

Fertility drugs and ovarian cancer risk: a critical review of the literature

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There is evidence that medications used for ovarian stimulation and *in vitro* fertilization may be associated with ovarian cancer. In this review, we attempt to describe this relationship according to the most recent epidemiologic data and to present the possible mechanisms on the molecular level that could potentially explain this correlation. Currently there is no proven relationship between any type of ovarian cancer and drugs used for infertility treatment. Overall, infertile women have increased risk for ovarian malignancies. Nulligravidas that received treatment are at increased risk for ovarian malignancy as compared to women that conceived after treatment. More studies with the appropriate statistical power and follow-up time, as well as with better adjustment for confounding factors, which coexist in infertile patients, are required to evaluate accurately the long-term effects of these drugs and procedures.

Keywords: ovarian cancer; ovulation induction; *in vitro* fertilization; infertility

Introduction

The process of *in vitro* fertilization (IVF) involves ovarian stimulation with a combination of drugs, oocyte retrieval, fertilization of the mature oocytes *in vitro*, and finally, transfer of the embryos back into the endometrial cavity, which has been adequately prepared for implantation. It is obvious that the main concern regarding the association between IVF and ovarian cancer is tightly related to the use of fertility drugs for the purpose of stimulating the ovaries to produce multiple follicles, a process known as superovulation. To date, there have been several studies that have tried to resolve the question of long-term effects of drugs used in the treatment of infertility and their possible connection with gynecological cancer. However, the majority of them involve a small number of women, for a limited follow-up period and without a detailed description of their treatments. The most commonly used drugs for infertility problems are the gonadotropins (biological or recombinant), clomiphene citrate, human chorionic gonadotropin (hCG), GnRH analogs (agonists and antagonists), and progesterone. Out of

these drugs, clomiphene citrate and gonadotropins cause excessive follicular development and multiple ovulation. In this paper, we perform a thorough review of the existing literature regarding the effects of fertility drugs on ovarian cancer risk.

Pathogenetic aspects of ovarian cancer

Several theories have been proposed to explain the association between ovarian cancer risk and fertility treatments. The theory of incessant ovulation, which implicates the repetitive damage and repair of the ovarian surface epithelium during ovulation in the pathogenesis of epithelial ovarian cancer, remains one of the most widely accepted.¹ Increased exposure to gonadotrophins increases the frequency of ovulation and because gonadotropins are used to treat infertility, such treatment might, theoretically, put patients at risk for ovarian cancer.² Finally, according to the follicle-depletion hypothesis, a diminished ovarian follicle reserve and advanced reproductive age often encountered in women suffering from infertility might increase the risk of developing ovarian cancer.³

Molecular and genetic aspects of ovarian cancer

Familial predisposition, genetic instability, immunologic, angiogenetic, and hormonal factors are related to the pathogenesis of ovarian cancer. Mechanisms that lead to ovarian cancer owing to genetic instability include deactivation of one or two alleles of tumor-suppressive genes, changes of the enzymes that act in DNA-repair, and increased oncogenic activity. The most commonly affected chromosome loci include 9p, 11q, and 22q.⁴

Mutations in the genes that encode metabolic and detoxification enzymes, such as GALT and GSTM, have been implicated in the development of ovarian cancer.⁵ Mutations in PTEN, a tumor-suppressive gene have been documented in certain histologic types of ovarian carcinomas.⁶ PTEN mutations as well as loss of heterozygosity (LOH) at locus 10q23.3 are quite common in ovarian endometriomas, as well as in endometrioid and clear cell ovarian cancers.⁷ K-ras is an oncogene that has been related to ovarian cancer. Mutations of K-ras are found in clear-cell ovarian carcinomas, especially in women with endometriosis. K-ras mutations were found in cancerous cells, but not in the neighboring cells with endometriosis or atypical endometriosis.⁸ According to those investigators, K-ras mutations are associated to malignant transformation of benign endometriosis to clear-cell carcinoma of the ovaries.⁸ In a rodent model, activation of the oncogenic K-ras or conditional PTEN deletion within the ovarian surface epithelium gave rise to preneoplastic ovarian lesions with an endometrioid glandular morphology. Furthermore, genetic recombination of the two mutations in the same model lead to the induction of invasive and widely metastatic endometrioid ovarian adenocarcinomas.⁹

Response of ovarian carcinomas to estrogen stimulation

Estrogens have been linked to the pathogenesis and growth of ovarian cancer. The key enzyme for estrogen biosynthesis or actually for the conversion of androgens to estrogens is aromatase. Tissue-specific aromatase expression is regulated by tissue-specific promoters located up-stream of a common coding region. Aromatase gene expression in malignant tumors of the ovary is primarily regulated by a promoter located in the 1.3/II region. These promoters

are stimulated by PGE₂ via a cAMP-PKA-dependent pathway. Thus, inflammatory substances such as PGE₂ often encountered in chronic inflammatory processes such as endometriosis may play an important role in inducing local production of estrogens that promote tumor growth.¹⁰

Physiologically, estradiol is being metabolized to estrone, a weak estrogen, by the action of the enzyme 17- β -hydroxysteroid dehydrogenase (17- β -HSD) type-2, which is being induced by progesterone in the endometrium. Seeger *et al.*¹¹ concluded that estradiol and its derivatives may have a variable impact on the survival and growth of ovarian cell lines and the quantification of these derivatives may be of prognostic value of the risk women have for the development of ovarian cancer. O'Donnel *et al.*,¹² have shown that the potential carcinogenic action of estrogen are mediated through estrogen receptors (ER- α). In ovarian cancer cell lines, genes controlled through ER- α mediated transcription had a three-fold increase in their expression, whereas there was no change in the expression of genes controlled by ER- β -mediated transcription.¹²

Growth factors such as TGF- α , TGF- β , and IGF-I have also been implicated to the development of ovarian cancer.¹³ Menopausal and premenopausal women with high-IGF-I serum levels are at increased risk of developing ovarian and other gynecological cancers (e.g., cervical and endometrial).¹⁴

Resistance to apoptotic mechanisms: deactivation of p53, Bcl-2 overexpression, Bax downregulation

Overexpression of antiapoptotic (Bcl-2) genes and underexpression of preapoptotic (Bax) factors, as well as deactivation of the p53 tumor-suppressive gene, through genetic mutations are often involved in the pathogenesis of malignancy. In a series of 109 patients with early stage epithelial ovarian carcinomas, the expression of p53 was inversely associated with tumor grade ($P = 0.014$), probability of persistent disease ($P = 0.016$), and cancer-specific survival rate ($P = 0.007$).¹⁵ Positive bcl-2 staining was associated with a favorable tumor grade distribution ($P = 0.034$), but not with the survival status.¹⁵ The combination of p53-bcl-2 expression was related to histopathologic subtype ($P = 0.032$), tumor grade ($P = 0.011$), persistent disease ($P = 0.014$), and risk of dying due to the disease ($P = 0.039$).¹⁵

The Bax status was not a prognostic factor, but the combination of p53-Bax expression showed an association with FIGO stage ($P = 0.014$), tumor grade ($P = 0.034$), persistent disease ($P = 0.006$), and risk of dying due to the disease ($P = 0.039$).¹⁵ The combined bcl-2-Bax expression was related to histopathologic subtype ($P = 0.045$) and tumor grade ($P = 0.022$).¹⁵

In a recent cohort study¹⁶ involving 77 healthy women, 161 women with benign gynecologic disease and 150 women with ovarian cancer, the levels of Bcl-2 were found to be elevated in the urine of patients with ovarian cancer and this finding may be of diagnostic and prognostic clinical importance.

Local tissue invasion and metastatic potential

Ovarian cancer has the ability to invade and spread to neighboring structures as well as in remote locations. The mechanism of tumor invasion involves the secretion of matrix metalloproteinases (MMPs), to penetrate the basal membrane and stroma. B-katenin and E-cadherin in combination with increased expression of MMPs probably play a role in the development of several malignant conditions including ovarian cancer.¹³ E-cadherin repression and the Wnt signal activation modulate β -catenin expression and translocation to the nucleus, which leads to changes in the gene expression and the susceptibility to epithelial-mesenchymal transition in epithelial ovarian cancer.¹³

Infertility drugs and ovarian cancer

Concerns about whether the use of fertility drugs increases a woman's risk of developing ovarian cancer arose initially by two studies^{17,18} suggesting that women who had taken fertility drugs had an increased risk of developing ovarian cancer. Whittemore *et al.*,¹⁷ were the first to examine the possible relationship between drugs used for infertility treatment and cancer. In their meta-analysis of 12 case control studies related to ovarian cancer, three out of 12 (including 526 cases and 966 controls) provided some information about fertility status and use of fertility drugs. According to their analysis, self-reported prior use of fertility medications was associated with an odds ratio of 2.8 (OR 2.8, 95% CI 1.3–6.1), for developing ovarian cancer as compared to no use. In that study, infertile women who took fertility drugs without ever being

pregnant, had a much higher risk to develop cancer (OR 27.0, 95% CI 2.3–315.6). In contrast, infertile women who had been treated for their problem and managed to get pregnant, had no increased risk of developing ovarian cancer (OR 1.4, 95% CI 0.52–3.6). However, editorials soon appeared to dispute the notion of an increased risk^{19,20} limited to the subgroup of nuligravid women, especially because the risk estimate was based on only 12 exposed cases and one exposed control.

Rossing *et al.*,¹⁸ examined 3,837 women who had been treated for infertility between 1974 and 1985 in a Seattle Medical Center. In that cohort, four invasive, five borderline and two granulosa-cell tumors were documented. The risk of developing ovarian tumor (of any type) in women who received fertility treatment was 2.5 times higher than the general population (95% CI 1.3–4.5). In women who received clomiphene citrate for 12 or more monthly treatment-cycles (5 of the 9 women), the relative risk was 11.1 (95% CI, 1.5–82.3). Clomiphene citrate use for less than a year was not associated with an increased risk of ovarian cancer. That study, despite its limitations raised serious questions, especially for the use of clomiphene citrate for more than 12 cycles.

Modan *et al.*²¹ studied a cohort of 2,496 infertile women treated between 1964 and 1974. In that cohort, 12 epithelial ovarian tumors were detected. The authors concluded that treatment with ovulation-inducing drugs did not appear to increase the risk for ovarian cancer (SIR 1.6, 95% CI 0.8–2.9).

In 2004, Brinton *et al.*²² reported on a cohort of 12,193 infertile women with a median follow-up period of 18.8 years. The results of that study were reassuring, as no positive connection between the use of clomiphene (SIR 0.8, 95% CI 0.4–1.5) and/or gonadotropin (SIR 1.1, 95% CI 0.4–2.8) and ovarian cancer had been established, even in the group of women with long follow-up period (more than 15 years). Moreover, no positive relationship had been shown between ovarian cancer and duration of treatment.

Most recently, Jensen *et al.*,²³ examined 54,362 infertile women with a median follow-up of 16 years. Analysis of the cohort revealed no overall increased risk of ovarian cancer after any use of gonadotropins (RR 0.83, 95% CI 0.50–1.37), clomiphene citrate (RR 1.14, 95% CI 0.79–1.64), human chorionic gonadotropin (RR 0.89, 95% CI 0.62–1.29), or

gonadotropin releasing hormone analogs (RR 0.80, 95% CI 0.42–1.51). Furthermore, the risk was not related to the number of cycles use, length of follow-up or parity.

Encouraging results regarding the effects of fertility drugs on ovarian cancer risk have also been revealed from a number of case-control studies.^{24,25} Mosgaard *et al.*²⁵ in a case control study including 684 patients and 1,721 age-matched population controls reported that nulliparous women had increased risk of developing ovarian cancer as compared to parous ones (OR 1.5–2.0). The subfertile nulliparous women who did not receive any treatment had a risk of 2.7 (OR 2.7, 95% CI 1.3–5.5) to develop ovarian tumors as compared to controls. The risk to develop ovarian cancer in nulliparous women who had received treatment was 0.8 (95% CI 0.4–2.0), whereas women who had already given birth after taking treatment was 0.6 (95% CI 0.2–1.3), as compared to subfertile women who had not been given any treatment. The authors concluded that in nulliparous women the risk of developing ovarian cancer is 1.5–2 times greater, whereas subfertility without treatment further increases that risk. The use of medical treatment did not seem to raise the risk for developing ovarian cancer in this group of infertile women.

In a meta-analysis of eight studies combining data from 1,060 patients and 1,337 healthy women there was a trend for increased risk for ovarian cancer in nulliparous women who used infertility drugs (OR 1.6, 95% CI 0.90–2.87), and for those who had been treated for more than 12 months (OR 1.54, 95% CI 0.45–5.27), nevertheless those risks were not statistically significant.²⁶

Similarly, Rossing *et al.*,²⁷ in a recent well-conducted case-control study that included 378 cases and 1,637 controls, reported a trend for increased risk of epithelial ovarian cancer in nulliparous women (OR 1.3, 95% CI 0.7–2.5) but not in parous women with a history of subfertility.

Nevertheless, all the case control studies are limited by the small number of patients reporting prior use of fertility drugs. For example, in a large case-control study,²⁴ based on 1,031 ovarian cancer cases and 2,411 hospital controls, only 15 cases and 26 controls reported prior fertility drug use.

In a recent meta-analysis of seven case-control and three cohort studies by Kashyap *et al.*,²⁸ women with ovarian cancer appeared to have a significantly

higher odds ratio of exposure to fertility drugs when they compared to normal controls (OR 1.52, 95% CI 1.18–1.97). When cases of ovarian cancer, however, were compared to infertile controls for exposure to infertility medications the OR (0.99, 95% CI 0.67–1.45) was not elevated. There is a trend, however, for untreated infertile controls to have a higher incidence of ovarian cancer than treated infertile patients when cohort data are considered (OR 0.67, 95% CI 0.32–1.41).

Another important aspect in the potential relationship between fertility drugs and cancer is the underlying cause of infertility; that is, different causes of infertility may impose different risk for developing ovarian cancer. Brinton *et al.*,²⁹ in a study that included 12,193 women with infertility treated between 1965 and 1988, tried to estimate the risk of developing ovarian cancer in those women as compared to women in the general population, and in relationship to the cause of infertility. Finally, medical records from 8,429 women were examined, with a median follow-up time of 18.8 years, whereas more than 80% of those had at least 15 years of follow-up. Subfertile women had almost double the risk of developing ovarian cancer as compared to the general population. (SIR 1.98, 95% CI 1.4–2.6). For women diagnosed with endometriosis, the risk was 2.5 times greater (RR 1.3–4.2); whereas in the group of women with primary infertility, the risk of developing ovarian cancer was even greater (RR = 4.19, 2.0–7.7).

Another question that has arisen is if fertility drug use is associated to certain histological types of ovarian cancer. Sporadic case reports have connected fertility drug use with clear-cell carcinoma, germ-cell malignant tumors, and malignant tumors of the granulosa cells.^{30,31} The rarity of those tumors makes the establishment of a possible true relationship very difficult. Granulosa-cell tumors are of increased interest, because animal and human *in vitro* models have shown that gonadotropins may be related to these tumors.^{32,33} In contrast, in a descriptive study from Finland,³⁴ a reduction in the frequency of granulosa-cell carcinomas of the ovary was noted in women who had been taking drugs for fertility treatment.

Others, however, have associated the use of infertility drugs to ovarian borderline carcinomas, with a relative risk of three to four as compared to the general population.^{18,26} Those findings, in correlation

with case reports of ovarian cancer diagnosed during or just after the end of treatment for infertility^{35,36} have lead to the suggestion that ovarian stimulation may provoke the development of “silent” tumors of high differentiation. Another possible explanation is that those findings could just reflect a detection bias due to intense and more thorough follow-up of those women. However, a recent case-control study by Cusido *et al.*,³⁷ which included 42 women with borderline ovarian tumors and 257 women with benign ovarian pathology, concluded that there is no evidence that ovulation induction treatment predisposes to the development of borderline ovarian tumors.

Studies focusing on the IVF procedure and cancer

Although these studies focused primarily on women exposed on infertility agents, a number of other studies have concentrated on exposures received during IVF. Venn *et al.* were the first to examine the incidence of various types of cancer—and especially gynecological ones—after IVF treatment in a cohort of 10,358 women who had been referred for IVF treatment in Australia between 1978 and 1992.³⁸ According to the authors, there was no increased risk of ovarian cancer in the IVF group. Although that study provided some reassurance, it had low statistical power. A second survey from the same investigators, which included almost 30,000 women, reached exactly the same conclusions.³⁹ According to the authors, women who had undergone IVF have no greater risk of suffering from ovarian cancer than the one expected from general population incidence rates. In a subsequent study,⁴⁰ 1,082 IVF cases were linked to the National Cancer Registry of Israel. Women that had undergone IVF treatments had higher than expected cancer rate as compared to the general population (SIR 1.91; 95% CI 1.18–2.91). Nevertheless, the authors concluded that this increase could not be attributed to IVF treatment, because when cancer cases diagnosed within 1 year of the IVF treatment were excluded from the analysis, the statistically significant excess risk of cancer disappeared (SIR 1.46; 95% CI 0.83–2.36).

Conclusions

It seems that till date there is no strong evidence to support a relationship between ovarian cancer and drugs used for infertility treatment. In most studies,

however, infertility itself seems to be an independent risk factor for gynecological cancer in general and nulliparous women seem to carry the biggest risk. When evaluating these studies one has to take into account that most are limited by small numbers of patients and/or short follow-up period. In addition is has to be taken under consideration that patients treated with fertility drugs in the past are just reaching the age of the peak incidence for ovarian cancer. Subsequent studies including larger populations, better adjustment for confounding factors, such as parity, contraceptive use, access to medical care, and type of gynecologic follow up may offer more accurate data in the future.

In summary, the existing literature on ovarian cancer risk associated with fertility drug treatment is reassuring but not definitive. Follow-up protocols for early detection of malignancy that include a detailed medical history and a meticulous physical examination must be established for those patients.

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Conflicts of interest

The authors declare no conflicts of interest.

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