The Controversial Association of the Treatment of Infertility With Fertility Agents and Development of Ovarian Cancer: What Should Patients Be Told?

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INTRODUCTION

Ovarian cancer remains the fifth leading cause of mortality in women.[1] There will be an estimated 23,400 new cases of ovarian cancer diagnosed in 2001 associated with 13,900 deaths. Unfortunately, despite enormous efforts, ovarian cancer does not have any curative therapy to date. The etiology of ovarian cancer still remains undefined as well. It has been suggested that family history, reproductive history, environmental factors, and diet may play a role in the development of ovarian cancer. Over the past decade, with the increased popularity and use of fertility drugs (FDs) for ovulation stimulation, there has been increased concern of a possible association between the use of FDs and ovarian cancer in both the literature and lay press. These concerns originated from the number of case reports, case-cohort studies, and case-control studies that suggested the possible association between FDs and ovarian cancer (Table 1).[2–12] However, conclusions from these studies have been inconclusive and have yet to definitively identify a causative relationship between FDs and ovarian cancer.

TABLE 1. SUMMARY OF REPORTS OF CASES OF OVARIAN CANCER ASSOCIATED WITH FERTILITY DRUGS[2-12]

Author	Study Design	Number of patients	Conclusion
Rossing et al	Case-cohort	3,837 infertility patients	Increased duration of CC may increase the risk of ovarian tumors
Venn et al	Case-cohort	5,564 exposed/4,794 unexposed	Small number of cases for conclusions to be drawn, long-term follow up needed
Whittmore et al	Case-control	2,197 cases/8,893 controls	Increased risk of ovarian cancer in women with history of FD treatment
Shushan et al	Case-control	200 cases/408 controls	Ovulation induction agents, specifically, hMG, may increase the risk of epithelial ovarian tumors
Mosgaard et al	Case-control	684 cases/1,721 controls	FDs were not associated with an increase risk compared to nontreated infertile women
Parazzini et al	Case-control	93 cases/273 controls	Elevated risk of ovarian borderline tumors in patients using FDs
Hull et al	Case report	1 case	Ovarian cancer 18 months after FD treatment with hMG
Grimbizis et al	Case report	2 cases	Supports potential association between ovulation stimulation with FDs and ovarian cancer
Ben-Hur et al	Case report	2 cases	Hyperstimulation ovarian syndrome may mask ovarian cancer and should be monitored closely
Nijmen et al	Case report	2 cases	Possible association between FDs and the risk of developing ovarian cancer
Carter and Joyce	Case report	1 case	FDs may act as promoters of ovarian carcinogenesis

CC=clomiphene citrate; FD=fertility drug; hMG=human menopausal gonadotrophin.

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PHARMACOLOGY

Fertility drugs are used in the follicular phase of the ovarian cycle to increase the serum concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which act to increase the maturation of multiple ovarian follicles and thus cause multiple ovulations (Fig.1).[13] The "threshold concept" suggests that the ovary will only respond to the additional FSH once above a threshold level.[14] Multiple ovulations will occur when the time during which the FSH serum concentration is above the FSH threshold is extended.[15] The general classes of fertility drugs that are used as indicated based upon the cause of infertility are antiestrogens, gonadotrophins, and gonadotrophin releasing hormone agonists.

TABLE 2. COMMON ADVERSE DRUG REACTIONS OF FERTILITY DRUGS

Fertility Drug	Adverse Drug Reaction
Clomiphene citrate	Hot flashes Visual disturbances Cervical mucus abnormalities Luteal phase defects Multiple births Enlargement of preexisting ovarian cysts
hMG	Ovarian hyperstimulation Nausea Vomiting Diarrhea Thromboembolism Multiple births
hCG	Headache Irritability Restlessness Fatigue Gynecomastia Pain at injection site
GnRH-AG (ie, leuprolide, goserelin)	Amenorrhea Dizziness Headache Insomnia Nausea Vomiting Irritation at injection site

hMG=human menopausal gonadotrophin; hCG=human chorionic gonadotrophin; GnRH-AG=gonadotrophin releasing hormone agonist.

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Clomiphene Citrate

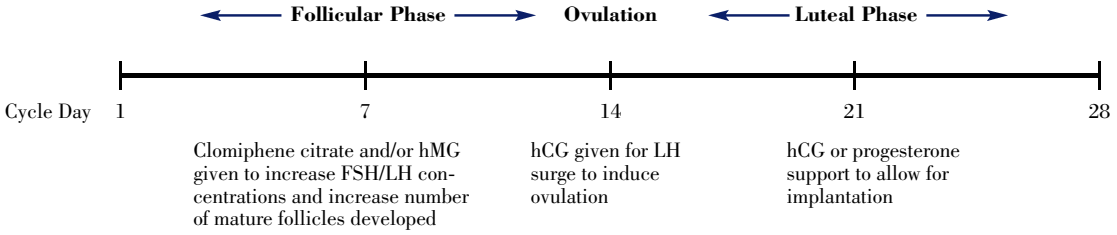
Clomiphene citrate (CC) (also known as Clomid or Serophene) is an antiestrogen agent that has been used in patients since the 1960s and was approved for the treatment of infertility associated with normogonadotrophic, normoprolactinaemic anovulation.[13] CC is a racemic, nonsteroidal triarylethylene compound that interacts with estrogen receptors at the hypothalamus, displacing endogenous estrogen and thus disrupting the endogenous estrogen negative feedback loop effect.[16] Ultimately, this will stimulate the release of FSH and LH to increase the maturation of multiple ovarian follicles and subsequent multiple ovulations. The usual dosage of CC can range from 50 mg/day to 250 mg/day usually given on days 3–7 of the menstrual cycle and up to 12 days in some patients.[13,16] The common adverse drug reactions (ADRs) associated with CC administration include hot flashes, visual disturbances, cervical mucus abnormalities, luteal phase defects, and multiple gestations (Table 2). The potential risk for development of ovarian cancer associated with CC therapy was first recognized in the study by Rossing and colleagues that found an increased incidence of borderline and invasive epithelial tumors after prolonged use of CC (12 cycles).[8]

Gonadotrophins

Human Menopausal Gonadotrophin and Human Chorionic Gonadotrophin

Human menopausal gonadotrophin (hMG) (also known as menotrophins, or Pergonal) is a combination of purified pituitary gonadotrophins, FSH and LH. This drug is purified from the urine of postmenopausal women. The primary indication for hMG is in patients with chronic anovulation secondary to pituitary insufficiency, and is not effective in patients with primary ovarian failure. hMG consists of 75–250 IU of FSH and LH per ampoule and is administered as an intramuscular (IM) injection for 9–12 consecutive

FIGURE 1. OVARIAN CYCLE AND ACTIVITY OF FERTILITY DRUGS



hMG=human menopausal gonadotrophin; FSH=follicle-stimulating hormone; LH=luteinizing hormone; hCG=human chorionic gonadotrophin.

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days during the follicular phase of the menstrual cycle.[16] Patients should be closely monitored during this treatment. Once follicles mature, 5,000–10,000 IU of human chorionic gonadotrophin (hCG) is administered IM to obtain adequate LH concentrations to induce ovulation. hCG is a gonad-stimulating polypeptide hormone secreted by the placenta, obtained from purified urine of pregnant women. Additional doses of hCG or progesterone are used for support during the luteal phase.[16] In general, hCG is well tolerated by patients with minor ADRs reported (Table 2).[12] On the other hand, among other minor ADRs (Table 2), hMG is associated with a serious ADR, ovarian hyperstimulation syndrome, classified from mild to severe (Table 3) that could delay or cause the misdiagnosis of ovarian tumors.[5,6,13] In addition, a meta-analysis conducted by Whitmore and colleagues suggested that the odds ratio of developing ovarian cancer was 2.8 for all women treated with FDs, compared to 0.91 for those with no prior history of FDs.[7] Furthermore, in the cohort of nulligravid patients, this odds ratio significantly increased to 27 for those that had received FDs compared to 1.6 that had no history of FD use.

Gonadotrophin Releasing Hormone Agonist

Gonadotrophin releasing hormone agonist (GnRH-AG) (also known as leuprolide, buserelin, or goserelin) decreases pituitary gland sensitivity, via pituitary receptor down-regulation, to gonadotrophin, thus decreasing the release of the pituitary gonadotrophins, FSH and LH, and ultimately suppressing ovulation. However, when GnRH-AGs are administered 3–4 weeks before gonadotrophin stimulation a "rebound effect" is set up that will increase the oocyte production from gonadotrophin stimulation.[16] GnRH-AGs are reasonably tolerated with few significant ADRs (Table 2).[13]

THE CONTROVERSY

Ovulation-induction medications were introduced just over 30 years ago and since that time there have been over 18 publications reporting 71 cases of ovarian cancer associated with the use of FDs.[16] Although there is a mortality of over 50% associated with the diagnosis of ovarian cancer, a recent pilot study by Rosen and colleagues found that less than 24% of the women surveyed understood that the treatment of ovarian cancer was not usually curative.[17] However, 80% of the women surveyed in this study were willing to accept a potential increased risk of ovarian cancer associated with the use of FDs. Another recent survey of reproductive endocrinologists and obstetrician/gynecologists by Shushan and Laufer reported that, although 70% of those surveyed were not convinced that there is an association or increased risk of ovarian cancer from ovulation induction FDs, 83% still addressed the risk while acquiring consent before treatment.[18]

Intuitively, considering two of the popular hypothesis for the etiology of ovarian cancer, the "incessant ovulation" and "elevated gonadotropin model," the association between FDs and ovarian tumors seems obvious. The "incessant ovulation" hypothesis proposes that with each ovulation, the ovary epithelium is disrupted or damaged, and there is no rest period to allow adequate time for repair, and these damaged epithelial cells could therefore be a source for neoplastic cells.[19] Similarly, the "gonadotrophin model" suggests that the continuous stimulation of the ovary by pituitary gonadotrophins, FSH and LH, while increasing the number of follicles as desired, may also increase the risk of malignant changes.[16] Both hypotheses suggest a more mitogenic vs mutagenic effect of FDs on the ovarian epithelium that may initiate or increase tumor growth.[20,21]

To date, retrospective studies have not attempted to delineate the relationship between treatment with FDs and ovarian cancer, but have attempted to demonstrate that a relationship exists. There have also been several

TABLE 3. CLASSIFICATIONS AND TREATMENT OF OVARIAN HYPERSTIMULATION SYNDROME[4]

Degree of Ovarian Hyperstimulation	Occurrence	Common Symptoms	Suggested Treatment
Mild	Relatively common	Bodyweight gain	Observation only
Moderate	Less common	Bodyweight gain Abdominal bloating Abdominal pain	Daily weights Abdominal girth measurements Monitor hematocrit
Severe	Relatively uncommon	Bodyweight gain Dyspnea Hypotension Oliguria Electrolyte imbalances Increased coagulability Ascites	All above plus: - Monitor fluid intake* - Maintain adequate urine output† - Reserve use of heparin for documented thrombosis - If ruptured, conservative surgical intervention as appropriate

* Restrict intake to maintain electrolyte balance.

† Suggest use of intravenous fluids and plasma expanders, not diuretics.

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TABLE 4. SUMMARY OF NEGATIVE STUDIES EVALUATING THE ASSOCIATION BETWEEN FERTILITY DRUGS AND OVARIAN CANCER[22,23]

Author	Study Design	Number of Patients	Conclusion
Potashnik et al	Retrospective cohort	1,197 infertility patients files	The association between FDs and increased risk for ovarian cancer was not confirmed
Venn et al	Case-cohort	20,656 exposed/ 9,044 unexposed	Transient increase in the risk for breast and uterine cancer associated with FDs but overall no difference. Unexplained infertility was associated with increased risk for ovarian and uterine cancer

FDs=fertility drugs.

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prospective case-control studies reported that have not found a relationship between FDs and ovarian cancer (Table 4).[22,23] There are limitations in the study design and data collection for both the retrospective and prospective studies. Common methodology limitations have included the small number of ovarian cancer cases, inconsistent reporting of FD use including dose and duration, prior oral contraceptive history, reproductive history, indication for FDs, adequate control arm (ie, infertile patients not treated with FDs), or sufficient duration of follow up. The type of study that is needed to definitively answer the question of whether there is a relationship between FD use and ovarian cancer will be a large prospective study that addresses not only the above limitations, but also clearly defines the causes of infertility, family cancer history, and has close monitoring throughout follow up for early detection.

WHAT SHOULD PATIENTS BE TOLD ABOUT FD TREATMENT?

The conclusions from the literature on whether or not a true relationship exists between treatment with FDs and the development of ovarian tumors still remain controversial. Although the numbers are small, the cases that have been reported cannot be ignored. Until conclusive results are reported from a well-designed prospective trial, that doubt and potential risk will remain. Despite its rarity, patients choosing to use FDs should be informed of the possible risk of ovarian cancer from their treatment. Moreover, these patients also need to be educated that, as of now, there is no cure for ovarian cancers, so that they completely understand the risk they are assuming with FD treatment.

Standard routine screening tools for ovarian cancer have not been established. However, annual transvaginal ultrasounds and monitoring serum CA-125 concentrations may assist in early detection of ovarian cancer. Women receiving ovulation stimulation should be counseled on the signs and symptoms of ovarian hyperstimulation syndrome. Also, if possible, the number of cycles of ovulation stimulation should be limited to less than 12. Although the risk for developing ovarian cancer from treatment with FD is real, it seems extremely rare, and at this time should not limit the use of FDs for the treatment of infertility.

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