Ovulation Induction and Ovarian Cancer: Is There a Link?

K R Rupinder, MD, K Pratap, MD

Department of O & G, Melaka Manipal Medical College, 75150 Melaka

Introduction

Ovarian cancer accounts for approximately 4% of all cancers occurring in women and ranks the fourth most frequent cause of cancer-related death in women. Despite aggressive treatment modalities the 5 year survival rate remains less than 30%[1]. Almost 2.5% of all live births/ year result from assisted reproductive techniques (ART)[2]. Concern has been expressed that exposure to fertility drugs (FD) might be associated with a risk of ovarian tumors. Given the grave prognosis of ovarian cancer and the increasing use of ART, for the past several years this has been a subject of much scientific debate. The likely magnitude of risk may be 2 – 3 times that of the general population, which is at most 4-5% in a woman's lifetime. Several case control and cohort epidemiological studies have attempted to address this issue but failed to specifically look at drug treatment as risk factor and research to date demonstrates conflicting results.

Review of Literature

Ovulation induction (OI) agents are commonly used in the treatment of infertility in patients with or without ovulatory disturbances. These agents include clomiphene citrate (CC), bromocryptine, gonadotropins (Gn), Gonadotropin releasing hormone (GnRH) and its analogues. In in vitro fertilization (IVF), combinations and different drug dosages of FD are given to stimulate production of multiple oocytes. Fertility drugs were first marketed since the 1960's. The first to hit the market was CC in 1967 followed 2 years later by human Menopausal Gonadotropin (hMG) & human Chorionic Gonadotropin (hCG)[3]. Until 1987, most IVF cycles used CC in combination with HMG followed by hCG. From 1987, GnRH agonists were introduced to replace CC. From 1990, the main drug regimen was GnRH agonist in combination with HMG or Follicular Stimulating Hormone (FSH) followed by hCG.

Commonly used ovulation induction agents:

1. **Clomiphene citrate (CC):** acts as an anti-estrogen directly on the hypothalamus, thereby stimulating the pituitary to produce more FSH and LH and leads to an increase in the circulating estrogen by 2 – 3 fold, doubling of ovulations/ cycle and increased progesterone levels.
2. **hMG/ FSH:** increases ovarian response by recruitment of new follicles; therefore multiple ovulation.
3. **HCG:** simulates function of LH in initiating ovulation.
4. **GnRH:** stimulates endogenous pituitary release of LH and FSH and subsequent folliculogenesis.

The FD could theoretically increase the risk of ovarian cancer by causing multiple ovulations and thereby increasing the trauma to the epithelial surface[4] or, a hyper-gonadotrophic state in itself may cause the transformation [5]; alternatively, the pathogenesis could be multi-factorial.

Studies done

Although initially it was thought that ovarian cancer risk might be increased by incessant ovulation 4, it was only 2 decades later that a report on 12 case-control studies suggesting that FD might not be safe had touched off much controversy[6]. It is reported that infertile women who had used FD were at a relative risk of 2.8 for invasive epithelial ovarian cancer and 4.0 for borderline ovarian tumor, compared to women of general population, in particular nulliparous women. Infertile

This article was accepted: 16 November 2005
Corresponding Author: Rupinder Kaur Ruprai, Department of O&G, Melaka Manipal Medical College, 75150 Melaka

women without FD use did not show an increased risk. The report concluded that:

- Women without children are just as protected from ovarian cancer by oral contraceptives (OC) as women who have children. Pregnancy, use of OCP, and breast-feeding, all have a protective effect against development of ovarian cancer. A woman's first pregnancy cuts her cancer risk by 40%, with each additional pregnancy reducing it by 14% more 3.
- Previous hysterectomy or bilateral tubal ligation (TL) has a protective effect on ovarian cancer risk.

The analysis only included a small number of women and provided no information about the FD prescribed, reasons for infertility, tumor size, or stage of the disease at diagnosis. Therefore, actual correlation between OI therapy and risk of ovarian cancer remained uncertain. Also, cases in this study included women whose exposure to FD's was most likely to have occurred in the 1950 - 1960's, a time when the currently popular drugs in question were not available.

Another case cohort study (between 1974 and 1985) found a significantly increased risk of ovarian tumors associated with long-term use of CC (_ 12 menstrual cycles). Ovarian tumors were twice as likely to develop in women with ovulatory abnormalities as in infertile women with other type of abnormalities. The risk of a borderline tumor was substantially higher than expected than in general population[7].

Subsequently another study found no association between CC use and ovarian cancer regardless of duration and use and concluded that[8]:

- There was no association between epithelial ovarian cancer and the use of the CC.
- The use of hMG might increase the risk of epithelial ovarian tumors by three fold.

A large multi-center prospective study[9] done to investigate the association between FD and ovarian cancer reported that:

- Compared to general female population, frequency of ovarian cancer was no greater than expected. Number of treatment cycles and type of FD did not show an association with increased incidence of ovarian cancer. There was no increase in risk in the women exposed to FD compared with those unexposed.
- Unexplained infertility was associated with an increased risk of ovarian cancer and this finding could be because for some women infertility may have been a presenting symptom when the underlying disease was cancer.

Drawbacks of this study were potential confounding factors not being adjusted for (parity, OCP use, and age at menarche, menopause and first birth). The number of treatment cycles prior to registration with IVF was not addressed. Short duration of follow up and borderline tumors were not included.

A review, which included papers published between 1966 and 1999 on association between ovarian cancer and FD's, suggested that the associations observed in most of these reports appear to be due to bias or chance rather than being causal. The most important sources of bias are inadequate confounder control for both parity and causes of subfertility[2].

Data collected[10] on infertility and FD from 8 case-control studies (between 1989 and 1999) concluded that infertility, but not FD use showed the strongest association with ovarian cancer. A link between ovarian cancer and certain specific causes of infertility (endometriosis and unknown causes of infertility) was pointed out. Some of these associations include:

- Among nulligravid women, attempts exceeding 5 years to become pregnant compared to that for less than 1 year increased the risk of ovarian cancer by 2.67 fold.
- Among nulliparous subfertile women, neither FD use nor more than 12 months of use was associated with increased risk.
- Nulliparous women who took FD and did not conceive were more likely to have non-invasive tumors (probably because they were under close surveillance), but not invasive types.
- Risk of cancer dropped with each successive pregnancy and risk associated with exposure to FD was greater in parous than nulliparous women.
- They found no association between FD use and overall risk of ovarian cancer.

Weaknesses of the study include a small number of cases using FD, and no details on infertility treatment, drug type, dose and number of cycles.

A meta-analysis review by Kashyap and Davis concluded that data obtained so far does not support an increased risk of ovarian cancer as a result of OI. There is a trend towards protection of infertile women from ovarian cancer via OI for patients who conceive [11].

A cohort analysis by Lerner-Geva et al concluded that cancer development and, as a consequence cancer existence, might not be caused by the OI, but rather provoked by the hormonal changes enhanced by it [12]. Its findings support the theory that underlying infertility may be associated with increased incidence of occult pre-existing malignancy.

Thus, results of studies showing an increased risk of ovarian cancer in women previously treated for infertility have been inconsistent and interpreted as evidence of a causal relationship [6,8,12]. No convincing evidence of increased risk of invasive ovarian cancer after treatment with FD's has emerged as seen in various studies [9-15]. However, increased incidence of borderline tumors has been significantly associated with use of FD's [6-8,10,13-16].

Factors that may modify the risk:

- **Nulliparity** increases the risk of borderline and invasive ovarian tumors [1,14]. Each intervening pregnancy reduces the risk by 19% [1,6,14] and this risk reduction is continued by further pregnancies [15,16].
- **Infertility** is an independent risk factor. It is important to note that women that do not have children may not be infertile. Subgroups of infertile population, namely nulliparous and women with unexplained infertility are at highest risk [8,9,16-18].
- **Exposure dosage:** Exposed nulliparous infertile women, and women with longer duration of FD exposures are at an increased risk [6,7]. More than 12 cycles of stimulation carry significant risk, especially for borderline tumors [7,8,18]. In 1995, guidance was issued to doctors by Royal College of Obstetricians and Gynaecologists (RCOG) to limit the prescribing of one drug (CC) to a maximum of 6 cycles [12].
- **Endometriosis:** The association with endometriosis is unclear. It has been postulated that both ovarian cancer and endometriosis share a common etiology, or that endometriosis is a pre-malignant lesion.
- **Polycystic Ovarian Syndrome:** Increased circulating levels of androgens and LH:FSH ratio, both have been implicated in carcinogenesis. Increased levels of LH may enhance oxidative stress. An indirect role of androgens has been proposed through conversion of androgens to estrogens and subsequent action of estrogens on ovarian receptors [15,16].
- **IVF techniques:** Striking short-term changes in hormone concentration could promote tumor growth in hormonally dependent pre-malignant lesion/ occult tumor, with only a brief time lag between exposure and cancer diagnosis. Traumatic injuries may occur due to repeated punctures of ovarian epithelium, resulting in high mitotic activity in the ovary, which may cause genetic changes which ultimately causes malignant transformation [2]. In addition, infertility itself compounds the risk.
- **Pelvic inflammatory disease (PID):** Each episode of PID promotes a greater inflammatory response, resulting in increased damage to ovarian areas and tubal structure. Tubal infertility was associated with 3-fold increase in risk of ovarian cancer [16].
- **Family history** shows strong positive association has been seen between first-degree relatives of infertile women for invasive epithelial ovarian cancer [12].
- **Genetic factors** can contribute to as much as 5 – 40% of all ovarian cancers [1,12].
- **Oral contraceptives:** The risk decreases with increased use of OC. Stable levels of estrogen and progesterone inhibit Gn's, thereby inhibiting ability to stimulate ovulation [1,16].
- **HRT:** An association between use of estrogen replacement therapy for > 5 years and risk of fatal ovarian tumors has been seen[6]. However, estrogen therapy lowers Gn levels and may also stimulate immune response [15]. Mortality falls with increasing time from last use of estrogen replacement, such that if not used for 15 years, women are at no increased risk of death from ovarian cancer 16.
- **Hysterectomy and Tubal ligation:** Both these procedures are postulated to protect against the risk by preventing carcinogens from ascending the genital tract. However, effects in decreasing the risk appear to wear off within 2 decades [16].
- **Breast-feeding:** Prolonged breast-feeding confers a protective effect. Low levels of estrogen and LH suppress ovulation [6,15].
- **Length of menstrual cycle:** Initiation and cessation of menstruation does not reflect initiation and cessation of ovulation. No significance of age at menarche (>12 years) and at menopause is seen [16].
- **Diet and Obesity:** Galactose and animal fat increase the risk where as, green vegetables and olive oil decrease the risk. Association between obesity and ovarian cancer risk are weak and inconsistent. However, obesity may affect serum hormone levels and therefore be a part of causal chain [19].

It appears that OCP, parity and breast-feeding, provide a reduction in risk for 2 or 3 decades after their cessation[15]. These protective factors suspend ovulation and inhibit Gn's.

Five theories have been proposed for causation and/ or progression of ovarian cancer:

1. **Fathalla's Incessant Ovulation Theory**[4]: trauma to the surface of the ovary that occurs with repeated follicular rupture and subsequent epithelial repair results in local trauma-induced genetic alterations instrumental in causing ovarian cancer.
2. **Genetic predisposition:** Both infertility and epithelial ovarian cancer are consequences of a common underlying genetic abnormality. It has been suggested that there are several more common mutations other than BRCA 1 & 2 genes, that could allow for sporadic ovarian cancers and that first-degree relatives of infertile women have an increased risk of developing ovarian cancer, but this is restricted to the relatives of infertile women without children (despite treatment) [20].
3. **Stadel's gonadotropin theory 5:** high levels of pituitary Gn's increase risk of ovarian cancer by either a direct stimulatory effect on ovarian surface epithelium (OSE) or indirect stimulation via steroidogenesis [21].
4. Theory by Risch 2: Ovarian cancer risk may be increased by excessive androgenic stimulation of OSE, such as in PCOS patients [16] and decreased by factors related to greater progesterone stimulation.
5. **Inflammation / Endometriosis Theory by Paulson**[2]: Inflammation (characteristic of endometriosis) might work in conjunction with, and in addition to ovulation and steroid hormones in mediating epithelial ovarian cancer risk [15,21].

Type of Ovarian Tumors Reported

Most ovarian cancers in relation to FD use have been of epithelial origin, however, granulosa cell malignancies have also been reported[2,6]. Other histological variants include: endometrioid carcinoma[7,20], Clear cell carcinoma[20], Malignant germ cell[22], and Sertoli-Leydig cell tumor (poorly differentiated) [14].

Borderline Ovarian Tumor

While the data regarding the possible association between FD and invasive ovarian cancer are inconclusive, there is evidence to suggest an association between OI and borderline ovarian tumors [6-8,13-17]. One reason for this is that these tumors are more common in young women and these women are under close surveillance during infertility investigation and treatment protocols.

There is evidence to suggest that rather than genetic germ-line mutation; these tumors might be associated with hormonal factors. The plausibility of this is heightened by the finding that estrogen receptor expression is a common feature of ovarian borderline tumors and that these lead to tumor promotion under the conditions of super-ovulation and high levels of estrogen induced by FD's [23]. This could imply that the differences between invasive and borderline tumors probably represent[2] different entities with different clinical behavior[13].

Fertility saving surgery can be performed safely in germ cell, borderline and early stage epithelial ovarian tumors in selected cases. A study analyzed the outcome of patients that received infertility treatment after conservative management of borderline ovarian tumors[24]. Recurrences observed remained histologically borderline. It concluded that OI might be considered after the diagnosis of a borderline ovarian tumor. A report stated the spontaneous pregnancy rates as 60 – 88% following fertility saving surgery[25]. Any increment in the rate of tumor recurrence following OI has not been demonstrated.

Conclusion

On balance, the current body of evidence is reassuring on this issue. Despite concern regarding the increasing use of FD, the incidence of ovarian cancer has remained stable in the past 2 decades[11]. However, there are limitations to the studies reporting to this association and a need for large prospective research before a causal relationship can be established. The current epidemiological data are insufficient to implicate conclusively specific fertility medications in ovarian carcinogenesis and provide reassurance that the observed link between the use of FD and ovarian cancer is casual, not causal.

References

1. Wakeley KE, Grendys EC. Reproductive technologies and risk of ovarian cancer. Curr Opin Obstet Gynecol 2000; 12 (1): 43-47.
2. Klip H, Burger CW, Kenemans P & van Leeuwen FE. Cancer risk associated with subfertility and ovulation induction. Cancer Causes and Control 2001; 11: 319-44.
3. Costigan K. Fertility shots: linked to cancer? Health 1993; Vol 7, Issue 5.
4. Fathalla MF. Incessant ovulation—a factor in ovarian neoplasia? Lancet 1971; 2: 163.
5. Stadel BV. The etiology and prevention of ovarian cancer. Am J Obstet Gynecol 1975; 123: 772-74.
6. Whittemore A, Harris R, Itnyre J & The Collaborative Ovarian Cancer Group. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case–control studies. II Invasive epithelial ovarian cancers in white women. Am J Epidemiol 1992; 136: 1184–03.
7. Rossing M, Daling J, Weiss N, et al. Ovarian tumors in a cohort of infertile women. N Engl J Med 1994; 331: 771-76.
8. Shushan A, Paltiel O, Iscovich J et al. Human menopausal gonadotropin and the risk of epithelial ovarian cancer. Fertil and Steril 1996; 65(1): 13-18.
9. Venn A, Watson L, Bruinsma F, Giles G & Healy D. Risk of cancer after use of fertility drugs with in-vitro fertilisation. Lancet 1999; 354: 1586-90.
10. Ness RB, Cramer DW, Goodman MT et al. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case–control studies. Am J of Epidemiol 2002; 155: 217-24.
11. Kashyap S, Davis OK. Ovarian cancer and fertility medications: A critical appraisal. Semin Reprod Med 2003; 21(1): 65-71.
12. Lerner-Geva l, Geva E, Lessing JB, Chetrit A, et al. The possible association between in vitro fertilization treatments and cancer development. Int J Gynecol Cancer 2003; 13: 23-27.
13. Shushan A, Paltiel O, Schenker JG. Induction of ovulation and borderline ovarian cancer- the hormonal connection? Eur J Obstet & Gynecol. 1999; 85: 71-74.
14. Venn A, Healy D, McLachlan. Cancer risks associated with the diagnosis of infertility. Best Practice and Research clinical Obstet & Gynecol 2003; 17(2): 343-67.
15. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst 1999; 91(17): 1459-67.
16. Edmondson RJ, Monaghan JM. The epidemiology of ovarian cancer. Int J Gynecol Cancer 2001; 11: 423-29.
17. Tourgeman DE, Lu JJ, Boostanfar R, et al. Human chorionic gonadotropin suppresses ovarian epithelial neoplastic cell proliferation in vitro. Fertil Steril 2002; 78(5): 1096-09.
18. Dor J, Lerner-geva L, Rabinovici J, Chetrit A, et al. Cancer incidence in a cohort of infertile women who underwent in vitro fertilization. Fertil Steril 2002; 77: 324-27.
19. Farrow DS, Weiss NS, Lyon JL, Daling JR. Association of obesity and ovarian cancer in a case-control study. Am J Epidemiol 1989; 129: 1300-04.
20. Nieto JJ, Rolfe KJ, MacLean AB, Hardman P. Ovarian cancer and infertility: a genetic link? Lancet 1999; 354: 649.
21. Murdoch WJ. Metaplastic potential of p53 down-regulation in ovarian surface epithelial cells affected by ovulation. Cancer Letters 2003; 191: 75-81.
22. Tewari, Krishnansu, Rose, Scott G, et al. Fertility drugs and malignant germ-cell tumor of ovary in pregnancy. Lancet 1998; 351(9): 107.
23. Abu-Jawdeh GM, Jacobs TW, Nilof J, Cannistra SA. Estrogen receptor expression is a common feature of ovarian borderline tumors. Gynecol Oncol 1996; 60: 301-07.
24. Beiner ME, Gotlieb WH, Davidson B, et al. Infertility treatment after conservative management of borderline ovarian tumors. Cancer 2001; 92(2): 320-25.
25. Ayhan A, Celik H, Taskiran C, Bozdag G, Aksu T. Oncologic and reproductive outcome after fertility-saving surgery in ovarian cancer. Eur J Gynecol Oncol 2003; 24(3-4): 223-32.

MCQ's for Ovulation Induction and Ovarian Cancer: Is There a Link?

1. Use of fertility drugs in relation to borderline ovarian tumors:
a. There is no risk of borderline ovarian tumors.
b. There is good evidence to support an association.
c. The clinical behavior of these tumors with use of fertility drugs is similar to that of invasive epithelial tumors.
d. Genetic germ line mutation is the underlying factor associated with their occurrence.
e. Detection of such tumors would imply a contraindication to use of fertility drugs.

2. The following have been implicated as risk modifiers with adverse effects with use of fertility drugs:
a. Length of menstrual cycle
b. Tubal ligation
c. Nulliparity
d. Exposure dosage
e. Obesity

3. The independent risk factor that modifies risk of ovarian cancer with fertility drug use is:
a. Infertility
b. Genetic predisposition
c. IVF techniques
d. PCOS
e. Endometriosis

4. The maximum exposure dosage of clomiphene associated with increased risk of borderline ovarian tumors is:
a. 6 cycles
b. 12 cycles
c. 1 year
d. 6 months
e. 24 months

5. Genetic predisposition for development of ovarian cancer with fertility drug use:
a. Contributes to as high as 80% of all ovarian cancers.
b. Could be a common underlying factor with infertility.
c. Plays an important role in pathogenesis of borderline ovarian tumor.
d. There is a weak association between first degree relatives of infertile women and invasive epithelial ovarian cancer.
e. It's an independent risk factor

6. With regard to fertility drugs used:
a. Malignancies have been reported with use of hMG.
b. HCG confers protective effects by inhibiting proliferation of ovarian epithelial cells.
c. Use of clomiphene for more than 1 year is not associated with an increased risk of ovarian cancer.
d. There is a well established relationship of gonadotropin use and ovarian cancer.
e. IVF techniques have shown negative association.