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Induction of ovulation and ovarian cancer: a critical review of the literature

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Objective: To critically examine the possible association between ovulation-inducing drugs and ovarian cancer.

Design: Medline literature review and cross-reference of published data.

Results(s): The studies that have adjusted for the effects of confounding factors such as duration of oral contraceptive use and number of pregnancies have noted an increased risk of ovarian cancer among infertile women who remain childless despite long periods of unprotected intercourse. Whether such women are at risk due to the primary basis for their infertility or factors such as ovulation-inducing drugs, has been the subject of several studies. Overall, the findings on ovarian cancer (especially invasive epithelial and non-epithelial) risk associated with fertility drug treatment are reassuring. However, a stronger association between fertility drug use and borderline tumors of the ovary has been observed.

Conclusion(s): Despite the overall reassuring findings of the available studies, there is a need for well-designed clinical trials to understand the possible carcinogenic effects of the ovulation-inducing drugs. (*Fertil Steril*® 2006; 85:819–26. ©2006 by American Society for Reproductive Medicine.)

Key Words: Ovarian cancer, ovulation induction, infertility

Epidemiological studies have linked epithelial ovarian cancer with both nulliparity (1, 2) and infertility (3, 4). In particular, concerns have been raised by some investigators regarding the risk of ovarian malignancy during or after ovarian stimulation. Other researchers have found no such association.

Induction of ovulation is most frequently used to restore ovulation in anovulatory patients with the aim of inducing unifollicular growth and release of a mature oocyte. Controlled ovarian hyperstimulation (COH) exposes the ovaries to supraphysiological levels of gonadotropins to result in multiple follicular development for assisted conception. The fundamental consideration is whether ovarian stimulation, under either or both circumstances, increases the chance of ovarian neoplasia as an independent risk factor. Although this is a seemingly straightforward question, ovarian cancer is a relatively rare outcome, and mostly occurs late in life, many years after normal childbearing age or fertility therapy.

In this article, we critically review the evidence in the medical literature relating the effects of fertility drug use to ovarian cancer risk. The relative strengths and weaknesses of

these studies and integration of available data in counseling infertile patients are presented.

COHORT STUDIES

Rossing et al. (3) examined a cohort of 3,837 infertile women from 1974 to 1985. A total of 11 cases of ovarian tumors were detected (four invasive epithelial, two non-epithelial, and five borderline tumors). Compared with the general population, the standardized incidence ratio (SIR; the ratio of the observed to the expected new cases) for invasive epithelial ovarian cancer was 1.5 (95% confidence interval [CI] 0.4–3.7) and was 3.3 (95% CI 1.1–7.8) for borderline tumors. Ever use of clomiphene citrate (CC) was associated with a relative risk of 2.3 (95% CI 0.5–11.4) compared with infertile women with no CC use. The risk was most pronounced in women with long-term use of CC (12 or more cycles) with a relative risk (RR) of 11.1 (95% CI 1.5–82.3) and was observed in both women with refractory infertility and those who became pregnant. There was no increase in risk of ovarian tumors associated with the use of hCG when cases were compared with the subcohort. This study was limited by small number of tumors with almost half of them being borderline tumors. Moreover, invasive epithelial, borderline, and granulosa cell (GC) tumors were

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all studied in one group despite the differences in tumor biology based on histologic subtype (Table 1).

Venn et al. (5) reported the largest cohort study evaluating the association between fertility treatment and ovarian cancer. They included 10,358 infertile women referred for IVF. Six malignant ovarian tumors were observed. A significant association was found between unexplained infertility and invasive epithelial ovarian cancers with a RR of 19.9 (95% CI 2.23–165) compared with the general population. About half of the women were given ovulation-induction agents and the other half received no treatment. There was no statistically significant difference in the incidence of ovarian cancer between the two groups. Relative to the general population, SIR of 1.7 (95% CI 0.55–5.27) was noted in the group treated with fertility drugs whereas the SIR was 1.6 (95% CI 0.52–5.02) in the unexposed group. Despite its large size, this study had major limitations. First, the follow-up was short for treated women (mean, 5.2 years) and second, even women who started but did not complete the IVF were included in the evaluation. Lastly, this study was limited by the young population of the cohort with a mean age of 39 years at the completion of the study. For these reasons, the effect of fertility drugs on ovarian cancer may have been underestimated.

Venn et al. (6) expanded the cohort to 29,700 women in 1999 with a follow-up of 7 years for the exposed group and 10 years for unexposed group. Women who underwent IVF were at no increase for ovarian cancer compared to the general population (SIR = 0.9). Again, women with unexplained infertility had significantly more ovarian cancers than expected (SIR = 2.6).

In a more recent article, Venn et al. (7) described the features of ovarian cancers in this cohort of 29,700 IVF patients. Twelve cancers of ovary were identified with the following histologic types: four serous, one mucinous, one seromucinous, three endometrioid, two clear cell, and one unknown type. A choriocarcinoma of the fallopian tube was also diagnosed in a woman with history of tubal infertility.

Modan et al. (8) studied a cohort of 2,496 infertile women treated between 1964 and 1974. Site-specific analysis revealed 12 ovarian cancers vs. 7.2 expected (SIR = 1.6, 95% CI 0.8–2.9). Sensitivity analysis revealed that nulliparity might have explained the increased risk of ovarian cancer. They concluded that treatment with ovulation-inducing drugs did not appear to increase the risk for ovarian cancer but its role could not be completely excluded.

Potashnik et al. in a prospective cohort study (9) followed 1,197 infertile women for a mean of 17.9 years. No increased risk of ovarian cancer was noted among those who had used fertility drugs compared with the unexposed group. The infertile group as a whole was not at higher risk compared with the general population. The SIR for the exposed group was 0.7 (95% CI 0.01–380) and for unexposed group was 1.4 (95% CI 0.02–7.49) compared to general population. As

with most of the available studies, this study had a low mean age at follow-up (44 years) and there was lack of control for confounding factors.

Doyle et al. (10) studied a cohort of 5,556 infertile women of whom 75% had received ovarian stimulation drugs. A total of six ovarian cancers were found in the cohort from 1990 to 1997. The RR was 0.59 (95% CI 0.12–3.00) for the exposed group. The data did not support a hypothesis linking infertility treatment involving ovarian stimulation with increased ovarian cancer during the follow-up period.

Recently, Brinton et al. (11) reported a retrospective cohort study of 12,193 women who were evaluated for infertility during the period of 1965 to 1988 at five clinical sites and identified 45 subsequent ovarian cancers in follow-up through 1999. The infertility patients had a significantly elevated ovarian cancer risk compared with the general population (SIR 1.98, 95% CI 1.4–2.6). When patient characteristics were taken into account and risks assessed within the infertile women, the rate ratios associated with ever usage were 0.82 (95% CI 0.4–1.5) for CC and 1.09 (95% CI 0.4–2.8) for gonadotropins. There were higher, albeit non-significant, risks with follow-up time, with the rate ratios after 15 or more years being 1.48 (95% CI 0.7–3.2) for exposure to CC and 2.4 (95% CI 0.7–8.3) for gonadotropins. Although drug effects did not vary by causes of infertility, there was a slightly higher risk associated with CC use among women who remained nulligravid, based on six exposed patients (rate ratio 1.75; 95% CI 0.5–5.7). They concluded that despite generally reassuring results, slight but nonsignificant elevations in risk associated with drug usage among certain subgroups of users, supported the need for continued monitoring of long-term risks.

CASE-CONTROL STUDIES

One of the first studies to draw attention to a possible association between fertility drugs and ovarian cancer was reported by Whittemore and co-workers (12) who performed a collaborative pooled analysis using original data collected from 12 case-control studies of ovarian cancer diagnosed between 1956 and 1986. Only 3 of the 12 studies had data on infertility, use of infertility drugs, and epithelial ovarian cancer. A 2.7-fold increased risk of ovarian cancer was observed in infertile women who had used fertility drugs and 27-fold increased risk in the women who had never been pregnant before. In this study, infertile women who had not used infertility drugs experienced no increased risk of ovarian cancer compared with women without history of infertility. This study has been criticized for major limitations. It includes outdated infertility treatments such as pituitary radiation, conjugated estrogen, and diethylstilbestrol (DES). No information on duration or type of infertility is provided and cases are not controlled for confounding factors such as oral contraceptive (OC) use or family history of ovarian cancer (Table 2).

TABLE 1**Selected cohort studies of ovarian cancer risk and fertility drugs.**

Author	Median age at end of follow-up (y)	Mean length of follow-up (y)	Total cohort size (no. of ovarian cancer)	SIR (95% CI): comparison with general population		RR (95% CI): drug use vs. no use		Confounding control
Rossing et al. (3)	41.5	11.6	3,837 (11)	No drug	1.4 (0.2–5.0)	Clomiphene	2.3 (0.5–11.4)	Parity, oral contraceptive, weight, cause of infertility
				Clomiphene	3.1 (1.4–5.9)	>12 cycles	11.1 (1.5–82.3)	
				hMG	5.6 (0.1–31.0)	hCG	1.0 (0.2–4.3)	
Venn et al. (5)	39	7	29,666 (13)	No IVF	1.2 (0.5–2.6)			Cause of infertility
				IVF	0.9 (0.4–1.8)			
Modan et al. (8)	50	21.4	2,496 (12)	No drug	1.6 (0.6–3.5)			Not indicated
Potashnik et al. (9)	44.8	17.9	1,197 (2)	Clomiphene	2.7 (0.9–5.8)	Treatment	0.5 (0.02–7.49)	Not indicated
				No drug	1.35 (0.02–7.49)			
Doyle et al. (10)	46	15.5	5,556 (6)	Treatment	0.68 (0.01–3.80)	Treatment	0.6 (0.1–3.0)	Parity
				No drug	1.7 (0.2–6.0)			
Brinton et al. (11)	47	19.4	12,193 (45)	Treatment	0.8 (0.2–2.2)	Clomiphene	0.8 (0.4–1.5)	Oral contraceptive, family history, parity
				No drug	2.1 (1.4–3.0)			
				Clomiphene	1.8 (1.0–3.0)			
				hMG	2.3 (0.7–5.3)	hMG	1.1 (0.4–2.8)	

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TABLE 2**Selected case-control studies of ovarian cancer risk and fertility drugs.**

Author	Type of controls	No. of cases (% treated)	No. of controls (% treated)	Comparison	OR (95% CI)	Covariates
Whittemore et al. (12)	Hospital and population	718 (2.8)	1,236 (0.9)	Fertility drugs vs. no infertility Nulligravids	2.8 (1.3–6.1) 27.0 (2.3–316)	Age, study site, family history
Ness et al. (13)	Population	1,060 (14.1)	1,337 (15.0)	Gravids Fertility drugs vs. no use Nulligravids	1.4 (0.5–3.6) 1.0 (0.8–1.3) 1.8 (0.7–4.4)	Cause of infertility, parity, family history
Franceschi et al. (14)	Hospital	195 (1.0)	1,339 (1.1)	Gravids Fertility drugs vs. no use	0.7 (0.5–1.0) 0.7 (0.2–3.3)	Oral contraceptive, parity, age
Shushan et al. (15)	Population	164 (12)	408 (7.1)	Fertility drugs vs. no use Clomiphene	1.3 (0.6–278) 0.9 (0.3–2.3)	Age, parity, family history, weight
Mosgaard et al. (16)	Population	684 (20.7)	1,721 (23.8)	hMG Fertility drugs vs. no use Clomiphene	3.2 (0.9–11.8) 0.8 (0.4–2.0) 0.7 (0.2–2.0)	Age, oral contraceptive, weight
Parazzini et al. (18)	Hospital	971 (0.5)	2,758 (0.4)	hMG Fertility drugs vs. no use >6 cycles	0.8 (0.2–3.7) 1.1 (0.4–3.3) 1.0 (0.2–3.8)	Oral contraceptive, family history, parity
Parazzini et al. (20)	Hospital	1,031 (1.5)	2,411 (1.1)	Fertility drugs vs. no use	1.3 (0.7–2.5)	Oral contraceptive, family history, parity

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Ness et al. (13) published a reanalysis of pooled data from seven case-control studies with 4,644 cases diagnosed from 1989 to 1999 and 7,182 population controls. Among nulligravid women with infertility for more than 5 years compared with those treated for less than 1 year, the risk of ovarian cancer was increased 2.67-fold (95% CI 1.91–3.74). However, no association between fertility drug use and the overall risk of invasive ovarian cancer was found (odds ratio [OR] = 0.97; 95% CI 0.76–1.25). In addition, increasing duration of fertility drug use (CC and hMG) was not associated with increased risk. Separate analyses of cancer in nulligravid and gravid women showed a nonsignificant increase in the OR for nulligravid women exposed to fertility drugs (OR = 1.60; 95% CI 0.90–2.87). However, Ness et al. found that fertility drug use was associated with a significantly increased risk of borderline serous ovarian tumors when analysis by histologic subtypes of cancer was performed (OR = 2.43; 95% CI 1.01–5.88). An elevated risk was not noted with any other borderline or invasive subtypes.

In the case-control study by Franceschi et al. (14), a medical diagnosis of infertility was not associated with an increased risk of ovarian cancer. The RR of ovarian cancer in the exposed infertile population compared with the unexposed population was 1.3 with 95% CI 0.7–2.4. However, this study was limited by lack of information on cause of infertility and type of fertility treatment.

Shushan et al. (15) conducted a case-control study on a combined case group of invasive and borderline epithelial ovarian tumors and a case group including only women with borderline tumors. Compared with women without a history of infertility, infertile women who had never used fertility drugs had a crude RR of 1.3 (95% CI 0.6–2.7) of an ovarian tumor, whereas the RR for infertile women who had ever used fertility drugs was 1.8 (95% CI 1.0–3.3). When adjustment was made for confounding factors, the risk associated with fertility drugs became nonsignificant. When the analysis was restricted to borderline tumors, the RR was 3.5 (95% CI 1.2–10.1). The adjusted RR with CC use was 0.9 ($P=NS$) for epithelial ovarian cancers and 1.3 ($P=NS$) for borderline tumors. However, the RR with hMG use was 3.2 (95% CI 0.9–11.8) for the combined case group and 9.4 (95% CI 1.7–52.1) for the borderline tumors. As mentioned earlier, this is contrary to the findings of Rossing et al. (3). The investigators provided no information on types of infertility. Although this study had the strength of including cases through Israel Cancer Registry with histologic verification in all cases, it was limited by lack of information on specific causes of infertility and the fact that 36% of cases had died before contact was established, which could have caused selection bias.

Mosgaard et al. (16) conducted the largest case-control study with 684 cases of epithelial and non-epithelial ovarian cancer and 1,721 controls. The risk of ovarian cancer was not increased among treated infertile women compared with

unexposed infertile women. The risks were similar between nulliparous (OR = 0.8) and parous women (OR = 0.6).

Mosgaard et al. in another case-control study (17), assessed the risk of borderline ovarian cancer among infertile women treated with fertility drugs. The analysis included 231 cases and 1,721 controls during the period 1989 to 1994. The OR for borderline ovarian cancer among infertile untreated nulliparous women compared with fertile nulliparous women was 1.9 (95% CI 0.76–4.89). The OR for borderline ovarian cancer among treated nulliparous women compared with untreated infertile nulliparous women was 1.5 (95% CI 0.51–4.39) and the OR among treated parous women compared with untreated infertile parous women was 1.5. They concluded that there was no statistically significant increase in the risk of borderline ovarian cancer among nulliparous women who were treated with fertility drugs compared with nulliparous untreated infertile women. The same was true about treated parous women compared with untreated parous infertile women.

Parazzini et al. (18) conducted a case-control study with 971 cases of invasive epithelial ovarian cancer and 2,758 hospital controls. In comparison with women who had never used fertility drugs, the multivariate OR for women who had taken fertility drugs was 1.1 (95% CI 0.4–3.3). This study showed reassuring evidence of the absence of a strong association between fertility drugs and subsequent risk of developing invasive epithelial ovarian cancer.

In another case-control study, Parazzini et al. (19) compared 93 patients with borderline ovarian tumor with 273 hospital-based controls. They found statistically significant increase in the risk of low malignant potential tumors in patients who had previously used fertility medications (OR = 27.5). This study was limited with very small number of cases (only four) who had used fertility medications.

Recently Parazzini et al. (20) published a study of 1,031 hospital cases of invasive epithelial ovarian cancer diagnosed from 1992 to 1999 and 2,411 hospital controls. A total of 15 cases and 26 controls reported use of fertility drugs. The corresponding OR was 1.3 (95% CI 0.7–2.5). The OR was 0.6 among nulliparous women and 1.9 among parous ones. An apparently stronger association, although not significant, was found between fertility drug use and ovarian cancer risk in parous women.

In a recent meta-analysis of seven case-control and three cohort studies, Kashyap et al. (21) systematically evaluated the literature regarding the relationship between assisted reproductive technology (ART) and ovarian cancer. This meta-analysis showed a significantly elevated risk for exposure of infertility medications and ovarian cancer in subjects who underwent ART compared with general population controls (1.52; 95% CI 1.8–1.97). When cases of ovarian cancer were compared with infertile controls for exposure to infertility medications, the OR (0.99, 95% CI 0.67–1.45) was not elevated. However, cohort data comparing outcome in

treated infertile patients with untreated infertile patients suggested that treated patients may tend to a lower incidence of ovarian cancer (OR = 0.67; 95% CI 0.32–1.41). There are several fundamental problems with this meta-analysis. First, it did not explore the possibility of a dose–response relationship between fertility medications and ovarian cancer. Second, the follow-up of these patients was limited. Third, invasive epithelial tumors, borderline tumors, and non-epithelial tumors were all studied in one group despite their different pathogenesis.

DESCRIPTIVE STUDIES

Since 1982, case reports on 66 women with a malignant or borderline ovarian tumor during or after infertility treatment have been published (22–33). Histologic types of these tumors include 34 invasive epithelial ovarian cancer, 16 borderline tumors, 15 GC tumors, and 1 malignant teratoma. The type of infertility is frequently not specified and few case reports included information on potentially confounding factors. Some concern has been expressed as to whether the association between fertility drugs and ovarian cancer can be explained by detection bias. One of the cases series (28) found that all of the women studied became pregnant after removal of their GC tumors. Thus, there was a concern that they actually had had their tumors before infertility treatment started. Furthermore, Lais et al. (34) found an increased frequency of ovarian tumors during microsurgery for infertility treatment. This finding may reflect an increased likelihood of detection of ovarian tumors in women undergoing infertility surgery rather than an effect of fertility drug use on ovarian cancer risk.

DISCUSSION

Two hypotheses have postulated ovulation as potential biologic promoters of ovarian cancer. The most widely accepted hypothesis suggests that epithelial ovarian carcinoma results from repeated ovulations, where the cumulative effects of each minor trauma to the ovarian epithelium can lead to malignant transformation (Fathalla's incessant ovulation hypothesis) (5). As a result of ovulation, the ovarian surface epithelium is also exposed to estrogen (E)-rich follicular fluid (FF). Support for this theory lies primarily in the well-established protective effects of multiparity, breast feeding, and OC use—all conditions in which ovulation is suppressed. The second hypothesis suggests that persistent exposure of the ovary to endogenous and exogenous gonadotropins in conjunction with secondarily elevated E₂ concentration, may be directly carcinogenic (35). Indirect support for this hypothesis is provided by the detection of gonadotropin receptors in experimentally induced ovarian tumors. Estrogens have been shown to stimulate cell proliferation in cells containing estrogen receptors (ER), and use of E replacement therapy has been suggested to cause an increased risk for ovarian cancer in several studies (35, 36). Alternatively, OCs may diminish the risk of premalignant genetic

abnormalities by decreasing the number of ovulations, which at subsequent stages, would otherwise respond to ER-mediated E action. Contrary to E, P has been proposed to exert a protective role against ovarian cancer (37). Epidemiological evidence has demonstrated a reduced risk of ovarian cancer for those women using progestin-only contraceptives (38). Decreased P receptor (PR) is found in ovarian malignancies (39), and PR expression is found to be related to improved survival in ovarian cancer patients (40), possibly through mechanisms of P-mediated inhibition of cell proliferation and induced apoptosis (41). The increased serum E-to-P ratio in women with oligoovulation may explain the increased incidence of ovarian cancer in this subgroup of infertile women (41).

There are now extensive clinical and epidemiological data linking endometriosis to an increased risk of ovarian cancer. Ness (42) has recently discussed similarities between the proposed etiology of ovarian cancer and the observed pathophysiology of endometriosis. The synchronous occurrence of endometriosis with endometrioid, clear cell, and mixed subtypes of ovarian cancers suggests transformation of endometriosis constituents into tumor cells. Such transformation can be due to loss of heterozygosity and somatic mutation of tumor suppressor genes, particularly PTEN/ MMAC/ TP53 (43). Nezhat et al. (44) have demonstrated an association between alterations in bcl-2 and p53 proteins with malignant transformation of endometriotic cysts. Endometriosis as a common cause of infertility can provide another possible explanation for ovarian carcinogenesis in this population.

Because subfertile populations have lower pregnancy rates than the general population, and low parity is an important risk factor for ovarian cancer, risk estimates for ovarian cancer reported in cohort studies that are solely based on comparison with general population are likely to be biased upward. Studies that have limited or no information on the specific types of infertility drugs are difficult to interpret. Instead, attention may be focused on the studies in which such information was available (3, 11, 13, 15). In these studies, increased crude risks in the range of 1.4–2.5 were found among infertile women who had ever used fertility drugs when compared to infertile women with no drug use. In the study by Rossing et al. (3), the risk of CC use was dose-dependent, with risk increasing with duration of usage. After controlling for the presence of ovulatory abnormalities, the RR associated with long-term use of CC (12 months or more) was 11.1 (95% CI 1.5–82). This was one of the few statistically significant findings and was similar in gravid and nulligravid women, as well as among women with or without ovulatory abnormalities. However, no such effect was found in Mosgaard et al. study (16). Shushan et al. (15) found no effect of CC use alone, but an increased risk with combined use of CC and hMG, especially for borderline tumors. Notably, none of the cohort studies had an extended length of follow-up greater than a median age above 50 years old, the age group in which most epithelial ovarian cancer

occurs. This may lead to a reduced observation of ovarian cancer based on length of follow-up.

In the three studies that have specifically examined the effect of fertility drug use on the risk of borderline tumors, a stronger association was observed than with the risk of invasive tumors (13, 15, 19). The plausibility of these results is heightened by the finding that ER expression is a common feature of ovarian borderline tumors (45). The high proportion of borderline tumors may also suggest that the increased risk is attributed to the increased medical surveillance and younger age of subfertile women. We should emphasize that the association between borderline tumors and ovulation-inducing drugs was not a consistent finding among different studies.

The relation between subfertility treatment and the risk of non-epithelial ovarian malignancies is even less clear. The study of Willemsen et al. (28) on fertility drugs and GC tumors suggests that these tumors may be present before administration of fertility drugs and that their growth may be triggered by increased gonadotropin levels. On the other hand, Unkila-Kallio and colleagues (31) showed that the incidence of GC tumors in Finland declined by nearly 40% from 1985 to 1994. In the same period of time, the use of CC and hMG increased 13-fold and 200-fold, respectively. They concluded this to be one piece of evidence that ovulation inducers were unlikely to cause GC tumors of the ovary.

In general, epidemiological studies on fertility drug use and risk of ovarian cancer are hampered by methodological problems, such as small study size, short follow-up time, and low prevalence of infertility and fertility drug use. This makes it possible that the effect of fertility drug use on ovarian cancer risk has been underestimated. In most studies there has been a lack of information on confounding factors such as OC use or family history of ovarian neoplasia. Furthermore, analyses have not always been performed separately for different types of ovarian tumors. Ideally, invasive epithelial tumors, borderline tumors, and non-epithelial tumors should be analyzed separately.

In summary, the findings to date on ovarian cancer (especially invasive epithelial carcinoma and non-epithelial neoplasia) risk associated with fertility drug treatment are reassuring, but not definitive. A stronger association has been observed between fertility drug use and borderline tumors of the ovary. This finding, however, is not consistent among the available studies to date.

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