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Research Paper

An Increased Risk of Borderline Ovarian Cancers Following Use of Fertility Medications

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Abstract
Women who are infertile and require ovarian stimulation and assisted reproductive technologies (ART) must deal with challenging difficulties. The greatest concern is the possibility that utilizing hormones will raise their risk of developing cancer. The inability to distinguish cancer risk from the underlying issue of infertility as a whole is one of the major obstacles to measuring cancer risk following ART. A key risk factor for breast, endometrial, and ovarian cancer is the failure to conceive or the delay of conceiving. Medline literature review and cross-reference of published data. The following keywords were used to search the published literature in Medline and Cochrane: ovulation induction, reproductive techniques, clomiphene, in vitro fertilization, fertility agents, female/adverse effects, female/toxicity, gonadotropins/adverse effects or gonadotropins/toxicity, and "neoplasms or cancer." The evaluation included 95 publications in all. The risk of endometrial cancer may rise with high doses or frequent cycles of clomiphene citrate, according to limited evidence, albeit the confounding effects of polycystic ovarian disease and obesity are not generally taken into account. The risk of borderline ovarian carcinoma was slightly raised in several studies by ART. Breast, cervical, endometrial, ovarian, thyroid, and melanoma cancers, as well as colon and melanoma, are not made more likely by fertility therapies. Fertility medications do not appear to significantly raise the chance of developing invasive ovarian, endometrial, breast, or other cancers, and being pregnant early in life is a very important protective factor, so women can feel at peace about this.

Keywords: *Borderline tumors, Ovarian Cancer, Individual Fertility Drugs.*

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I. Introduction

The prevalence of male and female infertility is rising, and more women are turning to assisted reproductive technologies (ART) to become pregnant. According to estimates, 1% of births globally are thought to be the product of ART, and given the sociodemographic trend toward delaying childbearing until later in life for social and personal reasons, these numbers will likely rise. In addition to being common causes of infertility, conditions such being overweight or obese, heavy smoking, anovulation, endometriosis and null parity are also on the rise. These conditions are also independently linked to a higher risk of cancer (Luke *et al*., 2015). Additionally, there is a widespread fear in both the general public and among specialists that ovulation-inducing medications may make women more susceptible to endometrial and breast malignancies that are sensitive to estrogen by increasing the levels of sex hormones. The risk of ovarian cancer is also thought to be increased by mechanisms including repeated ovulation and ovarian damage after egg harvesting. When the confounding effect of infertility is eliminated, a recent systematic review and meta-analysis4 indicated that ART does not appear to be linked to an increased risk of cervical, ovarian, or endometrial cancer. In order to encourage unimolecular development and the release of a mature egg, induction of ovulation is most usually utilized to restore ovulation in ovulatory patients. In order to produce multiple follicular developments for assisted conception, controlled ovarian hyper stimulation (COH) exposes the ovaries to supraphysiological doses of gonadotropins (Saso *et al*., 2015; Brinton *et al*., 2013) . The main question is whether ovarian stimulation, in either case or both, raises the likelihood of ovarian neoplasia as a separate risk factor. Ovarian cancer, however it may seem like a simple query, is a relatively uncommon event that typically manifests in later years, any years following the normal childbearing age or fertility treatment. Rossing *et al*., (1994) looked at a cohort of 3,837 infertile women. A total of 11 ovarian tumor cases were found (four invasive epithelial, two nonepithelial and five borderline tumors). 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 when compared with the general population. A relative risk of 2.3 (95% CI 0.5-11.4) was found between infertile women who had ever used clomiphene citrate (CC) and those who had never used it. With a relative risk (RR) of 11.1 (95% CI 1.5- 82.3) and being found in both women with refractory infertility and those who became pregnant, the risk was more pronounced in women with long-term usage of CC (12 or more cycles), when cases and the sub cohort were compared, there was no increase in the incidence of ovarian cancers related to the use of hCG. The study was constrained by the small number of tumors, nearly half of which were borderline tumors. Furthermore, despite the differences in tumor biology based on histologic subtype, invasive epithelial, borderline and granulosa cell (GC) cancers were all investigated in a single cohort.

The largest cohort study examining the relationship between reproductive therapy and ovarian cancer was published by Venn *et al*. (2001 & 2003)10,358 infertile women who were referred for IVF were among them. There were six malignant ovarian tumors found. Unknown infertility and invasive epithelial ovarian cancer were found to be significantly correlated, with a risk ratio (RR) of 19.9 (95% CI 2.23-165) when compared to the general population. Ovulation-inducing medications were administered to about half of the women, while the other half got no therapy. Between the two groups, there was no statistically significant difference in the incidence of ovarian cancer. In the group receiving fertility medication, a SIR of 1.7 (95% CI 0.55–5.27) was observed, whereas the SIR in the group not receiving treatment was 1.6 (95% CI 0.52-5.02). This study had many shortcomings despite its magnitude. First of all, the follow-up period for treated women was brief (mean, 5.2 years), and secondly, even those women who began IVF but did not complete it were taken into account when evaluating the results. The cohort's youthful population, with a mean age of 39 at the end of the study, was the final constraint on this research. The impact of reproductive medications on ovarian cancer may have been overestimated as a result of these factors.

Recently, Brinton *et al*., (2004) published the results of a retrospective cohort research that included 12,193 women who had been assessed for infertility at five clinical sites. They found that 45 ovarian malignancies had developed since then, with follow-up continuing through 1999. Comparing infertile patients to the general population, they had a considerably higher risk of ovarian cancer (SIR 1.98, 95% CI 1.4-2.6). The rate ratios related 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 when patient characteristics were included and risks were evaluated in the infertile women. With time, the hazards increased, however they were not statistically significant. After 15 years or longer, the rate ratios for exposure to CC were 1.48 (95% CI 0.7-3.2) and gonadotropins were 2.4 (95% CI 0.7- 8.3). Based on six exposed patients, there was a slightly greater risk linked with CC usage among women who remained nulligravid, despite the fact that drug effects were unaffected by the causes of infertility (rate ratio 1.75; 95% CI 0.5-5.7). They came to the conclusion that, despite overall encouraging findings, minor but insignificant increases in the risk of drug use among particular user groupings justified the necessity for ongoing monitoring of long-term dangers.

A medical diagnosis of infertility was not linked to a higher risk of ovarian cancer in the case-control study by Franceschi *et al*. The risk ratio (RR) of ovarian cancer in the exposed infertile group was 1.3 (95% CI: 0.7–2.4) compared to the unexposed population. The absence of data regarding the aetiology of infertility and the type of fertility treatment, however, hampered this study.

- Ness *et al*., (2002) compared 93 patients with borderline ovarian tumors to 273 hospital-based controls in a different case-control study. In patients who had previously taken fertility drugs, they discovered a statistically significant increase in the probability of low-grade possible malignancies tumors (OR 27.5). Due to the small number of instances (only four) that used fertility drugs, this study had certain limitations.

A study of 1,031 hospital cases of invasive epithelial ovarian cancer diagnosed from 1992 to 1999 and 2,411 hospital controls was just published by Kashyap *et al*.., (2004), a total of 15 cases and 26 controls disclosed using fertility medications. The corresponding OR was 1.3 (95% CI 0.7-2.5). Women who were nulliparous had an OR of 0.6, whereas those who were porous had an OR of 1.9. In porous women, there was an apparent higher link between the use of reproductive drugs and their risk of developing ovarian cancer; however, it was not statistically significant.

II. Materials and Methods

The following keywords were used to filter the published literature: ((OVULATION INDUCTION [TI] OR IVF [TI] OR "Reproductive Techniques, Assisted/adverse effects" OR clomiphene [ti] OR "in vitro fertilization"[ti] OR "Fertility Agents, Female/adverse effects" OR "Fertility Agents, Female/toxicity" OR "Gonadotropins/adverse effects" OR "Gonadotrop.

III. Results and Discussion

In an analysis of 11 trials with a total of 3,900,231 individuals, 118,320 of whom were provided ART, the incidence of gynecological cancer in the group getting ART was even lower (0.6%) than in the group not receiving ART (2.1%). 5. However, a few of the studies revealed an elevated risk of cancer in a few subgroups,

including women who had received many treatments with clomiphene citrate6. As a result, it's important to keep an eye on how infertility therapy affects women's health over time.

Table1 The major variations in hormonal therapies that prevent them from having equivalent cancer risks.

High endogenoussex steroids		**Hormonal contraception**	**Menopausaltherapy**	**Ovulationinduction**
Effect of or Main purpose	Overweight-obesity, sedentariety, early menarche, late menopause Estradiol (E2) Progesterone (P)	Ovulation Inhibition	Reduction of menopausal symptoms, prevention of hypoestroestrogenism consequences	Multiple (or sometimes single)ovulation induction Antiestrogens (clomiphene) or gonadotrophins
Usual composition		Mainly strong syntetic progestogens with a low dose of ethinil estradiol or estradiol	Very low dose natural estrogens and progesteroneor close to natural progestogens	High or very highestradiol levels produced by the ovaries
Estradiol levels	High physiological in premenopause, kept high after menopause(examp. obese);	Progesterone suppressed and mostly substituted by low dose ethinilestradiol or estradiol	Nowadays lower than premenopausal levels, but sometimes continuedmany year after natural menopause Substituted by progesterone or the progestogen two weeksmonth or all time time in continuous combined menopausal treatments	Natural progesterone (or diidrogesterone)supplemented
Progesterone or progestogens	Low or absent (anovulation orPCOS) High in ovulatingearly menarche, late menopausal	Completely inhibitedand substituted by the progestogen mostor all of the duration of treatment		Young not ovulatingor infertile or needing superovulation
Age and usual condition	Since puberty, higher levels after weight gain; usual lifetime condition of most female in industrialized countries	Young or premenopausal usually ovulating or not infertile	Postmenopausal, early menopause, hypoestrogenic conditions	Usually some days of supraphysiolgical estradiol exposure and two or few more weeks of progesterone after ovulation induction Observational, no RCT
Duration of exposure or treatment	Lifetime estradiolexposure Two weeks monthly progesterone exposurein ovulation age	Months to many years sometimes decades (expecially before firstfull time pregnancy) in fertile age	Months to many yearsafter menopause	Ovarian hyperstimulation syndrome, multiple pregnancies Maybe neutral
Number and quality of studies	Many large epidemiological	Many observational;no RCT	Many, some RCT but with E and P no more or infrequently used in Europe Thrombotic	Maybe neutral
Main risk	Estrogen or progesterone sensitiveCancers	Thrombotic	Slightly increased with E2+ syntetic progestogens;maybe neutral with micronized P; reduced if E2 only with Conjugated Equine Estrogen Neutral to protective ifwell balanced E +P	Maybe neutral
Breast cancer risk	Increased (obese postmenopausal, early menarche or late menopause, sedentaryhabits) Infertile	Neutral (slightlyincreased in older studies)	Neutral or maybeslightly increased	Not effective or countereffective (pregnancy or earlier pregnancyreduce female cancer risk)
Endometrialcancer risk	Highly increased (obese, early menarche or late menopause, sedentary habits, anovulation)	Greatly reduced	Not effective if properlyuse (global cancer risk, health and mortality notaffected or reduced in younger users)	
Ovarian cancer risk	Increased (obese, early menarche or late menopause, sedentary habits, infertile)	Greatly reduced		
Effect of givingup treatment	Advise that following or not the code against cancer rules is far moreimportant than any fertility drug effect	Countereffective(overall cancer risk is reduced in hormonal contraception users)		

A - Borderline tumors

Less malignant potential exists in borderline tumors. Patients do not think of them as ovarian cancer. They are substantially dissimilar to "genuine" ovarian cancer. Additional investigation is planned to confirm the finding in a wider sample of patients and to determine whether some women are more at risk than others. The numbers involved at this time are minimal.

In the IVF treatment group. Women who undergo multiple IVF cycles or high doses of ovarian-stimulating medications are found to be at an increased risk of developing ovarian cancer; therefore, these women should be informed of these risks when undergoing additional IVF treatment and may be advised to stop after three to six cycles (depending on which number of cycles would be associated with the high risk of ovarian malignancies).

With a frequency of 1.8-4.8 per 100,000 women years78, borderline ovarian tumors account for 15% of all ovarian cancer cases and have a low propensity for malignancy. They are noninvasive, indolent tumors that differ from invasive ovarian cancer in that they have a 95% 5-year survival rate and a great diagnosis (Romagnolo *et al*., 2016); they act differently from invasive malignancies because they are more prevalent in reproductive-aged women who do not have endometriosis, parity, or a history of surgery.

According to certain research, IVF treatment for infertility in women increased their chance of borderline ovarian tumors. It assessed the incidence of cancer in women who underwent IVF, taking into account infertile patients who did not use IVF as a reference population. A cohort of infertile patients was chosen based on a hospital registry. While 14 incidences of borderline ovarian tumors were found in 14,095 women who did not use IVF, 17 women out of the 7,544 who underwent IVF had such tumors. With an HR of 2.46 (95% CI 1.20-5.04), or 11 more borderline tumors per 10,000 women, women undergoing IVF had a higher borderline rate of ovarian tumors than those who did not. As a result, the evidence suggests that there is no appreciable rise in the risk of invasive ovarian cancer following use of fertility drugs, which should reassure infertile patients. (Grade B evidence, ASRM28), and no particular treatment has a different risk (Grade B evidence, ASRM). The greater risk with regard to borderline ovarian cancers is still up for debate. Numerous researches have indicated a slight increase, although the information is still insufficient (Grade C evidence, ASRM). However, it must be noted that these tumors typically have a favorable prognosis and are indolent. There is undoubtedly a need for more research (Kurta *et al*., 2012; Trabert *et al*., 2013). Figure 1 illustrates the management of borderline ovarian tumors.

B - Ovarian Cancer

Because ovarian cancer is a complicated condition with at least five distinct histological kinds, studies about it are subject to some limitations. Due to the low efficacy of screening with imaging techniques and/or serological analyses, high-grade serous carcinoma, the most prevalent kind frequently mistakenly referred to as "ovarian cancer," typically manifests after menopause and is typically discovered at a late stage. Any effects of ART may be significant given the terrible prognosis of this cancer. Breastfeeding, many pregnancies and oral contraception are protective factors (not frequently used in infertile patients). Women with infertility, nulliparity, late menopause, or a family history of ovarian cancer are at an elevated risk of developing invasive ovarian cancer regardless of the fertility treatments they receive.

Therefore, these confounding factors need to be taken into account when analyzing the association between the use of reproductive drugs and ovarian cancer. Ovarian cancer often develops after menopause, necessitating long-term monitoring. Because ovarian cancer has been linked to ovulation, it is conceivable that fertility medications could have a positive influence on the disease. According to the continual ovulation hypothesis, characteristics that lower ovarian cancer risk include multiparity and combination hormonal contraception. These factors are thought to lower lifelong ovulation rates. In contrast, using fertility drugs may increase your chance of developing ovarian cancer because they encourage multi-follicular ovulation, which raises the amount of epithelial inclusions on the ovarian surface epithelium and causes more mechanical trauma (Perr *et al*., 2015; Gronwald *et al*., 2016; Romagnolo *et al*., 2016).

C – Risk of Ovarian Cancer due to Individual Fertility Drugs

Whether anti-estrogens or gonadotropins were used, the majority of studies failed to detect any differences in the incidence of ovarian cancer based on these reproductive medicines. The largest study, which reviewed data on all the women tracked in Danish fertility clinics between 1963 and 199865, concentrated on the risk of cancer particularly associated with the use of fertility drugs. Women who received treatment with gonadotropins (risk ratio [RR] 0.83, 95% CI 0.50-1.37), CC (RR 1.14, 95% CI 0.79-1.64), hCG (RR 0.89, 95% CI 0.62-1.29), or gonadotropin-releasing hormone (GnRH agonist (RR 0.80, 95% CI 0.42-1.51), either singly or in combination, showed no overall increase in the risk of developing epithelia (Jensen *et al*., 2009; Kim *et al*., 2012).

Table 2 Drugs used to induce ovulation: consequences for patients and doctors as well as potential impacts on the risk of ovarian cancer.

	Ovarian cancer
Clomiphene	No meaningful increase in the risk of invasive ovarian cancer. (Grade B) Invasive ovarian cancer risk is not different with one fertility drug compared to another. (Grade B)
Gonado trophins	No meaningful increase in the risk of invasive ovarian cancer.(Grade B) Invasive ovarian cancer Risk is not different with one fertility drug compared to another. (Grade B) Maybe neutral (or reduced) Limited and principally from observational studies (Level 2-2 or lower). Infertility per se is a significant factor of risk (nulliparity, later pregnancies, lower Hormonal Contraception use; BRCA?) (Grade B) Detection and surveillance bias for borderline Ovarian cancers that arise in fertile age. *Same methodological issues
Progesterone	
Quality of evidence	
Main literature bias	

IV. Conclusion

The use of fertility treatments does not significantly increase the risk of cancer, doctors who specialize in this field can advise their patients. However, physicians and researchers must keep in mind that there are only a limited number of data available, most of which are derived from observational cohort and case-control studies that have the methodological problems already described. Breast, endometrial, and invasive ovarian cancers in particular are known to be at increased risk as a result of infertility. In these situations, fertility counseling is an excellent chance to improve the lifestyle choices that may have an impact on both fertility and cancer risk: such as height, weight, food, smoking, and exercise. Clomiphene may slightly raise the risk of endometrial cancer, especially when used in doses larger than 2000 mg and for longer than six cycles. The requirement for repeating cycles with clomiphene or the prevalence of PCOS and obesity among users are more likely causes of this increase.

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