Ovulation Inducing Agents and Cancer Risk: Review of Literature

Gianna Gabriella Impicciatore and Gian Mario Tiboni*

Sezione di Scienze della Riproduzione, Dipartimento di Medicina e Scienze dell'Invecchiamento, Facoltà di Medicina e Chirurgia, Università "G. d'Annunzio" Chieti-Pescara, Italy

Abstract: Over the past decades, the use of ovulation inducing drugs has been increasing. A possible causal link between fertility treatments (especially clomiphene citrate and gonadotrophins) and various types of malignancies, including cancers of female reproductive system, thyroid cancer and melanoma, has been postulated. The majority of the available studies on this subject suffers from methodological limitations, including the small number of outcomes, short and incomplete follow-up, and inability to control for potential confounders. Concerning ovarian cancer, while early studies led to the suggestion of an association between ovulation inducing agents and increased risk of malignancies, the majority of data do not support a causal link. An increased risk was recently observed in women giving birth after *in vitro* fertilization (IVF), but it appeared to be consequential to the infertile status rather than the effect of fertility drugs. More controversial are the results concerning breast cancer with some investigations suggesting an increased risk after exposure to ovulation inducing agents, especially clomiphene citrate, whereas others not supporting this concept. A possible trend towards an increased risk has been reported by some authors for endometrial cancer. Altogether, current data should be thus regarded as a signal for the need of further studies rather than being definitive in them.

Keywords: Cancer risk, clomiphene citrate, ovulation inducing agents, gonadotrophins, breast cancer, melanoma, ovarian cancer, thyroid cancer, uterine cancer, *in vitro* fertilization.

INTRODUCTION

Infertility is a common condition affecting between 15-20% of couples in developed countries [1]. The recurrence to infertility treatments, mainly IVF, has grown exponentially in recent decades, with exposure to ovulation inducing agents becoming common. In anovulatory women, ovulation inducing agents are given to restore ovulation, whereas during IVF programs ovarian stimulation aims at stimulating the growth of multiple follicles, an approach known as superovulation or controlled ovarian stimulation (COH). Clomiphene citrate (CC) and gonadotrophins (in their various preparations) are agents currently used as ovulation-stimulating drugs. GnRH analogs (agonist and antagonists), human chorionic gonadotrophin (hCG) and progesterone are commonly given in conjunction with ovulation inducing agents combination during controlled ovarian hyperstimulation to prevent premature LH surge, to ensure final maturation of eggs, and to support the luteal phase, respectively [2, 3]. These pharmaceutical agents have been referred in several epidemiological studies as fertility drugs (FD). It should be noted that ovarian stimulation regimens have undergone significant modifications over the years. Until 1987 most stimulated IVF cycles used CC in combination with human menopausal gonadotropins to induce multiple folliculogenesis followed by hCG for oocyte maturation before retrieval. Since 1987 GnRH agonists were introduced in COH and few years later GnRH antagonist came onto the market as alternative to GnRH antagonist to prevent untimely surges of LH [4, 5]. Currently, the most frequently used stimulation protocols are GnRH agonist long protocol, and GnRH agonist short protocol, GnRH antagonist protocol [6]. Two concepts are important for an optimized choice of protocol: the identification of ovarian response and the prevention of potential complications through the identification of patient at risk . It is well established that women who underwent gonadotropin stimulation fell into one of the three response categories high, intermediate or low responders [7]. Patients with PCOS (polycystic ovary syndrome) or PCO like features or with multifollicular ovarian appearance should be regarded as high responders. These patients are at risk of developing ovarian hyperstimulation syndrome (OHSS) which represents a potentially lethal iatrogenic complication of COH [8]. The management of high responders is mainly based on administration of FSH at low doses (100-150 IU/day). The use of GnRH antagonists should be favored, considering that this class of analogues have been shown to be safer than agonists in term of OHSS prevention. With regard to the intermediate responders, identified as those patients having a normal basal FSH and a normal ovarian volume with an adequate number of antral follicles, the first line of treatment may be represented GnRH agonist long protocol with the daily starting dose of FSH at 225-300 UI/day.

Despite their wide use, information on the potential long term effects of FD on the female reproductive system is limited. Recently, increasing attention has been focused on the possible cause-effect relationship between the use of ovulation inducing agent and the development of several malignancies, mainly of the ovary, breast, and endometrium. A link between ovulation stimulating drugs and these malignancies is theoretically possible considering that these drugs are known to raise circulating levels of estrogens and other sex hormones which are recognized as affecting the development and growth of ovary, uterine and breast cancer

*Address correspondence to this author at the Sezione di Scienze della Riproduzione, Dipartimento di Medicina e Scienze dell'Invecchiamento, Facoltà di Medicina e Chirurgia, Università "G. d'Annunzio", Chieti-Pescara, Ospedale "G. Bernabeo", Contrada Fontegrande, 66026, Ortona (Chieti), Italy; Tel: +39 085 9172289; Fax: +39 0871 540037;
E-mail: tiboni@unich.it

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and others cancer types, including thyroid cancer and melanoma, possibly.

In this article, the available studies assessing the possible effects of ovulation inducing agents, and fertility treatments on female cancer risk are reviewed.

Ovarian Cancer

Ovarian cancer is the fifth most frequent gynecological cancer and the leading cause of gynecological cancer deaths in Western Word [9]. The large majority (80-90%) of ovarian cancer derives from relatively pluripotent cells of the celomic epithelium. About 10% to 20% of epithelial ovarian neoplasms are borderline or low malignant potential tumors, which are characterized by a high degree of cellular proliferation in the absence of stromal invasion [10]. Among the invasive epithelial ovarian cancers (EOC), about 75-80% are serous, 10% are mucinous, and 10% are endometrioid. Less common types include clear cell, Brenner, small cell, and undifferentiated carcinoma [10]. Epithelial ovarian cancer is predominantly a disease of perimenopausal and postmenopausal women with the majority of cases occurring after the age of 40 [11]. The etiology is largely unknown being most likely multi factorial with genetic, environmental and endocrinological factors directly or indirectly related to carcinogenesis. To explain the epidemiology of EOC, three main hypotheses have been postulated which are not mutually exclusive; these included the incessant ovulation hypotheses, the gonadotrophin hypotheses, and the hormonal hypotheses [11-15]. The incessant ovulation hypothesis proposes that ovulation traumatizes the ovarian surface, because rupture of the ovulating follicle damages the OSE (ovarian epithelial surface), requiring the immediate repair. Over time, this process of continuous damage and OSE proliferation to repair the wound, increases the probability of spontaneous mutation and may lead to ovarian cancer development. The gonadothrophin hypothesis proposes a model in which excessive gonadothrophin exposure increases estrogenic stimulation of the OSE, possibly leading to malignant transformation. Gonadotrophins could act directly on the OSE enhancing transformation, or indirectly by stimulating estrogen production. The third hypothesis proposes that excess androgen stimulation of the OSE leads to increased risk of cancer, whereas progesterone exposure plays a protective role. Recently, two additional hypotheses have been postulated. According to the endometriosis hypothesis, endometriosis may act to promote the development of ovarian cancer if endometrial implants cause irritation and subsequent inflammation reactions [16]. A carcinogenic role for the exposure of the ovarian epithelium to environmental agents has also been postulated [17]. The evidence for and against each of these theories is explained in detail in the previous manuscripts [10-17]. These etiological hypotheses clearly implicate a role for fertility drugs, and more specifically for the ovulation inducing agents. Although, concern about potential carcinogenic effects has been raised by a number of case reports [18-23], epidemiological studies have produced varying results. The main studies focusing on the issue of ovarian cancer are summarized in Table **1**. The statistical parameter used in these studies includes: relative risk (RR) defined as the ratio of the probability of the event occurring in the exposed group versus a non exposed group, standardized incidence ratio (SIR) defined as the ratio of the observed number of cases to the expected number of cases multiplied by 100 and hazard ratio (HR) which is the limit of the number of events per unit time divided by the number at risk as the time interval decreases. The first case cohort study was performed by Ron and co-workers [24]. They evaluated the cancer incidence among 2,632 women treated for infertility between 1964-1974, and found no evidence of an association between ovulation inducing drugs and ovarian cancer. Five years later, Whittemore and colleagues [25] performed a meta-analysis of 12 case-control studies of the etiology of ovarian cancer diagnosed between 1956-1986. Only 3 of these, with 526 cases and 966 controls, have analyzed the possible link between infertility, infertility agents and ovarian cancer. A 2.7 fold increased risk of ovarian cancer was observed in infertile women who had used ovulation inducing drugs respect to women who had no history of infertility. The risk was essentially limited to the subgroup of women who had never been pregnant before (nulliparous), who experienced a 27 fold increase in risk associated with fertility drug use. Albeit was the first large case control study reporting on a possible association between EOC and ovulation inducing agents, it is flawed by some important limitations including lack of information about type, dose of fertility medications, and the duration of treatments [25]. Furthermore, another important aspect that should be taken into account in interpreting these findings is that infertile women treated so long ago received fertility drugs different from the ones used today. As in the US gonadotrophins and CC were first approved in the mid-1960s, it is more likely that the fertility medications prescribed for these women consisted of conjugated estrogens, progesterone, pregnant mare serum gonadotrophins and diethylbestrol. Finally the strongly increased risk in nulliparous was based on relatively few cases (only 12 cases) of ovarian cancer and one control.

Rossing and colleagues [26] examined the risk of ovarian cancer in a cohort of 3,837 women evaluated for infertility between 1974 and 1985, and detected 11 cases of ovarian cancer as compared with an expected number of 4.4 (standardized incidence ratio SIR 2.5). They also observed that the risk in developing borderline tumors, after fertility drug use, was substantially higher than the risk of invasive cancer (age standardized incidence ratio 3.3 versus 1.5). The authors reported an increased risk in infertile women treated with CC (relative risk RR 2.3) with respect to women without a history of CC exposure. In particular, it was found that long term use of CC (>12 cycles) was associated with a much higher statistically significant increase of the risk (RR 11). Interestingly, no statistically significant difference was noted between women with ovulatory problems and women without ovulatory abnormalities after treatment with CC. With respect to hCG exposure, no increased risk of EOC was observed. As major limitation, the study conclusions were based on a small number of ovarian tumors. Although, the results of these two early studies raised substantial concern, subsequent results from a number of studies did not support a link between infertility treatments and increased ovarian cancer [27-34].

Table 1. Summary of the Cohort Studies Focusing on Association Between Ovulation Inducing Drugs and Ovarian Cancer Risk

Authors	Total Cohort Size	No of Ovarian Cancer Detected (%)	Standardized Incidence Ratios (SIR) (95% CIs) *vs* General Population	Relative Risks (RR) (95%) Comparison of Drug Use *vs* No Use within Cohort
Venn *et al.* [35]	29,700	13 (0.04)	Clomiphene 2.46 (0.35-17.5) Clomiphene plus hMG 0.77 (0.19-3.07) hMG 1.14 (0.16-8.10) hMG plus GnRH agonist 0.48 (0.07-3.38)	
Klip *et al.* [36]	23,592	17 (0.07)	No IVF 1.4(0.4-3.2) IVF 1.4 (0.7-2.6)	
Jensen *et al.* [37]	54,362	156 (0.28)		Gonadothropins 0.83 (0.50-1.37) Clomiphene citrate 1.14 (0.79-1.64) hCG 0.89 (0.62-1.29) GnRH 0.80 (0.42-1.51)
Brinton *et al.* [38]	12,193	45 (0.36)	No clomiphene 2.1 (1.4-3.0) Clomiphene 1.48(0.7-3.2) Gonadothropins 2.46 (0.7-8.3)	

Note: studies with at least 10,000 patients are considered.

Reassuring results were reported by Venn and coworkers [35] who analyzed the possible impact of IVF on cancer risk. The study assessed 29,700 women who had referred to IVF. Interestingly the authors enrolled 20,656 undergoing IVF treatment with ovarian stimulation and 9,044 women undergoing IVF without treatment cycles. Thirteen ovarian cancers were observed during a follow-up period averaging 7.8 years. Interestingly, no significant difference in ovarian cancer risk between exposed and unexposed women was detected. Moreover, no association between the number of IVF treatment and the incidence of ovarian cancer was found, although it seems appropriate to note that the median number of IVF treatment cycles in this cohort was two, with only 30% of the women having four or more treatment cycles.

No difference in risk between treated and untreated subjects was also reported by Klip *et al*. [36]. They analyzed the incidence of ovarian cancer in a cohort of 25,152 women treated for subfertility and detected 17 cases of ovarian cancer during 5.6 years follow up. As point of strength, this study included detailed information on both causes of infertility and drug exposure. Similar figures were also reported in one of the most large cohort studies in this field. Jensen and coworkers [37] established a cohort of 54,362 women who attended infertility clinics during 1963-98. In this report patients were stratified according to the number of stimulated cycles, specific drugs, parity and use of oral contraceptive. Interestingly, the risk did not differ according to any use of ovulation inducing agents, number of cycle of use, length of follow-up since first use of drug and parity.

Unfortunately, not all the studies are in line with the concept that fertility drugs do not increased the risk of ovarian cancer. Studying 12,139 patients, Brinton and colleagues [38] reported similar cancer risk in patients unexposed and exposed to clomiphene or gonadotrophins, but detected an increase risk in extended follow-up with the standardized incidence ratio after 15 or more years resulting of 1.48 for exposure to clomiphene, and 2.46 for gonadotrophins. Similar results were observed by Sanner *et al.* [39] that performed a retrospective cohort study of 2,768 women who were assessed for infertility between 1961 and 1975 and detected an increased risk of invasive tumors associated with the use of gonadotrophins (RR 5.28) and borderline tumors after CC exposure (SIR 7.47). Albeit the duration of the follow up was the strength of this study (median follow-up time 33 years), the number of patients evaluated was not sufficiently large to yield reliable risk estimates. Since ovarian cancer is also affected by pregnancy factor [40-43], recently Kallen and co-workers have investigated cancer risk in women who have had an infant after IVF [44]. A total of 24,058 women who delivered an infant following IVF and a total of 349,061 women in the general population were studied using the cancer register. The women were categorized according to the diagnosis of the first cancer and the timing (before/after IVF) referred to that event. A high risk estimate for ovarian cancer after IVF was found but this increased risk is lower than that seen before IVF (2.13 versus 3.93). This finding was interpreted to reflect the effect of infertility and ovarian cancer rather than a direct effect of fertility drugs [44]. Regarding the issue whether FD have a preferential effect on certain ovarian cancer types such as clear cell, malignant germ cell, and granulose cells tumors, only few studies are available with contrasting results. The rarity of these tumors makes it difficult evaluating the reality of associations through epidemiological results [20, 45, 46].

In conclusion, the summation of evidence of association between fertility drug use and ovarian cancer suggests a non significant elevation in risk associated with drugs usage. Additional studies are needed to continue monitoring of long term effects.

Breast Cancer

Breast cancer is the most common malignancy in women in developed countries, accounting for 30-35% of all malignancies in females [47]. The etiology of breast cancer has been studied extensively with many investigations supporting the important role of endogenous and exogenous

hormones exposure [48]. Regarding the endogenous hormones, their influence is well defined for factors such as nulliparity, late age at first pregnancy, early menarche and late menopause. A possible relationship between exogenous hormones, such as hormone replacement therapy (HRT) and hormonal contraceptives, has also been established [49, 50]. In contrast less is known about the impact of infertility *per se*, and ovulation inducing agents on the risk of breast cancer. Theoretically, high estrogen levels during the follicular phase of ovulation cycles, unopposed by adequate progesterone (P), may lead to the development of breast cancer by affecting the proliferation of the cells of the breast epithelium [51]. Although, several clinical reports [52-57] suggested positive associations between ovarian stimulation and increased risk of breast cancer, these findings were not replicated in the majority of epidemiological studies that failed to provide consistent evidences, owing of methodological limitations, including the small size of the cohort studied, the short follow-up and the incomplete abilities to control for other correlates of risk, including well recognized reproductive risk factors. Table **2** summarizes the cohort studies with at least 25 observed breast cancers. In the largest follow-up study evaluating risk of breast cancer in patients treated with ovulation inducing agents, Jensen *et al.* [58] analyzed 54,362 women with infertility referred to all Danish infertility clinics, and found no overall increase in the incidence of breast malignancies after using clomiphene, gonadotrophins and hCG. However, they detected a higher breast cancer risk associated with the use of gonadotrophins among nulliparous women (RR 1.69), and after using progesterone (RR 2.9). It is possible, according to the authors, that the excess of breast cancer risk in nulliparous might be the result either of a genetic susceptibility to breast cancer and infertility or a specific susceptibility when exposed to ovulation inducing agents. Regarding the increased risk of breast cancer associated with progesterone, as it is not yet understood the specific role of this hormone in breast cancer, further investigations are needed to confirm or reject this data. Finally, in contrast of Burkmann *et al.* study [59], no relationship between the number of treatment cycles and risk of developing breast cancer was discovered.

Intriguing results were reported by Venn and coworkers [35] who failed to find a significant association between ovulation inducing agents and breast cancer risk. The standardization incidence ratio (SIR) was 0.91 in the exposed group (20,656 women undergoing IVF treatment with ovarian stimulation) and 0.95 in the unexposed group (9,044 performed IVF treatment without treatment cycle). However, approximately two-fold increased risk within one year of last treatment was found; 17 cases were observed compared with 8.7 expected, giving a SIR estimate of 1.96. This finding suggests a possible role of fertility medications to promote the rapid growth of pre-existing tumors, similar to the short term transient increase in breast cancer after a recent pregnancy [60]. Brinton *et al.* [61], performed a retrospective cohort study of 12,193 women evaluated for infertility between 1965 and 1988 and detected an increase in breast cancer risk when the follow-up was extended for more than 20 years. Although, this long term risk increase was based on small numbers, (29 breast cancers for clomiphene and 8 for gonadothropins), and was not statistically

Table 2. Summary of the Major Cohort Studies* Focusing on Association Between Infertility Drugs and Breast Cancer Risk

Authors	Population	No of Breast Cancer Detected	Standardized Incidence Ratios (SIR) (95% CIs) *vs* General Population	Relative Risks (95%) Comparison of Drug Use *vs* No Use Within Cohort
Venn *et al.* [35]	29,666	143	Clomiphene 0.85 (0.32-2.26) Clomiphene plus hMG 1.17 (0.85-1.62) hMG 0.99 (0.55-1.79) hMG plus GnRH agonist 0.94 (0.63-1.40)	
Jensen *et al.* [58]	54,362	331		Gonadothropins 1.20 (0.82-1.78) Clomiphene 1.08 (0.85-1.39) hCG 0.94 (0.73-1.21) GnRH 1.28 (0.75-2.19)
Brinton *et al.* [61]	12,193	292	No Clomiphene 1.3 (1.1-1.5) Clomiphene 1.3 (1.1-1.6) No hMG 1.3 (1.1-1.6) hMG 1.4(0.9-2.0)	Clomiphene 1.0 (0.8-1.3) ≥ 20 years of follow-up 1.4 (0.9-2.1) hMG 1.1 (0.7-1.6) ≥ 20 years of follow-up 1.5 (0.8-3.2)
Pappo *et al.* [62]	3,375	35	IVF treatments 1.4 (0.98-1.95) Women 40 years older 1.9 (0.97-3.30) ≥ 4 cycles 2.0 (1.15-3.27)	
Rossing *et al.* [63]	3,837	27		Clomiphene 0.5 (0.2-1.2)
Lerner Geva *et al.* [65]	5,788	131	Untreated 1.05 (0.79-1.35) Clomiphene only 1.40 (1.05-1.83) hMG only 0.66 (0.21-1.54) Clomiphene followed by hCG 1.06 (0.59-1.75)	Clomiphene 2.1 (0.99-4.3) hMG 0.6 (0.10-2.2) Clomiphene + hMG 0.8 (0.30-2.2)

* Studies with at least 25 observed breast cancer cases were considered.

the risk observed for other hormonal exposures, such as diethyl _stil _bestrol, that are known to have long latency effects on breast cancer. This prompted the suggestion that ovulation-inducing drugs might act as initiator of carcinogenesis. These data deserve monitoring in additional follow-up study to assess their biological plausibility.

Recently, a possible link between ovulation inducing agents and breast cancer was reported by Pappo *et al*. [62]. They examined the incidence of breast cancer in a cohort of 3,375 infertile women referred to their IVF unit between 1986 and 2003 and compared the observed number of cases with those expected in the general population. During the follow-up period, 35 women were diagnosed with breast cancer compared to 24.8 expected in the general population (SIR 1.4). Interestingly, they observed a higher risk in women older than 40 years at first treatment (SIR 1.9) and in those who received more than four cycles of therapy (SIR 2.0). When the analysis was restricted to women who were at the age of 40 or older and who underwent four or more IVF cycles, the SIR increased to 8.6. The major limitation of this study was the potential confounding effect of infertility. A higher incidence in infertile women with respect to the general population indeed could be attributable to infertility itself rather than infertility drug exposure. For this reason, the infertile women who have never used fertility medications would be the ideal comparison group. An increased risk of breast cancer for women exposed to ovulation induction was also supported by Calderon Margali *et al*. [27] Although, no details were given in this study about type of treatment, duration of therapy and dosages, the authors reported that women who were exposed to ovarian induction and waited more than 12 months to conceive, had two times higher risk of breast cancer with respect to the untreated women. In contrast, the results of the recent retrospective study show a protective effect of IVF on breast cancer [44].

More controversial are the data relative to the possible causative role of clomiphene citrate (CC) on cancer development. Two studies have found a preventive effect of CC on breast cancer development [63, 64]. Importantly, the risk decreased significantly with the duration of therapy. These findings were not confirmed by subsequent epidemiological studies. A significant increase of risk of invasive breast cancer after 20 years of follow up for women treated with clomiphene (RR 1.6) was detected by Brinton and associates [61]. Similar results were found by Geva and coworkers [65], who reported a hazard ratio of 1.45 between women who were treated with clomiphene and women who were not treated with ovulation induction. A possible explanation is that the antiestrogenic effect of clomiphene (clomiphene citrate binds to the estrogen receptor for long periods and blocks estrogen receptor to endogenous estradiol) may be overridden by the elevated estradiol levels induced by this drug.

In conclusion, given that breast cancer is widely recognized as having a hormonal etiology, and given that the large number of women being medically evaluated for infertility, further monitoring of the effects of ovulation-inducing drugs is warranted.

Endometrial Cancer

The etiology of endometrial cancer is multifactorial with both endogenous and exogenous hormones have a crucial role [66, 67]. Because of their influence on endogenous estrogen levels, nulliparity, late menopause, polycystic ovary syndrome (PCOS), obesity and the presence of estrogen secreting malignancies, are all well established risk factors for uterine cancer [67]. Concerning exogenous hormones, while the role of hormonal replacement therapy (HRT) and tamoxifene has been clarified [68, 69], less is known about the influence of ovulation inducing agents on the risk of endometrial cancer. In contrast to the fairly larger number of studies relative to ovarian and breast cancer, only few epidemiological studies examined the possible relationship between ovulation inducing agents and uterine cancer. Table **3** illustrates the largest cohort studies addressing this topic. Available literature delivers contradictory data, as most studies found no association [29, 57], while others indicated that ovulation inducing agents may increase the risk. Most of these studies presented some limitations, including low statistical power due to a low number of endometrial cancer cases, inability to control for potential confounders, and short or incomplete follow-up. An early study found no significant association between use of CC, HMG (human menopausal gonadotrophin) and hCG and endometrial cancer development [36]. A difference in estimates risk between the treated and untreated groups was initially reported with controversial results by Modan *et al.* [31] and Venn *et al.* [35] in their studies. Although, both studies showed an increased risk for endometrial cancer with respect to general population, Modan *et al*. [31] detected a major risk in treated patients (1,039 treated women versus 1,187 untreated ones SIR 4.8), while in the study by Venn *et al.* [35], cancers of uterus were significantly more common in patients unexposed to ovulation inducing drugs in comparison to women exposed (SIR 1.09 versus 2.64). Moreover, no association was found among the number of treatment cycles, the type of ovarian stimulation regime and the incidence of uterine cancer. These findings were not confirmed by subsequent studies. Althuis and coworkers [70] conducted a retrospective study of 8,431 US women evaluated for infertility during 1965-1968 and described 39 uterine cancers. Analysis of patients by questionnaire or by cancer and death registries suggested that infertile subjects had a significantly higher risk of developing uterine cancer with respect to women in the general population (SIR 1.56). The elevation in incidence ratio was more pronounced among CC exposed women (SIR 2.14). The risk raised with dose, menstrual cycle of use and with number of years elapsed since initial CC use, with rate ratio of 1.93 for more than 900 mg; 2.16 for 6 and more cycles of use and 2.50 for women followed for more of 20 years, respectively. Although, it was based on small number of cases in each subgroup, it is notable that the risk of uterine cancer was most strongly associated with CC use for nulliparous (RR 3.49) and obese (RR 6.02), but is not modified by parity at follow-up, attained age or hormone therapy replacement use. It is plausible that higher estrogen levels found in obese and nulliparous women act synergistically with clomiphene to

increase uterine cancer, however the authors cannot entirely exclude the possibility that these subgroups of women had more severe underlying diseases for which we were unable to account. Overall, these findings indicate that CC increases uterine cancer risk and provide evidence for both dose response and latency effect. The significant latency effect suggests that CC may be an initiator of carcinogenesis. It is likely that CC increases uterine cancer risk by indirectly increasing estrogen levels during the first half of the menstrual cycle [67]. Recent evidences suggest that CC may also impact uterine cancer risk by interacting directly with estrogen receptors [71], however the effect of CC on the uterus appears complex and requires further investigations. Regarding gonadotrophin, although the number of women with uterine cancers that used gonadothropin was very small (only three patients), evidence of higher risk for those exposed (SIR 1.26 compared with those unexposed) was detected [70]. Recently, similar results were detected by Silva at al. [72]; they followed up for over 20 years a British cohort of 7,355 women with ovulatory disorders and found no association between use of gonadotrophins and uterine cancer. Concerning clomiphene, their results showed no clear trends in the risk of uterine cancer with time since first treatment but indicated a positive trend with total cumulative dose and number of cycles of clomiphene. Indeed, women who were exposed to 2250 mg were 2.62 times more likely to develop cancer of the uterus compared with untreated women. A strong association between ovulation stimulation drugs and uterine cancer was detected by Calderon-Margalit and co-workers [27], reporting that women who received ovulation induction treatment had a 3-fold increased risk of uterine cancer compared with unexposed women (HR 3.32%). It should be however noted that after adjustment for age, ovulatory disorder, body mass index, the estimates of uterine cancer risk did not appreciably change. Also in this study women treated with clomiphene experienced a significantly increased risk of uterine cancer, with adjusted hazard ratio of 4.56%. This finding cannot be explained by other risk factors for uterine cancer such as nulliparity since all woman in this cohort gave birth, and nor can be attributable to ovulation disorders or obesity for which they controlled in multivariate analysis. Limitations of this study include the lack of information regarding type of treatment, dosage and number of cycle.

Detailed information on various types of ovulation inducing agents and number of cycle use was reported by Jensen *et al.* in their study [73]. In order to assess the association between uterine cancer and ovulation inducing agents, they used data from a large cohort of 54,362 women diagnosed with infertility who were referred to Danish fertility clinics between 1965-1998.

An increased risk, though statistically non-significantly, was observed after use of clomiphene (RR1.36), hCG (RR1.36), gonadotrophins (2.21), but not after GnRH analogs. The risk was not associated with time since first use but significantly increased with the number of treatments for both clomiphene (for >6 cycles RR 1.96) and hCG (for>6 cycles RR 2.18). Concerning gonadotrophins, the study from Jensen *et al*. [73] is the first study suggesting that this type of fertility drug may increase uterine cancer risk. Interestingly, the risk was primarily observed after 10 years of follow-up and this latency effect is in good concordance with the fact that uterine tumors generally grow slowly. Recent data from a control study conducted between 1992 and 2006 in Italy including 454 cases and 908 female controls found an OR of endometrial cancer for ever use of fertility drugs of 3.26 (95% CI, 1.07-9.95). The risk was higher for the duration of use 12 months or more (OR=6.10; 95% CI, 0.96-38.6), time since last use 25 years or less before the interview (OR=5.30; 95% CI, 1.12-25.1), and for age at first use less than 30 years (OR=5.14; 95% CI, 1.13-23.4) [74].

The available evidence does not allow any firm conclusion regarding the association between uterine cancer and ovulation inducing agents. Further scrutiny is warranted.

Melanoma

Cutaneous malignant melanoma represents roughly 5% of skin cancer and 1% of malignant tumors [75]. The possible dependence of malignant melanomas on hormonal influences has been speculated for many years. An increased risk has been found to be associated with low parity, late age at first birth, and use of oral contraceptives [76,77]. Data regarding the association between ovulation inducing agents and the risk of melanoma are limited. Although, several clinical reports suggested a relationship [78,79], the few epidemiological studies, that have addressed the issue,

Table 3. Summary of the Main Cohort Studies Focusing on Association Between Fertility Drugs and Uterine Cancer

Authors	Population	No. of Uterine Cancer Detected	Standardized Incidence Ratios (SIR) (95% CIs)*vs* General Population	Relative Risks (95%) Comparison of Drug Use *vs* No Use within cohoRt
Althuis *et al.* [70]	8,341	39	Clomiphene 2.14 (1.3-3.3) Clomiphene dosage≥900mg 2.26 (1.2-3.9) No of cycles ≥ 6 2.30 (0.9-4.8) Gonadothropins 1.26 (0.3-3.7)	Clomiphene dosage ≥ 900mg 1.93 (0.9-4.0) No of cycles ≥ 6 2.16 (0.9-5.2)
Silva *et al.* [72]	7,355	31	Clomiphene only 1.41 (1.09-1.79) Gonadothropins only 0.94 (0.31-2.20) Both 1.09 (0.74-1.55)	Clomiphene only 1.29 (0.87-1.92) Gonadothropins only 0.86 (0.31-2.20) Both 1.00 (0.61-1.61)
Jensen *et al.* [73]	54,362	83		Gonadothropins 2.21 (1.08-4.50) Clomiphene 1.36 (0.83-2.23) hCG 1.36 (0.83-2.23) GnRH 1.09 (0.47-2.52)

and the risk of melanoma are limited. Although, several clinical reports suggested a relationship [78,79], the few epidemiological studies, that have addressed the issue, provided conflicting data. Rossing *et al.* [80] assessed the risk of cutaneous malignant melanoma associated with the use of ovulation inducing agents in a cohort of 3,837 women evaluated at infertility clinics in Seattle between 1974 and 1985. They described 12 cases of melanoma in comparison with an expected number of 6.8 cases (SIR1.95). The observed increment was not statistically significant. An increase in risk was observed in women who had used clomiphene for 12 or more menstrual cycles (relative risk 2.2) and women who had used hCG (relative risk 1.7). However, it was unclear whether these increases were due to the effect of the drug or to some underlying abnormalities among the women. Controversial results were also reported by Young *et al.* [81], they focused on 3,186 women attending infertility clinics and detected a total of 14 melanomas. All cases were exposed to fertility medications, but women who developed melanoma had fewer cycles of exposure to fertility medications than other cohort members. No difference in risk between the exposed and unexposed patients emerged in Dutch IVF follow up study [36] and Venn and colleagues study [4]. These data were confirmed by Althuis and co-workers [82]. They reported the findings of a retrospective cohort study of 8422 women evaluated for infertility, and found no statistically significant association between fertility medications and cancer risk. However they detected an increased risk in women treated with clomiphene and followed for 15 or more years (Relative relative to non users of 2.08). Moreover, they also found that clomiphene use appeared to impart stronger effects on the risk of melanoma among women who remained nulliparous through follow-up. Similar results were also reported by Calderon Margalit *et al.* [27]. In their study, it was emerged that the treatment for ovulation in general was not associated with the development of malignant melanoma (multivariate hazard ratio 1.68), but women treated with clomiphene experienced a significantly increased risk of melanoma, with a multivariate-adjusted hazard ratio of 2.56. Finally, contradictory data emerged also from the largest study assessing the effects of these drugs on risk to develop melanoma. Hannibal *et al.* [83] analyzed a cohort of 54,362 women with infertility referred to Danish fertility clinics in the period 1963-1998 and detected 112 malignant melanoma. Although, in general their findings indicated that treatment with ovulation inducing agents was not related to melanoma risk for all ovulation inducing agents, after the adjustment for parity status, use of gonadothropins was associated with a borderline significantly increase melanoma risk (RR1.65).

In conclusion, the existing studies are insufficient for an estimation of the risk. Additional long term follow-up studies should be performed in order to monitor the potential association between use of ovulation inducing agents and malignant melanoma risk.

Thyroid Cancer

The greater incidence of thyroid cancer in women than in men, particularly during the reproductive years, may imply the potential role for female hormones in the etiology of thyroid cancer.

Increased thyroid cancer risk has been associated to factors such as high parity, and use of exogenous hormones such as oral contraceptives, estrogens, and hormone replacement therapy [84]. In contrast less is known about possible effects of fertility medications on thyroid cancer; indeed few reports have addressed the question with contrasting results.

The largest study assessing the effects of ovulation inducing agents on the risk of thyroid tumors has been the Hannibal study in Denmark [85]. They established a cohort of 54,362 women with fertility problems referred to Danish hospitals and private fertility clinics in the period 1963-1998 and detected 29 cases of thyroid cancer. Interestingly, they found that women who used clomiphene (RR 2.8) and progesterone (RR 10.14) had a significantly increased risk of developing thyroid cancer compared with women who never used clomiphene or progesterone respectively. In contrast the risk was not significantly increased after use of gonadotrophins (RR 1.43) and GnRH (RR 1.82). For all groups of ovulation inducing agents no significant association with the number of cycles of use and with years since first use was detected. These findings are in agreement with those previously published by Althuis and colleagues. Although, they reported that clomiphene and gonadothropins use did not significantly affects the risk of thyroid cancer, a higher risk was observed in nulliparous treated with clomiphene. The mechanisms behind a potential association between clomiphene and thyroid cancer are not completely understood. It is plausible that CC affect thyroid cancer simply increasing estrogen levels, which has been demonstrated to increase the level of TSH which in turn enhances mitotic activity in the follicular cells of the thyroid gland increasing the risk of malignant transformation [86]. In conclusion, even though thyroid cancer risk was not associated with ever use of any ovulation inducing agents the findings of this large cohort study showed that infertile women treated with clomiphene and progesterone may have an increased risk of thyroid cancer. Further investigations are needed to confirm or reject these data.

CONCLUSIONS

In view of the constantly growing number of women requesting fertility treatment, the question of whether ovulation inducing agents increase the risk of cancer has serious implications for the clinical practice. Studies examining whether ovulation induction is associated with an increased cancer risk present some limitations that should be taken into account in interpreting the available data. Overall the limitations include difficulties in achieving an adequate sample size, an accurate diagnosis of infertility, data about dosage, number of cycles and type of medication. Concerning cohort studies, most of them have been limited by the small number of detected cancers and by short follow-up period that makes difficult to assess the long term effects of FD. Furthermore in many of these studies the cancer experience of cohort of infertile women is related to the experience of the general population through the calculation of standardized incidence ratios (SIR). SIR compare the number of observed cancer in the cohort of interest to the number expected based on the incidence ratio in the general population and take into account age, race and calendar time

but have no information about the likely difference in other cancer predictors. Results based only on the SIR are the little value when determining the relationship between fertility treatment and hormone related cancer risk because of inability to adjust for recognized risk factors for ovarian endometrial and breast cancer such as nulliparity. Regarding case control study this is a retrospective study conducted focusing on large number of selected cancer cases that are related on retrospective assessment of fertility drug use usually through recall the patients. The major limitation is the lack of precise information about type, dosage of drugs, and indication to the treatment. Furthermore, the results are strictly dependent of the choice of a control group.

Although, current evidence is in general reassuring, larger population studies better adjustment for confounding factors such as parity, infertility, contraceptive use, early age at menarche and late age at menopause, and long term follow-up may offer more precise data in the future.

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