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Risk of cancer after assisted reproduction: a review of the available evidences and guidance to fertility counselors

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Abstract. – OBJECTIVE: Infertile women requiring ovarian stimulation and assisted reproduction techniques (ART) are faced with difficult issues. The fear that using hormones could increase their risk of cancer is the most significant. One of the main challenges for assessing cancer risk after ART is the difficulty to separate it from the underlying condition of infertility per se. The delay or the inability to achieve a pregnancy is an important risk factor for breast, endometrial and ovarian cancer. We analyzed the current literature on the topic.

MATERIALS AND METHODS: The published literature in Medline and Cochrane was screened using the following keywords: 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".

RESULTS: A total of 95 articles were evaluated. Limited evidence suggests that high doses or many cycles of clomiphene citrate could increase the risk of endometrial cancer, although the confounding factors of polycystic ovarian disease and overweight are not always considered. In some studies, ART modestly increased the risk of borderline ovarian cancer. Fertility treatments do not increase the risk of breast, cervical, endometrial and ovarian cancers, thyroid, melanoma and colon cancer.

CONCLUSIONS: Women can be reassured that fertility drugs do not appear to significantly increase the risk of invasive ovarian, endometrial, breast or other cancers, while achieving a pregnancy at an earlier age is a significant protective factor.

Key Words:
Fertility drugs, *In-vitro* fertilization, Ovarian stimulation, Cancer risk, Breast cancer, Ovarian cancer, Gynecological cancer, Thyroid cancer, Melanoma, Colon cancer.

Introduction

Male and female infertility is increasing in the general population and more women are relying on assisted reproduction techniques (ART) to conceive[1]. It is estimated that approximately 1% of births worldwide are the result of ART, and most likely these numbers will increase, due to the socio-demographic trend to postpone pregnancy at later ages for personal and social reasons[2]. Conditions such as being overweight or obesity, excessive smoking, anovulation, endometriosis and nulliparity are also on the rise, and besides being frequent causes of infertility they are also independently related to an increased risk of cancer[3]. Moreover, the concern that drugs used for ovulation induction could increase the risk of estrogen sensitive breast and endometrial cancers by raising the levels of sex hormones is widespread in the general population and among professionals. Mechanisms like multiple ovulation and ovarian trauma by oocyte retrieval are also believed to increase the risk of ovarian cancer. According to a recent systematic review and meta-analysis[4] ART does not seem to be associated with elevated cervical, ovarian or endometrial cancer when the confounding effect of infertility is neutralized. However, there are still methodological reasons for example the lack of valid exposure data, the need to adjust for a variety of meaningful confounders and the lack of relatively long follow-up periods that need to be considered before sound conclusions can be drawn. The aim of this study is to assess the available evidence correlating ART with the risk

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of developing cancer in the infertile population, after controlling for confounding factors that may introduce important biases. In order to give a more immediate message we considered together, for example, ovarian stimulation and ART. The main characteristics of the different treatments are summarized in Table I.

Materials and Methods

The published literature was screened using the following keywords: ((OVULATION INDUCTION[TI] OR IVF[TI] OR "Reproductive Techniques, Assisted/adverse effects"[Mesh] OR clomiphene[ti] OR "*in vitro* fertilization"[ti] OR "Fertility Agents, Female/adverse effects"[Mesh] OR "Fertility Agents, Female/toxicity"[Mesh] OR "Gonadotropins/adverse effects"[Mesh] OR "Gonadotropins/toxicity"[Mesh] OR "Clomiphene/adverse effects"[Mesh] OR "Clomiphene/toxicity"[Mesh]) AND (NEOPLASMS[MAJR] OR "Neoplasms/EPIDEMIOLOGY"[Mesh] OR Neoplasms/CHEMICALLY INDUCED[MH] OR cancer[ti] OR Breast Neoplasms/etiology[MAJR]) AND (REVIEW[PT] OR systematic[sb] OR guideline*)) NOT ("fertility preservation"[ti] OR Polycystic Ovary Syndrome/therapy[MH]) in Medline and the Cochrane. A total of 182 hits were found and 87 satisfied the inclusion criteria: peer reviewed papers, only published English literature, no abstracts, papers where the data of interest were clearly specified and collected.

Results

We discuss the incidence of cancer in women undergoing ART. Most of the 87 papers analyzed focused on gynecological cancers (breast, endometrium, ovary, cervix). Concerning gynecological cancers as a whole, the overall evidence is reassuring. In a review of 11 studies totaling 3,900,231 patients of whom 118,320 were offered ART, the incidence of gynecological cancer in the ART-treated group was even lower (0.6%) than in the group not receiving ART (2.1%)[5]. Some of the studies, however, showed an increased risk of cancer among certain sub-groups, such as women who received repeated treatment with clomiphene citrate[6]. It is, therefore, necessary to monitor the long-term effects of infertility treatment on women's health[7]. A possible increase in other cancers (thyroid, melanoma, colon and non-Hodgkin lymphoma) has also been investigated. Every woman may be particularly concerned by a specific tumor; we, therefore, present evidence divided according to anatomical sites.

Breast Cancer

Breast cancer is the most common and feared female malignancy, affecting one in eight women lifetimes. The causes of breast cancer are multifactorial and complex. Most are estrogen and progesterone sensitive and several hormonal aspects may influence breast cancer risk. These include both physiological conditions and pharmacological treatments. Precocious menarche and/or late menopause, which result in a more prolonged exposure to estrogens, have been linked to an increased risk[8], while pregnancies (especially at an early age) are protective possibly due to the prolonged exposure to natural progesterone. On the other hand, synthetic derivatives of progesterone are protective for the endometrium, but appear to be mitogenic on the breast[9,10]. Among pharmacological manipulations, both post-menopausal hormone replacement treatment and the use of hormones for birth control have been associated with an increased incidence of breast cancer[11-13]. During fertility treatments, ovarian stimulation temporarily induces supra-physiological estrogens levels, which also could theoretically increase the risk of breast cancer. However, the short period of time with high estradiol levels, even with multiple repetitive ovarian stimulation cycles, has not been shown to be a significant event for breast cancer risk. As ART use is increasing, the interest for a potential oncogenic risk is becoming more relevant. This is biologically plausible; however, there are several confounding elements, which are considered risk factors for the development of breast cancer, such as infertility itself, nulliparity, delayed childbearing, and a later menopause, all of which are often not properly controlled for [14]. There are also several aspects connected to the type of treatment administered that may influence breast cancer risk: the drug(s) administered, the dose and schedule, the woman's age and having achieved a full-term pregnancy or not. Even if most researches published so far do not include analyses for these different confounders (since the numbers become progressively smaller making statistical inferences less reliable) there are systematic reviews or meta-analyses describing breast cancer risk for specific treatments. All of these studies[15-20] have not found considerable differences in breast

Table I. Main differences among hormonal treatments that make their cancer risk not comparable.

	High endogenous sex steroids	Hormonal contraception	Menopausal therapy	Ovulation induction
Effect of or Main purpose	Overweight-obesity, sedentariety, early menarche, late menopause	Ovulation Inhibition	Reduction of menopausal symptoms, prevention of hypoestroestrogenism consequences	Multiple (or sometimes single) ovulation induction
Usual composition	Estradiol (E2) Progesterone (P)	Mainly strong syntetic progestogens with a low dose of ethinil estradiol or estradiol	Very low dose natural estrogens and progesterone or close to natural progestogens	Antiestrogens (clomiphene) or gonadotrophins
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 continued many year after natural menopause	High or very high estradiol levels produced by the ovaries
Progesterone or progestogens	Low or absent (anovulation or PCOS) High in ovulating early menarche, late menopausal	Completely inhibited and substituted by the progestogen most or all of the duration of treatment	Substituted by progesterone or the progestogen two weeks month or all time time in continuous combined menopausal treatments	Natural progesterone (or diidrogesterone) supplemented
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	Young not ovulating or infertile or needing superovulation
Duration of exposure or treatment	Lifetime estradiol exposure Two weeks monthly progesterone exposure in ovulation age	Months to many years sometimes decades (expecially before first full time pregnancy) in fertile age	Months to many years after menopause	Usually some days of supraphysiolgical estradiol exposure and two or few more weeks of progesterone after ovulation induction
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	Observational, no RCT
Main risk	Estrogen or progesterone sensitive Cancers	Thrombotic	Thrombotic	Ovarian hyperstimulation syndrome, multiple pregnancies
Breast cancer risk	Increased (obese postmenopausal, early menarche or late menopause, sedentary habits) Infertile	Neutral (slightly increased in older studies)	Slightly increased with E2+ syntetic progestogens; maybe neutral with micronized P; reduced if E2 only with Conjugated Equine Estrogen	Maybe neutral
Endometrial cancer risk	Highly increased (obese, early menarche or late menopause, sedentary habits, anovulation)	Greatly reduced	Neutral to protective if well balanced E +P	Maybe neutral
Ovarian cancer risk	Increased (obese, early menarche or late menopause, sedentary habits, infertile)	Greatly reduced	Neutral or maybe slightly increased	Maybe neutral
Effect of giving up treatment	Advise that following or not the code against cancer rules is far more important than any fertility drug effect	Countereffective (overall cancer risk is reduced in hormonal contraception users)	Not effective if properly use (global cancer risk, health and mortality not affected or reduced in younger users)	Not effective or countereffective (pregnancy or earlier pregnancy reduce female cancer risk)

cancer risk in patients undergoing ART when compared to either untreated infertile women or with the general population[21]. 19.158 women who underwent IVF treatment and 5.950 women who started other fertility treatments were included in a historical cohort[22]. After a follow-up lasting on average 21 years, IVF treatment was not associated with an increased risk of breast cancer compared to non-IVF fertility treatment. There was no increase in the risk of breast cancer in IVF patients compared to either the general population (SIR: 1.01, 95% CI 0.93-1.09) or to patients receiving non-IVF-related fertility treatments (hazard ratio: 1.01, 95% CI 0.86-1.19). In a cohort study regarding infertile women, breast cancer incidence was not statistically different in women treated with IVF *vs.* untreated women (HR 1.10, 95% CI 0.88-1.36)[23]. A recent large meta-analysis[24] of 8 cohort studies that included 1,554,332 women and 14.961 breast cancer cases demonstrated no increased risk of breast cancer in IVF patients *vs.* the general population (RR: 0.91, 95% CI 0.74-1.11) nor *vs.* the infertile female population (RR: 1.02, 95% CI 0.88-1.18). A cohort study of 12.193 infertile women followed for 30 years[25] found no increased risk of breast cancer after clomiphene citrate (hazard ratio: 1.05, 95% CI 0.9-1.22) or gonadotropins (hazard ratio: 1.14, 95% CI 0.89-1.44) exposure compared to infertile controls. Breast cancer is more frequent after menopause and ovarian stimulation might cause an increase in the incidence at a later age. For this reason, the length of follow-up may introduce a bias and affect results on cancer incidence after ART. Investigations with a relatively short follow-up may not capture an increase because this incidence tends to be manifested at a different age. Studies with a longer follow up (more than 10 years) show a greater breast cancer risk[24,25] while no association was found in two studies with a very long follow-up. In two cohort studies involving a very long follow-up (30 years), the usage of fertility drugs did not increase breast cancer risk (HR 1.05, 95% CI 0.90-1.22) and (HR 1.14, 95% CI 0.89-1.44)[25]. Similar reassuring results were reported for different types of ovulation induction drugs: clomiphene citrate (SIR 1.21, 95% CI 0.91-1.58), gonadotropins (SIR 0.4, 95% CI 0.11-1.6), or both (SIR 0.93, 95% CI 0.48-1.63) when compared to the general population[14]. Clomiphene citrate induces apoptosis in breast cancer cell lines *in vitro*[26] and tamoxifen reduces breast cancer risk, when administered continuously[27]. A high cumulative number (more than six) of clomiphene citrate cycles seems to increase the risk of breast cancer[14,25]. In a more recent study[28] there was no dose response relationship for CC and breast cancer and an increased risk of breast cancer was found in parous women (1.26 (95% CI 1.03, 1.54)) (p = 0.02) only. The possible breast cancer effect of gonadotropins could be mediated by the relevant increase in estrogens and progesterone. Estrogens stimulate the growth of breast cancer, but at high doses they are also an effective treatment for this disease. This has been termed the 'estrogen paradox'. The supraphysiological levels achieved in ART could, therefore, be protective and not necessarily detrimental due to apoptosis induced by estrogens via the ERα receptor[29].

Beginning ART treatment at a younger age correlates to an increased breast cancer risk[14,18,23]. Other studies show different data concerning age at first infertility treatment with regards to breast cancer risk[30,31], cumulative dose of CC[32] or hormonal cause of infertility[14]. In the study by van den Belt-Dusebout et al[22], also after a follow-up lasting on average 21.1 years, the risk of breast cancer in IVF-treated women was notably different compared to that of the general population (SIR, 1.01 [95% CI, 0.93-1.09]) and to that of the non-IVF group (HR, 1.01 [95% CI, 0.86-1.19]). Likewise, it was considerably lower for women who had 7 or more IVF cycles (HR, 0.55 [95% CI, 0.39-0.77]) compared to 1 to 2 IVF cycles and also after an insignificant response to the first IVF cycle (HR, 0.77 [95% CI, 0.61-0.96] for <4 *vs.* ≥ 4 collected oocytes). The extensive search for a possible association between ovarian stimulation and an increased risk of breast cancer failed to document it. Therefore, infertile patients can be reassured. However, continued follow-up including the adoption of new protocols and drugs such as aromatase inhibitors, is recommended. In conclusion, there is Grade B evidence with regards to the lack of association of fertility drugs for ART and breast cancer. A very large analysis[33] did not find any increase in breast cancer incidence (SIR 0.98, C.I., 0.94 to 1.01) despite an excess of breast cancer in *in situ* SIR 1.15, C.I. 1.02 to 1.29). As proposed by ASRM[34], patients can be reassured that fertility drugs are not associated with an increased risk of breast cancer.

Endometrial Cancer

Endometrial cancer is the most frequent gynecologic malignancy and its incidence increases with age. Type I endometrial cancer is hor-

mone-dependent, with prolonged unopposed estrogens considered as high risk, while progesterone as having a protective effect. Endometrial cancer is also observed as a side effect of prolonged tamoxifen treatment for breast cancer[35,36]. Given its hormonal susceptibility, it is plausible to enlist endometrial cancers among those whose incidence may be increased by ovarian stimulation for ART. Several studies have examined the relationship between endometrial cancer and the use of fertility medications, but the results are discordant. These studies are often limited by a small sample size, a short follow-up, and by several confounding factors such as the choice of the reference population, the age at which treatment was administered, the dose used, the number of cycles, the underlying diagnosis of infertility like ovulatory dysfunction, obesity or polycystic ovarian syndrome (PCOS) or other methodological limitations[37]. Overall, most studies showed that the use of fertility drugs was not associated with a significant increased risk for endometrial cancer. A study with a very long follow-up (26 years)[37] of a cohort of 12.193 women did not find an increased risk of breast cancer with clomiphene (HR 1.39, 95% CI 0.96-2.01), gonadotropins (HR 1.34, 95% CI 0.76-2.37), or both (HR 1.77, 95% CI 0.98-3.19). In addition, no increased incidence has been observed in a large recent longitudinal cohort study that evaluated the short-term risk of cancer among women of reproductive age undergoing ART treatments[38]. Women treated with ART had a statistically significantly lower risk for all cancers (for all women: SIR 0.78; CI, 0.73-0.83; women without prior ART: SIR 0.75; CI, 0.68-0.82), breast cancer, and all female genital cancers. In this study on 113,226 American women there was also a non-statistically-significant lower risk for endocrine and uterine cancer; and a non-statistically-significant higher risk for melanoma and ovarian cancer. A population-based cohort study including all women registered in the Medical Birth Registry of Norway did not find a global significant correlation, after correcting for multiple analyses[24], but clomiphene citrate only was associated with increased risk of ovarian and endometrial cancer. A meta-analysis[39] of six studies comprising 776,224 infertile patients, of whom 103.758 receiving fertility treatments, did not find an increased risk of endometrial cancer between treatment *vs.* non-treatment (odds ratio: 0.78, 95% CI 0.39-1.57). Another meta-analysis[4] found that women undergoing ART had a higher risk for endometrial cancer (RR 2.04, 95% CI 1.22-3.43). Compared to an untreated infertile cohort, the risk was not significant and even seemed reduced (RR 0.45, 95% CI 0.18-1.14). Therefore, infertility *per se* and not its therapy seems to be the main risk factor for endometrial cancer. A study on 2.431 women, who were followed for over 20 years, showed that the risk of endometrial cancer did not increase compared to the general population either with CC (SIR 1.07, 95% CI 0.39-2.33) or human menopausal gonadotropin (hMG) (SIR 2.16, 95% CI 0.43-6.32). In addition, the initial higher risk (SIR 5.0, 95% CI 2.15-9.85) was no longer significant in a subsequent multivariate reanalysis[14]. The recent analysis of a large population[33] also did not find any increased risk (SIR 1.12, 95% C.I. 0.95 to 1.30). Older analyses[40] reported a higher risk of endometrial cancer in infertile patients *vs.* the general population, with age at first use <30 years and last use less than 25 years (OR 3.26, 95% CI 1.07-9.95). However, no information with regards to the kind of fertility drugs used was provided. Endometrial cancer risk was shown in infertile women with ovulatory dysfunction, progesterone deficiency, and/or obesity[41,42]. Some data seem to indicate clomiphene as a risk factor. A registry-based cohort study[28] found an increased risk of endometrial cancer in women receiving clomiphene citrate (hazard ratio: 2.91, 95% CI 1.87-4.53), but not in women undergoing IVF (hazard ratio: 1.62, 95% CI 0.70-3.85) compared to the general population. This study, however, was limited by a lack of adjusting for confounding factors. According to the latest Cochrane review[43] to the use of clomiphene citrate in infertile women, it might increase endometrial cancer risk, especially in cumulative doses greater than 2000 mg and after a high number of cycles (more than 7). The reason for this increased incidence may be the presence of confounding factors, such as overweight or polycystic ovary syndrome, found in women who require treatment with CC, but the evidence at present available in the literature is actually not adequate to reach any solid conclusion. Data regarding exposure to gonadotropins were also inconclusive. Cochrane data analyzed more in detail reveal that six studies, that included infertile women and not a general population control group, established that exposure to ovary stimulating drugs did not result in an increased risk of endometrial cancer (RR 0.96, 95% CI 0.67 to 1.37; 156.774 participants; evidence of very low quality). The risk was found to be increased in fifteen studies in women

exposed to any ovary-stimulating drug (RR 1.75, 95% CI 1.18 to 2.61; 1.762.829 participants; evidence of very low quality) where the general population was used as the control. Five studies, limited to infertile women (92.849 patients), reported on the exposure to clomiphene citrate; there was a positive association (RR 1.32; 95% CI 1.01 to 1.71; 88.618 participants; evidence of very low quality), but only at a high dosage (RR 1.69, 95% CI 1.07 to 2.68; two studies; 12.073 participants) and with a high number of cycles (RR 1.69, 95% CI 1.16 to 2.47; three studies; 13.757 participants). Four studies reported an increased risk of endometrial cancer in women who needed clomiphene citrate compared to the general population (RR 1.87, 95% CI 1.00 to 3.48; four studies, 19.614 participants; evidence of very low quality). In these researches, anyway, it was not possible to determine if the association was due to the pathological conditions that requested clomiphene treatment or to the drug. When infertile women not treated with any stimulating agent were used as the reference, it was possible to observe that gonadotropins increased the risk of cancer of the endometrium (RR 1.55, 95% CI 1.03 to 2.34; four studies; 17,769 participants; evidence of very low quality). By analyzing two works (1595 participants) which used the general population as a reference group, it was possible to find that there was no variation in risk (RR 2.12, 95% CI 0.79 to 5.64: evidence of very low quality). The use of both clomiphene citrate and gonadotropins resulted in no relevant difference in endometrial cancer risk compared to unexposed infertile women (RR 1.18, 95% CI 0.57 to 2.44; two studies; 6345 participants; evidence of very low quality). However, a higher risk was found when compared to the general population, indicating that the key factor may be infertility, and not its treatment (RR 2.99, 95% CI 1.53 to 5.86; three studies; 7789 participants; evidence of very low quality). Infertile women who are overweight and obese with oligomenorrhea due to PCOS should be informed to be at increased risk for endometrial cancer and advised to adopt lifestyle changes to reduce their risk, such as weight loss and adequate endometrial protection with progesterone or progestogens. Clomiphene citrate and lately the aromatase inhibitor letrozole are first line treatments for up to 12 cycles for women with World Health Organization Group II ovulation disorders (hypothalamic pituitary dysfunction), such as PCOS, as recommended by contemporary guidelines[44,45]. According to the ASRM guidelines (grade B evidence), patients can be reassured that the increased risk of endometrial cancer is not linked to fertility drugs. Ovulatory PCOS infertile patients should be educated about healthy lifestyle changes: weight loss and exercise to reduce the underlying risks for endometrial cancer.

Epithelial and Stromal Ovarian Cancer

Ovarian cancer is a complex disease that includes at least five different histological types, thus any study relating to ovarian cancer has some limits. High-grade serous cancer (which is the most common type often identified with "ovarian cancer") generally appears after menopause and it is usually diagnosed at a late stage, since screening with imaging techniques and/or serological analyses has a limited efficacy[46]. This cancer has a poor prognosis and so any impact of ART could be relevant. Protective factors are multi-parity, breastfeeding and oral contraceptives (not frequently used in infertile patients). Independently of treatment for fertility issues, women with family history or genetic susceptibility to ovarian cancer, infertility and nulliparity, and late menopause, have an increased risk of developing invasive ovarian cancer[47,48]. When examining the relationship between the use of fertility medications and ovarian cancer, these confounding variables must, therefore, be considered. Long-term follow-up is necessary as ovarian cancer typically occurs after menopause. Ovulation has been proposed as a potential cause of ovarian cancer; therefore a potential promoting effect of fertility drugs is plausible. Incessant ovulation theory states that factors decreasing lifetime ovulation rates, such as multiparity or combined hormonal contraception, reduce ovarian cancer risk[49]. Conversely, the use of fertility medications could increase ovarian cancer risk by promoting multi follicular ovulation[46], thus increasing mechanical trauma and the quantity of epithelial inclusions of the ovarian surface epithelium.

It has been calculated, although inevitably in a very approximate way, that the hormonal stimulation used for a single cycle of IVF results in the production of a number of follicles and in an estrogen exposure similar to what occurs in two years of life[50]. Furthermore, the risk of ovarian cancer has not decreased but augmented in women with anovulation, ovulatory disturbances, or infrequent ovulation, whereas in accordance with the 'incessant ovulation' theory, the risk of ovarian cancer would have expected to be reduced in

these women[48]. It is also possible to hypothesize that in the absence of pregnancy the risk of ovarian cancer is already increased before ART. An explanation is that an underlying ovulatory disorder, or that the fact that the woman does not become pregnant , are themselves causes of cancer[51]. High doses of gonadotropins may have a predisposing effect directly or through the increased level of estrogens[52-54]. Nevertheless, these data do not prove the existence of a causal relationship between iatrogenic elevation of serum gonadotropin concentrations and the development of granulosa cell tumors. Other explanations are possible, such as the presence of the tumor before fertility treatment initiation, or that the onset of the tumor during fertility treatment was coincidental. This role of gonadotropins is in accordance with the protective effects of pregnancy and oral contraceptives. An additional hypothesis is that undiagnosed early ovarian cancer can cause infertility. The basis of this suggestion was observed in the epidemiological data indicating that patients with ovarian cancer had a higher rate of infertility[55]. As a result of recent theories[56,57] stating that epithelial ovarian cancer originates in the fallopian tubes and not in the ovary itself, a currently accepted treatment for women with severe tubal disease is salpingectomy before IVF. Older researches[55,58] indicated that ovarian cancer may be increased by ART. In some of these works, however, methodological aspects may have played a role: in some cases the reference population consisted of women in the general population, not of untreated infertile women which represent a group more suitable for comparison. In other researches the absolute number of cancers was low, while in others malignant and benign tumors were considered together. Unpredictable elements, such as the imprecise recording of medications and the duration of treatment, make these studies largely unreliable. And it must be considered that in the last years ovarian stimulation protocols have changed and do not resemble those used in some of these reports[59]. Analyses[38,60] conducted and published in the last years do not support the idea that ART may be linked to a higher risk of malignant invasive cancer. More in detail ovarian cancer risk is not increased in premenopausal women undergoing ART[24]. Similar conclusions were reached by reviews and meta-analyses[4,16,61-64] that evaluated the epidemiology of ovarian cancer and found no increase in its incidence. In more than 87,000 women, ovarian cancer was not increased by any treatment for infertility (hazard ratio [HR] 0.90, 95% CI 0.45-1.79) nor by IVF (HR 1.58, 95% CI 0.75-3.29)[37]. According to a cohort study[65], which included more than 54,000 infertile women with an average follow-up period of 16 years, invasive ovarian cancer did not increase with the use of CC (adjusted rate ratio [ARR] 1.14, 95% CI 0.79-1.64) or gonadotropin (ARR 0.83, 95% CI 0.50-1.37) compared to women who never used them. The largest systematic review, which included 11 case-control and 14 cohort studies, was published by the Cochrane Collaboration[66] and consisted of 182.972 women. Due to a very high heterogeneity among studies, it was impossible to obtain an overall relative risk. Women treated for infertility with any drug did not have an increased risk of invasive ovarian cancer: this was observed in cohort- and in case-control studies that analyzed women of a similar age, or untreated infertile women, as the reference group. When, in cohort studies, comparison was made with the general population invasive ovarian cancer incidence was more frequent. In one study SIR was 5.0 (95% confidence interval (CI) 1.0 to 15), but this was due to the occurrence of a very low number of cancers (three) and risk was lower when cancers diagnosed in the first year after treatment were not included (SIR 1.67, 95% CI 0.02 to 9.27). However, another study[67] on 26 cases showed an OR of 2.09 (95% CI 1.39 to 3.12). A long-term follow-up of a historical cohort in Sweden reported no overall excess risk of invasive ovarian cancer emerged compared with the general population[68]. Considering borderline ovarian tumors, some case-control studies found an increased risk after fertility drug treatment. One of these studies reported an OR of 28 (95% CI 1.5 to 516) but this was based on the occurrence of four cancers[69]. In a cohort study[70], the hazard ratio (HR) for a borderline ovarian tumor was 4.23 (95% CI 1.25 to 14.33) for infertile women treated with IVF compared to a non-IVF treated group who had a follow-up lasting over one year. There was no proof that the risk increased in women exposed to clomiphene alone or clomiphene plus gonadotropin, compared to untreated women. Risk was high during the first year after the IVF, which may be supported by the reported evidence that ovarian stimulation may induce growth in existing highly differentiated tumors[16]. One case-control study stated that the risk increased in users of human menopausal gonadotrophin (HMG) (OR 9.4, 95% CI 1.7 to 52). However, this estimate was based on only six cases. The conclusion of the Cochrane[66]

reported no conclusive evidence of an increased risk of ovarian cancer for women who are treated with fertility drugs, compared to infertile women not treated with fertility drugs, or to women in the general population. Of note, five studies showing an increase in the risk of ovarian cancer were of low methodological quality and subsequently their results are not reliable to conclude that the risk of cancer is definitive while on treatment for infertility. In one study that included over 25,000 women, the risk of ovarian cancer increased only when the follow-up was extended to more than 15 years (SIR 3.54, 95% CI 1.62-6.72). The analysis of the entire patient group showed no increase of invasive ovarian cancer when compared to the general population (standardized incidence ratio [SIR] 1.30, 95% CI 0.86-1.88)[70]. A higher risk of ovarian cancer after fertility drugs (SIR 1.91, 95% CI 1.18-2.91) had been used was shown in another investigation. However, with the exclusion of cancer cases, which had been diagnosed within one year of receiving treatment, this increase was no longer significant (SIR 1.46, 95% CI 0.83-2.36)[67]. A population-based cohort study that included 106.031 women followed for a period lasting on average 12 years, showed that history of IVF treatment remained independently associated with ovarian and uterine cancer after controlling for confounding variables such as maternal age and obesity [hazard ratio: 3.9, 95% CI 1.2-12.6], but this occurred over a 25-year period during which fertility drug use changed and it was based on only three women with invasive ovarian cancer following IVF[71]. The majority of data indicate that ovarian cancer risk comes from infertility per se and Brinton et al[37] did not find an association between ovarian cancer and fertility treatment when using infertile women as control group, even for women who had undergone at least four cycles of IVF. A meta-analysis [4] of nine cohort studies including 109.969 patients compared the ovarian cancer risk in women receiving fertility treatment with that in an infertile reference group and the general population. The risk of ovarian cancer in women receiving fertility treatment increased compared to the general population [relative risk (RR): 1.50, 95% confidence interval (CI) 1.17-1.92], but was similar to that of the infertile reference group (RR: 1.26, 95% CI 0.62-2.55). A recently published analysis[33] on a huge population (2.2 million person years of observation) did find an increased risk of ovarian cancer, both invasive (SIR 1.40, C.I. 1.24 to 1.58) and borderline (SIR 1.36, C.I. 1.15 to 1.60). The very interesting observation is that ovarian cancer increased only in women with conditions associated with ovarian cancer (low parity and/or endometriosis).

Risk of Ovarian Cancer due to Individual Fertility Drugs

Most studies could not find dissimilarity in the incidence of ovarian cancer according to the specific type of fertility drugs, whether anti estrogens or gonadotropins, utilized. The largest study, which focused on the risk of cancer linked specifically to fertility drug usage, examined data on all the women who were followed in Danish fertility clinics during the years 1963-1998[65]. Women who were treated 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 individually or when combined, demonstrated no overall increase in the risk of developing epithelial ovarian cancer. Furthermore, it was not possible to make any associations with the quantity of cycles of use, parity, or duration of follow-up. Reigstad el al[28] showed that women failing to conceive after clomiphene citrate therapy, have a higher risk of ovarian cancer warranting further investigation of this subgroup of women[28]. Trabert et al[72] which included 9.825 women who were referred for infertility, found that the risk for invasive ovarian cancer following the utilization of gonadotropins or CC did not increase, except for 517 women who were still childless after the use of CC (RR 3.63, 95% CI 1.36-9.72). Other investigations[14,68,73-75] did not find that a risk for ovarian cancer increased with the use of CC, gonadotropins, combined therapy, or other drugs for infertility. In conclusion, the overwhelming majority of reports did not find a significant effect on ovarian cancer risk after the exposure to any specific fertility drug.

The Special Case of BRCA Mutation Carriers

Fertility treatments for carriers of BRCA mutation should not be restrained or viewed as capable of modifying the risk for invasive epithelial ovarian cancer as this high-risk group may also be more likely to undergo fertility treatment whether for fertility preservation or diminished ovarian reserve. A recent matched case-control study (941 pairs with and without a diagnosis of cancer)[76] assessed the risk of ovarian cancer

in BRCA mutation carriers undergoing fertility treatment and found no significant relationship between fertility medication use and subsequent risk of ovarian cancer. Another cohort study[77] of 1,073 BRCA mutation carriers showed no association between fertility treatment and ovarian cancer, regardless of type of fertility treatment in the 164 (15%) patients that received fertility treatment in both BRCA1 and BRCA2 mutation carriers. These studies, even if relatively small in size, are reassuring.

Borderline Ovarian Tumors

Borderline ovarian tumors have a low malignant potential and represent about 15% of all ovarian cancers, with a 1.8-4.8 incidence per 100,000 women years[78]. They are noninvasive, indolent tumors that differ from invasive ovarian cancer in having an excellent diagnosis with a 95% 5-year rate of survival. They are more common in reproductive-aged women who have not been associated with parity, endometriosis or prior surgery, so they behave differently from invasive cancers. Some studies showed an increase in the risk of borderline ovarian tumors in infertile women who were treated using IVF. A large study[23] evaluated a cohort of infertile patients selected on the basis of a hospital registry and evaluated cancer incidence in women who underwent IVF including as a reference population infertile patients who did not use IVF. 17 women out of the 7,544 who underwent IVF were diagnosed with borderline ovarian tumors, whereas 14 cases were identified in 14,095 women who did not use IVF. Women undergoing IVF showed a higher borderline rate of ovarian tumors with an HR of 2.46 (95% CI 1.20-5.04), which indicates 11 additional tumors (borderline) per 10,000 women. The incidence was not affected by hysterectomy, endometriosis, sterilization or prior birth, which is in contrast to invasive ovarian cancer. Van Leeuwen et al[70] compared borderline ovarian tumors in more than 19,000 women undergoing IVF with 6,000 infertile women who did not use IVF and with the general population. After an average of 14.7-year follow-up and after adjusting for age, parity and fertility diagnosis, the risk of borderline ovarian tumors was increased in treated women (SIR: 1.79, 95% CI 1.16-2.56). Another cohort study[23] also found an increased rate of borderline ovarian tumors in women who received IVF, after controlling for confounders (hazard ratio: 2.66, CI 1.2-5.04). Three cohort and three case-control studies were identified through the largest review which evaluated borderline ovarian tumor risks after fertility drugs were used[66]. Three researchers[47,69,79] described an increase in borderline ovarian tumors with the use of a fertility drug: this consisted of a 2- to 3-fold excess. A true meta-analysis was not possible because of the excessive heterogeneity among findings. However, in the evaluation of individual drugs, the increase in risk for borderline ovarian tumors with CC alone, CC and gonadotropins, or gonadotropins alone was not significant. An increase in the risk of borderline ovarian tumors using fertility drugs has not been shown by some investigations[80]. The largest study addressing this question[81] was a retrospective case-cohort study of 96,545 infertile Danish women observed for an average of 11 years. 142 women had borderline ovarian tumors but the risk did not increase with fertility drugs use (RR 1.0, 95% CI 0.67-1.51). Though there was no association observed for CC, gonadotropins, hCG, or GnRH agonists, the risk of the increase of borderline tumors was associated with the use of progesterone (RR 1.82, 95% CI 1.03-3.24). However, the absolute risk was extremely small, given the low incidence of this disease. Despite possible surveillance bias, most borderline ovarian tumors have been diagnosed up to 7-9 years after fertility treatment, raising concern about such an association since there is a high general risk of bias: retrospective study design, a lack of accounting for potential confounding and estimates which are based on a minor number of cases. In conclusion, based on the available evidence, infertile patients may be reassured since there appears to be no significant increase in the risk of invasive ovarian cancer after fertility drug usage. (Grade B evidence, ASRM[28]) and the risk is not different for any specific treatment (Grade B evidence, ASRM). When considering borderline ovarian tumors, the higher risk remains an open question. A small increase has been shown through several studies but the data remains insufficient (Grade C evidence, ASRM). It must be stated, however, that these are generally indolent tumors and carry a relatively good prognosis. Further studies are definitely needed.

Cervical Cancer

A number of studies[4,24,28,71], which assess cervical cancer risk following the use of fertility medication, have consistently shown that risk

does not increase in comparison to both the general population and infertile patients. A subset of researches[37,82] found that IVF patients showed a decrease of cervical cancer, although the mechanism behind this phenomenon is unclear and is perhaps related to better access to care with more frequent cervical cytology screening in women undergoing fertility treatment.

In conclusion, there is reasonable proof that an increase in the risk of cervical cancer is not associated with fertility drugs (Grade B evidence, ASRM).

Thyroid Cancer

The incidence of thyroid cancers is not associated with ART treatments as reported in most papers [75,83]. An increase in the risk of thyroid cancer is observed in association with high parity and use of exogenous hormones (hormone replacement therapy and oral contraceptives)[84]. In a retrospective cohort of 8.422 women evaluated for infertility[41], neither clomiphene citrate (RR: 1.42, 95% CI 0.5-3.7) nor gonadotropin (RR: 1.1; 95% CI 0.2-4.9) demonstrated an increased risk of thyroid cancer (18 cases) (RR: 1.42; 95% CI 0.5-3.7). It is possible that clomiphene citrate use may have a stronger effect on thyroid cancer risk among women who remain nulliparous (RR: 4.23; 95% CI 1.0-17.1), although six out of 18 thyroid cancer cases in this work were missing parity data. Another recent retrospective cohort study[85] showed a non-significant increase in thyroid cancer risk with the use of clomiphene citrate (hazard ratio: 1.57; 95% CI 0.89-2.75), based on 55 cases of thyroid cancer in a cohort of 9,892 women. Thyroid cancer risk was greatest among those women who received more than 2,250 mg of clomiphene citrate (hazard ratio: 1.96; 95% CI 0.92-4.17), although gonadotropin administration was unrelated to increased risk (hazard ratio: 1.16; 95% CI 0.52-2.58). A Danish cohort study of 54,362 infertile women[86] showed a significant association between CC use and thyroid cancer, based upon 29 cases (RR: 2.29; 95% CI 1.08-4.82). This increased risk was primarily associated with CC use in parous women. An increased risk of thyroid cancer was not found after gonadotrophin use (RR: 1.43; 95% CI 0.54-3.83), but was observed following progesterone use (RR: 10.14; 95% CI 1.93-53.34), although only in two patients. In conclusion, there is insufficient evidence to suggest an association between fertility medication use and thyroid cancer and only some studies show that thyroid cancer could be related to clomiphene use. On the whole, there seems to be no effect of fertility drugs on invasive thyroid cancer risk (Grade B evidence, ASRM).

Melanoma

Most works[41,87] have not shown that the risk of melanoma increases with the use of fertility drugs. There has been in the last years an increase in the occurrence of malignant melanoma, particularly in women, and this has been linked to late age at first birth, low parity and to oral contraceptives[88]. Stewart et al[89] found that women giving birth following IVF had an increased rate of invasive melanoma *vs.* women who failed to conceive after IVF, based on 139 invasive melanoma cases (hazard ratio: 3.61; 95% CI 1.79-7.26). There was, however, no increased risk in women receiving non-IVF-related fertility treatment (hazard ratio: 1.39; 95% CI 0.88-2.20). Hannibal et al[88] showed that fertility treatment was not associated with malignant melanoma, except for an increased risk following use of gonadotrophins or gonadotropin-releasing hormone in parous women. Finally, the use of clomiphene citrate has been associated with increased risk of melanoma in some[73,85] but not all[88,90] studies. In conclusion, there is not enough evidence to suggest an association between fertility drugs and melanoma (Grade C evidence, ASRM).

Colorectal Cancer

There is insufficient evidence to suggest an association between fertility medication use and colon cancer. In a large cohort study[41], clomiphene citrate use did not significantly increase the risk of colon cancer (RR: 0.83; 95% CI 0.4-1.9). In a retrospective cohort study of 9,892 women followed for a median of 30 years that detected 91 colorectal cancers, clomiphene citrate use was unrelated to colorectal cancer risk (hazard ratio: 0.82; 95% CI 0.52-1.30)[85]. A cohort study in 19,158 women who underwent ovarian stimulation for IVF compared to two groups (women who received different fertility treatments and the general population) found 109 colorectal cancers after a 21-year follow-up. The risk of colon cancer for the IVF group did not increase compared to the general population (SIR: 1.00; 95% CI 0.80-1.23), however, non-IVF women had a reduced risk (SIR 0.58, 95% CI 0.36-0.88)[91]. In conclusion, there is reasonable evidence that there is no association between fertility drugs and an increase in the risk of colon cancer (Grade B evidence, ASRM).

Non-Hodgkin Lymphoma

Calderon-Margalit et al[73], evaluating the risk for non-Hodgkin lymphoma following fertility drug usage, showed that the risk increased with ovulation induction therapy (HR 2.86, 95% CI 1.14-7.20) but not with use of only CC. However, there is insufficient data to make any conclusion, although ART does not seem to have an association with an increase in the risk of lymphoma (Grade C evidence according to ASRM).

Conclusions

We reviewed the available literature on cancer risk in women undergoing ART: we tried to focus on the most relevant studies in terms of size and quality of the analysis. Further, we put them into proper perspective and tried to make the information available to readers through simple tables, focused on patient counseling. At the same time we included trials with discordant results to show that this question is far from being settled. Many confounding elements may explain the differences reported. Women considering ART should receive balanced and sound advice but no oversimplification. High estrogens levels may theoretically increase the risk of hormone dependent cancers: breast, endometrium, and ovary. There is a relationship between long lasting high circulating estrogen levels (notably after menopause) and breast cancer. However, the cancer effect of fertility drugs is very different from that of endogenous hormones, hormonal contraception or menopausal therapy[92]. This applies specifically to a possible link between endogenous estrogens and the risk of premenopausal breast cancer: data are unfortunately scanty and results are not always plausible[92]. After reviewing the available literature, infertile women may be at an increased risk of invasive ovarian, endometrial, and breast cancer; however, the use of fertility drugs does not appear to increase this risk[34]. Methodological limitations need to be considered and studied further before drawing definitive conclusions. These are duration of infertility treatment, which is very short compared with the average use of hormonal contraception or menopausal hormonal therapy, and conditions like obesity that increase endogenous sex hormones causing very long lasting and measurable effects on susceptible reproductive organs. The putatively ART-related cancers may occur many years from the usual age of ART treatments, making it difficult to determine a cause-effect relationship, considering that most studies have a short follow up. Assisted reproductive techniques were not so frequently used many years ago, as they are today. As these cancers are relatively rare, randomized trials would not be practical. Most studies are old or case-control, and the risk of selection bias may contribute to the uncertainty about this relationship. Cohort studies can potentially minimize selection bias, but may be limited by recall bias and/or the ability to precisely identify and quantitate exposure. In addition, infertility patients may undergo more surveillance and so a detection bias could increase the real risk. Other methodological problems include improper or lack of controls, multiple causes and different treatments of infertility. Therefore, the net effect of fertility drugs per se is very difficult to be properly evaluated[93]. Another limitation for the interpretation of the net effect on cancer risk from ART treatments is the lack of distinction on the type of drugs used whether antiestrogens (like clomiphene or tamoxifen or aromatase inhibitors) or gonadotrophins and the interindividual differences in ovarian reserve and response to fertility drugs due to pathological conditions or previous treatments[94]. Progesterone is given to support the luteal phase for at least two weeks until the pregnancy test and if confirmed, it is continued for an average of 8 more weeks. The risk of breast cancer of natural progesterone in pre menopause is controversial, it may be neutral or it could even be protective[95]. In conclusion, physicians involved in fertility treatments can counsel patients that their use is not associated with a significant cancer risk. Table II summarizes the main results and could be used as a guideline or support for this discussion. At the same time clinicians and researchers must consider that data are still limited and obtained principally from observational cohort and case–control studies with the above mentioned several methodological issues. Infertility per se is a recognized risk factor for female cancers including breast, endometrial and invasive ovarian cancer. In these instances, fertility counseling is a very good opportunity to improve those lifestyle factors that could affect both fertility and cancer risk: like weight, diet, smoking and physical activity. Clomiphene, especially when using doses greater than 2000 mg and for more than six cycles, could modestly increase endometrial cancer risk. However, this increase is likely due to common characteristics of users (PCOS and overweight) or to the need of repetitive cycles in clomiphene re-

Table II. Ovulation induction drugs, possible effects on the risk of cancer risk and implications for patients and physicians.

	Breast cancer	Endometrial cancer	Ovarian cancer	Other cancers
Clomiphene	No association with an increase in the risk of breast cancer. (Grade B)	No association with an increase in risk of endometrial cancer. (Grade B) Some biased evidence of maybe increased risk for total dose > 2000 mg and > 7 number of cycles	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)	No increase in the risk of cervical cancer. (Grade B) No increase in the risk of invasive thyroid cancer. (Grade B) No associated with an increase in the risk of melanoma. (Grade C) No increase in the risk of colon cancer. (Grade B) Not associated with an increase in the risk of lymphoma. (Grade C)
Gonado trophins	No association with an increase in the risk of breast cancer. (Grade B)	No association with an increase in the risk of endometrial cancer. (Grade B) but cause high estrogen levels	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 as above.
Progesterone	Maybe neutral (or controversial)	Highly protective - greatly reduced risk	Maybe neutral (or reduced)	Inconclusive evidence
Quality of evidence	Limited and principally from observational studies (Level 2-2 or lower).	Limited and principally some observational studies (Level 2-2 or lower).	Limited and principally from observational studies (Level 2-2 or lower).	Limited and principally come observational studies (Level 2-2 or lower) Sometimes few anedoctal cases
Main literature bias	Infertility per se is a significant factor of risk (nulliparity, later pregnancies, BRCA?) (Grade B) Methodological issues include heterogeneous treatment regimens, small sample sizes, inadequate information regarding duration and dose of treatment, retrospective analyses, and short follow-up periods.*	Infertility per se is a significant factor of risk (nulliparity, later pregnancies, lower hormonal contraception use; Lynch?) (Grade B); women who require clomiphene are mostly anovulatory PCOS and or obese (associated with endometrial cancer and clomiphene use). Gonadotrophins increase estrogen levels, are more recently used, and have short follow-up. *Same methodological issues	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	Poor literature data on cervical, thyroid, melanoma, colon cancer and lymphoma *Same methodological issues

Table continued

sistant cases. Some studies have found that there is a small increased risk that borderline ovarian cancer could develop, however the absolute risk is small. There is not enough evidence to suggest that there is an association between fertility medication use and cancers of the cervix, thyroid and colon or melanoma. Additional studies with longer follow-up are needed to determine

Table II ***(Cont.)*** Ovulation induction drugs, possible effects on the risk of cancer risk and implications for patients and physicians.

	Breast cancer	Endometrial cancer	Ovarian cancer	Other cancers
What to tell patients before ART	Breast cancers are caused by a multitude of genetic and environmental causes: the net effect of ART is neutral or negligible. Renouncing to ART because of the risk of cancer (in estrogen sensitive breast cancer survivors low estrogen increasing regimens with letrozole seem safer) is not effective or even counter-effective as pregnancy, or an earlier and lactation are protective. Follow code against cancer recommendations	Infertile women with PCOS and those overweight should mostly improve lifestyle (exercise, weight reduction) with or without ART Renouncing to ART because of the risk of endometrial cancer is not effective or pregnancy, or an earlier one, and maybe lactation are protective. Follow code against cancer recommendations	No meaningful increase in the risk of invasive ovarian cancer following the usage of fertility drugs in infertile women. (Grade B) Absolute increase in the risk of borderline ovarian tumors is small, as they are indolent and generally have a favorable prognosis. (Grade B) Renouncing to ART because of ovarian, or borderline ovarian, cancer risk is not effective or even countereffective. Follow code against cancer recommendations*	Available literature is globally reassuring about fertility drugs risk on cervical, thyroid, melanoma, colon cancer and lymphoma Follow code against cancer recommendations
Implications for doctors	Fertility drugs should not be denied or restricted because of the risk of cancer, (with the possible exception of lower estrogen increasing or letrozole, regimens in already breast cancer patients	Fertility drugs should not be denied or restricted because of cancer risk. Clomiphene should be used when necessary (World Health Organization Group II ovulation disorders)	There is not enough evidence to recommend against using fertility medications to avoid borderline ovarian tumors. (ASRM recommendation) There is insufficient consisten t evidence that a particular fertility drug increases the risk of borderline ovarian tumors. (Grade C) Inform of the possible small risk using absolute numbers of low-malignant potential cancers, and their favorable prognosis (ASRM recommendation)	Clomiphene should be used when necessary (World Health Organization Group II ovulation disorders) as it has been related with thyroid cancer in some studies
What to do before ART treatment	History (BRCA Lynch) Breast ultrasound Mammography (> 38 years old?)	History (Lynch, BRCA) Thorough diagnostic workup of any suspicious endometrial lesion (ultrasound, Hysteroscopy, Sono Hysteroscopy)	History (BRCA; Lynch) Thorough diagnostic workup of any suspicious (laparoscopy) adnexal mass (Ultrasound, CA 125 + HE4 magnetic resonance and/or laparoscopy)	History Pap smear Check thyroid function (ultrasound?)
Which follow up after ART	Breast ultrasound Mammography (closer follow up?)	Endometrial ultrasound Hysteroscopy and Biopsy if a suspicious bleeding or uterine abnormal image	Thorough diagnostic workup of any suspicious adnexal mass (closer follow up?) Long term follow up	Check thyroid function?? (ultrasound?)

Table continued

whether particular subgroups of women have an increased risk of developing cancer following fertility treatment. At this time, there is no reason for concern when using assisted reproductive techniques. Nonetheless, infertility consultation is a good opportunity to address lifestyle changes and cancer prevention strategies.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

Table II *(Cont.)* Ovulation induction drugs, possible effects on the risk of cancer risk and implications for patients and physicians.

	Breast cancer	Endometrial cancer	Ovarian cancer	Other cancers
How to reduce the risk after completing ART and renouncing to achieve pregnancy	Follow code against cancer lifestyle recommendations	Follow code against cancer lifestyle recommendations. Hormonal contraception	Follow code against cancer lifestyle recommendations. Hormonal contraception	Follow code against cancer lifestyle recommendations.

Quality of evidence and level of recommendation from (Practice Committee of the American Society for Reproductive Medicine Fertility drugs and cancer: a guideline Fertil Steril 2016; 106: 1617-26). The evaluation of the quality of the evidence was conducted using the following grading system: (1) Level I: Evidence which was obtained from at least one properly designed randomized, controlled trial. (2) Level II-1: Evidence which was obtained from well-designed controlled trials without randomization. (3) Level II-2: Evidence which was obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group. (4) Level II-3: Evidence which was obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence. (5) Level III: Meta-analyses, systematic reviews, opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees. The strength of the evidence was evaluated as follows: Grade A: There is good evidence to support the recommendations, either for or against. Grade B: There is fair evidence to support the recommendations, either for or against. Grade C: There is insufficient evidence to support the recommendations, either for or against.

***Summary from ASRM guideline 2016*[34]**

– The data assessing the association between fertility drugs and cancer are limited and principally come from observational studies (Level 2-2 or lower).
– Methodological issues include small sample sizes, heterogeneous treatment regimens, inadequate information about duration and dose of treatment, retrospective analyses, and short follow-up periods.
– Overall, there is fair evidence that women with infertility have an increased risk of breast, ovarian, and endometrial cancer. (Grade B)
– Based on available data, we can be reasonably reassured that there is no meaningful increased risk of invasive ovarian cancer following the use of fertility drugs in infertile women. (Grade B)
– Based on the available data there is fair evidence that the risk of invasive ovarian cancer is not different with one fertility drug compared with another. (Grade B)
– While several studies have shown a small increase in the absolute risk of borderline tumors after fertility treatments, there is insufficient consistent evidence that a particular fertility drug increases the risk of borderline ovarian tumors. (Grade C)
– It is important to note that any absolute increase in risk is small, and borderline ovarian tumors are indolent and generally have a favorable prognosis. (Grade B)
– There is fair evidence that fertility drugs are not associated with an increased risk of breast cancer. (Grade B)
– Overall, there is fair evidence that fertility drugs are not associated with an increased risk of endometrial cancer. (Grade B)
– Overall, there is fair evidence that fertility drugs are not associated with an increased risk of invasive thyroid cancer. (Grade B)
– Overall, there is insufficient evidence that fertility drugs are associated with an increased risk of melanoma. (Grade C)
– Overall, there is fair evidence that fertility drugs are not associated with an increased risk of colon cancer. (Grade B)
– Based on a single study, there is insufficient evidence that fertility drugs are associated with an increased risk of lymphoma. (Grade C)
– Overall, there is fair evidence that fertility drugs are not associated with an increased risk of cervical cancer. (Grade B)

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