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Review

Does ovulation induction increase the risk of gynecological cancer?

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Abstract

The risk of developing gynaecological cancer following ovulation induction therapy in infertile patients is not easy to determine due to many confounding factors. These include the fact that infertility in itself is a known risk factor for some of these cancers, that these patients are subjected to increased surveillance compared to the general population and that the drugs used for ovulation induction are sometimes used in combination. Notwithstanding these limitations, most of the studies have not confirmed a link between these drugs and invasive ovarian cancers, although some studies have suggested that the risk of borderline ovarian tumors may be increased. Investigations regarding breast cancer risk have produced inconsistent results and more information on the subject is warranted. On the contrary, many studies suggest that drugs used for ovulation induction may increase the risk of uterine cancers. More large well-designed studies are still needed to further clarify the effects on cancer risk of these drugs and will allow more in-depth subgroup analysis based on both patient and disease characteristics.

Key words: **Ovulation induction, cancer, ovarian cancer, breast cancer, endometrial cancer, gynecologic cancer, clomiphene citrate, gonadotrophins, HMG, controlled ovarian hyperstimulation, infertility, trophoblastic disease.**

Introduction

Ovulation induction agents are now widely used in the treatment of female infertility. They were originally introduced to induce ovulation in anovulatory infertile women (Roy et al., 1963). With the introduction of assisted reproduction (intra-uterine insemination IUI, in-vitro fertilization IVF and intracytoplasmic sperm injection ICSI), ovulation induction agents have also been used to produce "controlled ovarian hyperstimulation" (COH) in patients undergoing these procedures (Cohen et al., 2005). Other uses include the treatment of luteal phase insufficiency, unexplained infertility and repeated miscarriages (Minassian et al., 1988; Sallam et al., 2011; Ray et al., 2012).

Since its introduction, ovulation induction therapy has succeeded in achieving pregnancy in large numbers of couples who had previously been denied this privilege. It has also been estimated that by June 2012, over 5 million babies have been born following assisted reproduction (ESHRE, 2012). However, these ovulation induction agents are not without complications. In particular, the long term risk of gynaecological cancer has been a matter of concern. The aim of this paper is to review the evidence related to this risk.

We have conducted a review of the literature in major databases and included the results of well conducted randomized or cohort studies in order to reach conclusions based on the best currently available evidence.

Ovulation induction agents

The first preparation used for inducing ovulation was clomiphene citrate and is the most widely used (Roy et al., 1963). Its exact mechanism of action is not known but it is believed to have mainly anti-estrogenic effects with some estrogenic effects (ASRM Practice Committee, 2013). It can therefore be considered as a selective estrogen receptor modulator. As an anti-estrogen, it competes with estradiol for binding sites at the hypothalamus level,

leading to an increased secretion of GnRH and hence of FSH and LH from the pituitary, resulting in ovarian follicular maturation. This is followed by the preovulatorty LH rise, ovulation and the subsequent development of the corpus luteum (Sallam et al., 1983). Other anti-estrogens used for ovulation induction which exert similar effects on the hypothalamus include tamoxifen, epimestrol and cyclofenil (Villalobos et al., 1975; Tajima and Fukushima, 1983; Sallam, 1999). More recently, aromatase inhibitors such as letrozol have been used for ovulation induction. However, contrary to anti-estrogens, the aromatase inhibitors act peripherally by diminishing the production of estradiol secreted from the ovarian follicles. This hypoestrogenemia leads to a negative feed-back effect at the level of the hypothalamus stimulating GnRH release (Mitwally and Casper, 2001).

Gonadotrophins are also used for ovulation induction and controlled ovarian hyperstimulation (Sallam et al., 1982; Sallam, 1999). These include human menopausal gonadotrophins (HMG) obtained from urine of menopausal women and their purified derivatives as well as the more recent recombinant FSH preparations obtained by recombinant technology (Lunenfeld, 2004).

Other methods of ovulation induction include the administration of dopamine agonists (e.g. bromocryptin) for patients with hyperprolactinemia and laparoscopic ovarian drilling LOD) for anovulatory patients with polycystic ovarian syndrome resistant to clomiphene citrate therapy.

Infertility and the risk of gynaecological cancer

It is important to realize that infertility in itself is a risk factor in the development of some gynaeocological cancers, particularly endometrial and ovarian cancer. It is therefore important to take this fact into consideration when evaluating the risk of cancer associated with ovulation induction.

In 1997, Mosgaard et al. conducted a case control study of all Danish women (below the age of 60 years) diagnosed with ovarian cancer during the period from 1989 to 1994 (Mosgaard et al., 1997). The analysis included 684 cases and 1,721 age-matched controls. They found that infertility *per-se* implied an increase in the crude risk of ovarian cancer (OR = 1.54; 95% CI = 1.22-1.95). Infertile nulliparous women without treatment had an even higher risk compared with nulliparous women without infertility (OR = 3.13; 95% CI = 1.60- 6.08).

Similar results were reported by Modan et al. (1998) who studied 2,496 infertile women treated between 1964 and 1974. They used standardized incidence ratios (SIRs) to compare cancer risk with the general population and found that infertility patients demonstrated a higher cancer risk than the general population (SIR = 1.2, 95% CI = 1.0-1.5). Site-specific analysis revealed that the risk of endometrial cancer was significantly elevated (SIR = 4.85, 95% CI = 3.0-7.4), with a borderline increase in ovarian and breast cancers (SIR = 1.6, 95% Cl = 0.8-2.9, and SIR = 1.3, 95% Cl = 0.96-1.6, respectively).

Similarly, an Australian study conducted by Venn et al. (1999) compared a cohort of 20,656 women who were previously exposed to fertility drugs to 9044 women who were not. Although the incidence of breast and ovarian cancer was not greater than expected in the exposed group or the unexposed group, the incidence of uterine cancer was significantly higher in the unexposed infertile group (SIR = 2.47; 95% CI = 1.18-5.18). Subgroup analysis showed that women with unexplained infertility had significantly more cancers of the ovary and uterus than expected (SIR = 2.64; 95% CI = 1.10-6.35 and SIR = 4.59; 95% CI = 1.91-11.0, respectively) (Venn et al., 1999). A British study conducted by Silva Idos et al. confirmed these results. In a cohort 7355 women with ovulatory disorders, a higher incidence of cancers of the breast (Relative risk RR = 1.13; 95% CI = 0.97-1.30) and corpus uteri (RR = 2.02; 95% CI = 1.37, 2.87) was reported (Silva Idos et al., 2009).

In another study by Benshushan et al. (2001) the authors conducted a case-control study in which they compared women with a histologically confirmed diagnosis of endometrial carcinoma (n = 128) to a group of controls (n = 255). They constructed a multivariate logistic model and found that nulliparity and infertility were independent factors significantly associated with endometrial cancer (Odds ratio OR = 2.7; 95% CI = 1.1-6.5, P = 0.03 and OR = 1.8; 95% CI = 1.0-3.3, P = 0.05, respectively) (Benshushan et al., 2001).

In a larger study, Brinton et al. (2005) conducted a retrospective cohort study involving 12,193 infertile women and found that 581 of them developed cancer (SIR = 1.23; 95% CI = 1.1-1.3). Patients with primary infertility were at an even higher risk (SIR = 1.43; 95% CI = 1.3-1.6). Particularly elevated risks among primary infertility patients were observed for cancers of the uterus (SIR = 1.93) and ovaries (SIR = 2.73). Further analysis revealed that patients with primary infertility due to anovulation were particularly predisposed to uterine cancer (SIR = 2.42; 95% CI = 1.0-5.8), while those with tubal disorders were more predisposed to ovarian cancer (SIR = 1.61; 95% CI = 0.7-3.8). Primary infertility associated with male-factor problems was associated with unexpected increases in colon

(SIR = 2.85; 95% CI = 0.9-9.5) and uterine (SIR = 3.15; 95% CI = 1.0-9.5) cancers.

In a more recent study, Liat et al. (2012) studied a cohort of 2431 Israeli women (more than 84,000 women-years) who were treated for infertility during the period 1964-1974. Eighteen cases of ovarian cancer were observed as compared to 18.1 expected (SIR = 1.0; 95% CI = 0.59-1.57). For breast cancer, 153 cases were observed as compared to 131.9 expected (SIR = 1.16; 95% CI = 0.98-1.36), and for endometrial cancer, 30 cases were observed as compared to 17.8 expected cases (SIR = 1.69; 95% CI = 1.14-2.41). They concluded that infertility is associated with a significantly increased risk for endometrial cancer and a borderline increased risk for breast cancer, while ovarian cancer risk was not found to be elevated.

Infertility is not the only confounding factor making the interpretation of the studies difficult. This task is also difficult because of the small numbers, short follow-up periods, and imprecise information on drugs or indications for usage in many of the studies. Prospective studies are also limited by their inability to control for other cancer predictors, while retrospective studies may suffer from selective recall bias. It should also be kept in mind that cancers may also be over-diagnosed in infertile women population because of the close medical surveillance to which these patients are exposed.

Uterine cancer

The risk of uterine cancer seems to be increased with ovulation induction therapy, particularly in women using clomiphene citrate. A study conducted by Venn et al. of 29,700 Australian women referred for IVF therapy showed that the risk of uterine cancer was significantly elevated (SIR = 4.96; 95% CI = 1.24-19.8) (Venn et al., 1999). Subsequently, Althuis et al. published the results of a retrospective cohort study of 8,431 US women (145,876 woman-years) evaluated for infertility during 1965-1988. The results suggest that clomiphene citrate tends to increase uterine cancer risk (rate ratio RR = 1.79, 95% CI = 0.9-3.4). The risk increased with the dose (RR = 1.93, 95% CI: 0.9-4.0), the number of menstrual cycles of use (RR = 2.16, 95% CI = 0.9-5.2 for > 6 cycles), and the time elapsed since initial use (RR = 2.50, 95% CI: 0.9-7.2 for women followed for more than 20 years). The risk was more strongly associated with clomiphene citrate among nulligravid (RR = 3.49, 95% CI = 1.3-9.3) and obese (RR = 6.02, 95% CI = 1.2-30.0) women. The highest risk was found in women who were both obese and nulligravid (RR = 12.52, 95% CI = 1.5-108.0). The authors concluded that clomiphene citrate may increase the risk of uterine cancer, with higher doses leading to higher risk (Althuis et al., 2005).

Similarly, Calderon-Margalit et al. conducted a long-term population-based historical cohort study of 15,030 Israeli women who gave birth between 1974 and 1976, including 567 women treated with ovulation induction. The cancer incidence was analyzed using Cox's proportional hazards models to calculate the multivariate hazard ratio (HR). They found that women who used drugs to induce ovulation had an increased risks of cancer at any site (HR = 1.36, 95% CI = 1.06-1.74). An increased risk of uterine cancer was also found among women treated with ovulation-inducing agents (HR = 3.39, 95% CI = 1.28-8.97), specifically clomiphene citrate (HR = 4.56, 95% CI = 1.56-13.34) (Calderon-Margalit et al., 2009).

However, not all studies reported an increased risk of uterine cancer with ovarian stimulation, particularly in women undergoing IVF. An earlier study by Dor et al. of 5026 Israeli women who underwent IVF between 1981 and 1992 had reported that the risk of cancer in general and of uterine cancer was not increased (SIR = 0.76; 95% CI = 0.50-1.10 and SIR = 2.25; 95% CI = 0.25-8.11, respectively) (Dor et al., 2002). Similarly, in the more recent cohort study of Liat et al., although infertility per-se and the combined administration of clomiphene citrate and HMG were found to be associated with significant increased risk for endometrial cancer (SIR = 1.69; 95% CI = 1.14-2.41 and SIR = 5.0; 95% CI = 2.15-9.85, respectively), no excess risk was found to be associated with exposure to clomiphene citrate alone or HMG alone (SIR = 1.07; 95% CI = 0.39-2.33 and SIR = 2.16; 95% CI = 0.43-6.32, respectively) (Liat et al., 2012). A summary of the relevant studies is shown in table I.

Not all of the uterine cancers reported are of endometrial origin. In the study conducted by Venn et al. mentioned previously, 12 cancers of the uterus were identified. They included 8 endometrial adenocarcinomas, 2 stromal sarcomas and 2 leiomyosarcomas (Venn et al., 2001). In an attempt to understand the relationship between ovarian stimulation and possible uterine cancer, Chai et al. studied endometrial biopsies from 12 natural and 12 stimulated cycles. They found that the expression of estrogen receptor α (ERα) transcript was significantly reduced in stimulated cycles compared with natural cycles (but not that of ERβ or progesterone receptor, PR). Glucocorticoid receptor (GR) transcript was also significantly increased in the excessive responders. In stimulated cycles, the endometrium had a lower expression of PR protein in

Table I. — Risk of uterine cancer with ovulation induction therapy – summary of selected studies.

Study	Subjects	Group	Risk	SIR, RR or HR (95% CI)
Venn 1999	29700 (20,656 exposed to fertility drugs and 9044 not exposed)	Exposed v/s expected	Not increased	SIR = 1.09 (0.45-2.61)
		Unexposed v/s expected	Increased	SIR = 2.47 (1.18-5.18)
		Exposed v/s expected (within 1 year of IVF)	Increased	SIR = 4.96 (1.24-19.8)
Dor 2002	5026	IVF	Not increased	SIR = 2.25 (0.25–8.11)
Althuis 2005	8431 (145,876 woman-years)	Clomiphene – All patients	Borderline increase	RR = 1.79 (0.9-3.4)
		Clomiphene > 900 mg	Borderline increase	RR = 1.93 (0.9-4.0)
		Clomiphene > 6 cycles	Borderline increase	RR = 2.16 (0.9-5.2)
		Clomiphene in nulligravidae	Increased	RR = 3.49 (1.3-9.3)
		Clomiphene in obese women	Increased	RR = 6.02 (1.2-30.0)
		Clomiphene in nulligravidae and obese	Increased	RR = 12.52 (1.5-108.0)
Calderon-Margalit 2009	15,030	Any drug	Increased	HR = 3.39 (1.28-8.97)
		Clomiphene	Increased	HR = 4.56 (1.56-13.34)
Liat 2012	2431 (> 84,000 women years)	HMG + Clomiphene citrate	Increased	SIR = 5.0 (2.15-9.85)
		Clomiphene citrate only	Not increased	SIR = 1.07 (0.39-2.33)
		HMG only	Not increased	SIR = 2.16 (0.43-6.32)

glands, but a higher expression in stroma, while GR protein expression was significantly up-regulated in the stroma but not the glands. In addition, endometrial cells treated with high steroid concentrations had a reduced spheroid attachment rate compared to the controls. They concluded that high serum oestradiol levels affect the expression of steroid receptors in the endometrial cells and suppress spheroid attachment (Chai et al., 2011).

Ovarian cancer

In 1971, Fathalla suggested that the increased risk of ovarian cancer among infertile women may be due to the incessant ovulation whereby the ovarian cortex is bombarded by monthly ovulations without any rest due to pregnancy or lactation (Fathalla, 1971). From comparative ovarian oncology in domestic fowl, he observed that adenocarcinomas can be induced in the ovaries of hens by maintaining them throughout life in a stable environment with 12 hours of fluorescent lighting daily, without any seasonal variation to maximize their egg production. Based on this "incessant ovulation" theory, the use of ovulation induction or hyperstimulation could increase the risk of ovarian cancer in humans. In support of this theory, Burdette et al. studied the proliferation of ovarian surface epithelium (OSE) cells in CD1 mice, in response to ovarian stimulation by pregnant mare serum gonadotrophin (PMSG) and human chorionic gonadotrophin (hCG). These cells are thought to be the progenitors of 90% of ovarian cancers. They found that OSE proliferation was significantly higher in superovulated animals compared with control mice. In addition, apoptosis was also assessed in response to ovulation, and virtually no cell death within the OSE cells was detected (Burdette et al., 2006). Murdoch suggested that the integrity of DNA of OSE cells is compromised by reactive oxidants and inflammatory mediators generated during the ovulatory process and that malfunction in a damage-

recognition and/or repair mechanism is a determinant in the etiology of ovarian metaplasia and carcinogenesis (Murdoch, 2003).

However, ovarian stimulation *per se* does not seem to increase the risk of ovarian cancer in humans. In a case control study by Shushan et al., these workers compared 200 cases with histologically confirmed ovarian cancer to 408 matched controls (Shushan et al., 1996). They found that the overall risk of ovarian tumors was not higher in women who used ovarian stimulation therapy (OR = 1.31; 95% CI = 0.63-2.74). In the 1997 study by Mosgaard et al., the risk of ovarian cancer in nulliparous patients treated with ovarian stimulation was not increased (OR = 2.26; CI = 0.92-5.58) compared with nulliparous women without infertility. The risk was still the same when nulliparous infertile women who received clomiphene citrate were compared to nulliparous infertile women who did not receive the drug (OR = 0.83; 95% CI = 0.35-2.01) (Mosgaard et al., 1998).

Similar findings were reported in the retrospective cohort study of 12,193 infertile women conducted by Brinton et al. (2004) The risk of ovarian cancer was not significantly higher in those who received clomiphene citrate (SIR = 0.82; 95% CI = 0.4, 1.5) or gonadotrophins (SIR = 1.09; 95% CI = 0.4, 2.8). There were higher, but non-significant, risks with follow-up time, with the rate ratios after 15 or more years being 1.48 (95% CI 0.7, 3.2) for exposure to clomiphene citrate and 2.46 (95% CI 0.7, 8.3) for gonadotropins. Similar results were also reported in the previously mentioned study of Calderon-Margalit et al. where no association was noted between the use of ovulation-inducing agents and ovarian cancer (HR = 0.61, 95% CI: 0.08-4.42) (Calderon-Margalit et al., 2009).

However, not all studies have reached these conclusions, particularly in patients undergoing ovulation induction for assisted reproduction (IVF or ICSI). For example, Lerner-Geva et al., studied 1082 Israeli women who underwent IVF treatment and found that the risk of ovarian cancer was increased (SIR = 1.91; 95% CI = 1.18-2.91), although when cases that were diagnosed within one year of the IVF treatment were excluded from the analysis (SIR = 1.46; 95% CI 0.83-2.36), no significant excess risk of cancer was noted (Lerner-Geva et al., 2003).

In an attempt to clarify the issue, Kashyap et al. conducted a meta-analysis of studies performed in patients undergoing assisted reproduction (Kashyap et al., 2004). Three cohort and 7 case-control studies were included in their analysis. They found that case-control and cohort data showed a significantly elevated risk of ovarian cancer in patients exposed to infertility medications who underwent assisted reproductive therapy compared with general population controls (OR = 1.52; 95% CI = 1.18 to 1.97). However, when cases of ovarian cancer were compared with infertile controls for exposure to infertility medications, the odds ratio was not elevated (OR = 0.99; 95% CI = 0.67, 1.45) and cohort data comparing treated with untreated infertile patients suggests that treated patients tended to have a lower incidence of ovarian cancer (OR = 0.67, 95% CI = 0.32, 1.41). They concluded that ovarian cancer does not appear to be increased in treated infertile patients versus untreated infertile patients and that treated infertile patients may even have a lower incidence of ovarian cancer than untreated infertile patients (Kashyap et al., 2004). More recent studies confirm these findings. In the study of Liat et al. no significant excess risk of ovarian cancer was associated with CC or HMG use (SIR = 1.33; 95% CI = 0.57-2.63 and SIR = 0.74; 95% = 0.01-4.12) (Liat et al., 2012).

On the other hand, borderline ovarian tumors seem to be increased after ovarian stimulation and in IVF treated patients. In the subgroup analysis of the Shushan et al. study, the risk of borderline ovarian tumors was increased in women who had used HMG (OR = 9.38; 95% CI = 1.66-52.08) (Shushan et al., 1996). Similar results were reported by van Leeuwen et al. who conducted a nationwide historic cohort of 19,146 women treated with IVF in the Netherlands between 1983 and 1995 and compared them to a group of 6006 subfertile women not treated with IVF (van Leeuwen et al., 2011). The results showed that after a median follow-up of 14.7 years, the risk of borderline ovarian tumours was increased in the IVF group (SIR = 1.76; 95% CI = 1.16-2.56). The overall SIR for invasive ovarian cancer was not significantly elevated, but increased with longer follow-up after first IVF (P = 0.02); the SIR was 3.54 (95% CI = 1.62-6.72) after 15 years. The risks of borderline ovarian tumors and of all ovarian malignancies combined in the IVF group were significantly increased compared with risks in the untreated subfertile comparison group (SIR = 4.23; 95% CI = 1.25-14.33 and 2.14; 95% CI = 1.07-4.25, respectively). The authors concluded that ovarian stimulation for IVF may increase the risk of ovarian malignancies, especially borderline ovarian tumors (van Leeuwen et al., 2011). Not all studies on borderline ovarian tumors have reached these conclusions. Cusidó et al. conducted a case control study involving 42 women with a borderline ovarian tumor and a control group of 257 women with benign ovarian pathology. They found no significant differences between the borderline tumor and control groups (14.3% vs. 27.2%, respectively) in terms of

infertility history. In addition, they did not find any significant differences between the groups with respect to the type of drug used, whether clomiphene citrate (9.5% vs. 6.2%, respectively) or gonadotrophins (7.1% vs. 10.1%, respectively). They concluded that there was no evidence that ovulation induction treatment predisposes women to the development of borderline ovarian tumors (Cusidó et al., 2007).

Most of the ovarian cancers reported in association with ovulation induction are of the epithelial type. In the study of the 29,700 IVF patients conducted by Venn et al. (2001) 13 cancers of the ovary were identified with the following histologic types: serous (n = 4), mucinous (n = 1), seromucinous (n = 1), endometrioid (n = 3), clear cell (n = 2), and unknown type (n = 1). A summary of the relevant studies is shown in Table II.

Breast cancer

The incidence of breast cancer in women treated with ovarian stimulation with or without assisted reproduction is still debated with most of the studies showing no significant increase in the risk. In the Australian study conducted by Venn et al., of the cohort of 20,656 women previously exposed to fertility drugs and 9044 unexposed controls, the incidence of breast cancer was no greater than expected in the exposed group as well as in the unexposed group (SIR = 0.91; 95% CI = 0.74-1.13) (Venn et al., 1999).

Similarly, the study of Dor et al. of 5026 Israeli women who underwent IVF between 1981 and 1992, 27 cases of cancer were observed when 35.6 were expected (SIR = 0.76; 95% CI = 0.50-1.10). Eleven cases of breast cancer were also observed, whereas 15.86 were expected (SIR = 0.69; 95% CI = 0.46-1.66). The type of infertility, number of IVF cycles, and treatment outcome did not significantly affect risk for cancer. They concluded that in women treated with IVF, there is no excess risk for cancer in general and of breast cancer in particular (Dor et al., 2002). Similar results were reported by Terry et al., who, as a part of the Nurses' Health Study II, analyzed data from a prospective cohort of 116,671 female nurses (1,275,566 person-years). They found that women who suffered from infertility due to ovulatory disorder had a significantly lower incidence of breast cancer than women who conceived within 12 month of trying (HR = 0.75; 95% CT = 0.59-0.96). The incidence of breast cancer was lowest among women with infertility who received ovulation-induction therapy (HR = 0.60; 95% CI = - 0.42-0.85) (Terry et al., 2006).

Contradictory results were reported by Pappo et al. who performed a retrospective cohort analysis of 3,375 IVF-treated women and found a borderline increase in the risk of breast cancer (SIR = 1.4; 95% CI 0.98-1.96). Age (40 years or more) at IVF treatment (SIR = 1.9; 95% CI 0.97-3.30), hormonal infertility (SIR = 3.1; 95% CI 0.99-7.22), and number (4 or more) of IVF cycles (SIR = 2.0; 95% CI 1.15-3.27) were found to be risk factors to develop breast cancer compared to the general population (Pappo et al., 2008). Multivariate analysis revealed that women who underwent 4 or more IVF cycles compared to those with one to three cycles were at risk to develop breast cancer, although not significantly (SIR = 1.9; 95% CI 0.95-3.81). Similarly, in the study of Calderon-Margalit et al. mentioned previously, ovulation induction was associated with a borderline-significantly increased risk of breast cancer (multivariate HR = 1.42, 95% CI = 0.99-2.05) (Calderon-Margalit et al., 2009).

More reassuring results were reported in the more recent study of Liat et al. of the cohort of 2431 Israeli women (> 84,000 women-years), where no significantly increased risk of breast cancer was found in patients treated with clomiphene citrate, with HMG or both (SIR = 1.21; 95% CI = 0.91-1.58, SIR = 0.4; 95% CI = 0.11-1.6 and SIR = 0.93; 95% = 0.48-1.63, respectively). A summary of the relevant studies is shown in Table III.

Trophoblastic disease

The possible association between exposure to fertility drugs and the risk of developing persistent trophoblastic tumour (PTT) after ovarian stimulation was also studied. Petignat et al. conducted a systematic review of the literature and found 52 reported cases. PTT occurred in 15% of patients with singleton hydatidiform moles (HM) and in 42% of patients with HM in a multiple pregnancy of whom 15% had a metastatic disease. These results are similar to spontaneously conceived pregnancies. They concluded that there was no added risk of PTT, but as multiple pregnancies are more likely to occur, the overall risk may be increased (Petignat et al., 2002).

Recurrence of trophoblastic tumours has also been described in women undergoing IVF therapy. In 1994, Tanos et al. reported recurrence of gestational trophoblastic disease (GTD) following two attempts at in-vitro fertilization (IVF)/embryo transfer in a childless couple after 17 years of unsuccessful trials of ovulation induction. The patient was treated successfully in both instances and was advised to have ovum donation to prevent a third recurrence (Tanos et al., 1994).

Table II. — Risk of ovarian cancer with ovulation induction therapy – summary of selected studies.

Study	Subjects	Group	Risk	SIR, OR or HR (95% CI)
Shushan 1996	200 women with epithelial ovarian cancer and 408 healthy controls	Exposed v/s non-exposed	Not increased	OR = 1.31(0.63-2.74).
		HMG+/-clomiphene citrate v/s unexposed	Not increased	OR = 1.42(0.65-3.12)
		All tumors -HMG alone v/s unexposed	Not increased	OR = 3.19 (0.86-11.82)
		Borderline tumors – HMG alone v/s unexposed	Increased	OR = 9.38 (1.66-52.08)
Mosgaard 1997	684 cases and 1,721 controls	Treated nulliparous women v/s nulliparous women without infertility.	Not increased	OR = 2.26 (0.92-5.58)
		Treated parous women v/s v/s nulliparous women without infertility.	Not increased	OR = 0.73 (0.29-1.82)
		Treated nulliparous infertile v/s non-treated infertile	Not increased	OR = 0.83 (0.35- 2.01)
		Treated parous infertile v/s non-treated infertile	Not increased	OR = 0.56 (0.24-1.29)
Dor 2002	5026	IVF	Not increased	SIR = 0.57 (0.01–3.20)
Lerner-Geva 2003	1082 IVF patients	Exposed v/s expected	Increased	SIR = 1.91 (1.18-2.91)
		After exclusion of cases diagnosed within 1 year of IVF	Not increased	SIR = 1.46 (0.83-2.36)
Brinton 2004	12,193	Any drug v/s general population	Increased	SIR = 1.98 (1.4-2.6)
		Clomiphene v/s infertile controls	Not increased	SIR = 0.82 (0.4-1.5)
		Gonadotrophins v/s infertile controls	Not increased	SIR = 1.09 (0.4-2.8)
		Clomiphene v/s infertile controls > 15 years	Not increased	SIR = 1.48 (0.7-3.2)
		Gonadotrophins v/s infertile controls > 15 years	Not increased	SIR = 2.46 (0.7-8.3)
Calderon-Margalit 2009	15,030	Any drug	Not increased	HR = 0.61 (0.08-4.42)
Venn 1999	29700 (20,656 exposed to fertility drugs and 9044 not exposed)	Exposed v/s expected	Not increased	SIR = 0.88 (0.42-1.84)
		Unexposed v/s expected	Not increased	SIR = 1.16 (0.52-2.59)
van Leeuwen 2011	19,146 IVF and 6,006 non-IVF	Borderline tumors v/s general population	Increased	SIR = 1.76 (1.16-2.56)
		Invasive cancer v/s general population	Not increased	SIR = 1.30 (0.86-1.88)
		Invasive cancer after 15 years v/s general population	Increased	SIR = 3.54 (1.62-6.72)
		Borderline tumors v/s infertile non-IVF group	Increased (HR)	SIR = 4.23 (1.25-14.33)
		Invasive cancer v/s infertile non-IVF group	Increased (HR)	SIR = 2.14 (1.07-4.25)
Liat 2012	2431 (> 84,000 women years)	All drugs	Not increased	SIR = 1.0 9 (0.59-1.57)
		Clomiphene citrate only	Not increased	SIR = 1.33 (0.57-2.63)
		HMG only	Not increased	SIR = 0.74 (0.01-4.12)

Table III. — Risk of breast cancer with ovulation induction therapy – summary of selected studies.

Study	Subjects	Group	Risk	SIR or HR (95% CI)
Venn 1999	29700 (20,656 exposed to fertility drugs and 9044 not exposed)	Exposed v/s expected	Not increased	SIR = 0.91 (0.74-1.13)
		Unexposed v/s expected	Not increased	SIR = 0.95 (0.73-1.23)
		Exposed v/s expected (within 1 year of IVF)	Increased	SIR = 1.96 (1.22-3.15)
Dor 2002	5026	IVF	Not increased	SIR = 0.69 (0.46-1.66)
Pappo 2008	3375 women	IVF	Borderline increase	SIR = 1.4 (0.98-1.96)
		> 40 years	Borderline increase	SIR = 1.9 (0.97-3.30)
		Hormonal infertility	Borderline increase	SIR = 3.1(0.99-7.22)
		> or = 4 IVF cycles	Increased	SIR = 2.0 (1.15-3.27)
Calderon-Margalit 2009	15030	Any drug	Borderline increase	HR = 1.42 (0.99-2.05)
Liat 2012	2431 (> 84,000 women years)	HMG + Clomiphene citrate	Not increased	SIR = 0.93 (0.48-1.63)
		Clomiphene citrate only	Not increased	SIR = 1.21 (0.91-1.58)
		HMG only	Not increased	SIR = 0.4 (0.11-1.6)

Risk of cancer in the offspring

The risk of cancer in the offspring of women treated with ovarian stimulation drugs has also been studied and the results are reassuring. Klip et al. studied the offspring of a large (n = 9484) population-based historical cohort of women who underwent IVF in the Netherlands. They were compared to 7532 children whose mothers were diagnosed with subfertility disorders but who were conceived naturally. They found no increased risk for childhood malignancies in the stimulated group (SIR = 0.8; 95% CI = 0.3-2.3) (Klip et al., 2001). Similarly, Lerner-Geva et al. studied a cohort of 332 Israeli children born to women after IVF and found no cancer cases with respect to 1.7 cases that were expected (Lerner-Geva et al., 2000).

Conclusion

Based on the currently available evidence, the question of whether ovulation induction increases the risk of gynecological cancer cannot be definitely answered, but the results are generally reassuring. The risk of ovarian cancer does not seem to be increased with ovulation induction, although some concern has been raised regarding borderline ovarian tumors. More information is needed regarding the relationship between ovulation induction and breast cancer before firm conclusions can be reached. The reported increased risk of uterine cancer seems to be related more to the infertility status of the patients rather than to the ovulation induction *per-se*. The risk of persistent trophoblastic tumor and the risk of cancer in the offspring are not increased. Larger and longer cohort studies addressing the various confounding factors are needed in order to further clarify the issue.

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