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Review Article

Fertility drugs and breast cancer risk

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Summary

Purpose of investigation: Female infertility is a widespread problem in Western countries. During past years, an association between ovarian stimulation in unfertile women and breast cancer risk has been hypothesized. *Objective:* Purpose of the present investigation was to comment the most updated studies about an eventual relationship between fertility drugs and breast cancer risk. *Materials and Methods:* The authors performed a review of the current literature regarding the possible association between the use of fertility drugs and the enhanced risk of breast cancer. They searched digital databases including Pubmed, EMBASE, and the Cochrane Library. The literature search was performed using various combinations of keywords. They carefully analyzed only the full versions of all relevant studies. *Results:* Using various combination of keywords, the authors examined 930 papers. They considered only papers written in English. With these criteria they selected the studies that had been discussed in detail on the text. *Conclusion:* None of the works commented provides an indisputable evidence about a link between ovarian stimulation and breast cancer risk. On the contrary, most of them actually suggest a lack of interaction between them or even a protective role of ovarian stimulation.

Key words: In vitro fertilization; Clomiphene citrate; Fertility drugs; Infertility treatment; Breast cancer risk.

Introduction

Infertility, defined as the inability to conceive, or to get pregnant, within one year of regular sexual activity, with the same partner and without any contraceptive use, affects between 9% and 20% of couples in Western countries [1-3]. Many new drugs and techniques against infertility are now available or under investigation, but their side effects are not still completely known. Many authors suggest the hypothesis of a correlation between these drugs and cancer development [4, 5]. Fertility drugs, new reproductive techniques, and new fertility preservation strategies are increasingly investigated and used in patients with breast cancer, one of the most common tumors in younger women still in reproductive age [6, 7]. It is well know that one of the most important etiological agents for the development of breast cancer is the proliferative activity of endogenous and exogenous female hormones [8, 9]. Furthermore the use of hormone replacement therapy or hormonal contraceptives, could play an important role in the development of breast cancer [10, 11] as well as various other hormonal factors such as younger age at menarche, older age at menopause, postmenopausal obesity, late age at first birth, and nulliparity [12-16]. Endogenous and exogenous hormones drive cell proliferation. Fertility drugs stimulate ovulation and increase endogenous progesterone and estrogen levels acting on ovarian and breast tissues. During proliferation, cells can accumulate random DNA mutations and give rise to cancer [17]. Several studies evaluated the impact of fertility medications and techniques on breast cancer risk [18-21]. The aim of the present work was to clarify the possible link between infertility, exposure to ovarian stimulation drugs, and the occurrence of breast cancer.

Materials and Methods

The authors performed a review of the current literature regarding the possible association between the use of fertility drugs and the enhanced risk of breast cancer. They searched digital databases including Pubmed, EMBASE, and the Cochrane Library. The literature search was performed using keywords such as "ovarian stimulation", "cancer risk", " breast cancer risk", "gynecological cancer", "gynecological cancer risk", "clomiphene citrate", "progesterone", "gonadotropin-releasing hormone analogues", "human chorionic gonadotropin "infertility, "*in vitro* fertilization", "fertility drugs", "infertility treatment" variously associated together.

The authors carefully analyzed only the full versions of all relevant studies. The abstracted data included general information (title, author, year, geographical, and clinical setting) and the characteristics of patients. They evaluated all the selected information with a particular attention to the relationship between the occurrence of breast cancer and treatment with fertility drugs in infertile women. In particular they focused the attention on the type of infertility treatment regimen, the sample size, the number of breast cancer reported, the

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Table 1. — *Breast cancer risk and fertility drugs.*

Study	Year of publication	Population	Treatments	Results
Bernstein *et al.* [30]	1995	774 breast cancer cases, 744 controls	hCG	OR: 0.77, 95% [0.50-1.19] DR
Braga *et al.* [31]	1996	2,569 breast cancer cases, 2,588 controls	Definited as use of fertility drugs	OR: 1.08 [0.80-1.50] exposed *vs* unexposed. NIR
Rossing *et al.* [32]	1996	3,837 infertile women, 27 breast cancer cases	Clomiphene, hCG	RR= 0.50 [0.20-1.2] exposed *vs* unexposed DR associated with clomiphene
Modan *et al.* [33]	1998	2,496 infertile women, 59 breast cancer cases	Clomiphene, clomiphene-hMG, hMG	SIR in infertile women vs general population: 1.3 [1.00-1.60]. NIR
Potashnik *et al.* [34]	1999	1,197 women, 20 breast cancer cases	Definited as use of fertility drugs	SIR exposed 1.65 [0.94-2.68], SIR unexposed 0.80 [0.21-2.04]. NIR
Ricci *et al.* [35]	1999	3,415 breast cancer cases, 2,916 controls	Definited as use of fertility drugs	OR: 0.8 [0.50-1.10] exposed *vs* unexposed NIR
Doyle *et al.* [36]	2002	5,556 infertile women, 55 breast cancer cases	Definited as use of fertility drugs	SIR exposed 1.16 [0.84-1.56], SIR unexposed 1.15 [0.57-2.05]. NIR
Burkman *et al.* [37]	2003	4,575 breast cancer cases, 4,682 controls	Clomiphene, hCG, hMG, other drugs	Increased RR = 2.7; [1.00–6.9] associated with use of hMG > 6 cycles
Brinton*et al.* [38]	2004	12,193 women evaluated for infertility, 292 breast cancer cases	Clomiphene, Gonadotropins	SIR in infertile women 1.29 [1.1–1.4] Clomiphene > 20 years follow-up Increased RR for invasive breast cancer: 1.6 [1.0–2.5]
Gauthier *et al.* [39]	2004	92555 women, 6602 treated, 183 breast cancer cases	Clomiphene, chorionic gonadotropin, menotropin	RR = 0.95 [0.82-1.11] exposed *vs* unexposed. NIR
Terry *et al.* [40]	2006	116,671 women responded to a questionnaire about their medical histories. 61 breast cancer cases	Clomiphene	RR = 0.60 [0.42-0.85] exposed *vs* unexposed. DR associated with clomiphene
Lerner-Geva *et al.* [41]	2006	5,788 women, 131 breast cancer cases	Clomiphene, clomiphene-hMG, hMG	RR= 1.11 [0.79-1.57] exposed *vs* unexposed Increased RR: 1.49; [1.15-1.93] associated with clomiphene exposure
Jensen *et al.* [42]	2007	331 breast cancer cases, 1,226 controls	Clomiphene, gonadotropin, hCG, GnRH, progesterone	RR= 1.08 [0.85-1.39] exposed *vs* unexposed Increased RR = 3.36; [1.3–8.6] associated with progesterone exposure
Kotsopoulos *et al.* [43]	2008	1380 women with BRCA1-BRCA2 mutation	4% exposed to clomiphene and gonadotropin	OR = 1.21 [0.81-1.82] exposed *vs* unexposed. NIR
dos Santos Silva *et al.* [44]	2009	7,355 women, 174 breast cancer cases	43% ovarian stimulation treatments	SIR exposed 1.26 [1.03-1.53], SIR unexposed 0.99 [0.78-1.25]. NIR
Calderon-Margalit *et al.* [45]	2009	15,030 parous women, 530 breast cancer cases	Clomiphene, hMG, other fertility drugs	Increased RR = 1.65 [1.15-2.36] exposed *vs* unexposed
Orgéas *et al.* [46]	2009	1,135 infertile women, 54 breast cancer cases	Clomiphene, hCG, hMG, FSH	SIR = 3.00 [1.35–6.67] for women with non ovulatory infertility who received > 4 cycles of clomiphene
Fei *et al.* [47]	2012	1,422 women with breast cancer + 1,669 women breast cancer free; 288 women treated with fertility drugs	Clomiphene, FSH	Overall: non-statistically significantly DR of breast cancer, OR= 0.82; [0.63 - 1.08]
Lerner-Geva *et al.* [48]	2012	2431 women treated for infertility, 153 breast cancer cases, 30 years of follow-up	Gonadotropins	SIR = 1.16 [0.98–1.36]. NIR associated with exposure to gonadotropins

Abbreviations: hCG: human chorionic gonadotropin; OR: odds ratio; DR: decreased risk; NIR: not increased risk; RR relative risk; hMG: human menopausal gonadotropin; SIR standardized incidence ratio; GnRH gonadotropin-releasing hormone; FSH: follicle-stimulating hormone.

time of follow-up, and on the presence of confounding factors in the studies.

Results

Using various combination of keywords, the authors examined 930 papers. They considered only papers written in English. In this work they did not include all case reports and all the articles with a low sample size. Moreover other works were excluded according to the title and to the content of the abstract. With these criteria they selected the studies that have been discussed.

Clomiphene citrate and other fertility drugs

Clomiphene citrate is a selective estrogen receptor modulator (SERM) that increases the production of go-

nadotropins by inhibiting negative feedback on the hypothalamus [22]. This drug is in use since the 1960s and is still considered one of the most important starting treatment for the majority of women with infertility [23]. Gonadotropins are commonly used drugs in female infertility treatment and several associations among these different agents have been tested. For example, gonadotropin-releasing hormone (GnRH) analogues/agonists, progesterone or human chorionic gonadotrophin (hCG) are used as single agents or in combination with clomiphene citrate [24-29]. In recent years many studies have been published with the aim to investigate the relationship between breast cancer, infertility, and ovarian stimulation procedure made with these drugs [30-48]. The present authors will discuss more in detail some of these studies in the text. All studies are also described in detail in Table 1.

In the study of Calderon-Margalit *et al.* [45] an increased risk of breast cancer was observed in women exposed to clomiphene citrate. However, this risk occurred only among women who waited more than 12 months to conceive, and no association was found among primiparous patients. On the contrary in the prospective study of Terry *et al.* [40] an analysis limited to patient with infertility caused by ovulatory disorders, found a significant reduction in breast cancer incidence with clomiphene citrate use with the greater risk reduction among women who were subjected to treatment with clomiphene citrate for more than ten months. Brinton *et al.* [38] in a retrospective cohort study enrolled 12,193 women, who had been treated with clomiphene citrate or gonadotropins. This study did not find a significant increase in risk for clomiphene citrate use, although in a very large cohort. A slight increase in risk was documented in case of high dosage gonadotropins. For both drugs, statistically significant risk was found only when follow-up had been prolonged for more than 20 years. In the study of Lerner-Geva *et al.* [41] an increased risk of breast cancer was reported in a retrospective analysis of 5,788 patients, with an hazard ratio (HR) of 1.49 for developing breast cancer with clomiphene citrate. However, this association was limited to women with very severe infertility, resistant to other treatments. In the study conducted by Fei *et al.* [47] the authors analyzed women that used clomiphene citrate or follicular stimulating hormone (FSH). The results showed an overall non-statistically significantly decreased risk of breast cancer, [Odds Ratio (OR): 0.82; 95% CI = 0.63 - 1.08]. Women who used fertility drugs and conceived a 10+ week pregnancy showed a statistically significantly increased risk of breast cancer compared with unsuccessfully treated women (OR: 1.82; 95% CI = 1.10 - 3.00), although their risk was not increased compared with women who had not used fertility drugs (OR:1.13; 95% CI = 0.78 - 1.64). In a subgroup analysis of this study, women who used fertility drugs but had not obtained a 10+ week pregnancy showed a statistically significantly decreased risk of breast cancer (OR: 0.62; 95% CI = 0.43 - 0.89). In a cohort study Jensen *et al.* [42] enrolled 54,362 women divided in five fertility treatment groups (gonadotropins, clomiphene citrate, hCG, GnRH, and progesterone). The authors identified 331 invasive breast cancers during follow-up. The results showed no increased breast cancer risk associated with fertility drugs treatment. However, a four-fold increased risk of breast cancer was found after exposure to progesterone. The use of gonadotropins have a stronger effect on breast cancer risk among nulliparous women and similar risk patterns were present for ductal, lobular, and tumors of other histologies. In the study by Bernstein *et al.* [30] the results suggest that hCG may be an instrument for reducing breast cancer risk; 744 patients with newly diagnosed breast cancer and 744 controls were enrolled. Forty-five cases and 65 controls reported exposure to hCG. The OR were reduced substantially for both nulliparous and parous women but only the result for nulliparous women was statistically significant ($p < 0.05$). In their study Burkman *et al.* [37] compared patients with breast cancer to healthy controls. In general, they did not find an overall increased risk to develop breast cancer in association with the use of ovulation induction drugs. However women using hMG for ≥ six months or for at least six cycles had a relative risk (RR) of breast cancer ranging between 2.7 to 3.8.

The study of Lerner-Geva *et al.* [48] evaluated the possible risk for cancer development in infertile women with over 30 years of follow-up in a cohort of 2,431 women who were treated for infertility at the Sheba Medical Center, in Israel, during the period 1964-1974. Standardized incidence ratios (SIR) were calculated between the observed cancer cases and the expected cancer rates in the general population. For breast cancer, 153 cases were observed as compared to 131.9 expected (SIR = 1.16; 95% CI = 0.98-1.36). No excess risk associated with exposure to gonadotropins was observed. Infertility was found to be associated with a borderline increased risk for breast cancer.

Most of the results from these and other studies were collected from the meta-analysis by Zreik *et al.* [19]. The populations included women who were treated for infertility with clomiphene citrate and other various fertility agents. Eight case-control studies and fifteen cohort studies were included in the analyses and the authors concluded that the available data do not suggest higher risk of breast cancer in women who receive fertility treatments.

In vitro fertilization (IVF)

Another important application of these drugs (clomiphene citrate, gonadotropins, gonadotropin releasing hormones, and other new fertility agents) concerns their association with IVF. IVF is a technique that allows fertilization of eggs by sperm outside the body. Many studies evaluated the association between breast cancer risk and IVF and most of these have not demonstrated changes in the rate of breast cancer [49-61]. All studies are described in detail in Table 2. Only the most relevant studies will be discussed in the text.

Table 2. — *Breast cancer risk and IVF.*

Study	Year of publication	Population	Treatments	Results
Brzezinski *et al.* [49]	1994	950 women, 16 breast cancer cases	IVF	Twofold increase in the rate of breast cancer in women who were subjected to IVF compared to the general population
Venn *et al.* [50]	1995	10,358 women, 5564 exposed, 34 breast cancer cases	IVF	SIR exposed 0.88 [0.55-1.46], SIR unexposed 0.98 [0.62-1.56]. RR:1.11[0.56-2.20] exposed *vs* unexposed. NIR
Jourdain *et al.*[51]	1996	32 breast cancer cases	IVF	No statistical study
Venn *et al.* [52]	1999	29,700 women, 20,656 exposed, 143 breast cancer cases	IVF	SIR exposed 0.91 [0.74-1.13], SIR unexposed 0.95 [0.73-1.23]. IR within one year of last IVF treatment SIR 2.0 [1.20–3.10].
Dor *et al.* [53]	2002	Retrospective cohort of 5,026 women, 11 breast cancer cases	IVF	SIR exposed 0.69 [0.46–1.66] NIR
Lerner-Geva *et al.* [54]	2003	Retrospective cohort of 1,082 women, 5 breast cancer cases	IVF	SIR exposed 1.02 [0.33–2.39] NIR
Kristiansson *et al.* [55]	2007	647,704 women, 24 breast cancer cases exposed	IVF	SIR exposed 4.31 [2.89-6.43], SIR unexposed 4.12 [3.97-4.27]. RR: 0.93 [0.48-1.43] exposed *vs* unexposed
Katz *et al.* [56]	2008	7,162 treated women, 28 breast cancer cases	IVF	Age over 30 at the time of first IVF treatment, was the only parameter significantly associated with IR. RR: 1.24 [1.03-1.48] $p = 0.02$.
Pappo *et al.* [57]	2008	3,375 treated women, 35 breast cancer cases	IVF	SIR in exposed 1.4 [0.98-1.96]. IR associated with: Age ≥ 40 at IVF treatment SIR: 1.9 [0.97–3.30]; hormonal infertility SIR: 3.1 [0.99–7.22]; and ≥ 4 IVF cycles SIR: 2.0 [1.15–3.27].
Källén *et al.* [58]	2011	24,058 treated women, 91 breast cancer cases	IVF	RR: 0.76 [0.62-0.94] exposed *vs* unexposed DR
Stewart *et al.* [59]	2012	21,025 treated women	IVF	No overall increase in the rate of breast cancer; HR: 1.10 [0.88-1.36]
Yli-Kuha *et al.* [60]	2012	18,350 patients, 9,175 IVF women, 55 breast cancer in exposed patients, 115 in general population	IVF	IVF women had a slightly fewer risk of breast cancer but this difference was not statistically significant
Brinton *et al.* [61]	2013	87,403 women, 522 breast cancer	IVF	NIR of breast cancer

Abbreviations: IVF: in vitro fertilization; SIR standardized incidence ratio; RR relative risk; NIR: not increased risk; IR: increased risk; DR: decreased risk; HR: hazard ratio.

In their study Brzezinski *et al.* [49] demonstrated a twofold increase in the rate of breast cancer in women who were subjected to IVF for more tan six cycles compared to the general population.

Venn *et al.* [52] in a study that enrolled 29,700 patients, observed an increased risk of breast cancer in women who underwent IVF, but this risk was seen only within one year from last treatment. Moreover Pappo *et al.* [57] in a more recent study in which 3,375 women were enrolled, found that age ≥ 40 years at IVF treatment, hormonal infertility, and ≥ four IVF cycles, were actually connected with an increased risk for breast cancer compared to the general population.

A study conducted by Katz *et al.* [56], in which 7,162 women were enrolled, documented that age over 30 at the time of first IVF treatment was the only parameter significantly associated with increased breast cancer risk.

In their study Yli-Kuha *et al.* [60] enrolled 9,175 women who purchased drugs for IVF, 55 breast cancer were recorded in exposed patient and 115 in general population (cohort sizes: 18,350 patients). This work showed that IVF women had a slightly fewer risk of breast cancer but this difference was not statistically significant.

In a very recent retrospective cohort study, Brinton *et al.* [61] analyzed 87,403 women who underwent IVF or were treated for infertility: 522 of them developed a breast cancer during the period of observation. No significant relationships between IVF exposure and breast cancer risk was found. Another recent cohort study, conducted by Stewart *et al.* [59], did not find an overall increase in the rate of breast cancer in women treated with IVF, though an increased rate in women who commenced IVF at a young age was observed. Instead risk was not increased in women who commenced treatment at age 40 and required IVF.

Two studies [55, 58] investigated on the possible protective effect of a pregnancy after IVF on treated women. In the study conducted by Kristiansson *et al.* [55], pregnancy after IVF really seemed to be linked to a reduction of breast cancer risk, even if this advantage was seen only in regards to in situ breast cancer. Nevertheless, in the study conducted by Kallen *et al.* [58], 24,058 women were enrolled: an overall reduction of breast cancer risk could be seen in

women who had a pregnancy after IVF, but this reduction was stronger if the women experienced a multiple birth ($p = 0.04$). This study found a reduction in breast cancer risk also among women who were 30 years or older at birth.

Regarding this topic, two meta-analysis have been recently published by Sergentanis *et al.* [20] and by Li *et al.* [21]. The first of two [20] included eight cohort studies, for a total of 1,554,332 women; 14,961 of these women received diagnosis of breast cancer, among which 576 underwent IVF. This is probably the largest study about this matter. This work found no increase of breast cancer risk in women who received IVF. Although all the limits can be subjective (short follow up periods, not satisfactory adjustment of confounding factors and others), this meta-analysis has a notable statistical strength, and can be considered, in the present authors' opinion, a model for future studies in this field. The second meta-analysis [21] included eight cohort studies involving 746,455 participants. The overall combined RR for women with IVF treatment were 0.99 (95% CI, 0.74-1.32) for all-site cancer, 1.59 (95% CI, 1.24-2.03) for ovarian cancer, 0.89 (95% CI, 0.79-1.01) for breast cancer, and 1.07 (95% CI, 0.45-2.55) for cervical cancer. A beneficial effect was shown in the subgroup of breast cancer meta-analysis compared with women who gave birth (RR, 0.79; 95% CI, 0.65-0.95). This meta-analysis suggests that there is no significant association between IVF and cancer risk. A possible beneficial effect was shown in the subgroup of breast cancer meta-analysis.

Discussion

At present infertility is a very important problem, causing a rise in health and social costs. About 45% of the causes of this disorder are to be found in female illness (malformative, infective, endocrine, autoimmune or psychological) [1-3]. Ovarian stimulating drugs use is associated with dramatic and impressive increase in estradiol (E2) levels and the role of endogenous and exogenous female hormones in the development of breast tumors, due to their proliferative and oncogenic activity, is well established [9-11]. In fact it is known that abnormal exposure to estrogens and other ovarian stimulating agents may facilitate malignant activation of cell cycle regulatory proto-oncogenes in breast tissue, suggesting a direct association between infertility drugs and breast cancer onset [12-14]. However, despite the extensive use of fertility drugs and the large number of papers published on the topic, the impact of fertility treatments on breast cancer risk is still under investigation.

It is undeniable that all these works often give contrasting or even opposite results. In the past, some of them suggested an increased breast cancer risk in fertility drugs users [34,3 7]. On the contrary, other authors hypothesized a protective role of fertility medications on breast cancer [32, 40]. It can be due to the fact that many of these studies are affected by bias. In fact, investigations in this field suffer from some methodological limitations. Many studies present very small sample size, so that statistical significance could not be reached. Some other studies were based on imprecise information about clinical data of the patients enrolled. In addition, a lot of studies used SIR as statistical parameter to analyze breast cancer risk in infertile women. SIR is not a reliable parameter because it compares the number of breast cancer observed in infertile women with the number of expected breast cancer cases in general population, without considering all those factors influencing cancer risk probably present in these two groups of patients.

Finally it is not clear if there is a difference between certain subgroups of patients, for example between women who were treated for infertility but remained nulliparous and women who received fertility drugs but became pregnant [62].

In conclusion the present authors can say that, despite the controversies that still remain open, none of the studies analyzed provides an indisputable evidence about a link between ovarian stimulation and breast cancer risk. On the contrary, most of them actually suggest a lack of interaction or even a protective role of ovarian stimulation on breast cancer risk, as underlined in the three recent available meta-analysis [19-21].

Nevertheless this issue deserves further clarifications, not just to give an answer for a mere scientific curiosity, but also in order to give the possibility to all women to have a child, without making them feeling as they had to choose between satisfying this desire and running into an increased risk of breast cancer.

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