

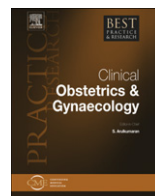


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Endometriosis, *in vitro* fertilisation and the risk of gynaecological malignancies, including ovarian and breast cancer

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There is evidence that endometriosis as well as drugs used in the process of *in vitro* fertilisation appear to associate with increased risk for gynaecological cancer. In this review, we attempt to describe this relationship according to the most recent epidemiologic data and to present the possible mechanisms on the molecular level that could potentially explain this correlation. There are data to support that ovarian endometriosis could have the potential for malignant transformation. Epidemiologic and genetic studies support this notion. It seems that endometriosis is associated with specific types of ovarian cancer (endometrioid and clear cell). There is no clear association between endometriosis and breast or endometrial cancer. More studies are needed to establish the risk factors that may lead to malignant transformation of this condition and to identify predisposed individuals who may require closer surveillance. Currently, there is no proven relationship between any type of gynaecological cancer and drugs used for infertility treatment. In principle, infertile women have increased risk for gynaecologic malignancies. Nulligravidas who received treatment are at increased risk for malignancy compared with women who had conceived after treatment. There is limited evidence that clomiphene citrate use for more than six cycles or 900 mg or treatment of women over the age of 40 could increase their risk for ovarian and breast cancer. More studies with the

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appropriate statistical power and follow-up time are required to evaluate accurately the long-term effects of these drugs and procedures.

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Introduction

Endometriosis is a disorder of the reproductive age defined as the presence of endometrial-like tissue (e.g., glands and stroma) outside of the endometrial cavity. Endometriosis is uncommon before menarche and it frequently regresses after menopause. The prevalence of endometriosis reaches 7–15% among women of reproductive age, but can increase up to 25–30% in women with infertility and to 40–70% in women with pelvic pain.^{1,2} Although endometriosis is considered to be a benign condition, it shares characteristics often encountered in malignancy, such as development of local and distant metastases, attachment, invasion and subsequent damage of adjacent tissues. Endometriosis, however, does not cause metabolic disturbance, does not have catabolic consequences and does not lead to death.

Studies that have investigated the overall risk of cancer in women with endometriosis have failed to demonstrate an increased risk for cancer in those women compared with population controls. In a study involving 64 492 Swedish patients hospitalised with the diagnosis of endometriosis, with an average follow-up of 12.7 years, the overall risk of cancer was similar to the general population (standardised incidence ratio (SIR) 1.04, 95% confidence interval (CI): 1.00–1.07).³ Similarly, no overall increased risk of cancer (age-adjusted relative risk (RR) 0.9, 95% CI: 0.7–1.2) was found after 13 years of follow-up in an epidemiological study of 1392 postmenopausal women with a self-reported history of endometriosis.⁴

Although endometriosis does not appear to be associated with an increased risk of cancer in general, evidence is accumulating suggesting a relation between endometriosis and specific types of cancer. To date, the main scientific interest has been focussed on the relationship between endometriosis and gynaecological cancer, with special emphasis on ovarian cancer.

Endometriosis and ovarian cancer

Sampson was the first to describe, back in 1925, a malignancy (ovarian carcinoma) derived by an endometriotic lesion.⁵ Since then, several studies have indicated a relation between endometriosis and ovarian cancer.^{3,6–16}

In a Swedish study involving 20 686 patients with endometriosis with an average follow-up of 11.4 years, the risk for developing ovarian cancer was about 2 times higher than in the general population (standardised incidence ratio (SIR) 1.9, 95% confidence interval (CI): 1.3–2.8). Furthermore, for women with long-standing endometriosis involving the ovaries, the risk was even higher (SIR 4.2, 95% CI 2.0–7.7).⁶ A more recent study from Scandinavia, which included 28 163 women with endometriosis, had also showed that these women had a 30% increase in the possibility of developing ovarian cancer.¹⁷

In the study by Melin et al.,³ with an average follow-up period of 12.7 years, an increased risk for ovarian cancer was documented in women with endometriosis compared with the general population (SIR 1.43, 95% CI: 1.19–1.71). Women with early diagnosed and long-standing endometriosis had a higher risk of ovarian cancer, with SIR of 2.01 and 2.23, respectively. Women who had a hysterectomy before or at the time of the endometriosis diagnosis did not show an increased risk of ovarian cancer, suggesting that hysterectomy or possibly tubal occlusion (ligation) may offer some protection. Both these studies,^{3,6} however, have been criticised that they have overestimated the risk of ovarian cancer in women with endometriosis, due to the fact that the cohorts were hospitalised patients with more advanced stages of endometriosis.

There is sufficient evidence to support that endometriosis is related to specific histological types of ovarian cancer. In a pathology review of 1000 consecutive cases, there was a strong correlation between endometriosis and endometrioid and clear cell ovarian carcinomas, whereas extraovarian

endometriosis was associated with adenocarcinomas and adenosarcomas.¹⁸ In a review of 556 patients with ovarian cancer, the frequency of endometriosis was significantly higher in patients with endometrioid, clear-cell and mixed-types tumours (26.3%, 21.1% and 22.2% respectively) compared with those with mucous or serous carcinomas.⁹

In another study,⁸ pathology slides from 79 patients with stage I epithelial cancer of the ovary were evaluated. Endometriosis was evident in 22 out of the 79 cases (28%). Ovarian tumours of endometrioid, clear cell and mixed type were associated with endometriosis in 39%, 41% and 50%, respectively. Thirty-two percent of the ovarian tumours developed in areas of endometriosis, with evidence of progression from benign to atypical endometriosis (characterised by cytologic atypia and architectural proliferation) to cancer.

These findings were confirmed by Ogawa et al.,¹⁹ who in 127 patients with primary ovarian carcinoma documented 37 patients with endometriosis. Out of 43 patients with clear-cell carcinoma 30 had endometriosis (70%), and out of seven patients with endometrioid carcinoma three had endometriosis (43%). By contrast, endometriosis was documented in only four out of 60 (7%) patients with serous carcinoma and in none out of 17 with mucinous carcinoma. Twenty-nine cases had atypical endometriosis and the transition from atypical endometriosis to carcinoma was evident in 23 cases. The authors concluded that atypical endometriosis could be a precancerous condition for ovarian carcinoma.¹⁹

Others, however, do not support this notion. Olson et al., in a group of 37434 postmenopausal women, which included a cohort of 1392 patients with a self-reported diagnosis of endometriosis,⁴ failed to document any increased risk of ovarian carcinoma (RR 0.8, 95% CI: 0.2–2.4). This study had an acceptable follow-up period of 13 years, but has been criticised by the fact that the cohort was small and included only three ovarian cancer cases. Other limitations of this study were the inclusion of only postmenopausal women and the fact that the diagnosis of endometriosis was not surgically confirmed.

The relationship between endometriosis and ovarian cancer was further explored in terms of causality by Viganò et al. by employing the nine criteria proposed by Austin Bradford Hill, which still stand as fundamental of causal inference.²⁰ The criterion of strength was not fulfilled, and there were mixed or insufficient data for four criteria (i.e., biological gradient, biological plausibility, analogy and coherence). The other four criteria (i.e., consistency, temporality, specificity and experimental evidence in animal model) were fulfilled, and the authors concluded that a causal relationship between endometriosis and ovarian cancer should be recognised, but that the low magnitude of the risk observed could be associated with the fact that ectopic and eutopic endometrium undergo malignant transformation with the same frequency.

Molecular and genetic aspects linking endometriosis to ovarian cancer

During the past several years, a significant amount of research on molecular and genetic factors that may connect endometriosis to ovarian cancer has been conducted. There is significant evidence to support the presence of common molecular pathways for the development of both conditions. On the other hand, the existing data highlight the possibility of endometriosis being a benign disease that may transform into a malignant one.

Both endometriosis and ovarian cancer share common pathogenetic factors such as familiar predisposition, genetic instability and a similar reaction to immunologic, angiogenetic and hormonal factors. Similar alterations in the immune response cascade and in the mechanism of inflammation have been observed in women with ovarian cancer and endometriosis.¹³

Mechanisms that lead to both ovarian cancer and endometriosis due to genetic instability include deactivation of one or two alleles of tumour-suppressive genes, changes of the enzymes that act in DNA repair and higher oncogenic activity. The most commonly affected chromosome loci include 9p, 11q and 22q.²¹

Mutations in the genes that encode metabolic and detoxification enzymes, like GALT and GSTM, have been implicated in the pathogenesis of endometriosis as well as in development of ovarian cancer.²² Mutations in PTEN, a tumour-suppressive gene, have been documented in endometriosis as well as in certain histologic types of ovarian carcinomas.^{23,24} PTEN mutations as well as loss of heterozygosity (LOH) at locus 10q23.3 are quite common in ovarian endometriomas, in atypical

endometriosis as well as in endometrioid and clear-cell ovarian cancers.^{15,24,25} K-ras is an oncogene that has been related to endometriosis and ovarian cancer. Mutations of K-ras are found in clear-cell ovarian carcinomas in women with endometriosis. K-ras mutations were found in cancerous cells, but not in the neighbouring cells with endometriosis or atypical endometriosis.²⁶ According to the investigators, K-ras mutations are associated with malignant transformation of benign endometriosis to clear-cell carcinoma of the ovaries.²⁶ In a rodent model, activation of the oncogenic K-ras or conditional PTEN deletion within the ovarian surface epithelium gave rise to pre-neoplastic ovarian lesions with an endometrioid glandular morphology.²⁷ The authors were able to demonstrate that a combination of the two mutations in the ovary leads to the induction of invasive and widely metastatic endometrioid ovarian adenocarcinomas.²⁷

The p-53 and c-erbB-2 genes have also been found to associate with endometriosis-related ovarian cancer.²⁸ The expression of these two oncogenes was significantly higher in the endometriosis-associated clear-cell tumours compared with those patients without endometriosis. These findings were in agreement with the report by Sainz de la Cuesta et al.²⁹ In their study, 17 out of 410 (4.1%) women with epithelial ovarian cancer had endometriosis, whereas six out of 521 (1.2%) women with endometriosis had atypical lesions. Of the 17 patients, 14 (82.4%) with endometriosis-associated ovarian cancer and six out of six (100%) women with atypical endometriosis had an over-expression of the p-53 gene. Only two out of 17 (11.8%) women with endometriosis had a mutation of the p-53 gene, and this difference was statistically significant.²⁹

Endometriosis and ovarian cancer: response to oestrogen stimulation

Oestrogens have been linked to the pathogenesis and growth of three common women's cancers (i.e., breast, endometrium and ovary). The key enzyme for oestrogen biosynthesis or, in fact, conversion of androgens to oestrogens is aromatase. Tissue-specific aromatase expression is regulated by tissue-specific promoters located upstream of a common coding region. Aromatase gene expression in malignant tumours of the breast, endometrium and ovary is primarily regulated by a promoter located in the 1.3/II region. These promoters are stimulated by PGE₂ via a cAMP/PKA-dependent pathway. Thus, inflammatory substances such as PGE₂ may play an important role in inducing local production of oestrogens that promote tumour growth.³⁰

Agents that block the function of this enzyme, 'aromatase inhibitors', have been used successfully in the treatment of breast cancer, whereas their roles in endometrial and ovarian cancers are less clear. Aromatase inhibitors have also been used in the treatment of endometriosis.^{31,32}

Oestrogen-induced triggering is similar in both endometriosis and oestrogen-dependent neoplasms. Normally, oestradiol is being metabolised to oestrone, a weak oestrogen, by the action of the enzyme 17- β -hydroxysteroid dehydrogenase (17- β -HSD) type-2, which is being induced by progesterone in the endometrium. In endometriosis, a local increase in oestradiol concentration has been described, attributed to an increased expression of cytochromal-P450 aromatase and a simultaneous insufficient expression of 17- β -HSD type-2, which has been attributed to a resistance of the endometriotic lesions to progesterone.³²

Ovarian cancer seems to be connected to oestrogen action as well. Seeger et al. concluded that oestradiol and its derivatives may have a variable impact on the survival and growth of ovarian cell lines and the quantification of these derivatives may be of prognostic value of the risk women have for the development of ovarian cancer.³³ O'Donnell et al.³⁴ have shown that the potential carcinogenic action of oestrogen are mediated through oestrogen receptor (ER- α). In ovarian cancer cell lines, genes controlled through ER- α -mediated transcription had a threefold increase in their expression, whereas there was no change in the expression of genes controlled by ER- β -mediated transcription.³⁴

Increased expression of ER- α has also been shown in active endometriosis.³⁵ Samples from 33 peritoneal and 37 ovarian endometriotic lesions were examined and analysed, using polymerase chain reaction (PCR) and *in situ* hybridisation (ISH). In active endometriosis lesions, higher ER- α than ER- β levels have been observed, a finding that is in contrast to what happens in the non-active lesions. These findings support the role of the increased expression of oestrogen receptors (especially ER- α) in the pathogenesis of endometriosis.³⁵

Growth factors such as TGF- α and IGF-I have also been implicated in the development of endometriosis as well as of ovarian cancer. Women with severe endometriosis have significantly higher IGF-I levels in their plasma compared with controls.³⁶ Moreover, menopausal and premenopausal women with high-IGF-I serum levels are at increased risk of developing ovarian, endometrial and cervical cancer.¹⁶

Resistance to apoptotic mechanisms: Bcl-2 over-expression, Bax down-regulation

Over-expression of anti-apoptotic (Bcl-2) genes and under-expression of pre-apoptotic (Bax) factors, as well as deactivation of the p53 tumour-suppressive gene, through gene mutations are often involved in the pathogenesis of malignancy. Spontaneous apoptosis is significantly decreased in the eutopic endometrium of women with endometriosis compared with healthy controls.³⁷ In addition, increased expression of the anti-apoptotic gene Bcl-2 and suppression of the pre-apoptotic gene Bax has also been noted during the proliferative-phase endometrium of those women.³⁷

Local tissue invasion and metastatic potential

Both endometriosis and ovarian cancer have the ability to invade and spread to neighbouring structures as well as in remote locations. The mechanism of tumour invasion involves the secretion of matrix metalloproteinases (MMPs) to penetrate the basal membrane and stroma. In endometriosis, a similarly increased action of MMPs is observed. The expression and localisation of several MMPs were evaluated by immunohistochemistry in women with endometriomas. MMP-1, -2 and -9 were strongly detected in both stromal and epithelial cells, whereas MMP-3 was mainly expressed in macrophages containing haemosiderin. Based on these results, the authors suggested that the destruction of the surrounding matrix by endometriosis might be caused by various MMPs, which are mainly produced in stromal cells.³⁸

In the study conducted by Ueda et al.,³⁹ the expression of E-cadherin, a- and b-katenin, MMP-2, MMP-9 and membrane-type-1-MMP (MT1-MMP) were evaluated in 35 women with endometriosis and in 12 normal controls. The expression of MMP-2, MMP-9 and MT1-MMP in coloured lesions was significantly higher in comparison to normal endometrium, whereas the expression of E-cadherin, a- and b-katenin was not suppressed in the endometriosis lesions. B-katenin, E-cadherin and P-cadherin in combination with increased expression of MMPs probably play a role in the pathogenesis of endometriosis and in the development of several malignant conditions, including ovarian cancer.

Endometriosis and breast cancer

The studies published so far, examining the association between breast cancer and endometriosis, have provided inconsistent results.^{4,6,17,40–44} Two Swedish cohort studies^{6,42} based on the hospital records of patients with endometriosis and one case-control study¹⁷ showed an increased risk for breast cancer. However, in a more recent publication³ including the cohort previously studied by Brinton et al.,⁶ with a longer follow-up, the previously seen association disappeared (SIR 1.04, 95% CI: 0.98–1.09). Furthermore, three cohort studies,^{4,43} two case-control studies^{40,41} and one recent population-based case-cohort study⁴⁴ showed no overall association between endometriosis and breast cancer.

Data on the association between endometriosis and breast cancer should be interpreted with caution, because of the lack of consistency between the studies and because of the small number of patients studied so far. Endometriosis and breast cancer are hormone-dependent conditions, and endometriosis is more common among nulliparous women and among women who have delayed childbearing, both well-known risk factors for breast cancer. Another possible explanation for the conflicting results could be that treatment of endometriosis (i.e., oral contraceptives or progestins) could potentially have an adverse effect on the breast. The aetiology of endometriosis in postmenopausal women may also differ from that in premenopausal women. In a recent study,⁴⁴ the authors concluded that women in whom endometriosis was diagnosed at a young age (<40 years) had a reduced risk for breast cancer than those in whom endometriosis was diagnosed at older ages (>40 years); this may be due to the stronger effect of altered endogenous oestrogen levels associated with endometriosis in older women and the anti-oestrogenic effects of the drugs used for endometriosis especially in younger women.

Endometriosis and cervical cancer

Two studies so far^{6,17} have reported data on the possible association between endometriosis and cervical cancer. Patients with endometriosis had a 40% reduced risk of cervical cancer compared with the general population. This has been attributed to the fact that patients with endometriosis have cervical smears (PAP tests) more frequently and manage to diagnose cervical cancer before the establishment of the disease.

Endometriosis and endometrial cancer

No association has been found between endometriosis and endometrial cancer in population-based studies.^{4,6} This observation remains the same even after the publication of the two more recent studies, the extended study of Melin et al.³ with a longer follow-up (RR 1.19, 95% CI: 0.96–1.46) and another cohort study by Brinton et al.⁴³ (RR 0.8, 95% CI: 0.3–1.9). Because of the small number of events, it is not safe to draw any definitive conclusions about the possible association between endometriosis and endometrial cancer.

The special case of *in vitro* fertilisation (IVF) and the risk of gynaecological cancer

The process of IVF involves ovarian stimulation with a combination of drugs, oocyte retrieval, fertilisation of the mature oocytes *in vitro* and finally transfer of the embryos back into the endometrial cavity, which has been adequately prepared for implantation. It is obvious that the main concern regarding the association between IVF and gynaecological cancer (e.g., ovarian, breast and endometrial) is tightly related to the use of fertility drugs to stimulate the ovaries to produce multiple follicles; a process known as super-ovulation. To date, there have been several studies that have tried to resolve the question of long-term effects of drugs used in the treatment of infertility and their possible connection with gynaecological cancer. However, the majority of them involve a small number of women, for a limited follow-up period and without a detailed description of their treatments. The most commonly used drugs for infertility problems are the gonadotropins (biological or recombinant), clomiphene citrate, human chorionic gonadotropin (hCG), gonadotropin-releasing hormone (GnRH) analogues (agonists and antagonists) and progesterone. Of those drugs, clomiphene citrate and gonadotropins cause excessive follicular development and multiple ovulation. Incessant ovulation, which causes a repetitive damage and repair of the ovarian surface epithelium, remains one of the main theories implicated in the pathogenesis of epithelial ovarian cancer.^{45,46} Furthermore, use of these drugs during the process of ovarian stimulation produces a precipitous rise in serum oestradiol and progesterone levels, hormones that are also related to breast cancer and to some other types of female cancer.

Ovarian cancer

Whittemore et al.⁴⁷ were the first to examine the possible relationship between drugs used for infertility treatment and cancer. In their meta-analysis of 12 case-control studies related to ovarian cancer, three out of 12 (including 526 patients and 966 women-control group) provided some information about the fertility status and use of fertility drugs. According to their analysis, the odds ratio for women using infertility drugs to develop ovarian cancer was 2.8 (OR 2.8, 95% CI: 1.3–6.1) compared with women in the control group. In that study, infertile women who took fertility drugs without ever being pregnant had a much higher risk to develop cancer (OR 27.0, 95% CI: 2.3–315.6). By contrast, infertile women who had been treated for their problem and managed to get pregnant had no increased risk of developing ovarian cancer (OR 1.4, 95% CI: 0.52–3.6).

Rossing et al.⁴⁸ examined 3837 women who had been treated for infertility between 1974 and 1985 in the Seattle Medical Center. In this cohort, four invasive, five borderline and two granulosa-cell tumours were documented. The risk of developing ovarian tumour (of any type) in women who received fertility treatment was 2.5 times higher than that in the general population (95% CI: 1.3–4.5). In women who received clomiphene citrate for 12 or more monthly treatment-cycles, the RR was 11.1 (95% CI: 1.5–82.3). Use of clomiphene citrate for less than a year was not related to ovarian tumours. The Rossing et al. study, despite its limitations, raised serious questions.

Mosgaard et al.,⁴⁹ in a case-control study including 684 patients and 1721 age-matched population controls, reported that nulliparous women had increased risk of developing ovarian cancer compared with parous ones (OR: 1.5–2.0). The subfertile nulliparous women who did not receive any treatment had a risk of 2.7 (OR 2.7, 95% CI: 1.3–5.5) to develop ovarian tumours compared with controls. The risk to develop ovarian cancer in nulliparous women who had received treatment was 0.8 (95% CI: 0.4–2.0), while women who had already given birth and, in parallel, had been taking treatment was 0.6 (95% CI: 0.2–1.3), compared with subfertile women who had not been given any treatment. The authors concluded that, in cases of nulliparous women, the risk of developing ovarian cancer is 1.5–2 times greater, while subfertility without treatment further increases that risk. The use of medical treatment did not seem to raise the risk for developing ovarian cancer in the group of infertile women.

In a meta-analysis of eight studies, which included data of 1060 patients and 1337 healthy women, there was a trend for increased risk for ovarian cancer in nulliparous women who used infertility drugs (OR 1.6, 95% CI: 0.90–2.87) and for those who had been treated for more than 12 months (OR 1.54, 95% CI: 0.45–5.27); nevertheless, these risks were not statistically significant.⁵⁰

In 2006, Brinton et al.⁵¹ reported on 12 193 infertile women with a median follow-up period of 18.8 years. The results of this study were reassuring, as no positive connection between the use of clomiphene and/or gonadotropin and ovarian cancer has been established and even in the group of women with long follow-up period (more than 15 years). Moreover, no positive relationship has been shown between ovarian cancer and the duration of treatment. Most recently, Jensen et al.⁵² examined 54 362 infertile women with a median follow-up of 16 years. Analysis of the cohorts revealed no overall increased risk of ovarian cancer after any use of gonadotropins (RR 0.83, 95% CI: 0.50–1.37), clomiphene citrate (RR 1.14, 95% CI: 0.79–1.64), human chorionic gonadotropin (RR 0.89, 95% CI: 0.62–1.29), or GnRH (RR 0.80, 95% CI: 0.42–1.51). Furthermore, risk did not differ according to number of cycles of use, length of follow-up or parity.

Another important aspect is the possible relationship between fertility drugs, the underlying cause of infertility and cancer; that is, different causes of infertility may impose different risk for developing ovarian cancer. Brinton et al.,⁵³ in a study that included 12 193 women with infertility treated between 1965 and 1988, tried to estimate the risk of developing ovarian cancer in those women compared with women in the general population and in relationship to the cause of infertility. Finally, medical records of 8429 women were examined, with a median follow-up time of 18.8 years, while more than 80% had at least 15 years of follow-up. Subfertile women had almost twice the risk of developing ovarian cancer (SIR 1.98, 95% CI: 1.4–2.6). In women with already diagnosed endometriosis, the risk was 2.5 times greater (RR 1.3–4.2), while the risk of developing ovarian cancer were even greater in the group of women with primary infertility (RR = 4.19, 2.0–7.7).

Another question that has arisen is if fertility drug use is associated with certain histological types of ovarian cancer. Sporadic case reports have connected infertility drug use with clear-cell carcinoma, germ-cell malignant tumours and malignant tumours of the granulosa cells.⁵⁴ The rarity of those tumours makes the establishment of a possible true relationship very difficult. Granulosa-cell tumours are of increased interest, because animal and human *in vitro* models have shown that gonadotropins may be related to these tumours.^{55,56}

In contrast to a descriptive study from Finland,⁵⁷ a reduction in the frequency of granulosa-cell carcinomas of the ovary was noticed in women who had been taking drugs for subfertility treatment.

Other studies^{58,59} have associated the use of infertility drugs to ovarian borderline carcinomas, with a relative risk of 3–4 compared with the general population. These findings, in correlation to case reports of ovarian cancer diagnosed during or just after the end of treatment for infertility,^{60,61} have led to the suggestion that ovarian stimulation may provoke the development of 'silent' tumours of high differentiation. Another possible explanation is that these findings just reflect a detection bias due to closer and more precise follow-up of those women.

Breast cancer

Despite the fact that infertility drugs have a recognised effect on ovulation and in other hormonal changes of the female reproductive system, only a limited number of studies have tried to illuminate the possible correlation between breast cancer and infertility drugs.

In their vast majority, both cohort studies^{62–65} and case-control studies have failed to show a relationship between infertility drugs and breast cancer. Serious disadvantages of these studies are the limited number of cancer cases, the unclear indications of issuing those drugs and the failure to control patients for simultaneous co-existence of other factors that may cause breast cancer.

In a cohort of 92 555 women from France followed up for approximately 10 years,⁶⁶ there were 6602 who have used fertility treatment. During the follow-up period, 2571 cases of breast cancer were diagnosed; among these women, 183 had previously taken infertility treatment. Analysis of the data showed no correlation between breast cancer and infertility treatment (RR 0.95, 95% CI: 0.82–1.11). Furthermore, no correlation has been established with the type of the treatment or the duration.

In a study published in 2003,⁶⁷ which included 4500 women with breast cancer, no relationship between the use of clomiphene citrate and development of breast cancer has been found; however, a tendency for increased risk in women who used gonadotropins for a long term (use for 6 months or more or at least six cycles) has been related with an OR ranging from 2.7 to 3.8.

A recent multicentre cohort study, with 292 cases of breast cancer documented during the follow-up period, failed to document increased risk for breast cancer after the use of either clomiphene or gonadotropin.⁶⁸ Despite that, there was a small, not statistically significant, increase in RR for women with longer follow-up of more than 20 years, with RR being between 1.4 and 1.6. However, when the analysis was limited to the cases with invasive disease, this difference reached significance (RR 1.6, 95% CI: 1.0–2.5).

By contrast, there are also data from the Nurses Health Study⁶⁹ to support a decrease in the risk of breast cancer in women who have used clomiphene citrate: RR = 0.40 (95% CI: 0.2–0.7). This risk has been further decreased with the longer duration of treatment ending in a RR of 0.21 for a 10-month use compared with women who had never used clomiphene. In addition, a retrospective study⁷⁰ concluded that there is a statistically not significant lower risk for developing breast cancer in women who used clomiphene citrate (RR 0.5, 95% CI: 0.2–1.2). Chemical similarities between clomiphene citrate and tamoxifen could provide a plausible explanation for these findings as they could both act as selective modulators of oestrogen receptors (SERM) on the breast.⁷¹

Endometrial cancer

Most studies have failed to prove any relationship between endometrial cancer and infertility drugs. Benschushan et al.,⁷² in a retrospective study that examined the exposure to infertility drugs (especially clomiphene) and its possible relationship with endometrial cancer, in comparison to healthy women, ended with the remark that only infertility (1.8 times) and nulliparity (2.7 times) increase the risk for developing endometrial cancer.

In another retrospective study, which included 8431 subfertile women in the USA,⁷³ only 39 cases of uterine/endometrial cancer have been observed. The authors found no increased risk due to gonadotropin use. The relative risk for women to develop endometrial cancer after the use of clomiphene citrate was 3.5 (95% CI: 1.3–9.3) in nulliparous women, 6.2 (95% CI: 1.2–30) in obese women and in women who were both nulliparous and obese the risk was 12.5 (95% CI: 1.5–108). There was a trend for an increase in the risk for endometrial cancer in women who had received more than 900 mg of clomiphene citrate (RR 1.9, 95% CI: 0.9–4.0) and in women who had been treated for more than six cycles (RR 2.16, 95% CI: 0.9–5.2). In both cases, the differences were not statistically significant.

Studies focussing on the IVF procedure and cancer

Venn et al. were the first to examine the incidence of various types of cancer – and especially gynaecological ones – after IVF treatment.⁷⁴ There was no increased risk of either ovarian or breast cancer in a cohort of 10 358 women who had been referred for IVF treatment in Australia between 1978 and 1992. Although that study provided some reassurance, it had low statistical power. A second survey from the same investigators, which included almost 30 000 women, reached exactly the same conclusions.⁷⁵ According to these authors, women who had undergone IVF have no greater risk of suffering from uterine, breast and ovarian cancer than those expected from general-population incidence rates. In a subsequent study,⁷⁶ 1082 IVF cases were linked to the National Cancer Registry of

Israel. Women who had undergone IVF treatments had a higher than expected cancer rate compared with the general population (SIR 1.91; 95% CI: 1.18–2.91). Nevertheless, the authors concluded that this increase could not be attributed to IVF treatment, because when cancer cases diagnosed within 1 year of the IVF treatment were excluded from the analysis, the statistically significant excess risk of cancer had disappeared (SIR 1.46; 95% CI: 0.83–2.36).

On the other hand, in a cohort of 3375 women, Pappo et al. reported a possible association between IVF therapy and breast cancer, especially in women over 40 years of age.⁷⁷ Furthermore, a recent case-control study examining the long-term risks of IVF treatment in a cohort of 7162 women concluded that women over 30 years who have been treated with IVF appear to have an increased risk of developing breast cancer (RR 1.24, 95% CI: 1.03–1.48) even after controlling for age at first pregnancy.⁷⁸ The authors suggested that ovarian stimulation might have a 'booster effect' on the breast at an older age.

In all of these studies, however, there was no subgroup analysis according to the type of infertility that leads to IVF treatment. Therefore, we are unable to draw any conclusion regarding women with endometriosis who underwent IVF and the subsequent risk for gynaecological cancer.

Discussion

Endometriosis, by definition, a benign neoplastic disease, seems to have the potential of malignant transformation as well. This is the assumption obtained from clinical, epidemiological and laboratory data collected since the first description of the disease. The hypothesis that endometriosis is associated with ovarian cancer and especially with two of its histological types, endometrioid and clear-cell carcinoma, is supported by several studies. A hormonal environment rich in oestrogen and poor in progesterone as well as additional genetic alterations seem to help the development of the disease and its evolution to a malignant state. So far, the exact molecular mechanisms that may lead to malignant transformation of endometriosis are not completely understood. More studies are required to identify those women with endometriosis who are at risk for developing ovarian malignancy.

It seems that there is no proven relationship between any type of gynaecological cancer and drugs used for infertility treatment. Infertility itself seems to be an independent risk factor for gynaecological cancer. Despite that, because of the fact that all of those studies include fewer patients and/or shorter follow-up period, more studies in the future must examine the long-term effects of drugs used for infertility treatment, and their relationship with borderline carcinomas and some histological subtypes of ovarian cancer. Special attention must be paid to nulliparous women who had been treated with infertility drugs as well as to women with endometriosis. Follow-up protocols for early detection of malignancy that include a detailed medical history and a meticulous physical examination must be established for these patients.

Practice points

- Women with endometriosis as well as nulliparous women who have been treated with infertility drugs seem to have an increased risk for developing gynaecological malignancies, especially ovarian cancer.
- Despite common belief, prolonged treatments with clomiphene citrate do not seem to carry significant risks for gynaecologic malignancies.
- All women scheduled to undergo assisted reproductive technology procedures need to be thoroughly informed about the risks and the benefits of each type of treatment.
- These women need to be under close surveillance for early detection of cancer according to widely accepted screening protocols.
- Detailed screening protocols need to be established for early detection of malignancy in these groups of patients. These protocols apart from a detailed medical history and a meticulous physical examination should include the appropriate laboratory and radiographic tests.

Research agenda

- As no specific markers for subsequent development of gynaecological malignancy currently exist, apart for the presence of the BRCA gene, more studies are required to identify women with endometriosis who are at risk for developing ovarian or other types of gynaecological cancer.
- Evaluation of the current screening protocols for ovarian malignancy and development of new ones should be undertaken to improve detection rate in women with endometriosis and those who had multiple fertility treatments.
- As the population ages, women who have been exposed to fertility drugs reach the peak age for the development of specific malignancies. More studies in the future should have adequate follow-up of these women to produce more reliable conclusions.
- Prospective randomised trials to evaluate the relationship between fertility treatments and cancer are not feasible and will never be performed. National and international web-based registries should be established that include detailed information about type of infertility, fertility treatments and treatment outcome. These registries should be connected to cancer registries all over the world to improve our ability to draw valid and reliable conclusions about the risks associated with infertility treatments.

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