Bilan avant induction de l’ovulation chez une femme à haut risque mammaire

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Women with a breast cancer susceptibility gene 1 (BRCA1) or breast cancer susceptibility gene 2 (BRCA2) mutation are at increased risk for developing breast and ovarian cancer. Various reproductive and hormonal factors have been shown to modify the risk of breast cancer. These studies suggest that estrogen exposure and deprivation are important in the etiology of hereditary cancer. Many patients are interested in the possibility of an adverse effect of fertility treatment on breast cancer risk. It is important to evaluate whether or not infertility per se or exposure to fertility medications increase the risk of breast cancer in genetically predisposed women.

We conducted a matched case-control study of 1,380 pairs of women with a BRCA1 or BRCA2 mutation to determine if a history of infertility, the use of fertility medications, or undergoing in vitro fertilization (IVF) were associated with and increased the risk of breast cancer.

Sixteen percent of the study subjects reported having experienced a fertility problem and 4% had used a fertility medication. Women who had used a fertility medication were not at significantly increased risk of breast cancer (odds ratio [OR] = 1.21; 95% confidence interval [CI] = 0.81-1.82) compared to non-users. Furthermore, there was no risk associated with a history of use of a fertility medication when the subjects were stratified by parity: (OR = 1.29; 95%
CI = 0.83-2.01 for nulliparous women and OR = 0.81; 95% CI = 0.30-2.22 for parous women).

The results of this study suggest that the use of fertility medications does not adversely affect the risk of breast cancer among BRCA mutation carriers. Given the small sizes of the exposed subgroups, these findings should be interpreted with caution and confirmatory studies are required.


The possible association between ovulation-inducing drugs and breast cancer development has been debated. Our aim was to evaluate the incidence of breast cancer in a cohort of women exposed to in vitro fertilization (IVF).

A retrospective cohort analysis was performed by linkage of the computerized database of all women treated at the IVF Unit at Assaf Harofeh Medical Center between 1986 and 2003, and the Israeli National Cancer Registry. The standardized incidence ratio (SIR) was computed as the ratio between the observed number of breast cancer cases and the expected cases, adjusted for age and continent of birth, in the general population. Tumor characteristics of the IVF patients were studied by reviewing original medical records.

35 breast carcinomas were diagnosed among 3,375 IVF-treated women, compared to 24.8 cases expected (SIR = 1.4; 95% CI 0.98-1.96). Age >or=40 years at IVF treatment (SIR = 1.9; 95% CI 0.97-3.30), hormonal infertility (SIR = 3.1; 95% CI 0.99-7.22), and >or=4 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. Multivariate analysis revealed that women who underwent >or=4 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). Of IVF-treated women 85% had ER(+) tumors and 29% had positive family history.

A possible association between IVF therapy and breast cancer development was demonstrated, especially in women >or=40 years of age. These preliminary findings need to be replicated in other cohort studies.

To assess the impact of infertility treatment with causes of infertility on incidence of breast cancer.

Historical prospective cohort study of 1135 women attending major university clinics for treatment of infertility in Sweden, 1961-1976. Women were classified as users of clomiphene citrate or gonadotropins, or a combination of both therapies. Standardized incidence ratios were calculated to estimate relative risk of breast cancer.

We observed 54 cases of breast cancer during 1961-2004, which did not significantly exceed those expected. Users of high-dose clomiphene citrate had an almost 2-fold increased risk (standardized incidence ratio, 1.90; 95% confidence interval, 1.08-3.35). This association was more pronounced among women referred for nonovulatory factors, with 3-fold increased risk (standardized incidence ratio, 3.00; 95% confidence interval, 1.35-6.67).

No overall increased risk for breast cancer was shown with infertility treatment. Women with nonovulatory causes treated with high-dose clomiphene citrate therapy may have an elevated risk for breast cancer.


Ovulation induction drugs may be associated with increased breast cancer risk. Results so far have been inconclusive.

To evaluate the association between infertility, exposure to ovulation induction drugs and the incidence of breast cancer.

Historical prospective cohort and nested case-control study.


Breast cancer incidence was determined through linkage with the National Cancer Registry database. Standardized incidence ratios (SIRs) and 95% confidence intervals were computed by comparing the observed to the expected cancer rates in the general population. In addition, a nested case-control study within the cohort was performed with interviews of breast cancer cases and two matched controls.
The study cohort included 120,895 women years of follow-up. Compared to 115.2 expected breast cancer cases, 131 cases were observed (SIR = 1.1; 95% CI 0.9-1.4). Risk for breast cancer was significantly higher for women treated with clomiphene citrate (SIR = 1.4; 95% CI 1.0-1.8). Similar results were noted when comparisons were carried out between treated and untreated women, and when multivariate models were applied. In the nested case-control study, higher cycle index (OR = 2.2; 95% CI 1.0-4.8) and treatment with clomiphene citrate (OR=2.7; 95% CI 1.3-5.7) were associated with higher risk for breast cancer.

Infertility and usage of infertility drugs in general are not associated with increased risk for breast cancer. However, for infertile women treated with clomiphene citrate, breast cancer risk is elevated.


Germline mutations in BRCA genes are associated with breast and ovarian cancer susceptibility. Because infertility is associated with breast and ovarian cancer risks, we hypothesized that the mutations in the BRCA gene may be associated with low response to fertility treatments.

We performed ovarian stimulation in 126 women with breast cancer by using letrozole and gonadotropins for the purpose of fertility preservation by embryo or oocyte cryopreservation. As surrogates of ovarian reserve, the oocyte yield and the incidence of low response were compared with ovarian stimulation according to BRCA mutation status.

Of the 82 women who met the inclusion criteria, 47 women (57%) had undergone BRCA testing, and 14 had a mutation in BRCA genes, of which two were of clinically undetermined significance. In BRCA mutation-positive patients, low ovarian response rate was significantly higher compared with BRCA mutation-negative patients (33.3 v 3.3%; P = .014) and with BRCA-untested women (2.9%; P = .012). All BRCA mutation-positive low responders had BRCA1 mutations, but low response was not encountered in women who were only BRCA2 mutation positive. Compared with controls, BRCA1 mutation- but not BRCA2 mutation-positive women produced lower numbers of eggs (7.4 [95% CI, 3.1 to 17.7] v 12.4 [95% CI, 10.8 to 14.2]; P = .025) and had as many as 38.3 times the odds ratio of low response (95% CI, 4.1 to 353.4; P = .001).
BRCA1 mutations are associated with occult primary ovarian insufficiency. This finding may, at least in part, explain the link between infertility and breast/ovarian cancer risks.


Women with a BRCA mutation have unique concerns about childbearing and future fertility. In a focus group conducted among unaffected carriers, the majority of women held positive attitudes toward preimplantation genetic diagnosis to reduce transmission to future offspring and further identified unmet needs for education and support for decision making.

Ormondroyd E, Donnelly L, Moynihan C (2012) Attitudes to reproductive genetic testing in women who had a positive BRCA test before having children: a qualitative analysis Eur J Hum Genet 20: 4-10

The scope of conditions for which preimplantation genetic diagnosis (PGD) is licensed has recently been expanded in the United Kingdom to include genetic predisposition to adult-onset cancer. This qualitative interview study explores reproductive decision making, knowledge of and attitudes to reproductive genetic testing (prenatal diagnosis and PGD) with 25 women aged 18-45 years who received a positive BRCA test in the United Kingdom before having children. In this cohort of younger women, BRCA testing was motivated by risk management decisions; for some, BRCA status has affected their later decisions about having children. The perceived severity of hereditary breast/ovarian cancer (HBOC) influences thoughts about passing on the mutation to children and willingness to consider reproductive genetic testing, but most participants do not believe HBOC is a condition for which pregnancy termination is justified. PGD is considered more acceptable and advantageous because it would prevent transmission to future generations, but women have concerns about selecting embryos and the fact that they and affected family members would not have been selected. Women would also be deterred by the need to undergo in vitro fertilisation (IVF) and ovarian stimulation for PGD. Awareness of reproductive testing options was very variable among the cohort. The findings highlight the complexities of reproductive decision making for young women who knowingly carry a BRCA mutation,
and the dilemmas inherent to reproductive genetic testing when the condition being tested for also affects a prospective parent. Counselling and psychological support for BRCA-positive women and couples concerning reproductive options are strongly indicated.


There are no data regarding the actual need for fertility preservation (FP) in breast cancer (BC) patients. Our study provides a practical needs assessment for reproductive medicine by analyzing an unselected cohort of young BC patients. This assessment considers oncological factors as well as the patient’s obstetrical and gynecological history and reproductive outcome after BC diagnosis. We aimed to identify how many patients are actually potential candidates for FP and how many patients might consequently use their cryopreserved gametes to achieve pregnancy.

Based on a prospective BC database, we analyzed all patients who were ≤ 40 years at initial diagnosis (time period of diagnosis: 1990-2007; n = 100; 7.7 % of the entire BC cohort; median age: 35.9 years).

Results: Using an algorithm of exclusion criteria considering disease-specific, therapy-specific and family history characteristics, 36 patients who received chemotherapy were identified as potential “classical” candidates for FP. After 5 years, 22 women were identified as potential candidates for using their cryopreserved gametes to achieve pregnancy; the majority of these patients were childless (n = 16, 72.7 %) and in their late reproductive years (n = 12, 54.5 %).

Our study demonstrates that in a cohort of young BC patients only a minority of women are candidates for FP. Young BC patients who wish to have children in the future usually carry risk factors both from oncological and reproductive medicine perspective. Due to this high-risk profile, the rarity of BC in young age and the limited number of patients who might actually have opted for FP, these women must be offered timely and multidisciplinary counseling in highly specialized centers.

The aim of the present study was to evaluate the possible risk for cancer development in infertile women with over 30 years of follow-up. Cancer development was assessed through linkage with the National Cancer Registry updated to 31 December 2005 in a cohort of 2431 women who were treated for infertility at the Sheba Medical Center in Israel during the period 1964-1974 and contributed more than 84,000 women years of follow-up. Standardized incidence ratios (SIR) were calculated between the observed cancer cases and the expected cancer rates in the general population. The mean age at the end of follow-up was 62.7 years. 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). No excess risk associated with exposure to gonadotropins was observed. Infertility was found to be associated with significant increased risk for endometrial cancer and borderline increased risk for breast cancer. Ovarian cancer risk was not found to be elevated. No significant excess risk was associated with treatment with ovulation induction.


Breast cancer development involves a series of mutations in a heterogeneous group of proto-oncogenes/tumor suppressor genes that alter mammary cells to create a microenvironment permissive to tumorigenesis. Exposure to hormones during infertility treatment may have a mutagenic effect on normal mammary epithelial cells, high-risk breast lesions and early-stage breast cancers. Our goal was to understand the association between infertility treatment and normal and cancerous breast cell proliferation.

MCF-10A normal mammary cells and the breast cancer cell lines MCF-7 [estrogen receptor (ER)-positive, well differentiated] and HCC 1937 (ER-negative, aggressive, BRCA1 mutation) were treated with the weak ER activator clomiphene citrate and hormones that are increased during infertility treatment. Direct effects of treatment on cell proliferation and colony growth were determined.

While clomiphene citrate had no effect on MCF-10A cells or MCF-7 breast cancer cells, it decreased proliferation of HCC 1937 versus untreated cells (P = 0.003). Estrogen had no effect on either MCF-10A or HCC 1937 cells but, as expected,
increased cell proliferation (20-100 nM; $P \leq 0.002$) and colony growth (10-30 nM; $P < 0.0001$) of MCF-7 cells versus control. Conversely, progesterone decreased both proliferation ($P = 0.001$) and colony growth ($P = 0.01$) of MCF-10A cells, inhibited colony size of MCF-7 cells ($P = 0.01$) and decreased proliferation of HCC 1937 cells ($P = 0.008$) versus control. hCG (100 mIU/ml) decreased both proliferation ($P \leq 0.01$) and colony growth ($P \leq 0.002$) of all three cell lines.

Although these data are preclinical, they support possible indirect estrogenic effects of infertility regimens on ER-positive breast cancer cells and validate the potential protective effect of pregnancy-related exposure to hCG.


To examine the impact of hormones used for controlled ovarian hyperstimulation (COH) on normal and malignant breast cell growth and proliferation.

In vitro study of cultured normal and malignant breast cell lines.

Academic medical center. None patients. Normal and malignant breast cell lines cultured in two- and three-dimensional (2D and 3D) systems and treated with follicle-stimulating hormone (FSH), luteinizing hormone (LH), or FSH with LH or human chorionic gonadotropin (hCG).

Effects of treatment on cell proliferation in 2D culture using the MTS assay and on colony growth in 3D culture.

Compared with untreated cells, normal MCF-10A cells showed a decrease in proliferation and colony size when exposed to a combination of FSH and hCG. The HCC 1937 cells treated with FSH and LH also showed a decrease in colony growth but no change in proliferation. None of the treatments had an effect on the proliferation or colony size of the MCF-7 cells.

Follicle-stimulating hormone, LH, and hCG do not appear to cause an increase in cell proliferation or colony growth in either normal or malignant mammary epithelial cell lines. The potential risk for mammary cell transformation associated with these agents may be related to indirect endocrine effects on breast cell physiology.

Fifty-two thousand new breast cancers occur each year in France, 7% in patients less than 40 years. The standard regimens of adjuvant chemotherapy for breast cancer now include anthracyclines and taxanes. These therapeutics advances have significantly improved the prognosis of these young women who may later wish to become mother and have biological offspring. The impact of chemotherapy on reproductive function should be accurately assessed and the ovarian reserve has to be taken into account. The estimated risk of chemo-induced amenorrhea and infertility has to be balanced with the expected results and risks of methods of fertility preservation. The place of different options for fertility preservation depends on patient age, presence or not of a partner and the time available before the initiation of treatment. For these breast cancer patients who will receive chemotherapy, new techniques of in vitro oocyte maturation seem promising. Even if some ethical and technical issues are unresolved, fertility preservation must now be part of the management of these young patients receiving adjuvant chemotherapy for breast cancer. This new approach must be multidisciplinary and complex.


Estimates suggest that by 2010, one in 715 people in the UK will have survived cancer during childhood. With increasing numbers of children cured, attention has focused on their quality of life. We discuss the causes of impaired fertility after cancer treatment in young people, and outline which patients are at risk and how their gonadal function should be assessed. With the report of a livebirth after orthotopic transplantation of cryopreserved ovarian tissue and the continued development of intracytoplasmic sperm injection for men with poor sperm quality, we assess established and experimental strategies to protect or restore fertility, and discuss the ethical and legal issues that arise.

Thanks to the recent advances in reproductive medicine, more and more young women with breast cancer may be offered the possibility of preserving their fertility. Fertility can be endangered by chemotherapy, by treatment duration and by patient’s age at diagnosis. The currently available means to preserve a young woman’s fertility are pharmacological protection with gonadotrophin-releasing hormone analogues during chemotherapy, and ovarian tissue or oocyte/embryo freezing before treatment. New future venues, including in vitro maturation, will improve the feasibility and efficacy of the fertility preservation methods in breast cancer patients.