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# Breast Cancer and Infertility

## Meme Kanseri ve İnfertilite

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**ABSTRACT**
Breast cancer is the most common malignancy among women and may accompany infertility. The relationship between infertility treatment and breast cancer has not yet been proven. However, estrogen exposure is well known to cause breast cancer. Recent advances in treatment options have provided young patients with breast cancer a chance of being mother
**Key words:** Breast cancer, infertility treatment, in vitro fertilisation

**ÖZET**
Meme kanseri kadınlar arasında en sık izlenen kanser türü olup infertiliteye eşlik edebilir. İnfertilite tedavisi ve meme kanseri arasında henüz ispatlanmış bir ilişki yoktur. Ancak östrojen maruziyetinin meme kanserine neden olduğu iyi bilinmektedir. Bununla birlikte, son zamanlarda yeni tedavi seçenekleri meme kanseri olan genç hastalara anne olma şansını sunmuştur.
**Anahtar kelimeler:** Meme kanseri, infertilite tedavisi, in vitro fertilizasyon

## Introduction

Breast cancer is the most common malignancy among women, especially in those of reproductive age. Approximately 6 and 7% of women diagnosed with breast cancer are under the age of 40[1]. The main risk factors for breast cancer include low parity, infertility, early age at menarche, and late age at menopause. As they have similar risk factors, infertility and breast cancer may coexist[2].

An association between infertility and breast cancer has been shown in several studies, but the results are conflicting[3,4]. It is well known that breast cancer risk increases with estrogen

exposure[5]. Infertility drugs induce ovulation by increasing estrogen concentration to supraphysiological levels.

There are two main questions to be answered in this article. The first one is; does infertility treatment cause breast cancer? And the second one; is it appropriate for breast cancer survivors to conceive?

## Infertility Treatment and Breast Cancer Risk

Infertility is described as the inability to conceive within one year. The female is responsible for infertility in 35-40% of cases. Ovulatory dysfunction is a major cause of infertility. Inducing ovulation with drugs to get a high number of good quality oocytes is the most often used assisted reproductive technology treatment, which is used for other ailments as well. The drugs used to induce ovulation are known to promote mitosis, enhance angiogenesis, increase estrogen and progesterone levels and promote the development of multiple follicles[6].

Long-term exposure to estrogen increases breast cancer risk[7]. Infertility drugs such as clomiphene citrate and gonadotropins induce high serum estrogen levels. In addition, Jensen et al. emphasized that progesterone use increased the risk of ductal breast cancer by 4-fold[8]. Also, high progesterone levels caused by multiple follicular ovulations may increase the risk of breast cancer. Taken together, infertility treatment causes high levels of estrogen and progesterone, which increase the risk of breast malignity.

## Infertility Drugs

**Clomiphene citrate:** Clomiphene citrate is the first-line option in infertility treatment. The association between clomiphene citrate use and breast cancer has been shown in many studies, but a recent meta-analysis did not confirm these results, and indicated that the previous studies did not use a long enough follow-up period[9]. It has been reported that approximately 900 mg of clomiphene citrate, or more than 6 cycles of use, might increase the risk of breast and ovarian cancer. However, more long-term follow-up studies are needed to verify this claim[10].

**Gonadotropins:** The relationship between gonadotropins and breast cancer is not clear. However, the link between breast cancer and infertility treatment in general has not yet been proven. The study by Burkman et al. revealed that gonadotropins increased the risk of this

cancer[11], and mentioned that the use of human menopausal gonadotropin (hMG) for 6 months or more could double or triple breast cancer risk. Gonadotropins lead to increased levels of estrogen during the induction of ovulation, but have no direct effect on breast tissue. FSH (follicle stimulating hormone), LH (luteinizing hormone) and hCG (human chorionic gonadotropin) do not increase cell proliferation in normal or malignant mammary epithelial cell lines[12], although breast cell transformation in infertile women may be associated with the indirect effects of these drugs. In a cohort study including 21.025 women who were followed for 16 years, Stewart et al. found that assisted reproductive technology (ART) treatment did not increase the risk of breast cancer, although the type and cumulative doses of the drugs used were not included in this study[13].

## Scanning for Breast Cancer before Treatment

2.7% of breast cancer cases are under the age of 35. Hormone therapy has not been proven to cause breast cancer; however, it could accelerate the process leading to breast cancer. Breast screening before beginning infertility therapy will benefit patients and doctors, and also will protect the doctor from medico-legal problems.

## Infertility Treatment in Women with Breast Cancer

The treatment of breast cancer has recently shown promising developments, and 88% of breast cancer patients now exhibit a 5-year survival[14]. Mastectomy is usually advised in patients with breast cancer. Sentinel node biopsy determines those patients required to undergo axillary dissection, while post-mastectomy radiotherapy significantly reduces loco-regional recurrence. In addition, adjuvant systemic therapy is often used as a complementary approach[15].

Patients with breast cancer should be made aware that hormone-therapy and chemotherapy carry the risk of fertility loss. Chemotherapy has gonadotoxic effects that can result in early menopause and infertility. Although not yet proven, a GnRH analogue may be effective when used in combination with cytostatic chemotherapy in protecting the gonads[16].

Individuals who want to have a child may be offered fertility preservation options before cancer treatment. Patients who desire to receive treatment for fertility should evaluate the breast cancer stage, recurrence risk and the possible side effects with an oncologist. Eligible patients should be directed to the in vitro fertilization (IVF) unit.

Patients with male partners are fortunate in that they are able to undergo ovulation induction and IVF treatment. However, patients who do not have time or a male partner could opt for cryopreservation of their ovarian tissue. Unfortunately, this method has a relatively low chance of producing a viable pregnancy. During this process, healthy embryos are frozen, and years later, transferred to achieve pregnancy in patients who survived cancer. If the patient does not have a male partner, she has the option of ovulation induction and freezing oocytes to keep until she finds a male partner; however, this option typically results in lower success rates of pregnancy.

The purpose of ovulation induction is to retrieve high numbers of oocytes immediately before chemotherapy. However, the routine use of gonadotropins in IVF cycles leads to very high estrogen levels in the blood. Also, the risk of adverse effects from gonadotropins is not acceptable in breast cancer patients. Therefore, in recent years, letrazole (aromatase inhibitor) has been used with success as an alternative therapy[17]. Letrazole may result in ovulation induction alone. Additionally, when letrazole is used in combination with gonadotropins, high numbers of oocytes can be obtained with less gonadotropins, which keeps blood estrogen levels lower. In addition, the use of analogs to trigger ovulation reduces the exposure to estrogen and produces better results[18].

Ovulation induction treatment can be initiated at the beginning of a cycle, or in the luteal phase, if the patient has limited time[19]. An approximately 15 day delay in the treatment of cancer patients, which would be used to continue with infertility treatment, should not negatively affect the cancer treatment. The final step for conception during infertility treatment is the embryo transfer, which requires at least 2 years of being cancer-free to overcome the high risk of breast cancer recurrence[20].

Adjuvant chemotherapy does not affect pregnancy outcomes after 6 months. Further, pregnancy is not known to worsen the prognosis of breast cancer[21,22]. According to observational studies, breast-feeding does not have any impact on breast cancer prognosis[23]. Moreover, some survivors who were not aware of cryopreservation prior to receiving chemotherapy might still have a chance at conceiving. The ovarian reserve in these patients is evaluated with AMH (antimullerian hormone), FSH (follicle stimulating hormone) and antral follicle count 2 months after the therapy. 50% of women under the age of 35 continue menstruation after chemotherapy. In Sutton's study, all spontaneous pregnancies after

treatment were found to be in patients under the age of 35[21]. Breast cancer patients diagnosed at an early stage may desire infertility treatment after cancer therapy. However, the patient's ability to conceive after cancer therapy is low as a result of the reduction in the ovarian reserve and oocyte quality, which is due to advancing age, chemotherapy and hormonotherapy[24]. In addition, young women with breast cancer are faced with a more invasive disease that has a poor prognosis[25].

## Conclusion

Breast cancer and infertility may coexist. However, infertility drugs have not been proven to be responsible for the development of breast cancer. Gynecologists could advise for breast cancer scanning before initiating fertility treatment. Young and early stage breast cancer patients could preserve fertility by using IVF and cryopreservation technology.

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