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*Review Article*

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# *Preservation of Fertility in Patients with Breast Cancer: Literature Review*

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**Abstract**

Oncofertility is a discipline about the possibility of maintaining reproductive function in patients with malignant tumors. This new medical discipline is based on two main principles - safety and efficiency. Breast cancer ranks first in the structure of oncological morbidity among the female population of the reproductive period. The article describes methods of preserving fertility in breast cancer and their effectiveness.

**Keywords:** Oncofertility; Breast cancer; Cryopreservation; Oocytes; Embryos; Ovarian tissue.

## Introduction

In recent years, the preservation of genetic material has become an important aspect of the treatment of patients of reproductive age with an established diagnosis of malignant neoplasms of various localizations. In 2021, 580,415 cases of malignant neoplasms were detected in the Russian Federation for the first time in their lives (including 265,039 and 315,376 in male and female patients, respectively). The largest share in the structure of oncological morbidity in women has malignant neoplasms of the organs of the reproductive system (39.9%). Among them, breast cancer ranks first, which corresponds to 21.7% of all diagnosed neoplasms in women [1].

According to world statistics, Breast Cancer (BC), as well as in the Russian Federation, is the first most common oncological disease among the female population; in 2020, 2,261,419 (24.5%) new cases of breast cancer were registered in the world [2]. Although the incidence of Breast Cancer (BC) increases with age, it is the most frequently diagnosed malignant neoplasm in women of childbearing age: 10.5% of new cases are diagnosed each year in patients younger than 45 years [3].

Treatment of breast cancer requires an integrated approach that includes a combination of radiation, chemotherapy and hormone therapy, and surgical treatment. Domestic and foreign experience shows that many methods of antitumor treatment lead to the development of gonadal insufficiency. A 2018 meta-analysis by the authors: Gerstl B, Sullivan E, Ives A, Saunders C, Wand H, Anazodo A showed that in patients after breast cancer treatment who received systemic therapy, the probability of pregnancy is 14%, and the pregnancy rate 40% lower than the pregnancy rate in the general population. The introduction of new methods of screening and treatment of malignant neoplasms increases the detection of early stages of the disease, and as a result leads to good treatment outcomes, as well as high rates of overall and disease-free survival. In this connection, the category of patients who, in order to implement the reproductive function, requires the use of fertility preservation methods is increasing.

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According to the World Health Organization (WHO), about 17.5% of the adult population suffers from infertility, that is, approximately one in six people in the world. Currently, the implementation of the reproductive function by modern women is assigned to a later age, so according to Rosstat, the average age of a woman at the birth of a child in 2021 was 28 years and 10 months, and the average age of the birth of her first child was 25.9 years. Approximately 20.3% of women give birth to their first child before the age of 25, 22.6% from 25 to 29 years old, 23.4% from 30 to 34 years old, 24% from 35 to 39 years old, 24% from 40 years old and older – 24% [4]. And according to the Institute for Social Analysis and Forecasting of the RANEPA, the average age of Russian women at the time of the birth of their first child in 2017 was 28.5 years [5].

High incidence rates among patients of reproductive age with breast cancer, a tendency to delayed childbearing forms a category of patients with a high risk of developing gonadal insufficiency. This leads to the need to develop and apply methods of preserving fertility in patients of reproductive age with an established diagnosis of a malignant neoplasm, including patients with breast cancer.

All patients of reproductive age with an established diagnosis of a malignant neoplasm are recommended to consult a fertility specialist before antitumor treatment [6]. Thanks to the joint and well-coordinated work of an interdisciplinary team: Fertility specialist and oncologists, it is possible to solve the issues of a personalized approach to each patient on an individual basis: Is it necessary to apply fertility preservation methods (bio - insurance) before treatment, what methods are appropriate and the timing of their implementation, these issues are widely discussed both in foreign literature, and in Russia, however, there is no study that would include the study of fertility preservation methods and their impact on oncological risks.

**The main methods of preserving fertility in breast cancer include:**

- Use of GnRH agonists;
- Cryopreservation of mature oocytes obtained using special ovulation stimulation protocols or in natural cycles;
- Cryopreservation of immature oocytes obtained in an unstimulated cycle and cultured by IVM;
- Cryopreservation of embryos (possible for patients who have a partner);
- Cryopreservation and subsequent autologous transplantation of a part of the cortical layer of the ovary, which contains primordial follicles.

**GnRH agonists**

Currently, the only pharmacological means of protecting the ovaries during chemotherapy are Gonadotropin- Releasing Hormone (GnRH) agonists; however, its effectiveness remains controversial (Rodrigez -Wallberg & Oktay 2012, Hickman et al. 2016 _ et al. 2016 Senra et al. 2017). The benefit of using a GnRH agonist is that it eliminates monthly menstrual bleeding during chemotherapy and therefore may prevent chemotherapy-induced metrorrhagia. A GnRH agonist binds GnRH receptors in the anterior pituitary gland (Blumenfeld & Evron 2015, Hickman et al. 2016.), stimulating the secretion of luteinizing hormone and Follicle-Stimulating Hormone (FSH). Prolonged activation of the receptor leads to desensitization and suppression of the secretion of gonadotropins. In the ovary, the GnRH agonist is believed to reduce vascularization, thereby reducing the concentration of chemotherapeutic agents.

The protective effect of GnRH agonists on the ovaries has been studied mainly in patients with lymphoma and estrogen receptor positive breast cancer (Rodrigez -Wallberg & Oktay 2012, Lumachi 2015). In patients with Hodgkin's lymphoma, negative results were reported in a 2-year follow-up study (Waxman et al. 1987) and two studies nearly three decades later (Demeestere et al. 2016 Hickman et al. 2016). One study found that in patients with breast cancer, specifically those with early-stage estrogen receptor-negative disease, the addition of a GnRH agonist to chemotherapy was associated with a higher pregnancy rate (Moore et al. 2015).

Most other studies with similar patients have reported preservation of ovarian reserve with GnRH prior to polychemotherapy (Hickman et al., 2016), although some noted that GnRH agonists were ineffective when tamoxifen was not included in the treatment protocol (Vitek et al. 2014 & 2015). In 2013, the American Society for Reproductive Medicine recommended the use of GnRH agonists in combination with other methods of fertility preservation (Practical Committee of the American Society for Reproductive Medicine, 2013, Lambertini et al. 2016).

In a meta-analysis (Senra et al. 2017) evaluated 13 randomized control trials of patients treated for breast cancer (n=1099) or lymphoma (n=109). The GnRH agonist had a significant protective effect against premature ovarian failure in the breast cancer group, but not in the lymphoma group. The rate of spontaneous pregnancy after completion of treatment was higher in women who received GnRH agonists in combination with chemotherapy than in women who received chemotherapy alone. However, in order to assess the effectiveness of GnRH, given their mechanism of action, it is recommended to start the administration of GnRH 3-4 weeks earlier than PCT. Cryopreservation of oocytes and embryos.

The first births from a cryopreserved oocyte were reported in Australia in 1986 (Chen 1986, Jadoul & Kim 2012). However, this method did not give optimal results for many years (Oktay et al. 2006b, Jadoul & Kim 2012). Vitrification, introduced in Japan and Australia in the late 1990s to freeze embryos and oocytes (Mukaida et al. 1998, 1999 & 2017), was abandoned until the early 2000s, when studies using improved protocols showed a high birth rate of 40% for vitrified oocytes (Kobo et al. 2008, Ata et al. that of pregnancy from fresh frozen oocytes (Grifo & Noyes 2010, Pavone et al. 2016). So far, the use of cryopreserved oocytes has not been associated with an increase in congenital malformations (Chian et al. 2008 Noyes et al. 2009, Jadoul & Kim 2012).

Today, cryopreservation of embryos is the most recognized method of preserving fertility and has become a routine clinical practice in the Russian Federation and around the world. After oocyte collection, oocytes can be fertilized in vitro sperm of a donor or partner, and the embryos are subjected to cryopreservation.

The advantage of this method is that embryos generally survive cryopreservation better than oocytes. Improvements in vitrification technology have resulted in even higher embryo survival rates. In 2012, the American Society for Reproductive Medicine accepted the method of oocyte cryopreservation as non-experimental [7].

According to the recommendations of the European Society for Human Reproduction and Embryology (ESHRE), cryopreservation of oocytes/embryos should be offered as a proven option for fertility preservation [8]. For ovarian stimulation, the GnRH antagonist protocol [8] is more commonly used than the GnRH agonist protocol, due to the short duration of stimulation, the large number of oocytes obtained, and the resulting high pregnancy rates [9-11]. According to international data in young patients with breast cancer, an ovulation trigger using a GnRH agonist gives better results, including a greater number of obtained mature oocytes and cryopreserved embryos, compared with the hCG trigger [12]. In addition, a systematic analysis shows that the GnRH agonist trigger reduces the risk of ovarian hyperstimulation [12].

The combination of letrozole during ovarian stimulation with gonadotropins significantly reduces peak estradiol levels without concomitant negative effect on oocyte maturation, which probably increases the safety of use in cases of estro-gen-sensitive cancers, but requires more in-depth study (for example, breast cancer and endometrial cancer of the uterus) [13]. Cryopreservation of oocytes and embryos enables pre-implantation genetic testing during IVF procedure, which helps to exclude the possibility of transmission of pathogenic clinically significant germ cell mutations (such as BRCA1 and 2) to subsequent offspring [14-16 ].

In this category of patients, the selection of healthy embryos helps to plan the birth of healthy offspring, however, there is an alternative method of IVF procedure using a donor oocyte and subsequent cryopreservation of the embryo. The ethical issue of embryo selection remains open because BRCA mutations are not lethal mutations, and their presence does not guarantee the occurrence of cancer.

During the last decade, the introduction of maturation in vitro (IVM) also increased the chances of a successful pregnancy. Immature oocytes can be retrieved simultaneously with mature oocytes and subsequently cultured in vitro for 24-48 hours to mature into metaphase II oocytes, maximizing the number of obtained oocytes suitable for fertilization [17,18]. The percentage of childbearing during cryopreservation of oocytes/embryos depends on the age of patients and the number of cryopreserved oocytes/embryos [7]. The birth rate after oocyte cryopreservation has been reported to range from 32.6% [19] to 42.1% [20]. Based on one oocyte, the fertility rate was 8.7% (women <30 years old) and 1.1% (women 43-44 years old) [21]. Recent data show that the presence of 10-12 oocytes results in birth rates of up to 61.9% and 43.4% in patients under 35 years of age and over 35 years of age, respectively [20,22]. In a study conducted in Spain in 2018, which included 1073 women (1172 stimulation cycles) diagnosed with breast cancer, who underwent ovulation stimulation and oocyte cryopreservation, after a mean storage time of 4.1±0.9 years, oocyte survival was 81.8 %, with the transfer of an average number of 1.4±0.1 embryos, the frequency of clinical pregnancy and childbirth was 41.4% and 31.2%, respectively [20]. In terms of embryo cryopreservation, the live birth rate per embryo transferred in breast cancer patients is comparable to that in the general population (45.0% vs. 38.2%) [23].

### Ovarian tissue cryopreservation

Oocytes and embryos may not be suitable for patients requiring urgent oncological treatment or for prepubertal children [24]. In these cases, the method of Ovarian Tissue Cryopreservation (OTC) may be offered.

OTC involves removal of ovarian tissue and cryopreservation of cortical fragments, which are then subjected to autologous transplantation to restore both endocrine and fertile ovarian function [25,26]. OTC may also be a useful option for patients who have undergone chemotherapy, as chemotherapy is no longer a contraindication to freezing, since the decrease in ovarian reserve depends on the type of chemotherapeutic agents and the number of courses performed [7].

In 2004, the first pregnancy after cryopreservation of ovarian tissue was reported [27]. Tsyba is a branch of the National Medical Research Center for Radiology of the Ministry of Health of Russia. To date, more than 300 children have been born after this procedure. Restoration of the endocrine function of the ovaries is observed in more than 90% of cases after transplantation within 4-9 months [28,29]. In a 2015 study by Italian scientists that included 111 patients in five major centers, the pregnancy and childbearing rates after cryopreservation of ovarian tissue for breast cancer were 29% and 23%, respectively [30]. In 2019, Swedish scientists in a large sample study reported CT in 418 prepubertal children. However, no pregnancies were registered in this study due to the short follow-up period [31]. In 2015, the first delivery after OTC and ovarian tissue transplantation in a prepubertal patient was reported [32]. In a large report from five leading European centers, fertility rates were 30% and 21%, respectively, among those who conceived naturally and those who underwent In Vitro Fertilization (IVF) with a low rate of recurrence of malignancies [7]. Overall, the birth rate is reported to be around 40% among survivors under 36 years of age [21]. Consequently, the updated ASRM and ESHRE guidelines recommend that OTC be considered as a non-experimental procedure that should be offered to certain categories of patients to preserve fertility [33,34]. Data Analysis Results European centers show that the chances of a successful pregnancy do not decrease, even if OTC is prescribed after chemotherapy [7]. In addition to positive reproductive outcomes, OTC also contributes to the restoration of ovarian endocrine function, which is manifested by the restoration of menstrual cycles and improvement of the hormonal profile [35].

OTC is currently performed using conventional slow freezing and vitrification [36,37]. A systematic review and meta-analysis shows the superiority of vitrification over slow freezing in terms of clinical outcomes in terms of survival of oocytes, cleavage embryos and blastocysts [10]. However, slow freezing has been shown to be more effective than vitrification in OTC. Cryopreservation of human ovarian tissue by slow freezing has been reported to produce tissues with more remaining primordial follicles compared with vitrification [39]. Looking at a number of studies, it is recognized that slow freezing better preserves the quality of follicles in cryopreserved ovarian tissue [40-42]. According to the EHSRE recommendations, the slow freezing protocol should be used for

cryopreservation of ovarian tissue, as it is well established [8].

In recent years, along with the development of the maturation Method In Vitro (IVM) in the treatment of infertility, several scientific groups have tried to combine IVM with OTC because immature antral follicles could not survive after cryopreservation. Accordingly, immature oocytes obtained transvaginal or extracted from ovarian tissue "ex vivo", can mature in vitro to obtain mature oocytes ready for IVF, which increases the chances of pregnancy success [43,44]. According to the latest data, the combination of OTC and IVM "ex in vivo" of retrieved oocytes results in a result comparable to the results of oocytes obtained after ovarian stimulation before cancer treatment in terms of the number of mature oocytes and childbearing [44]. However, there is a need to improve the results of the OTC procedure. During cryopreservation, there is a significant loss of follicles due to ischemia after ovarian tissue transplantation, which shortens the life of the graft [45,46]. About 80% of ovarian follicles are reported to be lost during a CT procedure followed by transplantation [47]. To enhance neoangiogenesis after transplantation, it is proposed to use several agents during transplantation, including angiogenic and antiapoptotic factors, antioxidants, and adipose-derived stem cells [48-51].

The method of cryopreservation of oocytes and embryos in breast cancer is widely used in modern medicine, and the method of cryopreservation of ovarian tissue in this nosology is not widely used, although this procedure has its advantages: the time frame of the technique does not require a delay in antitumor treatment, this is the only method applicable in girls in prepubertal age, as well as it allows you to save the pool of primordial follicles.

However, the safety of this technique is still being studied, it has been proven that in lymphoproliferative diseases there is a risk of autografting of ovarian tissue affected by tumor cells, which can lead to a relapse of the disease. To remove tumor cells from the ovarian tissue, photodynamic therapy methods are used with good results [14]. However, such studies do not occur in breast cancer. In the structure of all malignant ovarian tumors, metastatic ovarian tumors range from 14.7 to 21.1 %. One of the tumors that most often metastasize to the ovaries is breast cancer - 15.46% [52]. At the same time, with the localization of the primary tumor in the mammary gland, bilateral ovarian lesion is noted in 63.3% of cases.

Therefore, when carrying out cryopreservation of ovarian tissue, the question of exclusion of metastatic lesions remains open; for this purpose, routine methods of morphological research are used, which often do not give an accurate picture of micrometastases of breast cancer in the ovary. In the literature, there are studies studying the detection of metastases and micrometastases in the ovary of breast cancer using various immunohistochemical markers, and researchers have identified the most sensitive markers (GCDFP-15, E- cadherin, HER-2neu, mammaglobin, CEA, EMA, BER-EP-4) [53-55]. BRCA mutations and fertility preservation.

Women who carry BRCA1 and BRCA2 mutations have long been known to have an increased lifetime risk of developing breast cancer, contralateral breast cancer, and ovarian cancer. A prospective study conducted by American researchers in 2017 showed that the lifetime risk of breast cancer is about 70% for BRCA1 and BRCA2 carriers, and the lifetime risk of ovarian cancer is 44% for BRCA1 carriers and 17% for BRCA2 carriers [53]. By age 40, the reported cumulative risk of developing breast cancer is 24% for BRCA1 carriers and 13% for BRCA2 carriers, while the cumulative risk of ovarian cancer is 2% for BRCA1 carriers and 0% for BRCA2 carriers [53]. Women with a BRCA1/2 mutation are advised to have bilateral salpingo-oophorectomy before the age of 35-40 years after they have completed childbearing to reduce their risk of developing ovarian cancer and breast cancer [54].

According to data published in 2018 by US researchers, carriers of the BRCA mutation have a reduced reproductive potential, i.e. decreased ovarian reserve, lower AMH levels, and poorer response to controlled ovarian stimulation with letrozole protocols [55,56]. Also, BRCA1/2 mutation carriers have an earlier natural menopause, approximately 3-4 years earlier than healthy women [57]. The gonadotoxic effects of chemotherapy may be more pronounced in breast cancer patients with a BRCA 1/2 mutation, since insufficient DNA repair by homologous recombination makes the oocytes of these women more vulnerable to gonadotoxic therapy [58]. Given the potentially reduced ovarian reserve in breast cancer patients with BRCA1/2 mutations, the use of protocols with double ovulation stimulation may be beneficial [59]. Preservation of fertility in patients with breast cancer with a BRCA1/2 mutation using ovarian tissue cryopreservation has not been studied due to the risk of developing ovarian cancer [60].

**Conclusion**

The question of the safety of using various methods of ovulation stimulation remains debatable, it is known that an increased level of endogenous estrogen in the blood is associated with an increased risk of breast cancer. A meta-analysis conducted by English scientists, including more than 50 studies involving a total of 160,000 women, demonstrated a higher risk of developing breast cancer for women taking menopausal therapy for 5 years or longer [61].

For these reasons, there are some concerns about the safety of using ovulation inducing drugs. The use of ovarian stimulating drugs in patients with reduced fertility is associated with significantly higher levels of circulating estrogen for a short period, in contrast to MHT, which is used for a long time, but in small doses [61,62].

In 2015, Italian scientists conducted a systematic review and meta-analysis of cohort studies that assessed the relationship between hormonal infertility treatment and the risk of developing breast cancer [63]. A total of 20 studies were included, involving 207, 914 women receiving hormone therapy for infertility and 2347 breast cancers. Overall, no increased risk was found with the use of hormone therapy for infertility, but significant heterogeneity between studies was found [63]. In a subgroup analysis, looking at only seven studies with In Vitro Fertilization (IVF), no increased risk of breast cancer was found. In contrast, a moderately increased risk of breast cancer was observed in three studies where women were treated without IVF protocols. Overall, the meta-analysis did not support the hypothesis that hormonal fertility treatment is associated with an increased risk of breast cancer [63].

In 2014, a large US cohort study reported encouraging re-

sults on the long-term effects of ovarian stimulating drugs with clomiphene or gonadotropins [64]. After a median follow-up of 30 years, of 9892 women screened for infertility, 749 developed breast cancer. No risk has ever been associated with the use of clomiphene citrate. However, a significantly increased risk was observed in patients receiving a high cumulative dose of stimulant drugs (i.e. ≥2251 mg) and multiple IVF cycles (i.e. ≥6 cycles). The use of gonadotropins was not significantly associated with the risk of developing breast cancer, regardless of dosage, number of cycles, or age of patients [64].

Despite these encouraging results, for women with infertility, including those already diagnosed with breast cancer, an individual approach to ovulation stimulation is needed and more in-depth studies are required on the safety of using various protocols for ovulation stimulation.

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