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Preserving Fertility For Breast Cancer Patients: where do we stand today?

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Abstract

Introduction: Breast cancer is the most common malignancy in women of reproductive age. The advances in treatment have resulted in an increased survival rate. However, keeping in mind that most women have not completed their families, treatment-related infertility poses a serious concern. The purpose of this review is to analyse the current options for fertility preservation in young breast cancer patients. **Materials and Methods:** We conducted a comprehensive search of the PubMed database for citations regarding fertility preservation in breast cancer patients. The search terms included "fertility preservation; breast cancer; ivf; ovarian stimulation protocols; ovarian tissue cryopreservation; tamoxifen; BRCA ; GnRH; ovarian suppression; pregnancy and guidelines". **Results:** More than 7% of women diagnosed with breast cancer are younger than 40 years old. Almost all of breast cancer survivors (97%) are either hormone receptor positive or receive chemotherapy, which could result in infertility. Data from the National Survey of Family Growth (NSFG) suggest that half of these women might want children and would benefit from fertility preservation. Currently available fertility preservation techniques include mainly embryo cryopreservation or oocyte cryopreservation. Apart from the established techniques, ovarian tissue cryopreservation is a promising option, especially when there is no time for controlled ovarian stimulation. However, it is still considered experimental, despite very promising results. On the other hand, ovarian suppression during chemotherapy or hormonal manipulation has not been proven effective and it is not supported by recent guidelines. **Conclusions:**It is imperative that all breast cancer patients of reproductive age have access to fertility counselling, since fertility preservation may be an option for most survivors, who haven't competed their reproductive goals. Furthermore, multidisciplinary oncology boards combining breast surgeons, oncologists and reproduction specialists must be available for all breast cancer patients, since the time margin between diagnosis and cancer treatment is tight (4-6 weeks).

Key words: Breast Cancer, Fertility Preservation. IVF; Ovarian Stimulation. Tamoxifen, BRCA, GnRH, Pregnancy

Introduction

Breast Cancer is the most common malignancy in women of reproductive age. It is estimated that every year 235.000 women are diagnosed with breast cancer in the USA[1]. Despite its increased prevalence with age, about 7% of these women are below 40 years of age[2]. This fact in combination with the delayed childbearing due to socio-economic reasons has raised the need of family planning for breast cancer survivors, especially since it is no longer considered unsafe regardless of hormone receptor positive or negative disease. However, due to the gonadotoxic effect of chemotherapy the reproductive ability of breast cancer patients is likely to be compromised. Making things worse, pregnancy is not recommended for a minimum of 2 years after the completion of cancer treatment, further diminishing the possibility on natural conception. Data from the National Survey of Family Growth (NSFG) suggest that almost half of the breast cancer survivors want to have children after completing their treatment[3]. Hence, it is imperative that all newly diagnosed breast cancer patients of reproductive age are offered consultation by a multidisciplinary oncology board including a reproduction specialist and that they are presented with a suitable fertility preservation option before the initiation of cancer therapy.

Materials and methods

The purpose of this review is to provide the reader with a concise and up to date view of fertility preservation options for breast cancer patients. A comprehensive search of the PubMed database was conducted using the search terms: Breast Cancer; Fertility Preservation; tamoxifen; BRCA, controlled ovarian stimulation; ovarian tissue cryopreservation; guidelines; The most important and up to date studies were selected ensuring that all the latest information is presented in this review.

Predicting ovarian damage due to gonadotoxic chemotherapy.

Five-year survival for breast cancer patients younger than 40 years of age in the United States has increased from 75.2% in the 1970s to the current 86.9%[4]. Despite the fact that cancer treatment has prolonged the survival of breast cancer patients, major side effects such as gonadal toxicity cannot be avoided. Predicting chemotherapy induced preterm ovarian failure may be possible when taking into account the patients age, the treatment regiment and the cumulative dose. In the case of breast cancer, alkylating agents have the greatest gonadotoxic potential. Taxans cause an intermediate ovarian damage, whereas methotrexate and 5-fluorouracil are associated with a lower toxicity risk. The extent of anthracycline-related ovarian toxicity is controversial. According to previous findings, it is expected to be low[5]. Among women treated with adjuvant chemotherapy for breast cancer, the risk for premature menopause is significantly higher for women older than 35 years with newly diagnosed breast cancer.

Strategies for Fertility Preservation in BreastCancer Patients

Timing and schedule flexibility

A standard COS protocol, where pituitary suppression is achieved via GnRH agonists, has a duration of about 4 weeks. GnRH antagonists achieve immediate pituitary suppression, allowing for shorter COS protocols (of about 2 weeks). Furthermore, random start COS protocols have been developed, taking advantage of the presence of multiple waves of follicular recruitment within the same menstrual cycle, thus further increasing schedule flexibility. The use of GnRH antagonists allows initiation of ovarian stimulation during the luteal phase of the menstrual cycle. Random start COS protocols have comparable oocyte yield, oocyte maturity rates, fertilization rates and satisfactory pregnancy outcomes with early follicular phase start COS protocols[6-9].

Usually, cancer treatment can be safely delayed for 6-8 weeks[10-11]. It has been demonstrated that in early stage cancer, treatment can be safely extended for up to 12 weeks without alteration of the prognosis[10-11]. In such cases, performing more than one cycle is preferable in order to obtain more oocytes and increase chances of future pregnancy . Even when neoadjuvant therapy is necessary, a window of 2-3 weeks is available for at least one COS cycle. When the time frame does not allow ovarian stimulation and retrieval of mature oocytes, the option of ovarian tissue cryopreservation should be explored.

Embryo and Oocyte Cryopreservation

Embryo and oocyte cryopreservation are both established techniques of assisted reproduction, that can be used for fertility preservation purposes in breast cancer patients. Since most types of breast cancer are hormone sensitive, elevated E2 levels as a result of controlled ovarian stimulation (COS) could endanger the oncologic outcome of the patient. Hence, a few years ago, only natural cycle IVF was offered to breast cancer patients as a fertility preservation option[12]. Nowadays, COS protocols have been designed especially for breast cancer patients, minimising estrogen exposure and making sure there are no adverse effects on the oncologic outcome.

Many different COS protocols have been tried in the effort to optimise oocyte yield without increasing estrogen exposure. Tamoxifen and letrozole have both been used for ovulation induction, either alone or in combination with low-dose gonadotropins.

The function of aromatase inhibitors, such as letrozole or anastrazole , is to reduce the production of estrogens. E2 and estrone are produced via catalysis from androstenedione and testosterone respectively. Aromatase is the key enzyme in this conversion[13]. The inhibition of aromatase by AIs results in complete suppression of estrogen production[14], not allowing E2 levels to rise above those observed in natural menstrual cycles[15]. Furthermore, AIs result in an increased FSH production from the pituitary by blocking the negative feedback of estrogen on the hypothalamic-pituitary axis, increasing follicular growth[16]. In conclusion, AIs are both effective at preventing estrogen production and inducing ovulation.

The first attempts of fertility preservation in breast cancer patients included natural cycle IVF, with profoundly poor results. The function of tamoxifen is to antagonise the effects of estrogens both at the breast and the CNS, while it acts as an agonist in the uterus and bone. Tamoxifen blocks the negative feedback of estrogen in the hypothalamic-pituitary axis, resulting in an increase of endogenous FSH production, stimulating follicular development. The use of tamoxifen in breast cancer patients results in an obvious increase of the mature oocyte and embryo number compared to natural-cycle IVF, with the added benefit of reducing cycle cancelations[12].Tamoxifen can be used for COS alone on cycle days 2 through 5 of the patient's menstrual cycle or in combination with gonadotropins[17]. Combined treatment with tamoxifen and gonadotropins, results in an even greater number of cryopreserved oocytes/embryos [18].

The use of COS protocols which combine daily administration of letrozole with gonadotropins has been proven superior over the use of tamoxifen, regarding the number of both retrieved and fertilized oocytes[19]. The safety of the letrozole-gonadotropine protocol in breast cancer patients has also been demonstrated, since short-term follow-up has not revealed any increased risk of breast cancer recurrence[19]. AIs have also been used safely, as part of COS protocols, in endometrial cancer patients[20].

GnRH agonists are used instead of hCG in order to trigger final oocyte maturation. GnRHa are preferred to hCG in breast cancer patients undergoing COS due to their lower half life and fewer OHSS occurrences, combined with higher number of retrieved oocytes and higher maturation and fertilisation rates[21].

Ovarian Tissue Cryopreservation

Ovarian tissue is retrieved via laparoscopic surgery and it is cryopreserved. The obtained tissue can be used for auto-transplantation or for follicle aspiration. Although auto-transplantation of ovarian tissue is still considered experimental, several pregnancies have been published[22]. This particular technique should be avoided in BRCA mutation carriers in which it could result in the development of an ovarian cancer. On the other hand, in prepubertal breast cancer patients, ovarian tissue cryopreservation is currently the only available fertility preservation option. Furthermore, ovarian tissue cryopreservation should be considered when there is no time to perform COS for fertility preservation before the initiation of adjuvant or neo-adjuvant cancer treatment.

Immature oocyte retrieval and in vitro maturation

Immature oocyte retrieval and in vitro maturation (IVM) is a new approach to fertility preservation for breast cancer patients. Obtaining oocytes from unstimulated ovaries has many advantages over traditional techniques. Since there is no need for COS, E2 levels are kept low, oocytes can be obtained faster and the cost of COS drugs can be avoided[23]. Immature oocytes can either be cryopreserved at the immature stage and then maturated in vitro after being thawed or they can be cryopreserved after in vitro maturation. First estimates show that up to 50% of the retrieved immature oocytes can be matured in vitro[24, 25]. Hence IVM is a very promising technique for improving the mature oocyte yield of fertility preservation cycles in breast cancer patients. However in vitro maturation is considered experimental and there are no data yet regarding this technique's safety and pregnancy rates [26, 27].

Ovarian Suppression with GnRHa

The use of gonadotropin-releasing hormone agonists (GnRHa) as a fertility preservation option for women receiving gonadotoxic chemotherapy has been investigated in several trials with controversial results[28]. One of the largest trials (PROMISE trial) showed a reduced incidence of early menopause[29], while three other prospective randomised trials did not show any statistical benefit of ovarian suppression[30-32]. A meta analysis of six randomised controlled trials showed a statistically significant improvement in the proportion of ovulation after chemotherapy compared to controls, which however did not translate to an increased rate of spontaneous pregnancy in at least three of the studies[33]. Further meta analysis have shown a protective effect of GnRHa use during chemotherapy regarding the rate of Premature Ovarian Failure (POF) as well as the rate of spontaneous menstruation after chemotherapy[34-38]. However, so far there are no data regarding the efficacy of ovarian suppression on long term ovarian function or pregnancy rates[39].

Hence, both ASCO and ESMO in their current fertility preservation guidelines (2013), do not regard the use of GnRHa as a reliable method of fertility preservation and do not recommend its use but only in clinical trials[40-41]. However the use of GnRHa is recommended by ASCO due to other medical benefits such as a reduction of vaginal bleeding when patients have low platelet counts as a result of chemotherapy[40].

Assessment of ovarian reserve

One of the most important factors to take into account when choosing the most suitable approach for fertility preservation in women diagnosed with breast cancer, is ovarian reserve. Ovarian reserve together with the patient's age and the kind of treatment she is going to receive will determine whether she will be able to have children. Several markers of ovarian reserve have been evaluated over time. These include early follicular phase serum E2, FSH, anti-Mullerian hormone (AMH) and Inhibin B (InB) levels as well as measurement of antral follicle count and ovarian volume. Poor ovarian response to controlled ovarian

stimulation has been associated with decreased AFC and ovarian volume, low AMH, low InB, high FSH and high E2 in the beginning of the follicular phase[42-52].

AMH, which can be assessed at any time during the menstrual cycle and AFC are the most commonly used markers of ovarian reserve. At the same time they serve as good predictors for ovarian response to COS. However, there are mixed reports on the predictive value of AMH and AFC regarding cancer patients[53,54]. Lower responses to COS have been documented in cancer patients compared to healthy age-matched women[55], highlighting the effect of overall clinical status apart from ovarian reserve to the response to COS[56].

Keeping in mind the fact that neither AFC nor AMH can predict pregnancy or live birth after IVF[57], they are useful for informing patients regarding their expectations but they cannot predict the outcome of COS in cancer patients. However, they are valuable tools in developing an effective ovarian stimulation protocol, when their limitations are taken into account.

Apart from age and treatment toxicity, ovarian reserve is affected by the presence of malignancy itself. Cancer at higher stages may cause malnutrition, stress and an increased catabolic state affecting all organ systems[58]. Enhanced stress hormones and hypothalamic dysfunction lead to decreased levels of gonadotropins, impacting fertility[59]. The presence of gene mutations pose yet another important factor that can potentially affect ovarian reserve. DNA damage resulting from BRCA gene mutations has been shown to pose a risk for oocytes[60]. In a meta-analyses conducted by Friedler S et al, retrieved oocytes were significantly less in the cancer group than in the control group 11.7+/-7.5 vs. 13.5+/-8.4, p=0.002 (95% CI, -2.976; -0.621) while at the same time cancellation rates were higher[61].

Current Guidelines

Guidelines for fertility preservation strategies in women diagnosed with breast cancer have been provided by the National Comprehensive Cancer Network (NCCN), the American Society for Clinical Oncology (ASCO) and the American Society for Reproductive Medicine (ASRM)[40,62-64]. All three institutions recommend the discussion of infertility risks due to cancer therapy before the initiation of treatment. Furthermore, female breast cancer patients who opt for fertility preservation should be offered consultation with multidisciplinary oncology boards combining breast surgeons, oncologists, psycho-oncologists and reproduction specialists as soon as possible (within 24 hours as suggested by the NCCN guidelines)[62]. If deemed necessary referral to a mental health professional may assist women in the decision making process. Embryo cryopreservation should be offered to all women with a male partner or those willing to use a sperm donor. Oocyte cryopreservation is a viable alternative for women whithout a male partner, adolescent girls and those who have ethical concerns about embryo freezing. Oocyte cryopreservation is not considered experimental since 2012, according to ASRM guidelines[40,63]. Ovarian tissue cryopreservation, although promising, it is still considered experimental and should be offered only in a research setting with institutional review board (IRB) oversight. However it is the only available fertility preservation option for prepubertal girls. In case of minors, informed consent must be obtained from their legal guardians. Ovarian suppression using GnRHa has produced conflicting results so far, so alternative fertility preservation options should be offered, according to the NCCN guidelines, whereas ASCO guidelines do not recommended it for fertility preservation outside clinical trials[40].

BRCA mutations

One of the remaining challenges regarding fertility preservation for breast cancer patients is the presence of BRCA mutations. These women may request preimplantation genetic diagnosis (PGD) for BRCA mutations during in vitro fertilisation (IVF) to prevent

mutation transmission to the embryo[65], although this measure might arise ethical and moral concerns, since most BRCA mutations are neither lethal per se nor does their presence guarantee cancer development. Despite the fact that there are only few studies specific for women with BRCA mutations, there have been indications that BRCA 1 mutations could be related to diminished ovarian reserve[66]. Another important factor that has to be considered for women carrying BRCA 1 and BRCA 2 mutations is the fact that they are not candidates for ovarian tissue cryopreservation since they have an increased risk for developing ovarian cancer[67]. BRCA mutation carriers should not be discouraged from getting pregnant, since no statistically significant difference has been found in the risk of developing breast cancer between parous and nulliparous women[68].

Conclusions

Fertility preservation is a very important aspect for the quality of life of breast cancer patients of childbearing age, especially for the women who haven't completed their families before the initiation of treatment. It has been clearly demonstrated that adjuvant treatment for breast cancer has a negative influence on fertility. Hence, presenting young cancer patients with the option for fertility preservation before the initiation of such treatment is very important. A multidisciplinary approach, should be a part of the routine clinical management of breast cancer in young women.

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