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Fertility Preservation in Breast Cancer Patients Under Special Consideration of Ovarian Stimulation for Fertility Purposes

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Importance of fertility preserving methods

A. Socio-demographic changes in society

In the industrialized countries, two developments have been observed over the last few decades that have shifted the focus of research and reproductive medicine to maintaining fertility. With regard to social life, there is a trend of postponing the realization of the desire to have children to an ever later phase of life or a childbirth does not take place at all due to existing biological limits. In Germany, for example, between 1993 and 2013, the age of women at the birth of their first child rose from around 25 to 29.3 years.[1] It is well-known for a long period of time that women's fertility decreases steadily at the age of approximately 30 years.[2] However, the optimum fertility is around 25 years. At the same time, there is an almost constant increase in life expectancy in cancer patients, especially in women with breast cancer. One reason for this observation is the progress made in oncologic therapy, which is reflected in improved long-term survival in cancer. However, these successes are accompanied by a loss of fertility due to premature ovarian insufficiency, triggered by gonadotoxic side effects of chemotherapy and radiation.[3,4] At the same time, many women report that they still want to have children despite being diagnosed with cancer. Up to every 7 patient would even be willing to accept a loss in oncologic safety if she could still give birth to a child.[5]

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B. Epidemiologic aspects of breast cancer

Breast cancer is the most common malignancy in women around the world with 1.6 million new breast cancer patients being identified each year worldwide.[6] Overall, 4-6 % of the women diagnosed are under the age of 40, and about one out of five women possesses a premenopausal hormonal status .[7] Advancement in the adjuvant systemic and locoregional therapy has resulted in a significantly improved forecast.

The function of the ovaries can be damaged by the therapy resulting in a loss of germ cells and later on in infertility. The question of maintaining fertility is of great importance regarding the self-determination of the patients. The potential use of treatments for fertility preservation has to be a compromise between risks and costs of the therapy. The overall forecast, family planning, gonadotoxic effects of the planned therapy and psychological compounds should be considered before doctors make an indication for fertility preservation.

An interdisciplinary collaboration of an oncologist, gynecologist, psychologist, radiologist, radiation therapist and reproductive specialist is indispensable.

Fertility preserving methods for breast cancer patients

A. General considerations

Ovaries contain a limited number of gametes compared to testes with a maximum of 6.000.000 follicles at 20 weeks of gestation. At birth, there are only 1,000,000 follicles left, and at entry of puberty there are only 300.000 follicles. Finally, the stock of follicles is exhausted by entry in the menopause. During the stage of fertility only 300–500 oocytes ovulate.

The determining factors in the admission of a cytotoxic caused amenorrhea include the age of the woman at the time of the therapy, the ovarian reserve and the applied chemotherapy regimen. The gonadotoxic effect of the commonly used chemotherapies is shown in Table 1. As can be seen, there is a correlation between the cumulative dose of the radiation of the pelvis in the case of metastatic disease and damage of the ovarian function.

Table 1. Gonadotoxicity of several agents applied in breast cancer patients

high risk (POI risk >= 80%)	Cyclophosphamid Busulfan Melphalan
intermediate risk (POI risk 20-80%)	platin derivates Adriamycin
low risk (POI risk < 20%)	Vincristin 5-Fluorouracil Methotrexat Actinomycin D
unclear risk	Trastuzumab Pertuzumab tyrosine kinase inhibitors Pembrolizumab CDK4/6 inhibitors PARP inhibitors PDL1 antagonists

Damage to ovaries caused by oncologic therapy clinically appears as an ovarian dysfunction followed by abnormal estrous cycle. If the stock of follicles is irreversibly damaged due to adjuvant therapy, a secondary amenorrhea results including the proof of a lack of estrogen, a thin endometrial lining in sonography and loss of antral follicles (ovarian atrophy). Gonadotrophins can be measured in a hypergonadotropic range and Anti-Mullerian-Hormone (AMH) is beneath detection limit.

The current study situation concerning the duration of amenorrhea with partial damage to the stock of follicles appears inhomogeneous and varies highly between different authors.[8]

Sukuvanich *et al*. published the first prospective study examining the effects of different chemotherapy regimens evaluating the probability of amenorrhea post therapy depending on the women's age at the start of the therapy.[9] In the period from 1998 to 2002, 466 women aged between 20 and 45 years were examined. The rate of amenorrhea was determined at 6, 12 and 24 months after termination of therapy.

Overall, 111 women out of the examined collective received the AC–regimen (Dexorubicin, Cyclophosphamid, Paclitaxel),76 women were treated according the CMF–regimen (Cyclophosphamid, Methotrexat, 5-Fluorouracil) and 143 received the ACT–regimen (Doxorubicin, Cyclophosphamid, Paclitaxel). Also, 136 women gained other cytostatics (ACR-, FAC-, FACT-, as well as not further defined regimens).

The patients were divided into categories with respect to their age: 20-34 years (n=112), 35-39 years (n=142) and >40 years (n=212). The probability of amenorrhea was examined as well as the presumption of recurrent menses following amenorrhea. In only 11% of women aged 20-34 amenorrhea was reported six months after completed chemotherapy. Results slightly varied between different chemotherapy regimens. In relation to recurrence of menstruation following secondary amenorrhea the CMF-regimen showed worse outcomes than in the other chemotherapy schemes. All in all, the risk of premature ovarian insufficiency caused by chemotherapy in patients suffering from breast cancer appears to be low. However, regarding fertility preservation-especially in patients suffering from estrogen-sensitive breast cancer-it should be considered that a longer adjuvant endocrine therapy might be necessary. Meanwhile, the stock of ovarian follicles could be reduced, particularly if the therapy is initiated in the second half of the fourth life decade.

As the transposition of the ovaries out of the pelvis prior to radiotherapy as an additional fertility preserving technique is not a relevant issue for breast cancer patients we do not report on it in this review article.

B. Medical protection of ovarian function

In breast cancer patients, GnRH analogues (GnRHa), such as Leuprorelin, Buserelin or Goserelin, are used as medicamentous fertility-protective therapy. A depot injection is carried out every 28 or 84 days with a GnRHa during the entire period of chemotherapy (starting shortly before the initiation of chemotherapy, ending approximately 2 weeks after completion of chemotherapy). In this case, there might be a downregulation of the ovary with consecutively reduced intake of cytostatics. The main side effects are climacteric complaints. If the therapy lasts more than 6 months, the so-called add-back therapy with an estrogen and a progestin is recommended to counteract the serious consequences of a sexual hormone deficiency such as osteoporosis.[10] During the last years there has been a lively debate about the pros and cons of applying GnRH analogues in women with hormone receptor-positive breast cancer. GnRHa treatment was considered to desensitize the tumor for the following endocrine therapy that is obligatory in hormone receptor-positive diseases, worsening the patient`s prognosis. However, in recent years there has been increasing evidence that GnRHa can in fact reduce the risk of premature ovarian insufficiency (POI) without being associated with a deterioration of prognosis - regardless of the hormone receptor status. In 2012, a meta-analysis of seven randomized studies with predominantly breast cancer patients showed that the administration of a GnRHa during chemotherapy can

significantly reduce the risk of premature ovarian insufficiency.[11] Therefore, GnRHa as fertility preserving agents are recommended in the guideline of the German AGO (Arbeitsgemeinschaft Gynäkologische Onkologie) group.[12] Nevertheless, the application of GnRHa solely for preserving fertility cannot be regarded as an effective strategy for preserving female fertility. For this reason, this approach is not recommended by the guidelines of the American Society for Reproductive Medicine (ASRM).

C. Ovarian stimulation and cryopreservation of oocytes

Carrying out ovarian stimulation is aimed at gathering mature oocytes (MII-stage) to preserve them in fertilized or unfertilized conditions to create a fertility reserve. The required treatment should be implemented promptly to avoid any delay of oncologic treatment. The aim is to retrieve as many oocytes as possible. At the same time, the risk of ovarian hyperstimulation should be avoided.

Often there are several years between fertility protection and the wish to attempt pregnancy; therefore, even women in a steady relationship should think about cryopreservation of unfertilized oocytes to ensure independence of the women in the case of separation from the partner. In this situation, the opportunity of 'splitting' should be discussed with the patient in which fertilized and unfertilized oocytes are cryopreserved. The later use of fertilized oocytes is only permitted after approval of both partners.

Procedures for ovarian stimulation can be initiated regardless of the time of menstrual cycle ("random-start-stimulation").[13-16] A total of two weeks should be scheduled for the treatment. Starting ovarian stimulation in the luteal phase takes on average 1-2 days more than starting it in the follicular phase. To increase the number of obtained oocytes in individual cases double stimulation could be proceeded. Double ovarian stimulation protocols are developed to allow ovarian stimulation and retrieving oocytes twice in the same menstrual cycle.[17-19]

The success of this method and the number of retrieved oocytes during a menstrual cycle depends on ovarian reserve (antral follicle count, AMH concentration) and the patient's age. Vitrification represents an effective method for cryopreservation of oocytes achieving satisfying survival and fertilization rates.[20] The birth rate of cryopreserved oocytes depends on the age of the women. The application rate of cryopreserved oocytes is low based on current studies and according to Diaz-Garcia, stands at 4.8%.[21]

In Germany, embryo cryopreservation for fertility preservation is forbidden by law following the embryo protecting law "Embryonenschutzgesetz" enacted in 1990. In other countries, embryo cryopreservation is permitted by law and it is an established method for fertility preservation. The pregnancy rates after fertility preservation using cryopreserved 2PN-cells (pronucleus stage) or cryopreserved embryos are comparable.

The German-IVF-Register has reported the viability rate of 90,2% using thawed oocytes and a pregnancy rate of 20,1% per embryo transfer.[22] The antagonist protocol represents the preferred method for ovarian stimulation during fertility preservation including ovulation trigger by GnRH agonists. Depending on the stage of menstrual cycle, different protocols are used at the beginning of the treatment.

Starting in the early or middle follicular phase, the stimulation of oocytes can be performed with the aid of FSH, FSH/LH or HMG by default. From a follicle size of >13mm a prematurely ovulation is prevented through the application of an GnRH antagonist like Ganirelix or Cetrorelix. Finally, ovulation is triggered via a GnRH agonist (e.g. Triptorelin) after sonographic detection of 3 follicles >17mm or a leading follicle > 20mm (Figure 1).

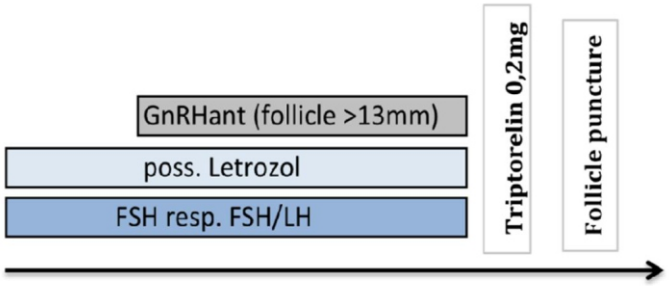

Figure 1. Scheme for ovarian cancer stimulation with the aim of oocyte cryopreservation in hormone receptor positive in breast cancer patients.

In contrast, commencing the treatment in the late follicle phase, an ovulation induction with HCG is performed if the sonographic examination reveals a follicle size >13mm. Subsequently, the stimulation is carried out following the "luteal phase scheme". Initiating the stimulation after ovulation has occurred, the stimulation is performed with FSH, FSH/LH or HMG introducing the antagonist after a new follicle reaches a size >13mm, following triggering ovulation by a GnRH agonist.

It is assumed that ovarian stimulation methods in patients suffering from hormone receptor-positive breast cancer could lead to hyperproliferation of tumor cells going along with supraphysiological serum concentrations of estrogen. In this situation stimulation protocols are complemented by aromatase inhibitors (off-label-use) like Letrozol.[23] Thereby, serum concentrations of estrogen during the treatment for fertility preservation could be reduced by half (also at agonist flair-up). As far as known, fetal outcome and pregnancy rates are unaffected by addition of aromatase inhibitors,[23-26] it seems to be unlikely that stimulation with gonadotrophins could have a negative effect on patients' prognosis, especially considering

the fact that the increase in the estrogen serum concentration during fertility preservation occurs over a period of approximately one week.

Further protocols are used for stimulation to retrieve oocytes such as double stimulation or progesterone primed ovarian stimulation.

D. Cryopreservation of ovarian tissue

A further method for fertility preservation is the ovarian tissue cryopreservation. The ovarian cortex is removed surgically and is cryopreserved afterwards. Upon completion of oncologic treatment and a recurrence and metastasis free interval of at least three years, the ovarian tissue can be thawed and transplanted back to the patient on the ovary or close to the ovary in the pelvic wall (see Figure 2). Using this technique the patients still have the opportunity to achieve spontaneous pregnancy. Up to now about 180 live births have been reported following ovarian tissue transplantation .[27]

During the operation, as much ovarian tissue as needed should be removed. A wedge excision including the ovarian stroma with a high number of dormant follicles and its subsequent cryopreservation is the most established method.[28] The advantage of this method is that it can be performed at any time during the menstrual cycle, so it does not require any delay in the initiation of oncologic treatmen

Greatest concern about this method is the fear of potential reimplantation of malignant cells. To reduce the risk, the removed ovarian tissue should be appropriately examined histologically to exclude malignant involvement. Due to the subtype of breast cancer, the risk for malignant cells in ovarian tissue has been reported to be low (ductal carcinoma) to medium (lobular carcinoma).[29,30]

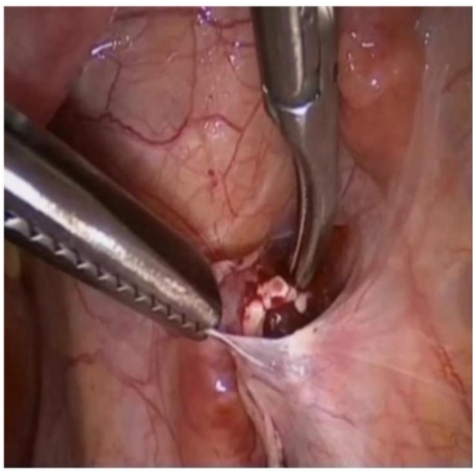

Figure 2. Laparoscopic transplantation of thawed ovarian tissue into a peritoneal pocket after completion of oncological therapy.

Previous data has showed that the use of cryopreserved ovarian tissue in everyday clinical practice is low, although this may increase in the next few years.[21] There are often several years between removal of ovarian tissue and transplantation.

The removal and subsequent transplantation of ovarian tissue can be regarded as the fertility preserving method of choice if the oncologic treatment has to be commenced immediately within few days.

In conclusion, fertility preservation is an emerging field in the treatment of breast cancer in young women to maintain reproductive health which carries a vital psychological significance for the self determination of the patient. For this reason, the possibilities of fertility preservation should be discussed with each woman of reproductive age diagnosed with breast cancer. The network FertiProtekt, for example, carried out 1.323 consultations in 2018 and 908 interventions for fertility preservation were done. Most women (About 40 percent of women) with the diagnosis of cancer who were sent to one of the cooperating oncofertility centers for fertility counseling suffered from breast cancer. Table 2 gives an overview of the value of existing fertility preserving methods available for breast cancer patients.

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Conflict of Interests

The authors declare no conflict of interest.

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Table 2. Value of the different fertility preserving methods being available for breast cancer patients

Method	Time frame	Pregnancy rate	Status
Ovarian tissue transplantation	immediately	20-25% (tissue activity rate 70-80%)	established
Cryopreservation of immature oocytes	immediately	10-15%	experimental
Cryopreservation of mature oocytes (MII)	10-14 days	10-15%	has to be optimized
Cryopreservation of pronucleus stage	10-14 days	25-35%	established, standard
Cryopreservation of embryos	10-14 days	25-35%	established, standard

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