Thieme

Fertility Preservation in Female Patients with Breast Cancer – a Current Overview

Fertilitätserhalt bei Patientinnen mit Mammakarzinom – eine aktuelle Übersicht

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ABSTRACT

Many premenopausal patients who develop breast cancer have not yet completed their family planning, so measures of fertility protection to preserve their fertile potential would be beneficial. Polychemotherapy causes irreversible damage to the ovarian follicles – irrespective of whether in a neoadjuvant or adjuvant setting – and this can sometimes result in permanent infertility. Depending on which cytostatic agents are used and on the age-related ovarian reserve of the woman, gonadotoxic risk must be classified as low, moderate or high. Options of fertility preservation include: a) cryopreservation of fertilised or unfertilised oocytes. After ovarian hyperstimulation, mature oocytes are retrieved by transvaginal follicle aspiration, after which they are cryopreserved, either unfertilised or on completion of IVF or ICSI treatment. During b) cryopreservation of ovarian tissue, about 50% of the ovarian cortex of one ovary is resected with the aid of a laparoscopic procedure and cryopreserved. The application of c) GnRH agonists as a medicinal therapy option is an attempt at endocrine ovarian suppression in order to protect oocytes, granulosa cells and theca cells from the cytotoxic effect of chemotherapy.

ZUSAMMENFASSUNG

Bei vielen prämenopausalen Patientinnen, die an einem Mammakarzinom erkranken, ist die Familienplanung noch nicht abgeschlossen, sodass für den Erhalt des fertilen Potenzials Maßnahmen der Fertilitätsprotektion sinnvoll sind. Durch eine Polychemotherapie – unabhängig ob im neoadjuvanten oder adjuvanten Setting – kommt es zu einer irreversiblen Schädigung der Follikel, was unter Umständen zu einer permanenten Infertilität führen kann. Abhängig von den verwendeten Zytostatika und der altersabhängigen Ovarialreserve der Frau, muss das gonadotoxische Risiko als niedrig, mittel oder hoch eingeschätzt werden. Möglichkeiten des Fertilitätserhalts sind: a) die Kryokonservierung von fertilisierten oder unfertilisierten Oozyten. Hierbei werden nach ovarieller Hyperstimulation reife Oozyten mittels transvaginaler Follikelaspiration gewonnen und im Anschluss entweder unfertilisiert oder nach erfolgter IVF- oder ICSI-Behandlung kryokonserviert. Bei b) der Kryokonservierung von Ovarialgewebe wird mithilfe eines laparoskopischen Eingriffs etwa 50% des Ovarkortex eines Ovars reseziert und kryokonserviert. Die Verwendung von c) GnRH-Agonisten als medikamentöse Therapieoption unternimmt den Versuch einer endokrinen Ovarialsuppression, um Oozyten, Granulosa- und Thekazellen vor dem zytotoxischen Einfluss der Chemotherapie zu schützen.

Introduction

The survival rate of cancer patients has been steadily rising over the past decades due to optimisation and efficiency of oncological therapy concepts [1].

Cancer is predominantly a disease of the older person, whereas adolescents and young adults are relatively rarely affected by it. In Germany, currently about 15 000 patients aged between 15 and 39 years are taken ill with cancer each year, with a total of 480 000 new cases [2]. Within this age range of under forties, breast cancer is the one most common form of cancer in Germany, with approx. 2500 new cases each year [2, 3]. In the age group of under 45-year-olds, the incidence in Germany from 2011–2012 was 120/100 000 [4]. Many of these women have not yet completed their family planning, due to, amongst other reasons, the rising age of the women when their first child is born [6].

In young breast cancer patients, tumour biology commonly shows an aggressive growth pattern and is associated with a poor prognosis [7]. For this reason, polychemotherapy – usually in a neoadjuvant setting – is an important therapy measure, particularly in young patients with breast cancer.

Focus is shifting to the long-term effects of oncological therapy, particularly in the light of the ever later realisation of the desire to have children. Premature ovarian failure (POF) is a common consequence of chemotherapy treatment. This cytotoxicity is reversible in organs with a high cell division rate, such as bone marrow, gastro-intestinal tract or thymus, for example. The ovaries, on the other hand, are damaged by chemotherapy to varying degrees because of their limited number of cells with no potential for replication or regeneration of the follicles [8, 9]. This can result in permanent infertility of the affected women, see ▶ **Tables 1** and **2**.

Premature Ovarian Failure

The effect of cytotoxic therapy on ovaries is explained, amongst other things, by the disturbance of steroid-producing granulosa cells and theca cells, resulting in destruction of the oocytes they enclose [10]. The histological correlate is a loss of follicular structures in the ovaries associated with fibrosis [11].

The degree of gonadotoxic effect of chemotherapy depends considerably on the substance used and the cumulative dose. Especially anthracyclines or alkylating agents, such as cyclophosphamide, are characterised by a high degree of cytotoxicity, as they do not have cell cycle specificity, unlike other cytostatic agents, and, in particular, have a cytotoxic effect particularly on non-proliferating cells [12]. Based on their gonadal toxicity risk, chemotherapeutic agents may be classified into various risk groups (▶ **Table 1**) [13]. In each case, the risk of persistent amenorrhoea after completion of chemotherapy is listed. ▶ **Table 2** shows amenorrhoea rates after chemotherapy, based on the examples of selected studies [14–16].

Cyclophosphamide is the best investigated chemotherapeutic agent and is the most discussed in connection with gonadal toxicity: There is a four-fold higher risk of developing premature ovarian failure as compared with other chemotherapeutic agents [17]. Furthermore, the patient's age plays an important role in the development and duration of ovarian failure: older women, who already have a physiological reduction of their primordial follicle pool, have a higher risk of developing infertility; in addition, cyclophosphamide already produces gonadal toxicity at lower doses than would be the case in younger women [18]. Other factors influencing chemotherapy-induced infertility include [19]:

- the individual ovarian reserve and pharmacokinetics with regard to metabolism,
- total dose,
- dose density,
- duration of treatment.

▶ **Table 1** Amenorrhoea rates after chemotherapy in premenopausal patients with breast cancer, overview, taken from [13].

Age (years)	Chemotherapy	Amenorrhoea rate (%)
> 40	6 × CMF, 6 × FEC, 6 × FAC	> 80 (high risk)
< 40	EC (dose dense)	
30–39	6 × CMF, 6 × FEC, 6 × FAC	20–80 (moderate risk)
> 40	4 × AC	
< 30	6 × CMF, 6 × FEC, 6 × FAC	< 20 (low risk)
< 40	4 × AC	

A = doxorubicin; C = cyclophosphamide; E = epirubicin; F = 5-fluorouracil; M = methotrexate

▶ **Table 2** Amenorrhoea rates after chemotherapy in premenopausal patients with breast cancer, selected studies [14–16].

Chemotherapy	Age (years)	Number of patients	Amenorrhoea rate (%)	Study
EC/Pac	mean age: 42	n = 80	46.6	Zhou, 2012
EC/Doc	< 35	n = 166	15	Fornier, 2005
TAC	premenopausal	n = 109	57.7	Martin, 2005
FAC	premenopausal	n = 409	52	Martin, 2005

EC = epirubicin, cyclophosphamide; Pac = paclitaxel; Doc = docetaxel; TAC = docetaxel, doxorubicin, cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide

A number of studies has dealt with establishing possible biomarkers for predicting chemotherapy-associated amenorrhoea in breast cancer patients [20–22]. In a multicentre, randomised study involving 124 premenopausal patients, Ruddy et al. [20] showed that anti-Mullerian hormone (AMH) levels measured before chemotherapy can serve as a biomarker for chemotherapy-associated amenorrhoea. Twelve months after completion of chemotherapy, 82% of the patients had amenorrhoea, with older age being the only significant marker (p = 0.0003). Eighteen months after chemotherapy and with an amenorrhoea rate still at 81%, both older age (OR 1.18, 95% CI 1.04–1.34, p = 0.008) and lower pre-chemotherapy AMH levels (OR 0.41, 95% CI 0.18–0.95, p = 0.04) were statistically significant predictors of amenorrhoea [20]. An increase of pre-chemotherapy AMH levels by 1 ng/ml would mean a 59% decrease in the risk for developing 18-month amenorrhoea. An increase in age by one year would result in an 18% higher probability of 18-month amenorrhoea [20].

Tamoxifen, given for the duration of at least five years as endocrine therapy for hormone receptor-positive breast cancer, is not associated with impairment of ovarian function [19]. Nevertheless, an age-related reduction of fertility must be assumed due to the duration of application of tamoxifen with its anti-endocrine effect. Pregnancy should be avoided during this time, if only because of the teratogenic properties of tamoxifen [23]. At the end of anti-endocrine therapy, the majority of the patients is perimenopausal to postmenopausal. For this reason, interruption of tamoxifen therapy may be considered together with the patient after about a two-year administration period in order first to fulfil the desire to have a child and then to complete tamoxifen treatment. This innovative approach is currently the subject of scientific reviews [24, 25].

The potential loss of fertility due to chemotherapy causes devastating emotional stress in many patients [26], commonly associated with episodes of depression, anxiety, grief, anger, relationship break-ups, and reduced quality of life in general [27, 28]. Accordingly, particular importance is attached to preserving ovarian function during and after chemotherapy, both with regard to fertility as well as maintaining healthy bone and cardiovascular systems.

Fertility Preservation Options

In May 2006, the network *Ferti*PROTEKT was founded in Heidelberg by a group of 40 university fertility physicians. After 10 years, the network now has the status of a registered society and has grown considerably in members. Fertility physicians and biologists of meanwhile over 100 university, as well as non-university, centres in Germany, Austria and Switzerland have combined forces to offer on a nationwide basis fertility preserving measures during chemotherapy and radiation therapy along the lines of uniform recommendations [29].

Cryopreservation of unfertilised and fertilised oocytes

If there is enough time for ovarian hyperstimulation before planned chemotherapy, mature oocytes can be harvested by transvaginal follicle aspiration. These can then be fertilised by IVF or ICSI treatment and cryopreserved in the pronuclear (2-pronuclear) stage. In Germany, only cryopreservation of fertilised oocytes is legally permitted, while in other countries embryos may also be preserved.

Stimulation can be initiated at any time, irrespective of the patient's cycle day ("random start"), and lasts about 14 days [30]. A stimulation protocol using an aromatase inhibitor (AI) in combination with gonadotropin administration has proven successful [31]. This results in lowering plasma oestradiol levels while at the same time inducing oestrogen production from androgens in the granulosa cells. Thus, both effects of the AI may be optimally utilised. On the one hand, measurable oestradiol (E2) levels in the blood are maximally suppressed, while on the other hand ovulation induction is supported [32]. Oktay et al. were able to show that, in the antagonist protocol, stimulation using FSH in combination with letrozole (third-generation AI) as compared with stimulation in the long agonist protocol resulted in a significant reduction of E2 levels (p < 0.001), with an unchanged number of harvested oocytes (p = 0.43) [32]. However, it must be pointed out that stimulation with letrozole is not recommended in every case, but only for hormone receptor-positive tumours. Furthermore, the patients must be informed about the off-label use of this stimulation protocol.

If the patient does not have a partner, then the oocytes are cryopreserved in an unfertilised state. This procedure should fundamentally be offered to every woman – irrespective of whether single, in a stable relationship or married – given the current high rates of separation and divorce. It must be ensured that the respective centre has at its disposal the appropriate possibility of cryopreservation.

With regard to cryopreservation, vitrification has particularly proven itself as an extremely fast process of freezing the oocytes in nitrogen (flash-freezing). With conventional methods, freezing is achieved significantly more slowly over several hours and carries a high level of risk of the formation of ice crystals. Cryopreserved fertilised oocytes have a high vitality of 73 to 95% after vitrification, similar to cryopreserved embryos or sperms, with a pregnancy rate of about 25% [33, 34].

In-vitro maturation

In-vitro maturation (IVM) is a relatively new extracorporeal technique of assisted reproductive medicine, which dispenses with controlled ovarian hyperstimulation, unlike classic IVF/ICSI, and therefore does not result in a delayed start to planned chemotherapy.

This technique involves harvesting immature oocytes from small antral follicles via transvaginal aspiration, if need be after a short stimulation with FSH and/or hCG. A high antral follicle count (AFC) is important here, so this method can only be used in a small subgroup.

This is followed by in-vitro maturation of the oocytes with subsequent fertilisation. In-vitro maturation of the oocytes is usually conducted over a period of 24 hours. There then follows an assessment of the stage of maturity and, if need be, fertilisation by conventional IVF or ICSI. Although accelerated in-vitro maturation could theoretically have negative effects, there has so far been no reports of an increase in malformation rates [36]. Disadvantages

of IVM as compared with conventional IVF or ICSI treatment include [36]:

- lower implantation and pregnancy rates per treatment cycle per embryo transfer,
- higher costs per achieved pregnancy,
- technically more difficult needle puncture with longer aspiration time,
- increased laboratory costs due to increased work volume,
- epigenetic and other foetal risks not entirely clarified.

In-vitro maturation is therefore still an experimental, non-standard procedure which so far almost no laboratory is providing.

Cryopreservation of ovarian tissue

Since its first successful use in Brussels in 2004, cryopreservation of ovarian tissue has established itself worldwide as an effective procedure [27]. Here, the first child was born after orthotopic, autologous transplantation of previously cryopreserved ovarian tissue and after spontaneous conception [39].

During cryopreservation of ovarian tissue, about 50% of the ovarian cortex of one ovary is resected by laparoscopy, prepared and preserved using cryoprotective agents. Cryopreservation of ovarian tissue is particularly suitable for younger patients, as their ovarian reserve and consequently their follicle density are very high. An upper age limit of between 35–37 years is recommended because up to this age range the majority of cases still has a sufficiently high ovarian follicle density. Before the procedure, the hormone status is examined from a blood sample and ultrasound examination of the uterus and the ovaries is performed.

Cryopreservation of ovarian tissue is particularly suitable when there is little time available before starting cytotoxic therapy: Whereas about two weeks must be planned for ovarian hyperstimulation with aspiration and cryopreservation of the oocytes, laparoscopy may be performed a few days before starting chemotherapy. The option of dispensing with hormonal stimulation, combined with a prompt conclusion of fertility protection, makes this method appear promising, especially in the group of breast cancer patients.

In the early days of establishing a method for re-transplantation of ovarian tissue, the attempt was made at heterotopic tissue transplantation, i.e. in the region of the forearm or in the abdominal wall [40]. Meanwhile, orthotopic re-implantation is usually preferred, i.e. in or at the residual ovary or in a peritoneal pocket in the region of the ovarian fossa. Resumption of endocrine function usually occurs within three to six months. Survival time of the tissue varies between a few months and several years [41, 42].

It should be noted that, particularly with breast cancer, there is – at least theoretically – a residual risk of re-induction of the cancer disease by persistent and, after re-implantation, reactivated micrometastases [33]. Particularly in early stages (I, II), re-transplantation of ovarian tissue is regarded as safe – malignant cells have been excluded both in histological as well as immune histological examinations of cryopreserved ovarian tissue [43, 44]. In the advanced stage (IV) on the other hand, the risk of reinduction of the cancer by ovarian metastases should at least be considered. In one patient, local recurrence on the side of the diseased breast about one year after re-transplantation of ovarian tissue has been reported. However, metastases were not detected in the ovary itself [45, 46]. This innovative procedure has been able to progressively establish itself in recent years and is meanwhile also being offered in Germany at selected centres [27].

Based on published cases and data submitted by the network *Ferti*PROTEKT, currently over 90 births worldwide have been documented [47, 48].

With this method, the live-birth rate percentage is 28.4% per patient, with simultaneously higher pregnancy rates [49]. Van der Ven reported a live-birth rate of 25%, with a pregnancy rate of over 30% [50]

Drug treatment – GnRH agonists

The rationale behind suppression of germ cell proliferation is to initiate cell cycle arrest with a limited treatment period using GnRH analogues, thus protecting the follicles from the gonadotoxic effect of chemotherapy. This concept is based on the observation that, with inactive gonads at a prepubertal age, fertility is less affected by chemotherapeutic agents than in the reproductive phase of life. At the start of treatment with GnRH agonists there is an initial release of gonadotropins ("flare-up" effect), lasting for about one week, so GnRH analogues should be administered the first time at least one week prior to the start of chemotherapy. Their use is on an off-label basis.

The benefit of GnRH analogues has been the subject of controversy for years. In a Cochrane analysis [52] based on the evaluation of four randomised studies from the years 1987 to 2007, the authors showed that patients profit from the use of GnRH analogues. Increased menstruation (RR 1.90, 95% CI 1.30–2.79) and ovulation rates (RR 2.70, 95% CI 1.52–4.79) were demonstrated after completion of chemotherapy [52]. A meta-analysis from 2011 [53], which included six studies until 2010, also found a protective effect from GnRH analogues on ovarian function.

POEMS (Prevention of Early Menopause Study), an international Phase 3 study by the Southwest Oncology Group (SWOG), examined the effect of goserelin on ovarian function during chemotherapy involving cyclophosphamide. Between 2004 and 2011, 257 patients were included in the study and followed-up for two years. The use of GnRH analogues was shown to be associated with a lower rate of premature ovarian failure ($p = 0.03$) in comparison with chemotherapy alone [54]. In addition, disease-free survival (DFS) and overall survival (OS) were examined, each over a period of four years, and shown to have experienced a positive effect from the addition of goserelin (DFS: 89 vs. 78%; OS: 92 vs. 82%, $p = 0.05$) [54].

Data obtained from the POEMS trial, however, should be assessed in a very critical light, because problems involving financing and recruiting resulted in a premature stop to the study. Furthermore, an excessively high drop-out rate also interferes with interpretation of the results. The study is therefore regarded as too "under-powered" for a reliable evaluation [55].

A meta-analysis from the year 2015 by Lambertini et al. [56] looked at 12 randomised studies involving a total of 1231 premenopausal breast cancer patients. Temporary suppression of ovarian function by GnRH analogues was associated with a lower risk of preterm ovarian failure (POF) (OR 0.36, 95% CI 0.23–0.57; $p < 0.001$) [56].

▶ **Table 3** Fertility preservation options in female patients with breast cancer [59].

Measure	Experimental vs. standard procedure	Ovarian stimulation (OS) required	Delayed start of chemotherapy	Surgical intervention	Preservation of ovarian function (OF)	Available in all centres	Comments
Cryopreservation of unfertilised oocytes	standard	yes	yes	yes	no	no	Duration of OS: 10–14 days
Cryopreservation of fertilised oocytes	standard	yes	yes	yes	no	no	Partner required
In-vitro maturation	experimental	no	no	yes	no	no	High AFC required, high costs, laborious procedure, practically no laboratory is currently offering this procedure
Cryopreservation of ovarian tissue	experimental	no	no	yes	yes	no	Not to be recommended at an advanced tumour stage, risk of micrometastases, no long-term data regarding OF
Ovarian suppression by GnRH analogues	experimental	no	no	no	yes	yes	Simple, favourable therapy, application before and during CT, few long-term data with regard to resumption and preservation of OF

AFC = antral follicle count; CT = chemotherapy; GnRH analogues = gonadotropin-releasing hormone analogues; OF = ovarian function; OS = ovarian stimulation

The PROMISE-GIM6 study is a multicentre, randomised Phase 3 study from 2015 [57]. Between 2003 and 2008, 281 patients were included in the study. The premenopausal patients were assigned to either the chemotherapy group (control group) or the chemotherapy + GnRH analogue (triptorelin) group. Primary endpoints were ovarian function, pregnancy rate and disease-free survival. Menstruation rates on completion of chemotherapy were reported to be 72.6% in the chemotherapy + triptorelin arm and 64% in the chemotherapy group (HR 1.28, 95% CI 0.98–1.68; p = 0.071). Five-year DFS was reported to be 80.5 and 83.7% for the chemotherapy + triptorelin arm and the chemotherapy group, respectively (HR 1.17, 95% CI 0.72–1.92 p = 0.519) [57]. In summary, the study reached the conclusion that GnRH analogues may be assumed to protect ovarian function while not affecting prognosis.

The authors Elgindy and co-workers reached a different result in 2015. In their report [58], ten randomised controlled studies, published between 1987 and 2015, were identified and assessed. The data of 907 patients were included in the meta-analysis, with 468 women having been additionally treated with a GnRH agonist during chemotherapy. No statistically significant differences were identified between those patients treated additionally with GnRH analogues and those treated with chemotherapy alone (68.4 vs. 59.9%). The patients did not benefit from the administration of GnRH analogues with regard to FSH levels (p = 0.27), nor anti-Mullerian hormone (p = 0.40), nor antral follicular count (p = 0.17) [58].

In the light of the contradictory statements regarding the efficacy of GnRH analogues, it is important to have a critical and detailed discussion with the patient [5].

▶ **Table 3** provides an overview of the above-mentioned options of fertility preservation.

Conclusions

1. All premenopausal patients who have not completed family planning should be informed about the options of fertility preservation before gonadotoxic chemotherapy.
2. Depending on tumour stage and tumour biology and possible time interval, the available measures should be discussed with the patient on an individual basis.
3. The various fertility-preserving measures may be combined.
4. Ovarian hyperstimulation may be started at any time, regardless of cycle day.
5. This applies to hormone receptor-positive, as well as hormone receptor-negative breast cancer in equal measure.
6. GnRH agonists still remain controversial, but should not be withheld from the patient.
7. Laparoscopic harvesting of ovarian cortex is a promising method which does not delay start of chemotherapy.

Conflict of Interest

The authors declare that they have no conflict of interest.

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