FertiPROTEKT – Network for Fertility Preservation
Techniques before Chemo- & Radiotherapy
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Introduction

Interest in fertility preservation techniques in young patients, predominantly oncology patients, has greatly increased in recent years, as these patients can be cured as a result of advances in oncological treatment.

The topicality of this subject had also been underlined by publications by the American Society for Reproductive Medicine Ethics Committee [1] and the American Society of Clinical Oncology [2].

Alongside the oncological indications for chemotherapy, patients can also require cytotoxic treatment for benign systemic diseases such as systemic lupus erythematosus (SLE).

After completion of oncological treatment, the fulfilment of the desire to conceive a child is a significant criterion for a patient’s quality of life. Approximately 70% of patients who have to be treated for a malignancy during the reproductive phase of their life say that they have a desire to conceive in the future after their illness [3, 4]. A web-based survey showed that only 51% of oncology patients had the feeling that their fears about their fertility were adequately perceived [5].

Advances in reproductive medicine have led to the development of new fertility preservation techniques, and oncologists, rheumatologists and specialists in reproductive medicine are required to present the appropriate fertility preservation options to patients and to incorporate them into their further treatment plans.

A survey of 26 German university hospitals conducted in December 2005 showed that fertility preservation methods were only performed at individual centres, and were only rudimentary in those centres.

In order to improve the care of young patients before chemotherapy, the situation led to the requirement for a network to be developed for the systematic establishment, optimization and coordination of fertility preservation techniques.

Establishment and Development of the FertiPROTEKT Network

By way of an invitation from Prof. M. von Wolff, Department of Gynaecological Endocrinology and Reproductive Medicine, Heidelberg University Women’s Hospital (=UFK) and Prof. Dr. Markus Montag, Department of Gynaecological Endocrinology and Reproductive Medicine at the UFK Bonn, a constitutional meeting of 30 university centres for reproductive medicine took place in Heidelberg in May 2006 to establish the FertiPROTEKT network. The purpose of the network is the pooling of expertise from oncologists and specialists in reproductive medicine.

At the launching meeting, the direction was set for the development of a national care structure and scientific compilation of treatment data.

From a network of 30 founding university centres in Germany and after integration into private Assisted Conception Centres in 2008, the network has developed into an establishment which now encompasses Germany, Austria and Switzerland with a total of 80 member centres. Hence, comprehensive counseling for patients prior to chemotherapy can now be alluded to in Germany. There are currently 3 and 6 member centres of the network in Austria and Switzerland respectively.

Membership in the FertiPROTEKT Network

To become a member of the FertiPROTEKT network, the centres must fulfil...
certain mandatory criteria permanently and demonstrably, so that a qualitative assured, consistent and patient orientated approach is guaranteed.

The membership requirements are stated in the network code, as shown in Table 1.

### Structure of the FertiPROTEKT Network

#### Management

During the development phase of the network, the coordinators Prof. M. von Wolff and Prof. M. Montag held the management positions of the network. At the workshop in Munich in March 2009, a management team consisting of 2 university coordinators (1 medical doctor, 1 biologist), as well as a 4-member steering committee (2 university medical doctors, 1 non-university medical doctor, 1 biologist) were elected in a ballot vote by the members of the centres who were present. The coordinators as well as the steering committee were each elected for 2 years. The organizer of the following meeting also belongs to the management team, however they only have an advisory function.

If decisions regarding the network have to be made, they are made by the coordinators only in consensus with the steering committee. Decisions are made by voting with absolute majority, and a wide consensus is generally aimed for.

The responsibilities of the coordinators and the steering committee are organisational and the preparation of workshops. If decisions have to be met which are of a significant structural relevance, they can only be made together with all FertiPROTEKT centres.

#### Workshops

After the constitutional workshop in Heidelberg in May 2006, all workshops initially took place at 6-monthly intervals in order to establish the fundamental structure of the network and to implement the fertility preservation methods in the individual centres. Since the meeting in Erlangen in January 2008, the workshops take place annually, and the decision as to in which centre the next workshops will take place is made together by all centres. The choice of key topics and the program planning of the next meeting rest with the management team.

#### Website

In 2007, websites with the addresses
- www.fertiprotekt.de
- www.fertiprotekt.ch
- www.fertiprotekt.at
- www.fertiprotekt.com were set up.

Since September 2008, the site is also available in English at www.fertiprotekt.eu and www.fertiprotekt.eu.

The website offers information for affected patients and interested doctors on the topics of the effects of chemotherapy/radiotherapy on fertility, treatment possibilities for the commonest illnesses and information about the network. The involved centres are listed in alphabetical order, so that patients seeking advice can find the contact address of a nearby centre. Only the centres involved have password access to the “Intranet” within the website. Figure 1 shows the annual number of “hits” on the German and English language websites.

#### Counselling and Treatment Documentation

With their participation in the network, the centres commit to document the counselling and treatment data of the presented patients. A national record of the consultations and treatments performed is therefore possible. The registry also provides information about complications occurring with fertility preservation methods [6] and the possible resulting postponement of oncological treatment.

#### Treatment Recommendations

One of the most important aims of the network was the development of treatment recommendations, both generally and for the individual fertility preservation methods and for the commonest illnesses.

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**Table 1. Compulsory membership requirements for participation in the network.**

1. Regular participation in workshops is compulsory. If a centre does not participate in a workshop on two consecutive occasions, it will be excluded.
2. The centre will be included in the address list on the FertiPROTEKT homepage and in return will promote the FertiPROTEKT network on its own homepage.
3. All fertility preservation techniques must be considered during patient counselling. If not all techniques are routinely offered in a centre, a cooperation with another centre must be arranged.
4. All counselled and treated patients must be correctly documented using the specified documentation forms. The documentation forms must be sent to the Heidelberg centre at a minimum of 8-monthly intervals.
5. The performance of fertility preservation treatments is not profit-oriented. The service is invoiced according to the Medical Fee Schedule (GOÄ), without a rate of increase.

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**Figure 1.** Annual number of “hits” on the FertiPROTEKT network German and English language websites.
The treatment recommendations were developed by study groups in outline before the meeting in Munich in March 2009 and, after discussion with the centres involved, were approved as the corporate treatment recommendations for the network.

These treatment recommendations are the basis of the counselling and treatment of patients within the framework of FertiPROTEKT and have since been published in open access [7].

Recommendations for Fertility Preservation Methods

The following fertility preservation methods are available:

Ovarian Stimulation and Cryopreservation of Unfertilised and Fertilised Oocytes

Indications & Requirements

- Postmenarchal women up to the age of 40 years with a sufficient ovarian reserve, who receive chemotherapy or another treatment which could lead to a significant chance of premature ovarian insufficiency or loss of ovarian function.
- The time until the start of chemotherapy is at least 2 weeks.

Success Rates

On average, 11.6 oocytes from 205 follicle punctures were collected in the FertiPROTEKT Network (STD: ± 7.7; 25% quartile: n = 6; 75%-quartile: n = 15). The fertilisation rate was 61.3%. If fertilisation was carried out on all oocytes, the following number of fertilised oocytes resulted in each age group: 18–25 years: 8.5 oocytes, 26–30 years: 7.3 oocytes, 31–35 years: 6.1 oocytes, 36–40 years: 5.1 oocytes [6, 8].

After cryopreservation of unfertilised oocytes, each thawed, surviving egg cell had an implantation potential of 6–8%. This applies to vitrification as well as to the new and adapted slow egg freezing protocols.

Efficacy

To assess the efficacy of hormonal stimulation in cancer patients before the start of chemotherapy, data from the German IVF Register (D·I·R) (www.deutsches-ivf-register.de) was consulted as a comparison. The D·I·R collects all the data mentioned from all German centres for reproductive medicine. With regard to the number of oocytes removed, if the D·I·R data are compared with our data analysis of stimulation treatment in cancer patients prior to chemotherapy, it can be seen that one to two more oocytes can be removed before chemotherapy per age group. The fertilisation rate in the D·I·R and in our collective was the same at around 60%.

Complication Rates

None of the patients developed an ovarian hyperstimulation syndrome (OHSS) as a result of stimulation, and none of the patients needed to have the start of their chemotherapy postponed beyond the time which had been planned for ovarian stimulation. 6 patients (2.9%) suffered one of the “relative” complications: two terminations of treatment due to no response, one where no puncture was performed, two failures to retrieve oocytes and one unsuccessful fertilisation. The complication rate was therefore 2.9% per stimulated patient.

Cryopreservation of Ovarian Tissue

Indications & Requirements

- Girls and women up to the age of 40 years, who receive chemotherapy or another treatment which could lead to a significant chance of premature ovarian insufficiency.
- With oncological disease: exclusion of ovarian metastases using appropriate diagnostic imaging.
- Exclusion of an oncological disease which is associated with a high risk of ovarian metastases (haematological neoplasias, metastatic breast cancer, ovarian cancer etc.)
- The time until the start of chemotherapy is at least 3 days.

Success Rates

15 births have been reported up to now. Spontaneous pregnancies occurred as well as pregnancies after IVF treatment. Successful teams [9] have achieved a pregnancy rate of ca. 30% per transplantation up to now, although the birth rate is lower. However, other teams report lower success rates, so it can be assumed that the success depends on the correct indication for cryopreservation, the age of the patient, the freezing technique and the transplantation technique.

A maximum age limit of ca. 35–37 years is recommended for the cryopreservation of ovarian tissue [10].

Complication Rates

Between 2007–2009 there have been 500 removals of ovarian tissue for cryopreservation performed, mostly laparoscopic, perioperative complications occurred in only 0.4% [6].

GnRH-Agonists (GnRHa)

Indication

Postmenarchal women up to the age of 40 years, who receive chemotherapy or another treatment which could lead to a significant chance of premature ovarian insufficiency.

As a definitive proof of efficacy is not yet available, other techniques should also be considered in addition to drug treatment.

Success Rates of GnRHa

12 studies carried out between 1966–2008 showed that out of 234 patients who received chemotherapy, 59% of cases had premature ovarian failure (POF) vs. 9% after a combination of chemotherapy with a GnRHa (n = 345) [11]. A summary of 9 studies (1980–2008) confirmed these results with a POF rate of 55.5% vs. 11.1% (n = 189 vs n = 225) [12].

In 2009 and 2010 three metaanalyses were published addressing the co-treatment GnRHa during chemotherapy to reduce ovarian damage [13–15]. Clowse et al. [13], 2009 and Ben-Aharon et al. [14], 2010 included 8 respectively 16 studies, including those with retrospective controls. Clowse et al [13] revealed that GnRHa are effective in preserving ovarian function (RR 1.68) and Ben-Aharon et al. [14] revealed that GnRHa are effective in reducing amenorrhoea (RR 0.26). Bedaiwy et al. [15], 2010 only included prospective randomized studies (n = 7) with 173 patients receiving GnRHa and 167 control patients. They calculated an odds ratio of 3.5 favouring the use of GnRHa.
On the whole, the evidence that GnRHa have a protective effect on the ovaries is becoming more established. Nevertheless, final confirmation is still awaited.

### Transposition of the Ovaries

**Indications**

Radiotherapy to the pelvis, which would lead to a significant chance of premature ovarian insufficiency.

Radiotherapy with 2 Gray leads to a loss of ca. 50% of the primordial follicles [16]. The chance of premature ovarian insufficiency occurring in women aged ≥20 years is almost 100% if they receive radiotherapy with 15 Gray [17].

**Success Rates**

According to the published literature, there is a success rate of up to 85% with this technique in patients with regular ovulatory cycles, and also in patients under the age of 40 after radiotherapy [18].

**Combination of the Techniques**

Fertility preservation procedures can be combined to increase their efficacy.

Ovarian tissue can be removed laparoscopically, and ovarian stimulation can be started ca. 1–2 days later [19]. The chance of pregnancy is almost doubled with this combination. Use of the luteal phase stimulation protocol is recommended if the stimulation is started after the 5th days of the cycle [20]. Additional administration of an aromatase inhibitor should be considered if breast cancer is present [21]. Short acting GnRHa are used for ovulation induction [22], which can be combined with a GnRHa depot. Chemotherapy can be started 1–2 days after follicle aspiration.

Starting chemotherapy before recovery of the ovaries after stimulation did not lead to more damage to the ovaries in an animal study [23].

In case of radiation of the pelvis, ovarian transposition can be combined with the removal of ovarian tissue for cryopreservation.

The decision for one or a combination of several of these techniques depends on the tumour characteristics, the planned oncological treatment regimen, the available time frame and the patient’s wishes. Treatment possibilities for the common diseases breast cancer, lymphoma and borderline ovarian tumours are specified here.

### Fertility Preservation Techniques in Breast Cancer, Hodgkin’s Lymphoma and Borderline Ovarian Tumours

#### Breast Cancer

**Risk of Treatment-Induced Amenorrhoea**

The risk of chemotherapy-induced amenorrhoea can only be roughly estimated because of the limited data available. Table 2 summarises the available studies and allows an approximate, age-dependent estimation of the risk. There is insufficient data for a risk calculation for taxanes, monoclonal antibodies, Avastin® (bevacizumab), lapatinib, Herceptin® (trastuzumab) and Gemzar® (gencitabine).

In the adjuvant situation, i.e., after tumour removal, the time from diagnosis to the start of chemotherapy is usually ≥2 weeks, therefore all available methods of fertility preservation can be offered in theory. In the neoadjuvant situation, ovarian stimulation should rather not be performed, as the tumour is still present during stimulation.

There is insufficient data about the risk associated with hormonal stimulation and receptor positive breast cancer. There is a theoretical risk of tumour progression with increased estrogen levels. However, one argument against this is that patients who do not undergo fertility preservation treatments maintain their menstrual cycles until chemotherapy, and therefore continue to have an endogenous estrogen synthesis. Furthermore,
a metaanalysis of 14 studies, which involved 1244 women, who became pregnant after recovering from breast cancer, did not show an increased risk of relapse for these women [25].

As the risk of relapse is still unclear, ovarian stimulation in a patient with receptor positive breast cancer must be discussed in detail with the patient after a careful risk-benefit analysis with the responsible oncologists.

Alternatively, the stimulation treatment can be combined with aromatase inhibitors [21]. The estrogen levels increase much less with this treatment. An increased risk of breast cancer relapse has not been found up to now in 79 patients who underwent this treatment [25]. If there are no concerns about giving ovarian stimulation, is can be combined with cryopreservation of ovarian tissue [19].

Treatment with a GnRHa should be possible without risk in receptor negative breast cancer patients. If receptor-positive breast cancer is present, is cannot be ruled out that the low estradiol values present under GnRHa treatment could lead to a reduced tumour cell sensitivity to the chemotherapy. However data concerning this theory is still lacking. As a result of this, GnRHa treatment in a patient with receptor-positive breast cancer must be discussed in detail with the patient after a careful risk-benefit analysis with the responsible oncologists.

Hodgkin’s Lymphoma

Risk of Treatment-Induced Amenorrhoea

The risk of chemotherapy-induced amenorrhoea can only be roughly estimated because of the limited data available. Table 3 allows an approximate, age-dependent estimation of the risk.

Fertility Protection Options

Possible fertility preservation methods are shown in Figure 3. Only treatments which are currently carried out by the German Hodgkin’s Study Group [28] are listed.

The risk of damage to the gonads with treatment according to the ABVD-regimen is low, and in such a case, fertility preservation techniques are not usually necessary.

If the patient is undergoing treatment according to the BEACOPP or BEACOPP-escalated regimen, an individual and age-related risk-benefit analysis should be carried out with the oncologists and the patient, and fertility preservation treatment should be started if necessary.

If ovarian tissue is to be cryoconserved and the patient has a mediastinal tumour, the increased anaesthesia risk should be taken into consideration. All forms of fertility preservation methods are otherwise possible, alone or in combination, in a time frame of ≥ 2 weeks.

Borderline Ovarian Tumours

In the case of unilateral disease and a desire to conceive, a macroscopically inconspicuous contralateral ovary with tube and uterus can be preserved; the advantage of adjuvant postoperative chemotherapy has not yet been demonstrated in prospective randomised studies. Chemotherapy comparable with the standard for invasive ovarian cancer is only recommended by the various centres for advanced stage and postoperative tumour residue or invasive implants [29].

Fertility Preservation Possibilities

Ovarian stimulation and cryoconservation of oocytes/pronuclear stage:

According to an analysis by the “Task Force for Fertility Preservation of the European Society of Gynaecological Oncology” (ESGO), ovarian stimulation to retrieve egg cells in patients who have undergone fertility perforation treatment appears to be associated with a significantly increased risk of relapse compared to a historic control group (OR 1.97,
Conclusions
A comprehensive tri-nation care structure for advising and treating young patients prior to cytotoxic treatment has arisen from the FertiPROTEKT network. The expertise from oncologists, specialists in reproductive medicine and reproductive biologists is combined to advise affected patients on the possible treatment options available to them and to integrate these into the total treatment concept.

Conflict of Interest
No potential conflict of interest to this article was reported.

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