Fertility Protection in Women exposed to Chemo- and Radiotherapy

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Summary

Increasing survival rates in cancer and the growing interest in life quality after cancer therapy has put fertility protection into the focus of attention. In many cancer therapies such as radiation of the pelvis, high dosage chemotherapy in hodgkin disease and breast cancer, bone marrow transplantation and others, the risk of developing secondary amenorrhoea and very early premature ovarian failure can reach 50% and more. Therefore, all young patients up to 35-40 years of age receiving cytotoxic therapies should be counselled by experienced specialists in reproductive medicine in an interdisciplinary setting. The patients can be offered cryopreservation of fertilized and unfertilized oocytes, cryopreservation of ovarian tissue and possibly GnRH-analogues. As the choice of the ideal technique is very complex and as some of the techniques are still experimental, counselling can only offered by trained specialists. The network FertiPROTEKT has been established in 2006 to offer profound information about this topic to patients and doctors to optimize all available fertility preserving techniques and to set up a network of specialized centres that offer nationwide counselling of patients. A list of the trained centres and comprehensive information about this topic can be found on the homepage of the network (www.fertiprotekt.de).

Introduction

Fertility protection techniques have becoming increasingly important during cytotoxic treatments due to the increased survival rates of patients who suffer from oncological diseases, to new developments in reproductive medicine and to the increased awareness of the quality of life after oncological illness. However, the fields of indication and fundamental knowledge (such as knowledge on the ovarian toxicity of the various types of chemotherapy) on many of the fertility protection techniques available are still largely inadequate, and further clinical and scientific evaluation is required.

The following article provides a critical illustration of the possibilities of fertility protection and their indication. The description is based on the experience and recommendations of the FertiPROTEKT network (www.fertiprotekt.de) and is supplemented by network data.

FertiPROTEKT

The FertiPROTEKT network was founded in 2006 in Heidelberg. It is coordinated by the physician and author of this article, and a biologist, associate professor Dr. Markus Montag, Dept. of Gynecological Endocrinology and Reproductive Medicine, Bonn. The aim of the network is to implement centers in Germany that are competent in the provision of fertility protective methods, nationwide. As the measures available are only carried out in very few centers and there has been hardly any clinical or scientific evaluation, many training courses are held for the personnel from the cooperating centers. A homepage for physicians and patients has been installed (www.fertiprotekt.de) with which all network centers are linked. Furthermore, since 2007 all counseling and treatments have been documented (Fig. 1, 2) and reported to a central registry. These measures enable transparent quality control, which guarantees the great competence of the roughly 45 centers listed on the homepage. Patients should therefore only be referred to centers listed on the homepage for counseling on fertility protection methods, in order to benefit from optimal individual treatment according to the guidelines of the network (Fig. 3).

As reproductive medicine is an interface for the various specialist disciplines, including specialist fields of oncology, there is intensive cooperation between the network and other professional associations, such as the German Hodgkin Study Group, the German Leukemia Network, and German Cancer Aid, amongst others.

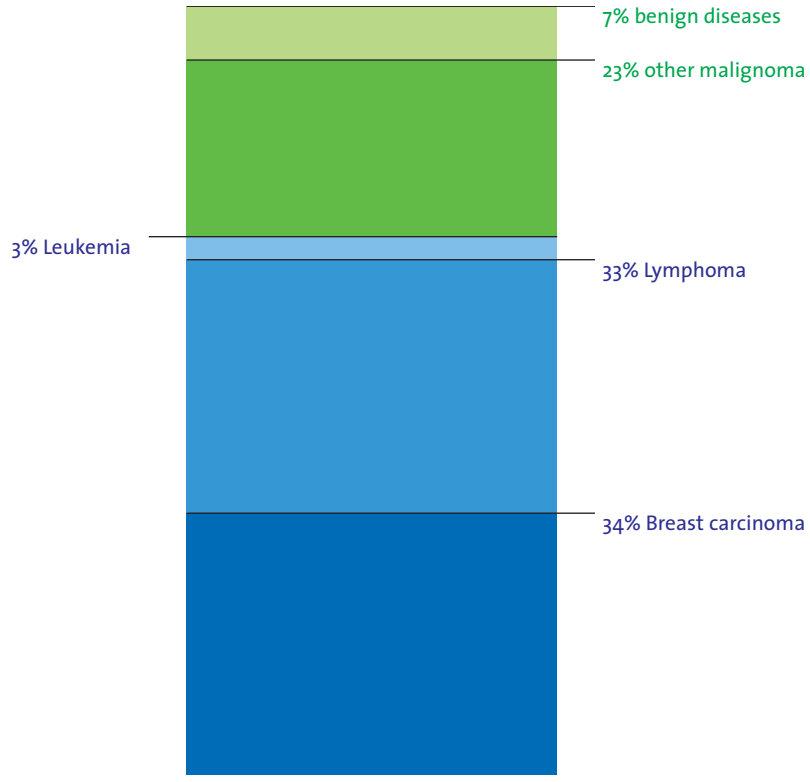

Figure 1: In 2007, counseling on fertility protection measures was provided at the network centers of FertiPROTEKT for the following clinical pictures

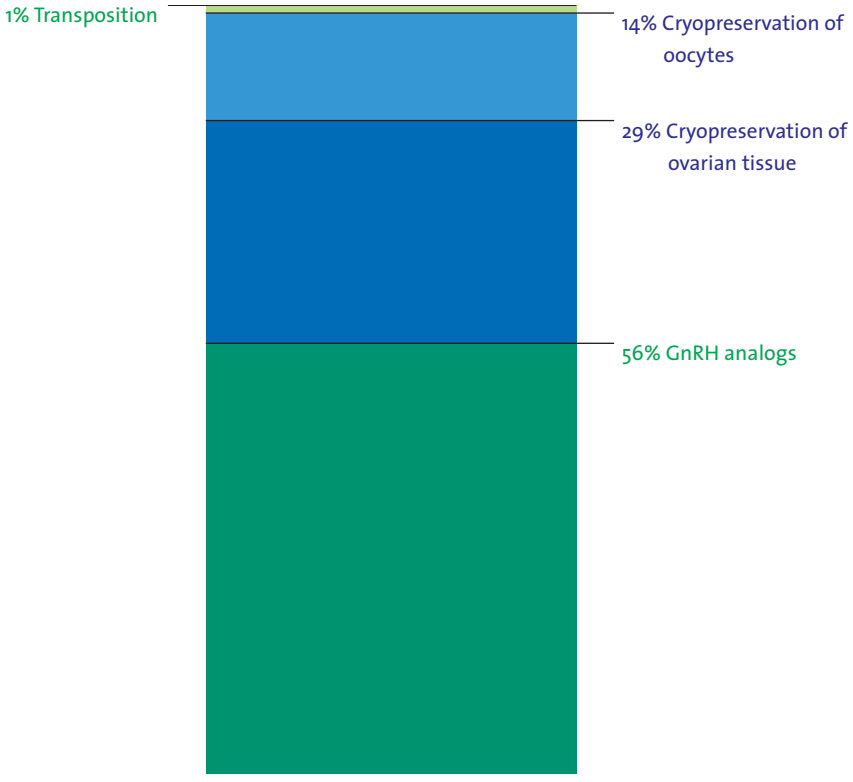

Figure 2: Fertility protection treatments, which were carried out at the network centers of FertiPROTEKT in 2007

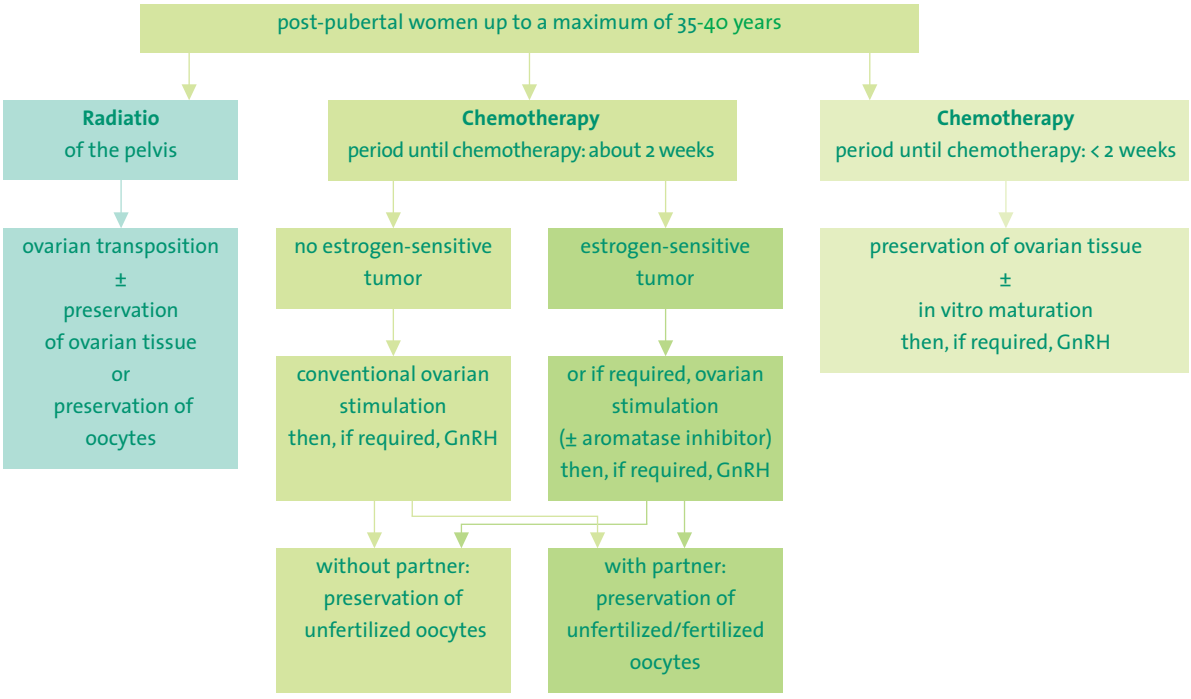

Figure 3: Present model for the performance of fertility protection techniques, according to the recommendations of the FertiPROTEKT network

Fundamentals of ovarian function

The ovary is a uniquely complex organ that unites somatic and germ cells in the follicles. In contrast with the testicles, female germ cells are present from birth onwards as a pool of one to two million primordial follicles, which cannot be renewed by stem cells and can therefore, not be regenerated after destruction due to cytotoxic treatment. However, current studies have thrown a shadow of doubt on this formerly accepted idea (Johnson et al. 2004), as it has been shown that in mice, proliferative stem cells were shown to cause new oocyte growth.

At the beginning of puberty, primary and secondary follicles develop continuously from the many primordial follicles. Anti-Müllerian hormone (AMH), increasingly produced in the granulosa cells, prevents the recruitment of too great a number of primordial follicles (Gruijters et al. 2003). Under the influence of the follicle-stimulating hormone (FSH), sonographically visible antral tertiary follicles develop cyclically from the small pool of preantral secondary follicles. The recruitment of several ripe tertiary follicles is prevented by the secretion of inhibin from the granulosa cells (Welt et al. 2002). Due to the significance of AMH, inhibin B and FSH in follicle genesis, these parameters were established as markers of ovarian reserve. Taking these parameters, as well as the number of sonographically determinable antral follicles and the relatively elaborate clomifene stimulation test into account, (Scott et al. 1995; Bukmann et al. 2001), the ovarian reserve can be estimated after cancer treatment. However, such estimations are only of limited value in the realization of prospective pregnancies; pregnancies should therefore generally not be delayed for too long.

While the number of primordial follicles decreases with age, the probability of amenorrhea due to cytotoxic therapy increases with age. Because of this, fertility protection measures can be dispensed with before cancer treatment in very young patients, but it is imperative that women of about 35 years of age consider such therapy.

Influence of cytotoxic treatment on uterine function and the course of pregnancy

If a patient becomes pregnant after cytotoxic treatment, the question arises as to the resulting degree of risk of miscarriage or premature birth.

Irradiation of the pelvis, particularly in prepubertal girls, reduces the volume of the uterus and the thickness of the endometrium (Bath et al. 1999).

The probability of a miscarriage appears to depend on the dose of radiation administered. A dose below 10 Gy after chemotherapy and irradiation of the whole body did not lead to miscarriage in five patients (Sanders et al. 1996). Radiation with 10-14 Gy, however, lead to an abort in six out of 16 pregnancies (38 %) and irradiation with 20-35 Gy, due to Wilms tumors, in nine out of 40 pregnancies (22 %) (Hawkins et al.1989). The risk of premature birth also increases after radiotherapy. Five out of eight pregnancies were ended prematurely after chemotherapy and whole-body radiation (Sanders et al. 1996). After radiotherapy of a Wilms tumor, the weight of the children born was 300 gm less on average than in unirradiated controls (Hawkins et al. 1989). Miscarriage and premature birth are thought to result from reduced elasticity of the uterus due to fibrosis and damage to the uterine vessels caused by irradiation.

There would appear to be no increase in the risk of miscarriage or premature birth after chemotherapy, in contrast with radiotherapy (Sanders et al. 1996).

Pregnancy – an unfavorable factor in tumor prognosis?

When considering the possibilities of fertility preservation after cytotoxic treatment, the risks of tumor recurrence due to pregnancy should also be critically evaluated. Such an evaluation is, however, extremely limited, as it is based on only a few studies with limited case numbers.

Most of the data refer to recurrent tumors after pregnancy following treatment of breast carcinoma as, according to several studies, about 5 % of women become pregnant after suffering from breast cancer (Sankila et al. 1994; Kroman et al. 1997; Velentgas et al. 1999). Theoretically, it would be most likely to expect a worse prognosis in the case of hormone receptor-positive breast carcinoma, due to their hormone dependency. In four studies on 91, 173, 53 and 438 patients after delivery, status post breast carcinoma, the prognosis was not worsened (Sankila et al. 1994; Kroman et al. 1997; Velentgas et al. 1999; Mueller et al. 2003).

However, when evaluating these encouraging figures, it should be taken into consideration that the patient collective was not very large, that there was no detailed evaluation for women with hormone receptor-positive tumor tissue, and that recurrence, even if it appears to be less frequent in pregnant women, takes on another ethical dimension for young mothers.

Significance of fertility protection measures in gynecology

In the field of gynecological oncology, women up to 35 years of age become ill, in decreasing order of frequency, from breast carcinoma, cervix carcinoma, ovarian carcinoma, and corpus carcinoma. Cervix carcinoma and corpus carcinoma play hardly any role in fertility protection treatments, as normally hysterectomy is performed and oocyte donation is not allowed in Germany. Ovarian carcinomas are also of less relevance, as ovarian carcinoma call for immediate operative intervention, usually in the form of bilateral adenectomy, and the prognosis is usually unfavorable. In the case of unilateral borderline tumors, it is often recommended that young mothers quickly fulfill their desire for a child, so that treatment can be completed by hysterectomy and bilateral adenectomy. In the case of subfertility, besides spontaneous conception, quickly performed in vitro fertilization (IVF) could be considered. Cryopreservation of ovarian tissue does not make much sense with a borderline tumor, as on the one hand, hysterectomy is often recommended, and on the other, a purely experimental xenotransplantation to obtain oocytes would be necessary.

Breast cancer is the most relevant oncological illness in which meaningful use can be made of fertility protection measures. According to calculations based on the Saarland cancer registry, every year about 440 patients up to the age of 34 become ill with breast cancer (von Wolff et al. 2007). Although this figure should be slightly upwardly corrected, as not all cancer cases are registered, it gives a realistic idea of the number of patients from the field of gynecological oncology that could benefit from counseling on fertility protection measures. About one third of all patients counseled by the FertiPROTEKT network have breast carcinoma (see Fig. 1). As chemotherapy leads to amenorrhea in up to 50 % of patients (Oktay et al. 2004), such counseling is justified because of the very high 5-year survival rate. However, about 50 % of all young women with breast carcinoma are hormone receptor-positive; therefore, the stimulation with gonadotropin and extraction of oocytes favored by FertiPROTEKT should only be carried out with caution. Stimulation with gonadotropins and simultaneous doses of aromatase inhibitors to lower the peripheral estrogen level should therefore be considered.

Significance of fertility protection measures in internal medicine

In the field of internal medicine, one differentiates between hematooncological illnesses and other internal oncological diseases that require ovarian toxic cytotoxic treatment. According to the Saarland Cancer Registry, the former occur in about 311 patients and the latter in about 180 patients per year (von Wolff et al. 2007). As in breast cancer, these figures should be corrected slightly upward, due to incomplete registration with the cancer registry. However, these data reflect the realistic number of patients from the field of internal medicine that come into question for counseling on fertility protection (see Fig. 1).

Patients with leukemia constitute a special category. Due to the fulminant development of the disease, these women are usually treated immediately with chemotherapy. This means that ovarian stimulation and the removal of oocytes is not possible before chemotherapy. Fertility protective measures, such as administration of GnRH analogs and cryopreservation of the ovarian cortex, cannot be performed until after induction chemotherapy. The removal of oocytes after induction chemotherapy is conceivable, but as no reliable data are available on the rate of potential deformities, such procedure can only be undertaken with the greatest caution, and only after thorough counseling of the patient.

The significance of fertility protection measures in pediatrics

Malignoma rarely occur in the second decade of life. According to the German children's cancer registry, which is almost complete, between the ages of 12-14 years about 79 such carcinoma are diagnosed that require counseling/therapy for ovarian-toxicity, as calculated by the author (von Wolff et al. 2007). Between the ages of 15-17 years probably a similar number of malignoma are diagnosed. Therefore, one can expect the number of illnesses in post-menarche girls up to the age of 17 years in Germany to be about 150-200 per year. The 5-year survival rate is very high in girls, making counseling on fertility protection methods expedient. However, the retrieval of oocytes before menarche is not possible, and any discussions with the girl and the parents must be conducted with great sensitivity. Close cooperation with pediatricians is also necessary, as many chemotherapies are only to a certain extent ovarian-toxic in childhood, and due to the large reserve of primordial follicles, only the ovaries of a small percentage of girls become insufficient due to cytotoxic treatment.

Fertility preservation surgery

Fertility preservation fertility is divided into two sections: surgery to preserve reproductive organs affected by tumors, and operations that protect the genitals from damage due to radiation. If a tumor affects a female reproductive organ and the organ is to be saved by surgical intervention, due to the very limited amount of data available it is necessary to assess the risks and benefits and patients must be thoroughly counseled. Only limited data is available on the following procedures: unilateral adenectomy with malignant germ cell tumors, borderline tumors, early stages of ovarian carcinoma (Ayhan et al. 2003), gestagen treatment of corpus carcinoma in stage FIGO Ia and low degree of proliferation (Gotlieb et al. 2003), and trachelectomy with cervix carcinoma (Bernardini et al. 2003). 500 operations and 100 resulting live births have taken place since the first trachelectomy was performed in 1994. As cervix carcinoma mainly infiltrate the parametria, the cervix, the parametria, the upper vaginal cuff, as well as the pelvic lymph nodes are removed. The technique is performed with FIGO IA1 to IB1 tumors. The rate of recurrence is 5 %, similar to that of a Wertheim-Meigs operation, whereby the prognosis appears to be worse with tumors > 2 cm. If pregnancy occurs, the rate of premature birth is relatively high, about 60 % of the pregnancies end prematurely (Beiner et al. 2007). If the small pelvis is to be irradiated, an ovarian transposition can be carried out to protect the ovaries. One or both of the ovaries are separated from the uterus and, usually after preparation of the stem of the vessel, are moved towards the diaphragm. In a small study, it was shown that the radiation dose could be lowered to less than 9 Gy when ovarian transposition was performed; only two out of 18 women in the study developed amenorrhea (Thibaud et al. 1992).

However, this data should not disguise the fact that even far lower doses of radiation cause damage to the ovaries; this does not immediately become apparent as amenorrhea, but appears later in the form of premature ovarian failure. Wallace and coworkers (2003) calculated that radiation doses of > 2 Gy destroy half of the oocytes. Disadvantages of transposition, which can also be performed by laparoscope to spare the vessels, are the necessary operative intervention and the fact that very often (about 25 %) patients develop ovarian cysts (Chambers et al. 1990). The risk of ovarian ischemia, which leads to amenorrhea in 4 % of all patients independent of radiotherapy (Chambers et al. 1990), is of limited relevance in comparison to the benefits of this treatment. It is, however, relevant that during transposition of the ovaries, which can reach as far as the diaphragm in individual cases, dissection of the tubes may be necessary. In this case, pregnancy at a later stage can only later be achieved by in vitro fertilization. At present, the FertiPROTEKT network is assessing an operative technique, whereby transposition can be performed without transection of the tubes. The ovary is returned to its original position after radiotherapy.

Cryopreservation of fertilized oocytes

If the patient is in a steady relationship, oocytes can be retrieved after ovarian stimulation that can be fertilized and cryopreserved by IVF or intracytoplasmatic sperm injection (ICSI) (see Fig. 3, Tab. 1). Thanks to the introduction of a new stimulation schema by the FertiPROTEKT Network, such a procedure only lasts about two weeks.

The advantage of these treatments lies in the high pregnancy rate that can be achieved with cryopreserved, fertilized oocytes. If for instance, ten pronuclear stage oocytes are cryopreserved, the cumulative pregnancy rate is about 50 %. However, the risk of this method lies exactly here, as it is not always possible to retrieve enough oocytes from all women. Ovarian function parameters are therefore used to attempt to determine whether this method is suitable for individual patients, or whether probably only few oocytes can be obtained, before stimulation treatment is commenced.

The risk of stimulation treatment in the case of receptor-positive breast carcinoma is a frequent point of discussion. As patients maintain their menstrual cycle before chemotherapy and estrogen levels are therefore principally increased, one would not expect stimulation treatment, which only lasts for a few days, to lead to tumor progression. There are, however, no data available to prove this assumption.

Cryopreservation of unfertilized oocytes

If the patient has no steady partner, the oocytes must be cryopreserved in an unfertilized state (see Fig. 3, 4 and Tab. 1). The cryopreservation of unfertilized oocytes has only become possible in the past few years, whereby, it is still unclear whether the oocytes should be frozen by vitrification (Isachenko et al. 2005) or by »slow freezing« (Borini et al. 2006). In vitrification, the oocytes are frozen ultra-rapidly by contact with liquid nitrogen, whereby no ice crystals develop to damage the oocytes. In the meantime, the effectiveness of cryopreservation of unfertilized oocytes appears to be similar to the cryopreservation of fertilized oocytes, although as yet, there are not sufficient data for evaluation.

The long-term aim of the FertiPROTEKT network is to preserve also unfertilized oocytes of patients in a steady relationship, in order to reduce the patient's dependency continuity of the relationship.

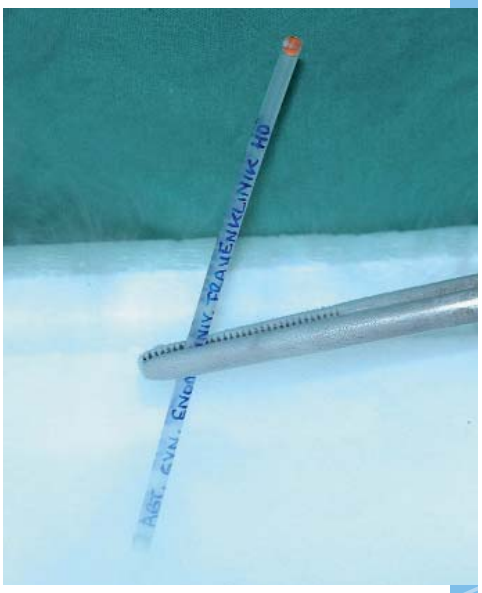

Figure 4: Vitrification, i.e. ultra-rapid freezing of so-called »straws« in liquid nitrogen, is one of the new cryopreservation techniques, which makes effective cryopreservation of unfertilized oocytes possible.

Cryopreservation of ovarian tissue

The first pregnancy following cryopreservation and re-transplantation of ovarian tissue was in 2004 (Donnez et al. 2004). Donnez and coworkers performed an orthotopic transplantation of ovarian tissue near to the ovary. In contrast with heterotopic transplantation (for instance on the forearm) (Oktay et al. 2004), it appears that this technique is becoming well established, as the conditions for follicle genesis appear to be better in the abdomen. In the meantime, several children have been born after transplantation and further pregnancies have been reported. This method is therefore a realistic alternative to cryopreservation of fertilized and unfertilized oocytes and can be used for girls in pre-puberty (see Fig. 3, 5 and Tab. 1). However, the present success should not disguise the fact that the available data is still very limited, and that a large quantity of ovarian tissue was transplanted, usually the equivalent of half an ovary. Hence, the tissue of at least 50 % of an ovary, 100 % would be even better, must be removed and cryopreserved to achieve a 50 % chance of pregnancy at the most, after retransplantation of the tissue.

Figure 5: Cryopreservation of ovarian tissue is an experimental technique with high development potential

Table 1: Estimated effectiveness of the various techniques of fertility protection. The still very limited chances of success in fertility protection in women require, as the case may be, a combination of different techniques.

Technique	Time required*	Achievable rates of pregnancy**
Cryopreservation of fertilized oocytes	About 2 weeks	About 20 % to a maximum of 50 %
Cryopreservation of unfertilized oocytes	About 2 weeks	About 20 % to a maximum of 50 %
Cryopreservation of ovarian tissue	A few days	Still unclear; with larger quantities of tissue, as the case may be, similar to cryopreservation of oocytes
GnRH analogs	A few days	The effect is still unclear
Transposition of the ovaries	A few days	Cannot be estimated

* The period required by each specific technique indicates the time from the patient's first visit to the commencement of cytotoxic treatment.

** The achievable, cumulative rates of pregnancy are dependent on the number of oocytes retrieved, the quantity of ovarian tissue removed, as well as the age of the patient. The rates of pregnancy are only a rough estimate made by the author, based on the experience of the FertiPROTEKT network and the data presently available.

The preservation of large quantities of ovarian tissue is necessary because most of the tissue degenerates during cryopreservation and transplantation. Even after successful transplantation of a large quantity of ovarian tissue, the patient will only have a small ovarian reserve, similar to during the premenopause, which is used up after some months, or at the most a few years. Therefore, only the tissue of young women up to 35 years of age should be conserved, and only if there is a high risk of amenorrhea-induced chemotherapy. For psychological reasons, cryopreservation of just a small amount of ovarian tissue should not be undertaken.

The risk of transfer of micrometastases via retransplantation has often been discussed. Although there are still too little data on the likelihood of this, the risk would appear to be very low in breast cancer and Hodgkin lymphoma if the tissue is carefully examined, in contrast with leukemia. As the FertiPROTEKT network is aware of this problem, all centers perform histological examinations on part of the ovarian tissue. Other tissue must be reserved for further tests before retransplantation. This tissue can be transplanted to immune deficient naked mice, for instance, to exclude contamination with micrometastases.

GnRH analogs

Despite the encouraging progress in cryopreservation of oocytes and ovarian tissue, an effective medicative ovarian protection during chemotherapy would be an ideal method of maintaining fertility (see Fig. 3, Tab. 1). First experiments using high doses of gestagen have been superseded by GnRH analogs, which have been successfully tested on animals and in the meantime, on the human system. Such treatment would mean far less damage to the ovaries of prepubertal girls during chemotherapy. As resting ovaries, i.e. ovaries that have not been stimulated by FSH, are much less susceptible to cytotoxic chemotherapy, the release of FSH is inhibited in post-pubertal women with the aid of GnRH analogs. However, there is international controversy over this type of treatment: on the one hand, the continuous recruitment of primary and secondary follicles is not controlled by FSH therapy, and on the other, although some clinical data support the efficacy of GnRH analogs (Blumenfeld et al. 2002) other data are contradictory (Waxmann et al. 1987; Raddatz et al. 2007). It will certainly take some years until a meta-analysis provides clarifies whether or not GnRH analogs are effective. As an overall trend towards effectiveness has been identified, this medication is nevertheless often administered to young women, particularly if other therapeutic alternatives of fertility preservation are lacking.

If GnRH analogs are indicated during chemotherapy, they should be administered one to two weeks before chemotherapy is commenced, as the initial release of FSH (»flare up«) can lead to undesired ovarian stimulation. According

to our tests, if the period before commencement of chemotherapy is less than five days, the »flare up« can be reduced by simultaneous administration of GnRH antagonists for five days.

Integration of the various fertility preservation techniques

As each method of fertility protection has only a limited effect on its own, combination of the different methods is the best solution (see Fig. 3).

Cryopreservation of oocytes or ovarian tissue is often combined with the administration of GnRH analogs. Cryopreservation of ovarian tissue combined with ovarian stimulation and preservation of oocytes is another possibility. Integration of the various therapeutic approaches is being tested at present by the FertiPROTEKT network, as the aim of every fertility protection intervention should be to achieve at least a 50 % chance of the patient becoming pregnant at a later stage.

Chemotherapy with lower ovarian toxicity

In addition to the establishment and optimization of fertility protection methods, only chemotherapeutics with low ovarian toxicity should be used. However, there is only rudimentary data on the ovarian toxicity of the various chemotherapies. For this reason, since January 2007 the highly reproducible ovarian function parameter anti-Müllerian hormone (AMH) has been determined for all patients of the FertiPROTEKT Network centers, before and after chemotherapy. The aim is to gain reliable data on ovarian toxicity.

In the long term, ovarian toxicity could be taken into consideration when choosing the type of chemotherapy to be used and the necessity of fertility protection measures could be assessed in individual cases. However, it will take at least two years until corresponding data is available.

Conclusion

Due to the progress in reproductive medicine, relatively effective fertility protection measures can be taken for women. Some techniques must, however, be further evaluated and their fields of indication better defined. The centers of the FertiPROTEKT network counsel patients thoroughly and carry out fertility protection techniques, which should be made available to all young women.

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Keywords
Cancer, chemotherapy, fertility preservation, ovarian stimulation, ovarian tissue

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Conflict of interest
The author declares that there is no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors (ICMJE; www.icmje.org).

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CME-Continuing Medical Education

Fertility protection in women exposed to chemo- and radiotherapy

Question 1
Which parameter is most suitable for the assessment of the ovarian toxicity of chemotherapy?
a. Inhibin B
b. FSH
c. AMH
d. Clomifene stimulation test
e. Ovarian volume

Question 2
Which of the following statements is correct, according to state-of-the-art scientific knowledge (in pregnancy ≥ 6 months after cytotoxic therapy)?
1. Chemotherapy leads to an increased probability of premature birth and miscarriage.
2. The rate of miscarriage increases after radiotherapy of the pelvis.
3. Irradiation of the pelvis leads to an increased rate of premature births.
4. The number of births with malformations increases after cytotoxic chemotherapy.
5. Irradiation of the pelvis leads to endometrial thinning.

a. Answers 1 and 4 are correct.
b. Answers 2, 3, 4 and 5 are correct.
c. All answers are correct.
d. Answers 2, 3 and 5 are correct.
e. Answers 1, 2 and 3 are correct.

Question 3
Which statement/s is/are correct?
1. Fertility protection measures often take more than 2 weeks to perform.
2. The probability of pregnancy with the aid of conserved ovarian tissue and germ cells is significantly higher than 50 %.
3. The obtainment and cryopreservation of fertilized oocytes is the technique that has been evaluated most thoroughly.
4. GnRH analogs have proved effective in protecting fertility.
5. The replacement of the ovaries after transposition usually enables spontaneous pregnancy.

a. Only answer 3 is correct.
b. Answers 3 and 5 are correct.
c. None of the statements are correct.
d. Answers 2 and 5 are correct.
e. All statements are correct.

Question 4
Which statement is correct?
a. Primary follicles develop from secondary follicles due to the influence of FSH.
b. Inhibin B prevents the recruitment of too many secondary follicles.
c. AMH plays an important role in the maturation of tertiary follicles.
d. FSH plays an important role in the entire follicle genesis.
e. AMH prevents the recruitment of too many primordial follicles.

Question 5
Which statement is *incorrect*?
a. It is estimated that a third of all patients who should undergo fertility protection measures come from the field of gynecological oncology.
b. Counseling on fertility preservation should only be carried out by specialists in the field.
c. A pregnancy shortly after breast cancer does not appear to increase the risk of recurrency.
d. Administration of GnRH analogs is the most frequent measure taken within the FertiPROTEKT network.
e. The younger the patient at the time of cytotoxic therapy, the greater the risk of amenorrhea.

Question 6
What percentage of oocytes is destroyed after irradiation of the ovaries with ≤ 2 Gray:
a. 10 %
b. 20 %
c. 30 %
d. 50 %
e. 80 %

Question 7
Which statement is correct regarding the cryopreservation and transplantation of ovarian tissue?
a. The risk of metastasis due to re-transplanted ovarian tissue is very low after cryopreservation of ovarian tissue following a breast carcinoma.
b. About 30 % of the ovarian cortex should be removed.
c. Cryopreservation of ovarian tissue can be recommended in women up to 40 years of age.
d. Heterotopic transplantation of ovarian tissue appears to be most favorable.
e. Retransplantation of ovarian tissue is also a long-term therapeutic alternative to avoid hormone replacement therapy.

Question 8
Which statement is *incorrect* with regard to GnRH analogs?
a. The effectiveness of GnRH analogs has still not been verified.
b. GnRH analogs should initially be applied one to two weeks before commencing chemotherapy.
c. The »flare up« of GnRH analogs can possibly be reduced by simultaneous administration of GnRH antagonists.
d. The only reason for the administration of GnRH analogs is the inhibition of recruitment of secondary follicles by a decrease in the concentration of FSH.
e. Despite lack of proof of their effectiveness, GnRH analogs are frequently used for fertility protection.

Question 9
Which statement is correct regarding cryopreservation of fertilized and unfertilized oocytes?
a. Often, no ovarian stimulation is required for the cryopreservation of oocytes.
b. The cryopreservation of unfertilized oocytes is now also possible.
c. The pregnancy rate after cryopreservation, which is often > 50 %, is mainly determined by the number of oocytes conserved.
d. Cryopreservation of oocytes is carried out as a fertility protection measure in about 50 % of patients.
e. Ovarian stimulation treatment worsens the prognosis in the case of breast carcinoma.

Question 10
Which statement is *incorrect* with regard to the FertiPROTEKT network?
a. To achieve effective protection the network recommends the combination of several fertility protection methods.
b. The network was founded in 2006.
c. The FertiPROTEKT network now has about 30 centers with trained specialists for counseling and carrying out fertility protection techniques.
d. Evaluation of the ovarian toxicity of chemotherapy is one of the network's long-term aims.
e. The network has a homepage, which provides physicians and patients with access to well-grounded information.