Options for Fertility Preservation in Cancer Patients

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Introduction

Increasing survival rates for cancer patients and an increasing awareness of the quality of life after chemo-/radiotherapy have focused attention on the preservation of fertility after cancer treatment. Due to great progress in reproductive medicine, measures that make it possible for affected women to have children after recovering from the disease can now be offered.

The effects of malignant disease on gonadal function are caused in most cases indirectly by the influence of cytotoxic therapy. Chemotherapy and/or radiotherapy very often lead to partial or complete impairment of the ovaries and spermatozoa, severely reducing or eliminating fertility. The gonadotoxic effects are strongly dependent on the patient’s age (older age correlating to higher risk), the type, dose and duration of chemotherapy and radiation therapy (Table 1, 2).

The aim of the present article is to provide basic information on fertility-preserving measures and to enhance awareness among medical staff treating affected patients that such measures are available. Our main focus is on fertility preservation for women, but options for men are also mentioned.

Options for Fertility Preservation in Women

In general, diseases that require treatment that is gonadotoxic represent an in-

Table 1. Infertility after Treatment with Different Cytotoxic Drugs

<table>
<thead>
<tr>
<th>Toxic effect on spermatozoa</th>
<th>Initiation of ovarian dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td></td>
</tr>
<tr>
<td>– Chlorambucil</td>
<td>– Chlorambucil</td>
</tr>
<tr>
<td>– Cyclophosphamid</td>
<td>– Cyclophosphamid</td>
</tr>
<tr>
<td>– Nitrosoureas</td>
<td>– Nitrosoureas</td>
</tr>
<tr>
<td>– Busulfan</td>
<td>– Busulfan</td>
</tr>
<tr>
<td>– Fludarabin</td>
<td>– Fludarabin</td>
</tr>
<tr>
<td>– Procarbazin</td>
<td>– Procarbazin</td>
</tr>
<tr>
<td>– CCNU</td>
<td>– CCNU</td>
</tr>
<tr>
<td>Moderate risk</td>
<td></td>
</tr>
<tr>
<td>– Doxorubicin</td>
<td>– Doxorubicin</td>
</tr>
<tr>
<td>– Vinblastin</td>
<td>– Vinblastin</td>
</tr>
<tr>
<td>– Cytarabin</td>
<td>– Cytarabin</td>
</tr>
<tr>
<td>– Cisplatin</td>
<td>– Cisplatin</td>
</tr>
<tr>
<td>– Topoisomerase-I-Hemmstoff</td>
<td>– Topoisomerase-I-Hemmstoff</td>
</tr>
<tr>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>– Methotrexat</td>
<td>– Methotrexat</td>
</tr>
<tr>
<td>– 5-Fluorouracil</td>
<td>– 5-Fluorouracil</td>
</tr>
<tr>
<td>– 6-Mercaptopurin</td>
<td>– 6-Mercaptopurin</td>
</tr>
<tr>
<td>– Vincristine</td>
<td>– Vincristine</td>
</tr>
<tr>
<td>Unknown risk</td>
<td></td>
</tr>
<tr>
<td>– Bleomycin</td>
<td>– Bleomycin</td>
</tr>
<tr>
<td>– Etoposid</td>
<td>– Etoposid</td>
</tr>
<tr>
<td>– Gencibatin</td>
<td>– Gencibatin</td>
</tr>
<tr>
<td>– Taxane</td>
<td>– Taxane</td>
</tr>
<tr>
<td>– Oxaliplatin</td>
<td>– Oxaliplatin</td>
</tr>
<tr>
<td>– Irinotecan</td>
<td>– Irinotecan</td>
</tr>
<tr>
<td>– Antibody</td>
<td>– Antibody</td>
</tr>
<tr>
<td>– Small molecules</td>
<td>– Small molecules</td>
</tr>
</tbody>
</table>

Table 2. Radiotoxicity and Ovarian Insufficiency. Adapted from [Demewood MD 1986]

<table>
<thead>
<tr>
<th>Risk of Sterility</th>
<th>Ovarian radiation dosage (Gy) (Patient age in years [y])</th>
</tr>
</thead>
<tbody>
<tr>
<td>No effect</td>
<td>0.6</td>
</tr>
<tr>
<td>Some risk</td>
<td>1.5</td>
</tr>
<tr>
<td>60%</td>
<td>2.5–5 (15–40y)</td>
</tr>
<tr>
<td>70%</td>
<td>5–8 (15–40y)</td>
</tr>
<tr>
<td>100%</td>
<td>&gt; 8 (15–40y)</td>
</tr>
<tr>
<td>100%</td>
<td>2.5–5 (&gt; 40y)</td>
</tr>
</tbody>
</table>
dication for measures to protect the ova-
ry. Fertility-preserving measures have to be
customized to match the patient’s in-
dividual clinical situation. Aspects to be
taken into account include the time avail-
able before the start of oncological ther-
apy, patient’s age, relationship status, po-
tential ovarian involvement in the cancer,
and gonadotoxic measures that are to be
used (Fig. 1). If possible, it should be en-
sured that operations are carried out as
fertility-conserving surgeries. In terms of
radiotherapy, attention must be paid to
sufficient gonad protection by the choice of
treatment fields and lead aprons.

Transposition of the Ovaries
(Ovariopexy)
In patients with Hodgkin or non-Hodg-
kin lymphomas, cervical carcinoma,
colorectal carcinoma, or other solid ma-
lignancies which require radiotherapy to
the pelvis, the ovaries can be surgically
repositioned away from the radiotherapy
field before starting treatment. The ova-
ries are laparoscopically mobilized after
transsection of the ovarian ligaments or
by opening the retroperitoneum via bilat-
eral division of the peritoneum along the
infundibulo-pelvic ligament, so that a
transsection of the fallopian tube is not
necessary in most cases. Subsequently,
the mobilized ovary is fixed cranio-later-
to the peritoneum of each paracolic
gutter. Ovaries can be marked with radiopa-
queline metal clips, so their location can
be checked during treatment. The pro-
portion of patients < 40 years of age who
recover regular ovulatory cycles after
radiotherapy with this technique is up to
85% [2]. The success rate with this method
depends on applied radiation dosage and
scattered radiation. Rare complications
include pain during ovulation, cyst for-
malation, thrombosis, and ischemia [3].

GnRH Analogues
Gonadotropin-releasing hormone (GnRH)
agonists may be utilized to inhibit the re-
lease of follicle-stimulating hormone in
postpubertal women, inducing transient
hypogonadotropic hypogonadism and
placing the ovaries in a “resting” state.
Hereby, it is anticipated that follicles can
be protected and fertility be preserved.
The latest meta-analysis including only
randomized controlled studies (n = 6) re-
ported a reduced rate of premature ovar-
ian failure with GnRH agonist adminis-
tration, with an odds ratio of 3.5 [4]. Pre-
liminary results of the most recent study
of LHRH analog during chemotherapy
to reduce ovarian failure in early stage,
hormone receptor-negative breast cancer
(Prevention of Early Menopause Study-
[POEMS]- SWOG S0230) show a re-
duced rate of premature ovarian failure
by using LHRH analogue (OR = 0.3;
95%-CI: 0.10–0.87; p = 0.3 [unadjusted
analyses]) [5]. On the other hand, other
studies on administration of GnRH ago-
nists in adjuvant chemotherapy for breast
cancer and lymphoma did not demon-
strate a significant benefit [6, 7]. When
used, GnRH analogues should be admin-
istered at least 1 week before starting
chemotherapy due to the initial increase
in the release of gonadotropins (known
as the “flare-up” effect), and administra-
tion should continue for at least 1–2
weeks after the last chemotherapy cycle.
If the time window before the start of
chemotherapy is less than a week, it is
possible to combine GnRH agonists with
GnRH antagonists in order to reduce
flare-up [8]. Side effects of GnRH ana-
logues can include menopausal symp-
toms (although this is also possible with
chemotherapy alone) and a reduction in
bone mass if the drug exposure is longer
than 6 months. It should also be noted
that possible negative effects of GnRH
analogue on the prognosis for patients
with estrogen receptor-positive diseases
(e.g., breast carcinoma) have not yet
been clarified. This method is currently
regarded as safe, noninvasive, and easy
to administer [9] and may be considered
on an individual basis in combination
with other fertility-protecting measures
if possible. Statements regarding the
chance of pregnancy cannot be made at
the present time and must be discussed in
detail during the information talk with
the patient. Further randomized prospec-
tive studies are lacking.

Cryopreservation of Unfertilized
and Fertilized Oocytes
Therapeutic cryopreservation of unfer-
tilized and fertilized oocytes is a well-
established assisted reproductive tech-
ique (ART) and is especially applicable
in the frame of fertility preservation
prior to gonadotoxic therapy. Ovarian stimu-
lation to harvest oocytes can be carried out
with most postmenarchal women aged
≤ 40 years. With the development of new
protocols, stimulation can begin at any
point during the menstrual cycle of the
patient, so that the working time frame
requires only 2 weeks prior to start of
cytotoxic therapy. Use of GnRH-antag-
nists and ovulation induction with a
GnRH-agonist prevents ovarian hyper-
stimulation syndrome, which would re-
quire postponement of chemotherapy.
Cytotoxic therapy can begin 1–2 days
after follicle puncture [10].

Freezing pronuclear stage zygotes using
traditional slow cryopreservation has
been well established, especially in

Figure 1. Planned Approach at German University Reproductive Centers. Mod. from [1]. * CHT = Chemotherapy treat-
ment
options for Fertility Preservation in Cancer Patients

Cryopreservation of unfertilized oocytes. Despite publication of the first birth after cryopreservation of unfertilized oocytes with a slow freezing protocol in humans 1986 [14], this technique was considered controversial due to the low survival rates of the cells. Based on improved survival rates due to slight modifications of slow freezing and vitrification protocols, the cryopreservation of unfertilized oocytes now represents an effective ART. Pregnancy rates can be achieved comparable to those resulting from IVF treatment using fresh eggs [15]. In a randomized controlled trial, pregnancy rate was compared with surplus slow freeze and vitrified oocytes. Results demonstrated that vitrification leads to a better survival of oocytes (81% vs. 67%; \( p < 0.001 \)), higher rate of fertilization (77% vs 67%; \( p = 0.03 \)), and higher pregnancy rate per thawed oocytes compared to slow freeze oocytes (5.2% vs 1.7%; \( p = 0.03 \)) [16]. However, other clinics report equivalent success of the two freezing methods in observational studies [17], and it is likely that clinic-specific success rates vary with different cryopreservation protocols. Today, over 1000 children worldwide have been born through cryopreservation of unfertilized oocytes. Based on available data, no increased risk of congenital anomalies has been observed [18]. The malformation rate of children born by cryopreserved oocytes does not differ from those after spontaneous conception. Due to these advances, the American Society for Reproductive Medicine no longer considers cryopreservation of unfertilised oocytes experimental, but an established method for retaining fertility [19].

Risks associated with ovarian stimulation are low. In the complication register of the FertiPROTEKT network no shift of chemotherapy due to complication was required in 205 stimulations. In patients with hormone-dependent tumors, such as hormone receptor-positive breast cancer or hormone-dependent genital tumors, ovarian stimulation should be critically discussed because of increased estradiol levels. In consultation with the oncologist, gonadotropins, antiestrogens (e.g., tamoxifen) or aromatase inhibitors (e.g., letrozole) could be administered during ovarian stimulation to reduce the unwanted rise of estradiol and to carry out an antiestrogenic effect on the tumor cells with a reduced risk of cancer progression [10].

One point against cryopreservation of zygotes or unfertilized oocytes as an option for fertility preservation in cancer patients is the need of hormonal stimulation to achieve more than 1 oocyte. Stimulation is accompanied with a delay of the chemotherapy because normally the start of the stimulation procedure, which already needs at least 10 days, is at the beginning of the follicular phase. When the patient is in the luteal phase, it is necessary to wait until bleeding occurs. An alternative is already to initiate the ovarian stimulation in the luteal phase together with the administration of Gonadotropin-Releasing Hormone antagonist (GnRH-antagonist), which is administered to induce immediate luteolysis. The success of this application was already shown by von Wolff et al in 2009 [20] and recently at the Meeting of the European Society of Human Reproduction and Embryology in 2014, where the results of 674 cases of luteal phase stimulation were presented [21].

In-vitro maturation

In-vitro maturation (IVM) involves obtaining immature oocytes, maturing them, and then fertilizing them. Immature oocytes from small antral follicles are obtained by transvaginal aspiration after short stimulation with follicle-stimulating hormone (FSH) and/or human chorionic gonadotropin (HCG), if necessary. Harvested oocytes are matured in vitro into fertilizable metaphase II oocytes and can then be cryopreserved. It is unnecessary to expose patients to high-dose gonadotropin therapy with this method, and the time required before follicular puncture is shorter than with conventional stimulation, making it easier to avoid a delay in the start of chemotherapy. Immature oocytes can also be obtained during processing of biopsied ovarian tissue. IVM of oocytes during cryopreservation of ovarian tissue offers an additional option of fertility preservation without additional risk and expense for the patient [22]. However, with the exception of results from a few research groups, data on pregnancy rates with this procedure are still very limited and the reported rates are lower than those with conventional in-vitro fertilization (IVF) [23, 24].

Cryopreservation of Ovarian Tissue

Cryopreservation of ovarian tissue has been investigated as a method of fertility preservation for more than a decade and has recently achieved considerable success. Over 25 live births have been reported following transplantation of cryopreserved ovarian tissue ([25] and personal communication). Technically, ovarian extraction is a simple procedure. Ovarian tissue can be obtained using minimally invasive techniques during laparoscopy, with unilateral ovariectomy or partial ovariectomy. Cryopreservation of ovarian tissue can be carried out independent of menstrual phase and, therefore, does not lead to any delay in oncological therapy (Table 3). In centers that offer cryopreservation of ovarian tissue,

| Table 3. Comparison of the Fertility Preservation Options in Women |
|-----------------|-----------------|-----------------|
| Characteristics  | Time required   | Pregnancy rate  |
| Cryopreservation of ovarian tissue | Laparoscopy, retransplantation | Immediately | Over 25 live births worldwide |
| Cryopreservation of unfertilized oocytes | Stimulation | 10–14 d | 20–30% |
| Cryopreservation of fertilized oocytes | Partner, stimulation | 10–14 d | 20–35% |
Options for Fertility Preservation in Cancer Patients

The procedure can be performed 1 day after the patient’s first visit. After the tissue has been removed, it can be processed immediately or transferred in specific transportation containers to a center that is specialized in the cryopreservation of ovarian tissue with an associated cryobank.

A transport duration of 4–5 hours before cryopreservation is possible without any problems [26]. In addition, the viability of the tissue appears also to be preserved for longer periods of time (overnight transport), as the first live birth in Germany after re-transplantation of cryopreserved ovarian tissue has demonstrated [27].

In general, cryopreservation of ovarian tissue involves similar cryogenic processes as those utilized for cryopreservation of oocytes or embryos. “Slow freezing” is currently recommended for freezing ovarian tissue due to current higher efficiency with this method. In all previously published births following retransplantation of cryopreserved ovarian tissue, the tissue underwent slow freezing [22]. Of note, however, experimental tests demonstrate increasingly better results for vitrification [28]. The main purpose of cryopreservation of ovarian tissue is to preserve viable ovarian tissue for potential reimplantation if ovarian function fails following cancer treatment. Ovarian tissue is usually reimplanted at the natural site (orthotopically), in a peritoneal pocket, or in the residual ovarian bed, in order to allow spontaneous conception. The first reimplantation of ovarian tissue in Germany was performed in 2007 at the Department of Gynecology at Erlangen University Hospital [29]. Resumption of hormonal function in reimplanted tissue has now been documented on many occasions, and there have been over 25 recently reported births following orthotopic reimplantation of cryoconserved ovarian tissue. The first birth after reimplantation of cryoconserved ovarian tissue in Germany occurred on October 10, 2011 [30]. The first international surveys of birth rate per ovarian tissue transplantation report a success rate of approximately 15%, which is likely to increase in the future.

The possibility that tumor cells may be concurrently reimplanted is a problem that must be discussed with the patient. To date, there have been no cases in which this has been confirmed, although considerable caution is advised regarding cryopreserved tissue from patients with leukemia, borderline ovarian tumor, or with a high risk of ovarian metastases (e.g., in adenocarcinoma of the cervix or stage III–IV breast cancer) [31, 32]. An option for these patients could be the maturation of follicles in vitro without transplantation. The ability of primordial follicles of ovarian tissue to fully mature in vitro and produce fertilizable, viable ova has only been demonstrated in a few animal model reports. Total in-vitro maturation of human oocytes from cryopreserved ovarian tissue is not yet possible [33]. However, it is quite conceivable that in the next few years this technique will be successful in humans [34].

Another option is ovarian tissue xenotransplantation. Ovarian tissue is transplanted into a surrogate host, such as immunodeficient mice (e.g., SCID mice), which do not have rejection reactions against foreign tissue. Follicles that mature can be punctured to obtain oocytes. This method has been used experimentally to test the vitality of frozen ovarian tissue and to assess any malignant contamination [32] (Table 4).

### Table 4. Comparison of the Fertility Preservation Options in Women

<table>
<thead>
<tr>
<th>Options for Fertility Preservation</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryopreservation of ovarian tissue</td>
<td>– No treatment delay&lt;br&gt;– Only way to preserve fertility in prepubertal girls&lt;br&gt;– Treatment of women without a partner&lt;br&gt;– No unwanted estrogen peak&lt;br&gt;– Can be used in chemo- and radiotherapy&lt;br&gt;– Restoration of fertility and endocrine function</td>
<td>– Risk that tumor cells may be reimplanted&lt;br&gt;– Limited experience</td>
</tr>
<tr>
<td>Cryopreservation of unfertilized oocytes</td>
<td>– Treatment of women without a partner&lt;br&gt;– Can be used in chemo- and radiotherapy</td>
<td>– Treatment delay&lt;br&gt;– Not for prepubertal girls&lt;br&gt;– Unwanted estrogen peak</td>
</tr>
<tr>
<td>Cryopreservation of fertilized oocytes</td>
<td>– Established method with high pregnancy rate&lt;br&gt;– Can be used in chemo- and radiotherapy</td>
<td>– Partner&lt;br&gt;– Treatment delay&lt;br&gt;– Not for prepubertal girls&lt;br&gt;– Unwanted estrogen peak</td>
</tr>
</tbody>
</table>

### Combination of Different Techniques

To increase the effectiveness of individual measures, a combination of the described fertility preservation strategies could be considered. For example, when 2 weeks are left before starting chemotherapy, ovarian stimulation could be performed and on the day of oocyte retrieval, ovarian tissue could also be harvested for cryopreservation at the same time [35]. Removing ovarian tissue first and starting ovarian stimulation approximately 1–2 days later is an alternative approach. The partial removal of ovarian tissue does not substantially affect the average number or quality of oocytes retrieved after ovarian stimulation [36]. Moreover, GnRH analogues could also be administered simultaneously with the induction of ovulation in these patients, thereby protecting remaining follicles.

### Options for Fertility Preservation in Men

In men, cryopreservation of ejaculate or testicular tissue are established means of creating a fertility reserve. A therapeutically effective method that protects testicular function from gonadotoxic effects of chemotherapy or radiotherapy has to be developed [37]. Hormonal suppression of spermatogenesis in cystotic chemotherapy (e.g., using GnRH analogues) has been attempted, but does not provide sufficient gonadal protection [38]. In radiotherapy, shielding of the testes from radiation or removal of the radiation field offers an effective measure to prevent unwanted damage and is widely practiced.
Cryopreservation of Sperm

Cryopreservation of an ejaculate is the established method of choice. Multiple sperm donations can be provided and a frozen depot created and maintained in reproductive medical centers, prior to the start of gonadotoxic treatment. This reserve could be used for ART-measures at a later date. Spermatozoa are relatively cryoresistant and post-thaw survival rate is high. Many pregnancies have been achieved using this method [39].

For prepubertal boys, cryopreservation of sperm is inappropriate because provision of an ejaculate is not yet possible. For adolescent boys undergoing puberty, germ cells can be obtained for cryopreservation through extraction from testicular biopsies or by electroejaculation. However, both methods are invasive procedures [40].

Cryopreservation of Sperm from Testicular Tissue (TESE)

A testicular biopsy could be performed to isolate spermatozoa from testicular tissue when no spermatozoa are found in the ejaculate. With this method, sperm cells are present in up to 75% of cases. TESE is an established process and is combined with intracytoplasmic sperm injection (ICSI) for later fertility. However, the success rate depends on the amount of viable spermatozoa present in testicular tissue at the time of cryopreservation [41].

The so-called Onco-TESE is particularly useful in patients with unilateral or bilateral testicular tumors, as well as patients with azoospermia before or after gonadotoxic therapy. Even for long-term survivors of oncological diseases with azoospermia, Onco-TESE can be offered as an opportunity for future fatherhood [42].

Experimental Approaches

Recovery of testicular tissue via biopsy provides a method for recovery of germ-line stem cells before the start of treatment which can be maintained through cryopreservation. This is currently the only conceivable method to preserve fertility for prepubertal boys and, therefore, the cryopreservation of immature testicular tissue should be considered for these patients. After a successful treatment, the tissue or the germ line stem cells contained therein could be used for process-

Conflict of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

References:

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