

Review

The effect of cancer treatment on female fertility and strategies for preserving fertility

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Abstract

Aggressive chemotherapy and radiotherapy in young patients with cancer has greatly enhanced the life expectancy of these patients, but these treatments often cause infertility because of the massive destruction of the ovarian reserve resulting in premature ovarian failure (POF). This review focuses on the effect of cancer treatments on fertility and on the various surgical and assisted-reproduction innovations that are available to provide the patient with the option of future pregnancies. As the emerging discipline of fertility preservation is steadily attracting increasing interest, developments in the near future promise to be very exciting. However, in everyday routine work, better interdisciplinary cooperation between gynecological and pediatric oncologists, surgeons, immunologists and endocrinologists is necessary so that individualized options for fertility preservation can be offered in advance of surgical procedures or cancer treatments. GnRH analog treatment can preserve fertility in some patients, but not in all. At present, cryopreservation of ovarian tissue appears as a very promising method of providing the cancer patient with a realistic chance of preserving fertility—a prospect that is also extremely important to patients for psychological reasons.

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Contents

1. Introduction	149
2. The effect of cancer treatment on female fertility	149
2.1. Radiotherapy-induced ovarian damage	149
2.2. Chemotherapy-induced ovarian damage	150
2.2.1. Effects of age	150
2.2.2. Various regimens	150
2.3. Combination chemotherapy	150
3. Fertility preservation options for female cancer patients	150
3.1. Ovarian transposition (oophoropexy)	150
3.2. Ovarian suppression	151
3.3. Apoptotic inhibitors	151

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3.4.	Cryopreservation of embryos	151
3.5.	Cryopreservation of oocytes	152
3.5.1.	Cryopreservation of mature oocytes (after gonadotropin stimulation)	152
3.5.2.	Cryopreservation of immature oocytes (without gonadotropin stimulation)	152
3.5.3.	Cryopreservation of immature oocytes after in vitro maturation (IVM) (without gonadotropin stimulation)	152
3.6.	Cryopreservation of ovarian tissue	152
3.7.	Construction of reconstituted human oocytes (artificial gametes)	153
4.	Conclusions	153
	References	153

1. Introduction

It is estimated that in 2010, every 250th adult will be a survivor of childhood cancer [1]. In the developed or Westernized countries, women are using better methods of contraception and are delaying childbearing for social or financial reasons, so that an increasing number of women are anxious to preserve their fertility when early-stage cancers are discovered [2,3]. In addition, increasing numbers of patients with non-malignant autoimmune diseases, such as rheumatoid arthritis or systemic lupus erythematosus, as well as hematological diseases [4], are being successfully treated with chemotherapy or radiation therapy.

Cytotoxic therapy often results in premature ovarian failure (POF) [5]. Patients with POF have to face years of menopause and psychological problems, or else years of hormone replacement therapy. However, this substitution therapy is not capable of replacing the reproductive function of the ovaries.

This article reviews the literature on the topic, discusses the effects of cancer treatment on female fertility, and presents the options currently available – thanks to advances in assisted-reproduction technology – for maintaining fertility in women undergoing this type of treatment.

2. The effect of cancer treatment on female fertility

2.1. Radiotherapy-induced ovarian damage

Ionizing radiation has adverse effects on gonadal function at all ages. The degree and persistence of the damage depends on the dose, the irradiation field and the patient's age, with older women being at greater risk of damage [6].

Cranial irradiation for brain tumors with doses to the hypothalamic–pituitary area in excess of 30 Gy can in time cause hypogonadotropic hypogonadism in children [7].

The ovaries are exposed to significant doses of radiation when radiotherapy is used in the treatment of cervical and rectal cancer, and with craniospinal radiotherapy for central nervous system malignancies. This can also happen when the pelvic lymph nodes are irradiated for hematological malignancies, such as Hodgkin's disease, and with total body irradiation before bone-marrow transplantation [6].

Gosden et al. demonstrated that there is dose-related depletion of primordial follicles in mouse ovaries after increasing radiation doses of 0.1, 0.2 and 0.3 Gy. This explains sterilization with total depletion of the primordial follicle reserve after exposure to high doses of radiotherapy, and premature ovarian failure at lower doses that cause only partial depletion of the primordial follicle reserve [8].

Various reports have been published on the radiation dosage necessary to cause loss of ovarian function. Lushbaugh and Casarett have shown that women under 40 years of age are less sensitive to radiation-induced ovarian damage, with an estimated dose of 20 Gy being required to produce permanent ovarian failure, in comparison with 6 Gy in older women [9]. Chiarelli et al. observed a dose-dependent and distribution-dependent relationship between the risk of premature ovarian failure and the total dose of abdominal pelvic irradiation: with doses <20 Gy, the relative risk was 1.02; at 20–35 Gy, the relative risk increased to 1.37; and with doses >35 Gy, the relative risk of premature ovarian failure was 3.27. The percentage of women who suffered infertility correlated with increasing dosages of abdominal pelvic irradiation; treatment with 20–35 Gy caused a 22% rate of infertility and doses >35 Gy led to a 32% rate of infertility [10].

There is also a known radiation effect on the uterus and subsequent pregnancy outcomes. Uterine radiation is associated with infertility, spontaneous miscarriage and intrauterine growth retardation [11]. Direct effects on the uterus after irradiation include irreversible changes in the uterine musculature and blood flow, as well as hormone-resistant endometrial insufficiency. A review by Critchley and Wallace [12] indicates that physiological sex steroid replacement therapy may improve uterine characteristics in some patients after irradiation at a young age.

It is also known that there is a higher rate of obstetric complications in patients who have received radiation treatment, in comparison with the general population; complications include spontaneous abortions (38% versus 12%), preterm labor (62% versus 9%) and low-birthweight infants (62% versus 6%). However, as long as radiation is not administered during pregnancy, there is no risk of subsequent teratogenicity [13]. These findings confirm studies on women exposed to the atomic bomb and on offspring conceived and born to them following exposure, which have shown that the incidence of spontaneous

abortion is greater, but that the children do not suffer from an increased rate of mutations or major congenital anomalies in comparison with the normal population [14]. Fenig et al. [15] reported an increase in low-birthweight infants and spontaneous abortions, especially if conception occurred less than a year after radiation exposure. They advised delaying pregnancy for a year after the completion of radiation therapy.

2.2. Chemotherapy-induced ovarian damage

All chemotherapeutic drugs act by interrupting vital cell processes and arresting the normal cellular proliferation cycle. Frequently, chemotherapeutic agents are used in combination because of synergistic effects, but this also leads to an increase in their adverse effects. In animal experiments, Meiorow et al. demonstrated that regular menses and a normal reproductive outcome after chemotherapy are not certain indicators of whether the ovarian follicular reserve has survived the treatment unaffected [16]. The authors also postulated that patients who recover from ovarian failure after high-dose chemotherapy or radiotherapy treatments should not delay childbearing for too many years. These patients should try to conceive after a few years of a disease-free interval, but not <6–12 months after the treatment, due to the possible toxic effects of the treatment on growing oocytes [17].

The risk of chemotherapy-related amenorrhea depends on the patient's age, the specific chemotherapeutic agents used and the total dose administered.

2.2.1. Effects of age

Older women have a higher incidence of complete ovarian failure and permanent infertility in comparison with younger women [6,18]. This can be explained by the larger primordial follicle reserve, which declines with age.

2.2.2. Various regimens

(1) Alkylating agents. These substances have a severe effect on human fertility. Known effects are ovarian fibrosis and follicular and oocyte depletion [19]. According to Meiorow [17], alkylating agents are associated with the greatest risk among all chemotherapeutic agents for inducing ovarian failure (odds ratio (OR) 3.98 in comparison with unexposed patients). In a study that examined the development of ovarian failure after cyclophosphamide treatment for lupus erythematosus, the POF incidence was 26%, with the major determining factors being the patient's age at the start of therapy and the cumulative dose [20]. Animal experiments have also shown an increase in abortions and fetal malformations (10 times higher than in the control group) in pregnancies resulting from oocytes exposed to cyclophosphamide at different stages of oocyte maturation [6]. Meiorow also indicated that the effect of cyclophosphamide in mice is not an "all-or-nothing" phenomenon

and that it causes follicular destruction in exponential proportion to increasing doses [16].

- (2) Cisplatin and analogs. Meiorow estimated that cisplatin causes ovarian failure with an odds ratio of 1.77 [17]. Studies of cisplatin treatment in female mice have demonstrated that different types of chromosomal damage are induced, with genetic effects in the oocytes resulting in early embryonic mortality and marked aneuploidy [21].
- (3) Vinca alkaloids. These substances are known aneuploidy inducers. According to Meiorow, the OR for ovarian failure was about one [17]. Many animal experiments have shown high levels of aneuploidy in oocytes exposed to vinblastine [22], which means that these damaged oocytes could produce malformed fetuses.
- (4) Antimetabolites. Insufficient data are available on the effects of antimetabolites on female germ cells.
- (5) Anthracycline antibiotics. Adriamycin and bleomycin are female-specific mutagens and have been shown to induce dominant lethal mutations in maturing/preovulatory oocytes in female mice. Etoposide induced preferential pericentric lesions and aneuploidy in oocytes [22].

2.3. Combination chemotherapy

In everyday practice, women are rarely subjected to just one chemotherapeutic agent, so that the results of single-agent administration cannot be determined [18]. Studies that have monitored pregnancies in women exposed to chemotherapy before conception have not reported increased rates of miscarriage or congenital abnormalities in comparison with the general population. Since these pregnancies occurred long after treatment had ceased, it can be assumed that there are correction mechanisms within the oocyte or that there are undetected miscarriages at a very early stage due to dominant lethal mutations [17].

3. Fertility preservation options for female cancer patients

3.1. Ovarian transposition (oophoropexy)

For patients undergoing gonadotoxic radiotherapy, transposition of the ovaries out of the field of irradiation can maintain ovarian function. The most common indications are Hodgkin's disease, cervical and vaginal cancer, and pelvic sarcomas. The ovarian dose after transposition is reduced to approximately 5–10% of that in in situ ovaries [23].

Laparoscopic procedures are currently conducted for ovarian transposition, as they offer the following advantages: there are fewer adhesions; radiotherapy can be initiated immediately postoperatively and it is possible to repeat the laparoscopy if postoperative assessment of the ovaries shows that the radiation dose will still be significant.

Various rates of ovarian function preservation and ability to conceive after radiotherapy and oophoropexy have been

reported, ranging from 16 to 90% [23]. The variations are due to the inability to calculate and prevent scatter radiation, concomitant use of chemotherapy and different doses of radiation administered [4]. Complications are relative rare and include benign ovarian cysts, chronic abdominal pain, adhesions and two reported cases of ovarian metastasis. To minimize the risk of ovarian metastasis, such a procedure should be performed regardless of the histological type in patients with an early invasive cervical cancer, with a tumor size of <3 cm, with tumor confined to the uterine cervix and with absent macroscopic extrauterine spread [23].

Oophoropexy is still an established method that has certainly been underestimated. It should be offered to all children or young women receiving radiotherapy or combined chemoradiotherapy. In some cases, in vitro fertilization (IVF) or surgical orthotopic retransposition may be necessary to achieve a pregnancy.

3.2. Ovarian suppression

When it was noticed that the premenarchal female gonads appear to be less sensitive to cytotoxic therapy, investigators attempted to render the germinal epithelium quiescent using a *gonadotropin-releasing hormone (GnRH) agonist*. GnRH agonists act on the hypothalamic–pituitary axis to suppress ovarian function [24].

However, contradictory results on the effects of GnRH agonists have been published and there has been intensive debate regarding the existence of follicle-stimulating hormone (FSH) receptors in the primordial follicles and GnRH analog receptors in the human ovary [25]. Meirow was unable to demonstrate a protective effect of GnRH after ablative chemotherapy and radiotherapy in patients undergoing bone-marrow transplantation [26]. Waxman et al. found that buserelin was not effective for fertility preservation in humans. However, it is possible that complete pituitary ovarian suppression was not achieved, which might be a necessary prerequisite for these drugs to work [27].

Blumenfeld and other research groups – although in studies including small numbers of patients – were able to demonstrate that the GnRH agonists are well tolerated and may protect long-term ovarian function [28,29]. Blumenfeld has reported on what is probably the largest group of women (55 lymphoma patients) who were started on GnRH analogs 7–10 days before chemotherapy treatment. The rate of POF was 5% in the GnRH analog/chemotherapy group versus 55% in the group receiving chemotherapy alone [28]. However, in a recent study from the same group investigating the effect of the CHOP chemotherapy regimen (cyclophosphamide, adriamycin, oncovine and prednisolone) in young women with intermediate-high grade non-Hodgkin's lymphoma there was no significant difference between those patients who received concurrently fertility preserving measures (GnRH analogs or contraceptive pills) versus the remainder concerning regular menstrual cycles recovery or pregnancies [30].

Treatment with GnRH analogs should begin at least 10 days before the start of chemotherapy, due to the initial flare-up effect, which causes undesirable ovarian stimulation. Administration should continue throughout the chemotherapy period in the form of depot injections, so that the down-regulating effect remains at least for 2 weeks after the end of chemotherapy. In the case of estrogen-sensitive tumors, tamoxifen therapy can be initiated after the GnRH analog treatment.

The protective role of *GnRH antagonists* has been investigated mainly in rodents experiments but only with contradictory results, with a study even suggesting a depletion of the ovarian follicles through a direct effect on the ovary in a murine model [31].

The *oral contraceptive pill* has been investigated as an agent for suppressing the ovaries during chemotherapy as a result of the decline of serum gonadotropin levels inhibiting the follicular growth in the ovary. The German Hodgkin's Lymphoma Study Group found in a retrospective study a possible protective effect of oral contraceptives in younger women undergoing gonadotoxic chemotherapy and has started a randomized phase II trial with the aim to define a standard co-treatment for the reduction of infertility rates in young female patients during chemotherapy for Hodgkin's Lymphoma [18].

3.3. Apoptotic inhibitors

When mice oocytes were exposed to doxorubicin in vitro, they underwent a series of changes that produced apoptotic bodies. Apoptosis also plays a significant role in the process of normal germ-cell depletion, so that the existence of a genetically predetermined pathway has been suggested that can be aberrantly activated by chemotherapeutic drugs [32]. As a logical consequence, the use of apoptosis inhibitors could potentially stop the apoptotic process and protect the patient from POF.

Administration of sphingosine 1-phosphate, a known apoptosis inhibitor, in mice treated with doxorubicin was found to protect the oocytes from apoptosis. The oocytes of mice that lacked the enzyme for generating ceramide and acid sphingomyelinase, early messengers in the apoptosis sequence, were also more resistant to doxorubicin-induced apoptosis [32]. Sphingosine 1-phosphate also preserved the fertility of irradiated female mice, without any genomic damage for the offspring [33].

The research shows that these agents are promising, but that they are still at a very early experimental stage. It is also known that many cytotoxic drugs act by producing apoptosis at the tumor level. Therefore, further studies have to clarify the negative effect on the reduction of cancer mass by the use of apoptosis inhibitors as a co-treatment during cancer therapy.

3.4. Cryopreservation of embryos

This is the most successful approach with regard to fertility preservation. The human embryo is very resistant to damage

caused by cryopreservation. The post-thaw survival rate of embryos is in the range of 35–90%, while implantation rates are between 8 and 30%; if multiple embryos are available for cryopreservation, cumulative pregnancy rates can be more than 60% [34]. Delivery rates per embryo transfer using cryopreserved embryos are reported to be in the range of 18–20% [34]. However, this approach requires in vitro fertilization and a participating male partner. Today with the modern ART possibilities the male infertility factor is a problem only in the very rare cases of complete non-obstructive azoospermia, and in these cases frozen sperm from a donor can be used. If many mature oocytes are retrieved, there is an opportunity to carry out several attempts at embryo transfer from a single cycle. This option may not be acceptable to prepubertal, adolescent girls.

Stimulation agents should be of concern only in patients with estrogen-sensitive cancers (e.g., breast cancer). In such cases, alternative stimulation regimens can be used—for example, tamoxifen or aromatase inhibitors [35], even if these regimens are less effective without added gonadotropins. Although these medicaments should not be used during pregnancy, studies with tamoxifen and letrozole demonstrated that its short-term use for ovulation induction does not adversely affect oocyte and embryo development. Moreover, no detrimental effect on fetal development was demonstrated. Anyway, clomiphene, a related compound of tamoxifen, has been safely used for ovulation induction for almost four decades [31].

3.5. Cryopreservation of oocytes

The following alternatives are available with regard to the cryopreservation of oocytes.

3.5.1. Cryopreservation of mature oocytes (after gonadotropin stimulation)

Oocyte banking is more problematic than cryopreservation of sperms or embryos. The first obstacle is the sensitivity of oocytes to chilling, probably because of the sensitivity of the spindle apparatus and the higher lipid content of the cells. Cooling and exposure to cryoprotecting agents (CPAs) affect the cytoskeleton and may aggravate the already high incidence of aneuploidy in human oocytes [36]. Exposure to CPAs also causes hardening of the zona pellucida, so that all oocyte cryopreservation protocols involve intracytoplasmic sperm injection (ICSI) as a precaution. Fertilization has to be carried out about 3–5 h after thawing while the oocyte remains fertile.

Further disadvantages of this method are that cancer patients may not have more than one opportunity for oocyte harvesting before undergoing potentially sterilizing treatment, since a cycle of controlled stimulation requires several weeks, and there is normally a delay of a few months before treatment cycles. The success of the method is also dependent on the total number of eggs harvested (<10 oocytes means very low chances of pregnancy).

However, with the introduction of ICSI and the publication of reassuring data [37], efforts to cryopreserve oocytes have resumed in recent years, with conventional slow cooling–rapid thawing protocols and later with vitrification. To date, more than 4300 oocytes have been cryopreserved and more than 80 children have been born, mostly with the conventional slow cooling method. The overall live birth rate per cryopreserved oocyte is about 2%, which is much lower than that with IVF using fresh oocytes [38].

These data were confirmed by a recent metaanalysis from Oktay et al., who found that the live birth rate per injected oocytes was approximately 2% for the most commonly used slow freezing technique. Pregnancy rates were one third to one fourth of the success rates seen with unfrozen oocytes [39].

3.5.2. Cryopreservation of immature oocytes (without gonadotropin stimulation)

An alternative strategy that allows a longer recovery time and avoids depolymerization of the spindle is to cryopreserve oocytes at the germinal vesicle stage, when the chromatin is diffuse and the cell is still at prophase I. However, immature oocytes do not appear to cryopreserve better than those at the metaphase II stage. Furthermore, they have to undergo incubation for 24–48 h in culture for meiotic maturation [38].

3.5.3. Cryopreservation of immature oocytes after in vitro maturation (IVM) (without gonadotropin stimulation)

Oocytes are recovered for IVM from fresh tissue or follicular aspirates, before the dominant follicle emerges during the mid-follicular phase of the menstrual cycle (normally 8–10 mm in diameter). Cryopreservation difficulties include the different optimal times of equilibration for the oocyte and its smaller cumulus cells. At present, the reported success of IVM in young women with polycystic ovaries is a pregnancy rate of approximately 25–30% per cycle, with a high miscarriage rate [40].

Oocytes can thus be recovered from unstimulated ovaries as well as from children, and egg harvesting is less expensive and risky and can be repeated frequently. However, this procedure requires further advances in cryotechnology.

In conclusion, it can be stated that although in men who face cancer treatment semen cryopreservation provides an easy and effective method of preserving fertility and has already yielded thousands of pregnancies, the cryopreservation of oocytes currently has significant limitations and there have only been a small number of reported pregnancies.

3.6. Cryopreservation of ovarian tissue

The cryopreservation of ovarian cortical strips has recently emerged as an easy, fast and inexpensive technique and has already yielded the first two livebirths after orthotopically transplanted ovaries [41,42]. One embryo could also be generated from a subcutaneously implanted

ovary from a breast cancer patient [43]. The idea of cryopreserving ovarian tissue is based on the finding that the ovarian cortex harbors primordial follicles that are more resistant to cryoinjury than mature oocytes, because the oocytes they contain have a relatively inactive metabolism and lack a metaphase spindle, zona pellucida and cortical granules [44]. The clinical indications are almost identical with those for the oocyte, but there are fewer logistical restrictions and there is a greater fertility potential, because of the far larger number of oocytes preserved.

Ovarian tissue cryopreservation may be the only acceptable method for any prepubertal or premenarchal female patients receiving chemotherapy or pelvic radiotherapy [2]. Follicular viability after cryopreservation and thawing has been demonstrated in several studies [45].

The risks of ovarian tissue cryopreservation include reimplantation of the primary tumor and malignant transformation [46]. Shaw, first reported transmission of lymphoma from a donor to a graft recipient with fresh and cryopreserved mouse ovarian tissue samples [46]. However, most of the malignant diseases encountered during the reproductive years in the human do not metastasize to the ovaries, with the exception of blood-borne malignancies, such as leukemias, neuroblastoma and Burkitt's lymphoma [45]. Kim et al. examined the risk of cancer relapse by transplanting frozen-thawed ovarian tissue from lymphoma patients to immunodeficient mice. None of the ovarian grafts from non-Hodgkin's or Hodgkin's lymphoma patients resulted in recurrences, whereas cancer spread was found in one of five animals transplanted with lymph nodes from a patient with Hodgkin's disease [47]. A histological assessment for micrometastases should therefore always be carried out on a small portion of the harvested tissue prior to cryopreservation. Another risk is the possibility of malignant transformation of the cryopreserved tissue after transplantation. In rats, heterotopic autotransplantation of cryopreserved ovarian tissue in the spleen resulted in the formation of sex cord stromal tumors [48].

3.7. Construction of reconstituted human oocytes (artificial gametes)

The construction of artificial gametes may be made possible by transferring the nucleus of somatic cells into enucleated oocytes and inducing chromosomal halving (haploidization). A simplified overview of the process includes the following steps: an immature oocyte at the germinal vesicle stage is enucleated by aspiration of the karyoplast. A somatic cell is isolated and inserted into the perivitelline space of the enucleated oocyte, the ooplast. Union of the cells is achieved through electrofusion. Artificial oocytes, either from human cells or from mouse cells, have been obtained, although to a limited extent and in certain experimental conditions [50].

Despite the possible promise of the method, centrosome evaluation, the conservation of the correct chromosome

number and genetic assessment of the manufactured oocytes – whether or not the recipient oocyte can engender the proper genomic imprinting that normally occurs during gametogenesis – need to be further examined [49].

The genetic information for the offspring comes from three sources: paternal, maternal and ooplasm donor (the latter in the form of mitochondrial DNA). Although this method is aimed at ensuring a normal biparental genomic contribution, it is technically similar to reproductive cloning, in which the aim is asexual reproduction [50]. These methods are still ethically extremely controversial, and in many countries they are illegal. However, artificially created gametes could in the future provide an ultimate solution for the treatment of infertility.

4. Conclusions

Young female cancer patients are still being poorly counseled with regard to the negative impact of the treatment on their fertility and on their options for fertility preservation. This review has focused both on the effect of cancer treatments on fertility and on the various surgical and assisted-reproduction innovations that are available to provide the patient with the option of future pregnancies. As the emerging discipline of fertility preservation is steadily attracting increasing interest, developments in the near future promise to be very exciting. However, in everyday routine work, better interdisciplinary cooperation between gynecological and pediatric oncologists, surgeons, immunologists and endocrinologists is necessary so that individualized options for fertility preservation can be offered in advance of surgical procedures or cancer treatments.

A not negligible aspect of the premature ovarian failure after chemotherapy, is the additional psychological stress, feelings of loss of control, depression and low self-esteem that is caused by the prospect of definite infertility. Therefore, these patients should be referred not only to reproductive specialists, but also to psychosocial providers who can diminish the impact of infertility on these young cancer survivors.

GnRH analog treatment can preserve fertility in some patients, but not in all. At present, cryopreservation of ovarian tissue appears as a very promising method of providing the cancer patient with a realistic chance of fertility preservation—a prospect that is also extremely important to patients for psychological reasons.

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