

Planning for fertility preservation before cancer treatment

The ability to have one's own biological children is an important and emotional topic for most patients of reproductive age who are diagnosed with cancer. Concerns about infertility are often not addressed during discussion of cancer treatment options and many patients are reluctant to raise this topic. However, infertility is a source of anxiety and depression among cancer survivors and can dramatically affect self-esteem. Indeed, the American Society of Clinical Oncology (ASCO) has issued recommendations that encourage oncologists to discuss fertility with young patients who require treatment.¹

Cancer among patients younger than 40

In the United States, 8% of the women diagnosed with invasive cancer in 2001 were younger than 40 years.² About 25% of the 220,000 new cases of breast cancer each year will occur in premenopausal women, most of whom will be treated with adjuvant chemotherapy.³

Among men and women younger than 40 years, the most commonly diagnosed cancers are breast cancer, melanoma, cervical cancer, non-Hodgkin's lymphoma (NHL), and leukemia.³ Treatment response rates and survival for these cancers are continually improving; 5-year survival rates now exceed 80% for childhood leukemia and are 75% for NHL.⁴

Because of this improved outlook, long-term adverse effects of cancer treatment, such as organ toxicity, impaired reproductive capacity, genetic abnormalities, and secondary malignancies, are assuming greater clinical significance. Although surrogacy and adoption are often options, many cancer survivors voice a preference for parenting their own biological children.

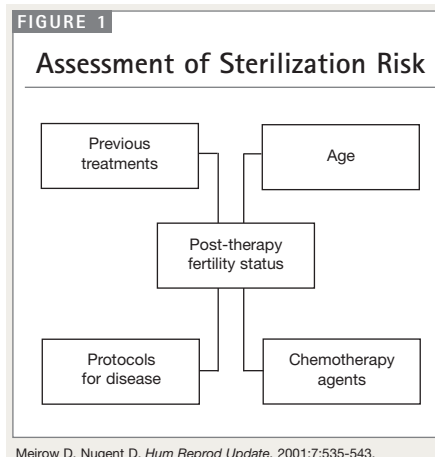
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Effects of treatment on fertility

Cancer treatment consists of chemotherapy (including the traditional chemotherapy agents and biological agents), radiation therapy, hormonal therapy, or some combination of these therapies. The effects of therapy on reproductive potential are multifactorial (FIGURE 1). The effects of chemotherapy on

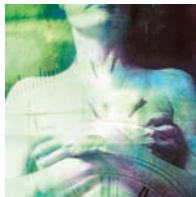


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KEY POINT

Improved awareness of the negative effects of cancer therapy on fertility and reproduction is desperately needed.

TABLE 1

Effects of Antitumor Agents on Sperm Production

Effect on Sperm	Antitumor Agents/Treatment
Prolonged azoospermia	Radiation to testes, chlorambucil, cyclophosphamide, procarbazine, melphalan, cisplatin, carboplatin
Azoospermia likely	BCNU, CCNU, busulfan, ifosfamide, nitrogen mustard, actinomycin D
Temporary reductions in sperm count when given alone; additive with other agents	Doxorubicin, thiotepa, cytosine arabinoside, vinblastine, vincristine, amсарine, bleomycin, dacarbazine, daunorubicin, epirubicin, etoposide, fludarabine, fluorouracil, 6-mercaptopurine, methotrexate, mitoxantrone, thioguanine
No effect on sperm or unlikely to affect sperm	Prednisone, interferon
Unknown effect on sperm (partial list only)	Oxaliplatin, irinotecan, trastuzumab, bevacizumab, cetuximab, erlotinib, imatinib, paclitaxel, docetaxel

BCNU, carmustine; CCNU, lomustine. Adapted from Lee SJ, et al. *J Clin Oncol.* 2006;24:2917-2931.

TABLE 2

Risk of Permanent Amenorrhea

Level of Risk	Antitumor Agents/Treatment
High risk (>80%)	Stem cell transplant, external beam irradiation to fields including the ovaries, breast cancer adjuvant combination chemotherapy regimens containing cyclophosphamide, methotrexate, fluorouracil, doxorubicin, and epirubicin in women >40 years
Intermediate risk	Breast cancer adjuvant chemotherapy regimens containing cyclophosphamide in women 30-39 years, or doxorubicin/cyclophosphamide in women >40 years
Low risk (<20%)	Combination chemotherapy regimens for NHL, ALL, AML; breast cancer adjuvant chemotherapy regimens containing cyclophosphamide in women <30 years, or doxorubicin/cyclophosphamide in women <40 years
Very low risk or no risk	Vincristine, methotrexate, fluorouracil
Unknown risk (partial list)	Paclitaxel, docetaxel, oxaliplatin, irinotecan, trastuzumab, bevacizumab, cetuximab, erlotinib, imatinib

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; NHL, non-Hodgkin's lymphoma. Risk assessment is based on rate of amenorrhea. Because some therapies compromise follicle reserve, fertility may be compromised before the cessation of menses. Adapted from Sonmezer M, Oktay K. *Oncologist.* 2006;11:422-434.

reproductive organs depend on age, sex, and chemotherapy protocol (doses, number of cycles, intervals between treatments). For patients receiving radiation, the effects depend on size/location of the radiation field, total dose, and dose-intensity.

The effect of therapy on reproductive capacity in both men and women is not an all-or-nothing event, but a continuum of little or no effects to prolonged or permanent sterility (TABLES 1 AND 2).^{1,5}

MALE PATIENTS. In men, infertility may result from the disease itself (eg, testicular cancer, and possibly, Hodgkin's lymphoma, although the latter is controversial), anatomic problems, primary or secondary hormonal insufficiency, or, most commonly,

germinal stem cell depletion. Measurable effects on germinal stem cells from chemotherapy or radiation therapy include compromised sperm numbers, motility, and morphology, and DNA integrity. In the absence of a heritable cancer syndrome, there is no evidence that a history of cancer increases the incidence of congenital abnormalities or cancer in male offspring.⁶

FEMALE PATIENTS. In women, age is likely the single greatest factor in determining the impact of cancer therapy on ovarian function. Female fertility may be adversely affected by treatments that decrease the number of primordial follicles, affect hormone balance, or interfere with the function of the ovaries,

fallopian tubes, uterus, or cervix.

Maintenance or resumption of cyclic menses is not a reliable measure of fertility because chemotherapy may compromise follicle reserve and, thus, fertility long before cessation of menses. Reductions in follicle reserve may result in premature ovarian failure and menopause even in patients who received chemotherapy at a very young age.

In vitro studies have shown that cytotoxic agents exert an immediate effect on ovarian follicles, targeting the pregranulosa cells and oocytes.⁷ Even though primordial follicles are not very metabolically active, many cancer agents induce their death by triggering cell suicide mechanisms. There is also evidence of injury to end artery blood vessels and of cortical fibrosis in human ovaries exposed to chemotherapy. It has been proposed that such injury causes relatively nonhomogeneous follicle loss throughout the ovarian cortex; however, more studies on human ovaries and experimental models are needed.⁸

ALL PATIENTS. Among chemotherapy agents, the alkylators (cyclophosphamide, ifosfamide, nitrosureas, chlorambucil, melphalan, busulfan, and procarbazine) pose the greatest risk of significant or permanent effects on fertility in both men and women. In addition, the gene mutations, chromosomal breaks, and aneuploidy induced by these agents pose a serious concern of increased risk of abortion and of birth or genetic defects in offspring conceived soon after chemotherapy.

However, risk to offspring is not increased when conception occurs after sufficient time—usually more than 6 months—has elapsed post-chemotherapy. Women who have received chemotherapy should be advised to allow a safe period between completion of treatment and conception to allow for repair mechanisms to function within oocytes.⁹

Patients who have undergone ablative chemotherapy or total body irradiation (TBI) with hematopoietic stem cell transplant (HSCT) represent a unique group of cancer survivors. Because of high treatment-related morbidity, HSCT is more frequently used for treatment of malignancies among young, reproductive-age patients. A number of studies have shown that the risk of ovarian failure after transplant is nearly universal.^{10,11} Additionally, these patients also may experience reproductive end-organ toxicity due to subse-

quent graft-versus-host disease.^{12,13} Furthermore, the TBI that is sometimes used as part of the conditioning regimen may produce uterine damage.¹⁴

Options for preserving fertility

MALE PATIENTS. Because of advances in fertilization and sperm banking technologies, all men, even those with extremely low sperm counts and motility, should be considered candidates for sperm cryopreservation (TABLE 3).¹ Studies have reported that having banked sperm may help men to cope emotionally with their diagnosis even if the samples are never used.^{15,16} Ideally, sperm should be collected before initiation of cancer therapy; it is important to note, however, that men with testicular cancer or Hodgkin's lymphoma may have particularly poor sperm quality. Hormonal therapy has not been successful in preserving fertility or speeding the recovery of spermatogenesis. Testicular tissue or spermatogonial cryopreservation and transplantation, or testis xenografting are considered experimental and have not been reported clinically.¹⁷

The female partners of former cancer patients can become pregnant with current assisted reproductive technologies, even when the patient has poor semen or a limited number of cryopreserved semen samples. The high success of in vitro fertilization with intracytoplasmic sperm injection makes cryopreservation of all samples containing any live sperm worthwhile.¹⁸

FEMALE PATIENTS. Differing approaches may be needed to preserve fertility in women, depending on the underlying disease and type of therapy, amount of time available, patient age, and whether the patient has a partner (TABLE 3). Options may include collection and cryopreservation of embryos, oocytes, or ovarian tissue, and ovarian transposition; however, these may not be covered by insurance plans.

When time does not allow for ovarian stimulation, in vitro maturation of unstimulated immature oocytes may be an option, but this approach is considered experimental. Ovarian stimulation prior to oocyte harvest must be timed so as not to interfere with other therapy and increase the risk for morbidity (infection, bleeding, clotting, etc). In women with estrogen-sensitive cancer, such as breast and endometrial malignancies, aromatase inhibitors used in conjunction with ovarian stimulation may reduce estrogen exposure and attenuate the potential risk of high estrogen levels.¹⁹

KEY POINT

The effects of cancer therapy are multifactorial—no 2 patients are alike.



KEY POINT

Several experimental techniques for fertility preservation have shown promising results.

Embryo freezing is an established technology; oocyte cryopreservation remains experimental, although techniques are improving.²⁰ Decisions to cryopreserve ovarian tissue must take into account not only patient age but risk of ovarian involvement from the underlying cancer²¹; such risk may be low (Wilm's tumor, early-stage breast cancer, nongenital rhabdomyosarcoma, osteogenic sarcoma, Ewing's sarcoma), moderate (stage IV breast cancer, stage I-III lobular cancer, adenocarcinoma of the cervix, or colorectal cancer), or high (leukemia, neuroblastoma, stage IV lobular breast cancer).

Although it is not widely used, transplantation of cryopreserved ovarian tissue after chemotherapy-induced ovarian failure has been successful in providing a return to ovarian function²² and fertility.²³ One case study describes a 28-year-old woman who had ovarian failure after chemotherapy for NHL. Ovarian tissue was harvested midway through treatment and transplanted 24 months after cessation of menses. The patient experienced spontaneous menstruation after

resumption of ovarian hormone secretion, conceived after in vitro fertilization, and delivered a healthy baby.²³

Surgical transposition of the ovaries outside the irradiation field prior to initiation of pelvic radiation has been used for decades and is the most commonly used fertility preservation practice today (FIGURE 2). This approach may be considered for patients who will not be receiving high-dose systemic chemotherapy.⁹ Surgery is effective in protecting the ovaries from irradiation damage, but fertility may be affected by scatter radiation as well as by damage to the ovarian vasculature during surgery or by torsion of the transposed ovary.

The misperception of greater ovarian toxicity in adult women compared with prepubertal girls led to a belief in the possible role of suppression of the pituitary-gonadal axis as a means to protect the ovaries.⁹ However, administration of a gonadotropin-releasing hormone (GnRH) agonist during chemotherapy treatments in order to protect the ovaries has been evaluated with mixed results and a small randomized study did not

TABLE 3

Fertility Preservation Options

	Use (Routine vs Experimental)	Timeframe for Referral/Initiation	Potential for Success
Male Patients			
Sperm cryopreservation ¹	Routine	Anytime before cancer treatment	Established
Testicular tissues/spermatogonial cryopreservation ¹⁶	Experimental	Anytime before cancer treatment	No clinical experience
Hormonal therapy	Experimental	Anytime before cancer treatment	Unsuccessful
Female Patients			
Embryo cryopreservation	Routine	Before chemotherapy begins	Established
Surgical transposition ⁹	Routine	Before pelvic radiation begins if no chemotherapy administered	Established
Oocyte cryopreservation ¹⁹	Experimental	Needs minimum of 2 weeks for stimulation	Over 200 live births; success rates lower than with fresh oocytes
Transplantation of cryopreserved ovarian tissue ^{21,22}	Experimental	Can be performed at any time before, and sometimes after, chemotherapy	Successful return of ovarian function and fertility shown in case studies
Ovarian stimulation with aromatase inhibitors ¹⁸	Investigational	Requires minimum of 2 weeks	Controlled studies show equal success rates to standard IVF; no increase in recurrence in short-term follow-up
GnRH agonist administration ^{23,24}	Experimental	During chemotherapy treatment	Mixed results; no benefit in women undergoing high-dose chemotherapy with HSCT

GnRH, gonadotropin-releasing hormone; HSCT, hematopoietic stem cell transplant; IVF, in vitro fertilization.

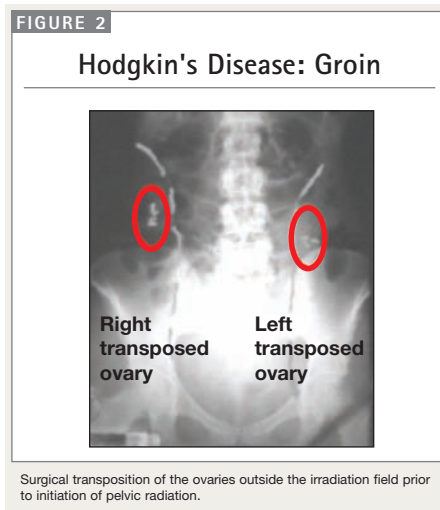
show benefit.^{24,25} In female patients undergoing high-dose chemotherapy with HSCT, GnRH analogs do not protect fertility.⁹

Regardless of the method used to preserve fertility, subsequent pregnancies should be considered high risk because of potential morbidity arising from prior chemotherapy (eg, increased risk of cardiac toxicity from prior treatment with doxorubicin).

CHILDREN. Impaired future fertility may be of little importance to children but can be traumatic during adulthood, prompting parents to inquire about fertility preservation for their children with cancer. Unfortunately, because of their sexual immaturity, fewer options for fertility preservation are available to prepubertal children.

Guidelines from ASCO

In June 2006, ASCO issued recommendations regarding fertility preservation in cancer patients.¹ The guidelines encourage oncologists to address the possibility of infertility with patients treated during their reproductive years and to be pre-



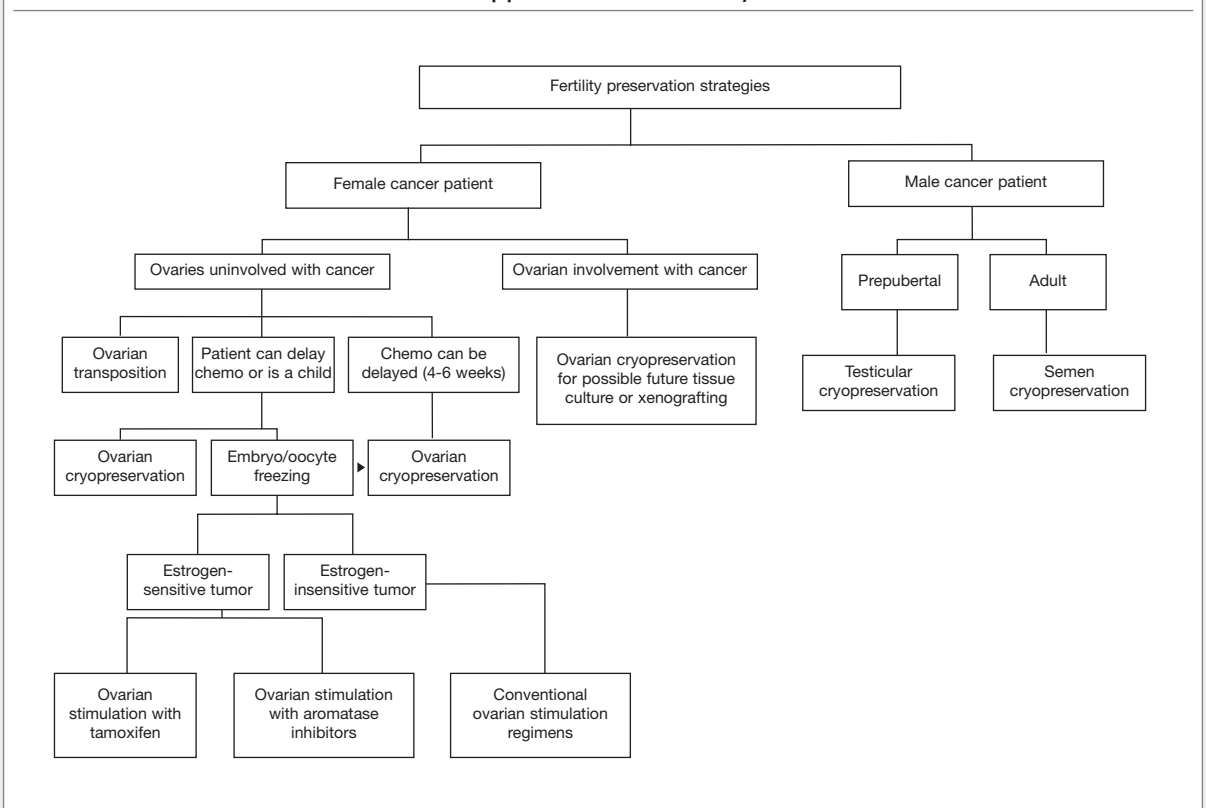
KEY POINT

After chemotherapy, any pregnancy should be considered high risk.

pared to discuss fertility preservation options or to refer patients to reproductive specialists. Although these guidelines represent a positive step forward, additional effort is needed to encourage providers to discuss fertility preservation as part of the standard workup for all cancer patients with reproductive potential.

FIGURE 3

Individualized Approaches to Fertility Preservation



Adapted from Oktay K, Sonmezer M. *Hum Reprod.* 2004;19:477-480.



KEY POINT

All patients of reproductive age diagnosed with cancer should be evaluated for and advised of fertility preservation options.

Health care team effort

Early referral, before treatment begins, is critical to proper assessment of fertility risks and planning for fertility preservation. Oncologists should be encouraged to collaborate with reproductive endocrinologists and to individualize treatment (FIGURE 3).²¹ Given the complexity of the few options available for fertility therapy following cancer treatment, it is imperative that clinicians realize the risk of sterility associated with cancer therapy and include assessment and planning for preservation of fertility before initiating treatment wherever possible. ■

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