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SPECIAL ARTICLE

Effect of Cancer and Its Treatment on Fertility and Fertility Preservation

Nares Sukcharoen MD.

Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

ABSTRACTS

Many young people receive cancer therapy which effects their future reproductive function. Sperm cryopreservation can be easily undertaken in any post-pubertal male. Oocyte cryopreservation is only at an experimental level. Cryopreservation of ovarian tissue with a view to maturing oocytes in vitro or in vivo appears to be a promising option for the future. Embryo cryopreservation is suitable for couples and is readily available and of proven effectiveness. If gonadal failure is already established, the use of donor sperm or donor oocytes is a relatively simple option. In the patients with premature gonadal failure, hormone replacement therapy should be recommended. Therefore, patients of reproductive age who are diagnosed with cancer should be informed of the long-term consequences of cancer and its therapy even if they do not readily ask for such information.

Key words : cancer, cancer treatment, chemotherapy, radiotherapy, surgery, fertility, reproduction

Over the past 30 years, the treatment success rates for cancers in the young people have increased substantially and a majority will survive their disease. With increased success rates, more patients are being cured and living normal life spans. One of the greatest concerns of these patients who receives therapy for cancer remains the eventual effect on the reproductive capacity. This article reviews the effect of cancer and cancer treatment, including surgery, chemotherapy, and radiotherapy on fertility. This review also provides update information of fertility preservation before cancer treatment, fertility restoration after cancer treatment and guideline for patient counseling.

Both cancer and its treatment interfere with normal sexual and reproductive function (Table 1).

Cancer itself can exert a harmful effect on fertility. Testicular and ovarian cancer directly involve the gonad, and prostate, endometrial, and cervical cancer directly involve the reproductive tract. Moreover, Hodgkin's disease is associated with abnormal testicular function. Furthermore, even patients who have normal gonadal function at the time of diagnosis can suffer gonadal injury secondary to the cancer treatment itself. Surgery, radiation, and chemotherapy can damage reproductive function. Gonadal failure, manifested as infertility and sexual dysfunction, has been documented in 40% to 70% of these patients.[2] Some effects are temporary, but some are permanent; some are preventable, but some are unavoidable. These consequences can have substantial effects on the patient's self esteem and quality of life.

Table 1. Reproductive consequences of cancer and cancer therapy[1]

Cancer	Direct gonadal involvement
	Reproductive tract involvement
	Hypothalamic and pituitary involvement
	Concern about inheritable cancer susceptibility
Surgery	Removal of the gonad
	Genital mutilation
	Failure of emission and retrograde ejaculation
	Impotence and loss of orgasm
Radiotherapy or chemotherapy	Germ cell depletion
	Loss of gonadal hormones
	Mutagenic changes in germ cells
	Teratogenic effects on fetus
Chemotherapy	Seminal transmission of drug
Radiotherapy (cranial)	Loss of gonadotropic hormones

Effect of cancer itself on fertility

Even before treatment is begun, cancer can exert a harmful effect on fertility. Any cancer in its advanced stages, especially if accompanied by malnutrition and decreasing overall physical and performance status, may have harmful effects on gonadal function. In males, Hodgkin's disease and testicular germ cell tumors have been associated with abnormal testicular function as manifested by abnormal semen values and abnormal hormonal status. These alterations in testicular function show no relation to the stage of the disease, the predominant cell type of lymphoma, or the age at presentation.[3] The presence of testicular cancer has also been associated with abnormal semen measurements, even before cancer treatment. Abnormal semen values have been noted in 50% to 70% of patients with testicular tumors after orchiectomy, but before additional therapy.[4] In general, ovarian function does not appear to be affected by the presence of Hodgkin's disease. However, advanced-stage lymphomas and leukemias have been associated with anovulation and amenorrhea.[5]

Effect of cancer surgery on fertility

Female

Surgical treatment for malignancies of the ovaries, uterine cervix, and uterine corpus can strongly affect female fertility, although the fertility preservation is often possible for lower staged malignancies. Only in the case of hysterectomy and bilateral oophorectomy are patients rendered totally incapable of reproducing. As with any pelvic surgery, pelvic cancer surgery can disrupt fallopian tubal function through the formation of peritubal adhesions.

Ovarian cancer

Conservative surgery for ovarian cancer is reserved for early staged lesions affecting only one ovary or for tumors of low malignant potential. In these patients, further fecundity depends on the reserve of the remaining ovary. Oocyte donation now allows the oophorectomized woman with a functioning uterus the ability to carry a viable pregnancy.

Cervical cancer

Cervical conization for in situ cervical cancer and precancerous lesions does not usually impair fertility.[6] Surgical management of higher staged lesions usually involves simple or radical hysterectomy. In these cases,

in vitro fertilization with a uterine surrogate also provides a means to bear a genetic child, if the patient retains functioning ovarian tissue.

In the uterine malignancies in women of reproductive age requiring hysterectomy, surrogacy offers the only alternative for childbearing.

Male

Testicular cancer accounts for only 1% of all cancer but it is the most common malignancy among men aged 15 to 35 years old. Radical orchiectomy of the involved testicle followed by ipsilateral iliac and retroperioneal lymph node irradiation to the level of the diaphragm is the usual treatment for pure seminomas. Nonseminomas are treated with radical orchiectomy followed by chemotherapy. Retroperitoneal lymph node dissection (RPLND) between orchiectomy and chemotherapy is controversial.

Removal of one testicle with cancer should cause no direct injurious effect on the remaining testicle. However, RPLND that involves the removal of the lymphatic drainage of the testes (the para-aortic and or inter-aortocaval nodes). It is often indicated in the treatment of non-seminomatous germ cell testicular tumors. Specifically, dissection in the area from the twelfth thoracic vertebra to the third lumbar vertebra (T12 to L3) can damage sympathetic chain ganglia and nerve fibers responsible for the initiation of seminal emission, bladder neck closure, and ejaculation.[3]

Effects of chemotherapy on fertility

Chemotherapy exerts its anti-cancer effect by killing rapidly dividing cells. Several strategies to accomplish this goal include interrupting deoxyribonucleic acid (DNA) synthesis and interfering with folate metabolism. Successful therapy for most cancers depends on systemic administration of one or more agents. Common side effects of these agents include nausea, alopecia, and leukopenia, which are short-lived and usually begin to self-correct when therapy ceases. The very high mitotic and meiotic activities in normal spermatogenesis make the germinal epithelium of the testicle highly susceptible to the damaging effects of chemotherapy when compared with other tissues. Testicular damage also occurs soon after initiating treatment; however, its effects can persist for months or years after function has returned to other tissues. Unfortunately, many men who undergo chemotherapy develop azoospermia and, somewhat less commonly, decreased libido and erectile dysfunction for an unknown period.[7]

In contrast, age or prepubertal status may be protective of ovarian function. Although alkylating agents caused a 50% reduction in the fertility of boys, no deleterious effect was observed in girls.[8] The resistance of the immature ovary may be due to an increased supply of oocytes or the smaller percentage of these cells undergoing meiosis compared with the constant cell division in the testicular germinal epithelium. The ovaries of a newborn girl contain a finite number of oocytes (about 2 million), which decreases with age. These oocytes arrest in the diplotene portion of the first meiotic prophase, a process that may be completed years later. However, cytotoxic agents can induce follicular agenesis and cause premature ovarian failure in older women. Older women are more sensitive because their supply of oocytes is more depleted at the time they begin therapy. From 2 million follicles at birth, 200,000 follicles remain at puberty and approximately 400 remain at the time of menopause.

Female

Chemotherapy is associated with the destruction of primordial follicles and their replacement by fibrous tissue. Chronic damage to follicles causes their atresia, leading to either temporary cessation of ovulation, oligomenorrhea, or permanent sterility with the features of premature menopause.[9]

An assessment of the effects of chemotherapy on ovarian function is hampered by the inability to easily estimate the size of the germ cell population. Therefore, menstrual and reproductive histories are important in assessing the functional status of the ovary. Information on the patient's menstrual cycle during and after therapy, as well as oral contraceptive use and laboratory symptoms of ovarian failure, should be noted. Hormonal measurements are most definitive in the

diagnosis of primary ovarian failure; FSH measurements are the most sensitive, but LH and estradiol levels are also useful.

Chemotherapy can often induce temporary amenorrhea which may last a few months or up to 3 years. Some of the temporary dysfunction is a result of direct ovarian damage and some is mediated through the hypothalamic-pituitary-gonadal axis. Direct ovarian damage includes loss of maturing follicles, failure of follicular recruitment, or failure of developing follicles to ovulate.

The effect of chemotherapy depends on several variables, including the type of drug, the total dose, the regimen, and the age of the patient, especially in relation to puberty (patients are less susceptible before puberty).(Table 2) While it is difficult to predict the reproductive outcome after cancer treatment for individual patients.

Table 2 . Likelihood of developing ovarian failure due to chemotherapy [10]

Definite	Cyclophosphamide
	L-Phenylalanine mustard
	Busulfan
	Nitrogen mustard
Unlikely	Methotrexate
	5-Fluorouracil
	6-Mercaptopurine
Unknown	Doxorubicin
	Bleomycin
	Vinca alkaloids
	Cispaltin
	Nitrosoureas
	Cytosine arabinoside

Male

The least serious effect on the testes is when mature sperm cells are destroyed but stem cells are spared. Sperm production from stem cell to mature spermatozoa takes about 12 weeks, and azoospermia will reverse after about three months. With partial destruction of stem cells, sperm production may not resume for several years; if all stem cells are destroyed, irreversible azoospermia results. The induced azoospermia can be either temporary or permanent, depending on the ability of surviving stem spermatogonia to proliferate, differentiate, and produce spermatozoa, which in turn depends on the nature of the cytotoxic agent and dose. The probability that spermatogenesis will recover decreases with the duration of azoospermia. The age at treatment is not a major factor in the recovery from gonadal damage in men. Nowadays, all curative chemotherapy employ combinations of agents. Different combinations vary with regard to their sterilizing potential. The expected outcome for spermatogenesis with various chemotherapeutic agents is shown in Table 3.

Table 3. Likelihood of developing sterility due to chemotherapy [10]

Definite	Chlorambucil
	Cyclophosphamide
	Nitrogen mustard
	Busulfan
	Procarbazine
	Nitrosoureas
Probable	Doxorubicin
	Vinblastine
	Cytosine arabinoside
	Cisplatin
Unlikely	Methotrexate
	5-Fluorouracil
	6-Mercaptopurine
	Vincristine
Unknown	Bleomycin

Leydig cell dysfunction is also encountered. Leydig cells are responsible for testosterone production and secretion, which are necessary both for libido and also for spermatogenesis.[11] Following chemotherapy, FSH and LH tend to be elevated and serum testosterone levels in the low normal range.

Effects of radiotherapy on fertility

Ionizing radiation damages DNA during replication and leads to the prevention of cell division.

Female

Radiation damage to the ovaries is age- and dose-related (Table 4), and manifests as either transient amenorrhea or premature ovarian failure. Similar to damage from chemotherapy, radiation damage is more likely in older women, either due to the larger pool of follicles or the higher proportion of oocytes involved in active meiotic replication. Permanent menopause can be caused in women at least 40 years old by total radiation exposure of 4 to 7 Gy in one to four fractions with 50% probability level for permanent sterility in young women being approximately 20 Gy over a 6-week period. The greater the number of fractions, the lower the risk.[13]

Table 4. Risk of ovarian failure after radiotherapy [10]

150 cGy	<40 years : minimal risk
	>40 years : some risk
250-400 cGy	<40 years : 60% ovarian failure; 40% temporary amenorrhea
	>40 years : 100% ovarian failure
500-800 cGy	<40 years : 60-90% ovarian failure
>800 cGy	Always permanent failure

Uterine malignancy requiring radiation is rare in the reproductive age group. Apart from the effect of radiotherapy on the ovary, it may also affect the uterus. Compared with women with premature ovarian failure not exposed to radiation, those who received whole abdominal irradiation in childhood had a significantly smaller uterine length, implying that radiation therapy may have an irreversible effect on uterine development and vasculature. The endometrium was also unresponsive to physiologic serum levels of estradiol and progesterone by exogenous administration.[14] This finding may be important in women undergoing in vitro fertilization using donated oocytes, where exogenous estrogen and progesterone are used for preparation of the endometrium.

Male

A single radiation dose to the testes of normal adults diminishes sperm count after a lag period of about 7 weeks.[15] Dose/toxicity curves on ionizing radiation show temporary oligospermia to occur with exposure to 10 to 30 cGY and irreversible azoospermia at exposures of 200 cGY. After exposure to intermediate doses of radiation, the return of spermatogenesis is variable in quality and may require up to 30 months after exposure. Single testicular doses of 8 to 10 Gy, given as total body irradiation in preparation for bone marrow transplantation, generally produce permanent azoospermia; however, occasionally spermatogenesis does recover 6 to 8 years later.[17]

Table 5. Effects of radiation on spermatogenesis recovery time (10)

<50 cGy	Less than 12 months
50-100 cGy	9 to 18 months
100-300 cGy	Up o 30 months
300-400 cGy	Up to 5 years
>400 cGy	Often permanent sterility

Specific administration of radiotherapy can have an effect on the subsequent toxicity, notably the specific radiation field administered and the method of delivery. Fractionated doses of ionizing radiation cause greater damage on the testicle.[18] Small doses may preferentially damage germinal epithelium, and spare other tissue. Altering the fields of external radiation to decrease the scatter effect on the testis to less than 100 cGy and the use of a lead or composite shield to protect the testicle(s) should always be attempted to minimize the chance of irreparable testicular injury.[3]

Gonadal dysfunction after cranial irradiation

Areas of the body often treated with radiation alone are the central nervous system (CNS) and the pituitary. Cranial radiation therapy can damage the CNS, including the hypothalamic-pituitary-gonadal axis, which may lead to precocious puberty, hyperprolactinemia and gonadotropin deficiency. Hyperprolactinemia tends to be more severe in females than males. Radiation therapy can also cause deficiencies in anterior pituitary hormones after treatment for a variety of disorders (nasopharyngeal cancer, pituitary tumors, and brain tumors) and in children who receive prophylactic cranial radiation for acute lymphoblastic leukemia and in patients who have undergone whole body irradiation. Anterior pituitary hormone deficiency occurs in a well-defined order with increasing doses of radiation. Growth hormone production is the most susceptible.[19]

Fertility preservation

There are many strategies for protecting fertility in cancer patients, such as, hormonal suppression of gonadal activity, attempts to limit the toxicity of the

therapy itself (for example, using fewer cycles of chemotherapy or using shielding during radiation therapy), cryopreservation of gametes and/or embryos, etc.

Choice of regimen

It is sometimes possible to choose between nearly equally curative regimens on the basis of their sterilizing potentials. The principle to be followed is to minimize the doses of the agents that are most sterilizing. In addition, preparative regimens for bone marrow transplantation that use bulsulfan and cyclophosphamide rather than total body irradiation also appear to be less sterilizing to men.[17]

Gonadal shielding

Except when they must be irradiated because of neoplastic involvement of anatomic inclusion within the irradiated target. The gonads are outside or are shielded from the direct radiation beam. Nevertheless, scatter may reach the gonads, which in both males and females are highly sensitive to damage. Even at moderately low doses, possible additive effects from chemotherapy and genetic damage to the germ cells suggest the radiation dose should be reduced even more if feasible.

Hormonal methods

The susceptibility of testicular germinal epithelium to anti-cancer agents is well known and is most likely due to the rapid turnover in this cell population. One approach to minimize damage has been to medically slow down or arrest cell turnover. Since spermatogenesis does not begin until puberty, attempts have been made to medically induce a prepubertal state through the use of gonadal steroids, GnRH analogues, or GnRH analogues combined with antiandrogens.[20] Ovarian suppression with oral contraceptives as a protectant initially appeared promising, but its effectiveness was not confirmed.[21] This strategy has been investigated for the enhancement of recovery of spermatogenesis and fertility following chemotherapy. However, there is no clinically reliable method for hormonal protection of gonadal function.[22]

Modified nerve-sparing surgery

Surgery in the treatment of testicular, prostate, and bladder cancer can produce neurologic dysfunction resulting in failure of emission, retrograde ejaculation, impotence, and loss of orgasm. Ejaculatory dysfunction after retroperitoneal lymph node dissection (RPLND) is either manifested as a failure of emission, or retrograde ejaculation in which emission takes place, but the bladder neck fails to contract and the ejaculate travels in a retrograde fashion into the bladder. Modification of the standard node dissection spares the areas below the inferior mesenteric artery and allows preservation of emission and normal ejaculation.[23] Modified templates have allowed preservation of ejaculation in 75% of patients.[3]

Gamete or embryo cryopreservation

Cryopreservation of gametes or embryos is an option to consider when contemplating therapy that may damage a patient's reproductive organs.

Sperm cryopreservation

Semen cryopreservation is an extremely important procedure for men desiring preservation of fertility potential after chemotherapy or radiotherapy. Before the advent of assisted reproductive technology (ART), only about 30% of women whose partner was a cancer patient achieved at least one pregnancy using artificial insemination of the cryopreserved sperm.[24,25] This low success rate was a result of the limited number of samples available, the poor quality semen of some cancer patients, and the loss of motility on freezing and thawing. Currently, in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) can offer these couples to achieve a pregnancy.[26] With the development of these techniques, only one or two samples need to be stored. Although men diagnosed with testicular cancer or Hodgkin's disease may have semen impairment before treatment,[4] there is usually sufficient sperm present for ICSI. Therefore, sperm cryopreservation is considered to be a method of fertility preservation for cancer patients.

When cancer is suspected, although the exact diagnosis, stage, and treatment regimen have not yet been decided. The cryopreservation procedure should

be initiated because the cryopreservation of at least three semen samples with at least a 48 hour period of abstinence between samples is recommended. This usually requires 5 to 8 days to complete to avoid possible increased genetic damage in sperm collected after the start of therapy.[27] Furthermore, the technique is easy to use, readily available in any reproductive center, relatively cheap and poses no risk to the patient. The only negative point is that it may delay treatment until samples have been collected and stored.

Oocyte cryopreservation

Oocyte cryopreservation is still experimental and not widely available. Oocytes can be cryopreserved as mature oocytes, immature oocytes and ovarian tissue.

Mature oocyte cryopreservation

Mature oocyte cryopreservation involves ovarian stimulation for 10 to 14 days, followed by oocyte retrieval, as for routine IVF. The eggs are frozen until they are required to create embryos, then thawed and fertilized using standard IVF techniques.[28] Although there have been births reported from thawed cryopreserved mature oocytes,[29] the low success rate has precluded routine clinical application of this technique. Other drawbacks include time required for a stimulation cycle, which may not be available if the need for cancer treatment is urgent, and the need for high doses of hormones is not suitable in women with estrogen-sensitive tumors, such as breast cancer.

Immature oocyte cryopreservation

An alternative approach is the use of immature oocytes collected in unstimulated cycles and subsequently frozen. Immature oocytes appear to be less susceptible to damage than mature oocytes during freezing, and this technique does not require a period of hormonal stimulation before oocyte retrieval.[30] Immature oocytes have been successfully matured in vitro, with subsequent pregnancy,[31] however there is little experience to date with fertilization of frozen-thawed, in vitro matured oocytes.

Ovarian tissue cryopreservation

The potential for cryopreservation of pieces of ovarian tissue has advantages over the current techniques of embryo or oocyte freezing. As the ovarian cortex of young women contains hundreds of thousands of oocytes, even a small portion will contain several hundred follicles.[32] The collection, cryopreservation and subsequent retransplantation of this tissue has resulted in live births in mice and sheep, but it has not yet been shown to restore fertility in human.[33]

The advantage of freezing ovarian wedges is that it can be performed at any time in the cycle, does not require hormonal stimulation, and can be performed laparoscopically. Autotransplantation of this tissue after thawing could restore ovulation. A possible risk is the transmission of cancer via ovarian graft which has been observed in mice.[34]

Instead of autotransplantation, it is possible to extract primordial follicles from frozen-thawed ovarian tissue. It is estimated that it will be several years before this treatment is readily available.[33] The collection and cryopreservation of ovarian tissue is relatively easy and could be offered to young women who understand that these is no guarantee of success.

Embryo cryopreservation

Embryo cryopreservation has proven to be one of the most successful additions to IVF technology, and is readily available in any reproductive medicine center. In the young female, oocytes can be matured in vivo and fertilized in vitro by partner, or donor sperms, and the embryo frozen and stored for future transfer. However, controlled ovarian hyperstimulation and oocyte retrieval would delay cancer treatment by 2-3 weeks. Furthermore, the live birth rate from this treatment is still low.

Unfortunately, embryo cryopreservation may not be possible for some patients. Several weeks are required for an IVF cycle, but cancer treatment may need to start immediately, and hormonal stimulation is required in IVF, which may be unsuitable for women with hormone-sensitive tumors. The ethical implication of embryo cryopreservation are also significant. Many young women with cancer do not

have a partner. In conclusion, in vitro fertilization is not an option for girls and young women. Oocyte donation later in life is a realistic option.

Optimization of fertility after cancer treatment

Men whose sperm count recovers after cancer therapy usually achieve normospermic levels, but some men remain oligospermic for extended periods. In cases of infertility with oligospermic counts, management of the patient should be the same as in those from a normal population with male factor infertility. Intrauterine insemination with the patient's sperm can be done at the female partner's midcycle LH surge. ART procedures appear to offer the most promise.

In women who have ceased menstruating following chemotherapy and have symptoms of ovarian failure, there is nothing that can be done to restore fertility. In women who have regular menstrual function following chemotherapy, infertility should generally be treated as in a normal population, except in those who received abdominal radiotherapy in childhood. These patients have increased rates of adverse pregnancy outcomes, including fetal or neonatal deaths, premature deliveries, and low birth weights due to radiation damage to the uterus, and there is a need for closer monitoring of these pregnancies.

ART procedures, including IVF and ICSI, are important in achievement of pregnancies from stored semen following the completion of chemotherapy, either as the primary modality or following unsuccessful attempts with artificial insemination. In addition, ART has a role in the optimization of fertility in men who are oligospermic following therapy and in utilization of sperm obtained from men with retrograde ejaculation.

The advantage of IVF over artificial insemination is that since insemination is usually performed with only 100,000 motile sperm per oocyte, and fewer have been used successfully samples with low counts and post-thaw motility can be used.[26] Furthermore, multiple oocytes can be fertilized in a single IVF cycle, and the embryos that are not transferred can be frozen for use at a later time. However, IVF requires hormonal induction of multiple ovulations, and the implantation of several fertilized oocytes increases the risk of multiple births and fetal loss. However, the success rate of IVF is still low.

Since freezing and thawing may result in complete loss of sperm motility, IVF may not be possible in some cases, but ICSI can be used instead.[35] The fertilization rate is about 80%, and the pregnancy rate is from about 30%.[36]

Oocyte or sperm donation

If reproductive failure is irreversible, sperm or oocyte donation can be considered. Sperm donation has been practiced and cancer-treatment sterility has been a common indication for its use. Oocyte donation is now widely practiced. The treatment is not different from any woman with ovarian failure. The greatest limiting factor is the availability of oocyte donors. This technique is readily available through most reproductive medicine units.

Management of ejaculatory dysfunction

Retrograde ejaculation

When retrograde ejaculation is present, sperm may be recovered from the bladder by direct voiding or by catheterization with irrigation.[37] Urine is often spermicidal because of its acidic pH and hyperosmolarity relative to semen.[38] For greater sperm survival, it is important to ensure a dilute, slightly alkaline urine and then to dilute the voided semen-urine mixture with buffering media to reduce harmful urine components. Therefore, the patient is instructed to increase his fluid intake and ingest sodium bicarbonate or potassium citrate for 48 hours before semen collection. Once collected, the semen samples are processed for artificial insemination or in vitro fertilization.

Failure of emission

Failure of emission is generally treated with one of three modalities: sympatho-mimetics, vibratory stimulation, or electroejaculation.

1. Sympathomimetic agents may enhance seminal

emission, and partially or completely convert the patient from retrograde to antegrade ejaculation. The medications act by causing release of norepinephrine from nerve terminals and by stimulating adrenergic receptor sites in the bladder neck.[39] Drugs, such as pseudoephedrine HCl, ephedrine sulfate, phenylpropanol-amine HCl, or imipramine HCl, should be given sequentially as 2-week trials until improvements in semen volume and sperm count are observed. Pregnancies have been reported. In general, medical therapy must be combined with some additional techniques to circumvent retrograde ejaculation.

2. Vibratory stimulation involves the application of a vibrator to the glans penis to induce a reflex ejaculation. It has a substantial success rate in spinal cord injured patients; however, because of the deficits in the sympathetic nervous system, results are often poor in patients after retroperitoneal lymph node dissection (RPLND).
3. Electroejaculation is a technique adapted from veterinary medicine where a rectal probe is used to electrically stimulate the prostate and seminal vesicles and produce emission and ejaculation. Because they have intact rectal sensation, patients after RPLND require general anesthesia. These procedures successfully produce an ejaculate in more than 90% of patients with all types of ejaculatory dysfunction,[40] although the subsequent pregnancy rate is low. Although most patients will have some antegrade ejaculate, catheterization should always be done to collect any retrograde semen.[41] Almost 30% to 40% of couples who attempt pregnancy are successful, but the fecundity rate per intrauterine insemination cycle is about 10%.[42] IVF or ICSI can be used to enhance pregnancy rates.

Hormonal deficiency from irreversible testicular damage or ovarian failure

Apart from the loss of fertility, ovarian failure always results in estrogen deficiency, with its associated symptoms. Women in whom premature menopause has been induced should be offered hormone replacement therapy. This requires both estrogen and progestogen if the uterus is present, and can be administered either by sequential or combined continuous regimens. If a hysterectomy has been performed, estrogen alone will suffice.

Testicular damage usually manifests as azoospermia, but damage to the Leydig cells, with consequent deficiency of testosterone, can also occur. Testosterone replacement may be required either orally or administered by injection or implant.

Offspring of cancer survivors

Of even more concern than simple recovery of fertility is the possibility of inducing mutations or chromosomal aberrations in the children of cancer survivors. The obvious question is whether the children of former cancer patients have an increase in the frequency of spontaneous abortion, genetic diseases, congenital anomalies, or a greater tendency to develop cancer in the future. So far, there is no firm evidence that any of these consequences occur more frequently than they do in the general population.[43] A lack of increase in the number of structural or functional abnormalities among the offspring fathered by cancer survivors who underwent chemotherapy 1 or more years before conception was reported.[44]

The use of radiation that interferes with DNA function and replication invokes similar concerns. Studies of children of Japanese survivors of the atomic bombings have not disclosed a significant germ cell effect after the single high dose of radiation.[45] It should be noted, however, that radiation therapy gives a different exposure to patients. For example, therapy is usually given in several doses.

Nearly all of these fail to indicate any significant increase in birth defects or genetic disease in offspring conceived after chemotherapy.

Cancer in the offspring of cancer survivors

Many cancer survivors fear that their children may develop cancer; these fears are based on the hereditary nature of some childhood cancers

otherwise termed "familial cancers." The overall risk of cancer in the offspring of survivors of cancer was not statistically increased relative to cancer in the offspring of control subjects or to the general population. The only exception that had a significantly increased relative risk (RR =2.9) was that with known familial cancers, such as retinoblastoma.[46]

Recommendations for the patient and clinician

Patients of reproductive age who are diagnosed with cancer should be informed of the long-term consequences of cancer and its therapy even if they do not readily ask for such information. The possibilities of sterility and genetic risk should be presented to the patients.(Table 6) In addition, the disease or treatment may have psychological and physical effects on sexual desire, erectile function, and the ability to achieve orgasm. The risks of cancer treatment-induced premature menopause should be presented to women. It is important to explain the benefits of prompt initiation of estrogen replacement therapy if ovarian failure is induced.

When attempting to maximize the preservation of fertility, pretreatment counseling of the patient and spouse or partner is essential. If patients are well informed about the potential for sexual and reproductive dysfunction during and after chemotherapy, psychological distress and anxiety may be avoided or at least decreased. It often is also reassuring for patients to know in advance that there are options for producing a family even if they are subsequently rendered permanently infertile.

Table 6. Guidelines for reproductive and genetic counseling of couples seeking pregnancy after cancer diagnosis and treatment [1]

1.	Discuss risk of infertility after cancer treatment, the option of sperm banking, and the possibility of healthy children if fertility is preserved.
2.	Explain options for gamete or embryos cryopreservation.
3.	Inquire about family history of cancer.
4.	Strongly encourage birth control during cancer treatment up to 6 months after the end of treatment; becoming pregnant or producing a pregnancy is contraindicated.
5.	Discuss theoretical concerns about mutational damage.
6.	Discuss the limited data for humans regarding congenital malformations and genetic disease, which indicate to measurable excess above the background level 4% risk for any pregnancy.
7.	Recommend that any pregnancy following therapy should be monitored with ultrasound and amniocentesis offered because of the theoretically increased genetic risk.

In conclusion, because cancer treatment may cause ovarian or testicular failure, or at best uncertainty, the possible effects need to be discussed at length, and most patients benefit from non-directive, informative and supportive infertility counseling. In appropriate circumstances, pretreatment cryopreservation of gametes should be considered. Sperm cryopreservation is readily available, but oocyte cryopreservation is still experimental. For a couple in a stable relationship where time permits, embryo cryopreservation is an option.

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