Effect of cancer and cancer treatment on human reproduction

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Cancer affecting children and individuals of reproductive age is associated with dilemmas concerning the ability to have a child and whether this child will be healthy. This is particularly true in light of the recent advances in the early detection of cancer and its effective treatment, which has improved survival rates. Both the cancer itself and its treatment have tremendous adverse effects on human reproduction and may result in the complete termination of reproductive ability both in men and women. Even in situations when conception is successfully achieved following cancer diagnosis and treatment, there are concerns regarding the potential increased risk of adverse obstetric and perinatal outcomes. This is especially true when pregnancy occurs shortly after cancer treatment. Moreover, there is a potential risk of chromosomal abnormalities and malformations in the offspring due to possible genetic defects in the germ cells induced by chemotherapy and radiotherapy. In addition, there is (at least theoretically) an increased risk of cancer developing in the offspring, particularly with hereditary cancer syndromes. A multidisciplinary team aware of the possible consequences of cancer treatment on reproduction is very much needed to provide optimal care for these patients after proper counseling regarding the potential adverse effects of cancer treatment on reproduction.

Expert Rev. Anticancer Ther. 7(6), 811–822 (2007)

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KEYWORDS:
cancer, chemotherapy, fertility, radiotherapy, reproduction

This is the first of a series of three articles discussing cancer and human reproduction from a clinical perspective. This article will present a general overview of how cancer and its treatment affect reproduction in men, women and their offspring. A review of the available literature is presented to summarize the nature and extent of the adverse effects.

The second article will deal with the different approaches to minimizing the reproductive damage caused by cancer and its treatment, as well as the various options for preserving human fertility. The third article will present details on the management of reproductive issues in cancer patients, including fertility enhancement by ovarian stimulation, assisted reproduction and contraceptive needs, as well as management of reproductive and hormonal deficiency, in particular delayed or absent puberty, menopause and andropause.

Epidemiology of cancer survival during childhood & in the reproductive age group

Although cancer is one of the leading causes of death worldwide, during the last few decades, major advances in the science and technology of cancer treatment have made this disease curable in a significant group of patients, or at least controllable in a good proportion, with long periods of survival following disease remission. The early detection of cancer and accurate diagnosis of the extent of the disease, with the continuous discovery of a stream of effective anticancer therapies and collaborative research to find the best management strategies have all lead to escalating numbers of cancer survivors worldwide.

Even though survival rates vary significantly according to the cancer type and its stage at diagnosis, the 5-year relative survival rate is around 63% for all cancers combined. Estimates from the National Cancer Institute indicated that, as of January 2000, almost

10.1586/14737140.7.6.811

ISSN 1473-7140

10 million Americans were living with a history of cancer and about 1,372,910 people were diagnosed with cancer in 2005, of whom 4% (~55,000) were under the age of 35 years [1,101,102].

The most common cancers diagnosed in people under the age of 40 years are breast cancer, melanoma, cervical cancer, non-Hodgkin lymphoma and leukemia [102]. It is estimated that in less than 3 years, one individual in almost every 250 adults will be a childhood cancer survivor, forming a pool of more than 1 million individuals in the USA. Although the incidence of childhood cancer has been constant during the last 50 years, effective treatment, long remission and the natural increase in the number of births over the years all added to the pool of childhood cancer survivors. This number is expected to increase further, particularly owing to the fact that more than 20,000 children and young individuals during their reproductive age are exposed to known mutagens in the form of chemotherapy and/or radiotherapy for cancer treatment every year [2]. This is particularly important for women who are using better methods of contraception and are delaying childbearing for social, financial or career reasons. Increasing numbers of these women become very anxious about preserving their fertility when early-stage curable cancers are discovered [2–9].

Cancer has been estimated to complicate approximately 0.02–0.1% of all pregnancies [10] and the incidence is expected to rise with the concomitant increasing age of childbearing and early detection of cancer. A population-based retrospective review of infant birth and death certificates and maternal and neonatal discharge records in California for the years 1992 through 1997 found the frequency of primary neoplasms diagnosed during pregnancy to be 19 per 100,000 live singleton births [11]. The most frequent cancer associated with pregnancy and delivery is believed to be breast cancer (3.7 per 100,000 deliveries), thyroid cancer (3.3 per 100,000 deliveries), cervical cancer (1.6 per 100,000 deliveries), Hodgkin disease (1.0 per 100,000 deliveries) and ovarian cancer (1.5 per 100,000 deliveries) [12].

In the past, cancer survivors tended to be most concerned with disease recurrence and treatment side effects. As survival rates have increased, however, patients are now also concerned about quality-of-life issues, in particular preserving reproductive potential [13].

Mechanisms of deleterious effects of cancer & cancer treatment on human reproduction

Cancer, in particular genital cancer, and cancer treatments (surgery, chemotherapy and radiotherapy) have tremendous impact on human reproduction through a direct effect on the gonads, as well as through effects on the endocrine glands. Evidence suggests that the disease process itself may influence gametogenesis [13].

When considering the effect of cancer and its treatment on human reproduction, there is a major difference between male and female reproduction due to the limited number of gametes in the female gonads (oocytes in the ovaries) with the absence of replication and formation of new oocytes in contrast to the male gametes (sperm in the testicles), which are continuously produced throughout male reproductive life.

In order to understand the different underlying mechanisms through which cancer and its treatment might affect human reproduction, a brief description of the basic concepts of human gametogenesis (formation and development of oocytes and sperm) is needed.

Female gametogenesis

In the female, it is believed that the peak number (~6–7 million) of oocytes or follicles (each oocyte exists inside one ovarian follicle) in both ovaries, is found when the female is a fetus at 5 months gestation. Beyond that point, there is no further proliferation of those germ cells (oocytes). On the contrary a progressive decline in that number of oocytes occurs due to the process of apoptosis (programmed cell death) that leads to follicle atresia. This process continues throughout the female reproductive life until menopause, which occurs when depletion of almost all the ovarian follicles and oocytes is attained. Premature ovarian failure takes place when menopause (depletion of ovarian follicles) occurs before the age of 40 years. It occurs in up to 0.9% of women in the general population. At birth, the number of oocytes decreases to approximately 2 million and at puberty there are less than half a million oocytes left in the ovaries (~300,000). Throughout the female reproductive life, approximately 1000th of these follicles (300–500 follicles) will develop into mature oocytes, whereas the rest will become atretic [14].

It is important to mention here that the rate of follicular atresia (oocyte loss) is not the same throughout the female's reproductive life. Accelerated follicular atresia occurs at a much higher rate at older age, usually by the mid-to-late thirties, until menopause. Such an accelerated rate of follicular atresia is associated with deterioration in the quality of the oocytes (with an increase in the rate of chromosomal abnormalities (i.e., aneuploidy), reduced inhibin production and increased follicle-stimulating hormone levels [15]. However, it is interesting that the central principle of age-dependent follicle depletion has been challenged by recent data suggesting that ovarian stem cells are present in female mice and could presumably lead to the replenishment of the follicles [16]. Obviously, such a theory cannot be supported in the human female in whom ovarian follicles have three major developmental phases in the lifecycle of the ovary: the phase in which embryogenesis starts *in utero* (gonadotropin independent), the pubertal/adult phase (gonadotropin dependent) and the postmenopausal phase [17].

Male gametogenesis

The testis consists of the sperm-producing component (seminiferous or germinal epithelium), arranged in tubules, and endocrine components (testosterone-producing Leydig cells) in the interstitial region between the tubules. Germinal stem cells exist in the testicles from birth. However, they do not develop into the haploid gametes (spermatozoa) until puberty. The first production of sperm is called spermarche [18].

In the prepubertal testis, there is a continuous turnover of early germ cells that undergo spontaneous degeneration before reaching the haploid stage. Such continuous cell division and turnover could probably explain the high vulnerability of the prepubertal testis to cytotoxic therapy. After puberty, the germinal stem cells undergo continual self renewal and differentiation into mature spermatozoa (within ~67 days) throughout life. Therefore, there are always germ cells in various developmental stages in the testicles [18].

The loss of germ cells has secondary effects on the hypothalamic–pituitary–gonadal axis. Inhibin secretion by the Sertoli cells declines and, consequently, serum FSH levels rise [18]. The recovery of sperm production after cancer treatment depends on the survival of the spermatogonial stem cells and their ability to differentiate. If treatment is limited to cytotoxic agents that do not kill stem spermatogonia, normal spermatozoa production is usually restored within 3 months after cytotoxic therapy [19].

Direct effect of cancer on human reproduction

Obviously, a direct effect is clear when the malignant tumor involves the genital system (e.g., ovaries and uterus in the female and testicles in the male). However, different mechanisms have been postulated to explain the adverse effects of cancer itself on human fertility (BOX 1). Cancer, in general, evokes a systemic response in the body. Cytokines, including interleukins, tumor necrosis factors and other substances secreted by the malignant tumor tissue or produced by the body defense cells, may mediate this systemic response. This theory can explain why semen parameters can improve after testicular cancer treatment [20]. Stress associated with cancer diagnosis is believed to impair fertility through disturbances at the hormonal levels [21]. Systemic effects, such as fever, have also been implicated, particularly in adversely affecting semen parameters, as seen with Hodgkin disease [22]. However, the assumption that the associated fever and other systemic effects could explain the decline in sperm parameters has not been validated. An immunological mechanism has been postulated by Redman and colleagues who found sperm agglutinins in 31% of patients with Hodgkin disease but not in healthy control subjects [23]. Systemic disturbances in the balance between subpopulations of T lymphocytes occur in patients with Hodgkin disease, and it is hypothesized that these disturbances could be a cause of dyspermia in these patients [24]. In addition, there is evidence of a shared etiology for the malignant process and reduced fertility in testicular cancer as part of the testicular dysgenesis syndrome. This syndrome is most probably the result of disturbed male gonadal development during early embryonic life, the result of environmental factors and genetically programmed susceptibility [25].

Effect of cancer treatment on female reproduction

Cancer treatment affects the different stages of female reproduction, including maturity and achievement of puberty, fertility and pregnancy.

Box 1. Suggested mechanisms behind effects of cancer on human reproduction.

- Direct effect through tissue destruction (malignant tumors of the genital system), for example, ovarian and uterine cancer in women and testicular cancer in men
- Cytokines and other toxic substances produced by the malignant tumor
- Cytokines and other toxic substances produced by the body defense cells in response to the malignant tumors
- Systemic effects induced by the malignant tumor (e.g., fever and cachexia)
- Immunological mechanisms

Chemotherapy

Chemotherapeutic agents work by interrupting cell division; they target vital cell processes needed for the cellular proliferation cycle. The three main determinants of chemotherapy-induced ovarian damage include the woman's age, the type of chemotherapeutic agent and the regimen (dose and duration) [26].

Age

As explained earlier, older women, particularly those in their late thirties and older, have a higher incidence of complete ovarian failure and permanent infertility in comparison with younger women, who have a larger ovarian follicle reserve [27,28].

Chemotherapeutic agents

It is clear that the higher the dose and longer the treatment regimen of chemotherapeutic agents, the greater the risk of ovarian failure. However, certain agents are much more deleterious to ovarian function than others. It is important to notice here that the risk of chemotherapeutic agents does not involve only ovarian failure due to depletion of ovarian follicles and oocytes, but also a direct effect on oocyte chromosomal integrity. Even when ovarian failure does not happen, a higher risk of chromosomal damage could happen in the oocytes [29]. This would obviously increase the risk of having malformed fetuses. However, it is important to mention here that such a risk is mostly theoretical as a significant proportion of the available data comes from studies in animal models, in particular the mouse. This could make it difficult to extrapolate accurate conclusions for application in the human.

TABLE 1 summarizes the risk of ovarian failure and oocyte damage in association with various commonly applied chemotherapeutic agents (as well as radiotherapy).

Radiotherapy

The three most important determinants of gonadal damage induced by radiotherapy include the cumulative dose, the irradiation field and the patient's age. TABLE 1 summarizes the damaging effect of different types and doses of radiotherapy on ovarian function.

Table 1. Risks of ovarian damage with permanent amenorrhea (ovarian failure) in women treated with modern regimens of chemotherapy and radiotherapy.

Cancer treatment	Effect on ovarian function
Bone marrow transplantation, including hematopoietic stem cell transplantation with cyclophosphamide/total body irradiation or cyclophosphamide/busulfan; external beam radiation to a field that includes the ovaries; CMF, CEF, CAF for six cycles in women aged 40 years or older (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin)	High risk (>80%) of ovarian failure and complete cessation of menstruation
Chemotherapy with CMF, CEF, CAF, six cycles in women aged 30–39 years old (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin and epirubicin); AC for four cycles in women aged 40 years and older (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide)	Intermediate risk, 20–80% may end in ovarian failure
ABVD; CHOP for four to six cycles; CVP; AML therapy (anthracycline/cytarabine); ALL (preagent); CMF, CEF, CAF for six cycles in women under 30 years old (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin and epirubicin); AC for four cycles in women under 40 years old (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide)	Lower risk (<20%)
Vincristine, methotrexate and fluorouracil	Very low or no risk
Taxanes, oxaliplatin, irinotecan, monoclonal antibodies (trastuzumab, bevacizumab, cetuximab) tyrosine kinase inhibitors (erlotinib, imatinib)	Unknown risk

NB: These are general guidelines based on the best available literature. Additional factors, particularly pretreatment ovarian reserve, specific treatment regimen and age determine individual risk for immediate infertility or for premature ovarian failure after resumption of menses or the resumption of ovarian function after temporary ovarian failure.
ABVD: Doxorubicin/bleomycin/vinblastin/dacarbazine; AC: Doxorubicin and cyclophosphamide; ALL: Acute lymphocytic leukaemia; AML: Acute melocytic leukaemia; CAF: Cyclophosphamide, doxorubicin and fluorouracil; CEF: Cyclophosphamide, epirubicin, fluorouracil; CHOP: Cyclophosphamide/doxorubicin/vincristine/prednisone; CMF: Cyclophosphamide, methotrexate and fluorouracil; CVP: Cyclophosphamide/vincristine/prednisone.
Adapted from [7].

Age

As with chemotherapy-induced gonadal damage, older women are also more vulnerable to radiotherapy-induced gonadal damage [27]. Lashbaugh and Casarett observed that women under 40 years of age are more resistant 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 [30].

Radiotherapy dose & field

Effect on the ovaries

Radiation doses, in the range of 30–70 Gy (usually applied for cervical and rectal cancer, and with craniospinal radiotherapy for central nervous malignancies) can cause a mutagenic, embryotoxic, embryolethal and teratogenic effect [4]. Radiation field can include the gonads (e.g., pelvic lymph nodes) and radiation for hematological malignancies or the gonads can be affected when the radiation field includes the whole body as with total body irradiation (TBI) before bone marrow transplantation. TBI of more than 10 Gy administered in a single dose before puberty causes a high rate of ovarian failure (55–80%), whereas fractionated TBI is less damaging to the ovaries even at higher doses. With fractionated TBI of more than 15 Gy, ovarian failure is present in all cases [4]. Wallace and colleagues estimated the dosage at which half the follicles are lost in humans to be 4 Gy [31]. Chiarelli and colleagues observed a dose-dependent and distribution-dependent relationship between the risk of premature ovarian failure and the total dosage of abdominal pelvic irradiation: with doses of less than 20 Gy the relative risk was 1.02; with irradiation of 20–35 Gy the relative risk increased to 1.37; and with doses of more than 35 Gy the relative risk of premature ovarian failure was 3.27 [32].

Effect on the uterus

In a comprehensive and detailed recent review, Critchley and Wallace have addressed the impact of cancer treatment on uterine function [33]. Uterine irradiation is associated with increased risk for infertility, spontaneous pregnancy loss and intrauterine growth retardation [34]. However, the problems of irradiation-induced uterine damage, which may lead to preterm labor and intrauterine growth retardation, are possibly encountered only in women who have been treated prepubertally [33]. There are also increased rates of obstetric complications in patients who have undergone radiotherapy in comparison with the general population, including spontaneous abortions, preterm labor and low-birth-weight infants. This is believed to be due to irreversible changes in the uterine musculature and blood flow, as well as hormone-resistant endometrial insufficiency [33]. Critchley and Wallace indicated that physiological sex steroid-replacement therapy might improve uterine characteristics in some patients after irradiation at a young age [33]. Obviously, with modern techniques of fertility preservation, such as oocyte and embryo cryopreservation before cancer treatment, a gestational carrier (another woman who carries the pregnancy in her uterus) provides an option when the radiation-induced damage to the uterus is beyond repair by sex hormones.

Effect on offspring

It is interesting that in contrast to some chemotherapeutic agents that cause chromosomal abnormalities and can result in malformed fetuses, as long as the radiation is not administered during pregnancy, there is no risk of subsequent teratogenicity [35]. In support of this, in female survivors of the atomic bombs in Hiroshima and Nagasaki, offspring conceived and born to them after exposure did not suffer a higher rate of mutations or major congenital anomalies in comparison with the normal population [36,102]. Swerdlow and colleagues confirmed that there was no excess of stillbirths, low birth weight, congenital malformations, abnormal karyotypes or cancer in the offspring of women treated for Hodgkin disease [37].

Another important risk that has been studied is that of cancers developing in offspring of childhood cancer survivors. Sankila and colleagues assessed the risk of cancer among 5847 offspring of 14,652 survivors of cancer in childhood or adolescence diagnosed since the 1940s and 1950s, using data from national cancer and birth registries in Denmark, Finland, Iceland, Norway and Sweden [37]. The offspring were followed up for a diagnosis of cancer for 86,780 person years and standardized incidence ratios were calculated. Results: among the 5847 offspring, 44 malignant neoplasms were diagnosed. The authors found no evidence of a significantly increased risk of nonhereditary cancer among the offspring of survivors of cancer in childhood [38].

Other treatments

Bone marrow transplantation

Bone marrow transplantation has become widely used in the treatment of oncohematological malignancies. The procedure includes high-dose chemotherapy, with or without body irradiation. In a survey of 38,000 male and female patients who had received high-dose chemotherapy or TBI with allogeneic/autologous stem cell transplantation, the fecundity rate was found to be extremely low, with only 129 pregnancies reported (<0.4%) [39].

Evaluating the effect of cancer treatment on female fertility (ovarian reserve tests)

After discussing the different variables that determine the fertility outcomes following cancer diagnosis and treatment, it is important to review different ways of assessing fertility potential in the female, often called 'ovarian reserve'. This is certainly important before (to help with counseling and the determination of the various treatment strategies) and after (to help determine the extent of damage to female fertility) applying cancer treatment.

Testing for ovarian reserve

The term 'ovarian reserve' denotes the available pool of primordial follicles in the ovary, which is a major determinant of female fertility potential. Both biochemical and biophysical tests have been suggested to test for ovarian reserve [40]. It is important to mention that there is no general consensus on which ovarian reserve test(s) would be the best in predicting the extent of damage to female fertility or the outcome of fertility treatment. Usually the decision as to which test(s) to select depends on the clinician's judgment. However, it is usually advisable that decisions are not made based on only one test or one value. TABLE 2 summarizes these tests.

Puberty

Radiation in excess of 30 Gy of the hypothalamic–pituitary area for brain tumors was found to cause early or even precocious puberty [41]. Conversely, children who have received larger doses of cranial irradiation are at risk of developing hypogonadotropic hypogonadism [42].

Pregnancy

Cancer diagnosis during pregnancy

The use of chemotherapy, radiotherapy and surgery in the treatment of pregnant cancer patients should be weighed carefully against the risk to the unborn child. This often raises conflicts between optimal maternal therapy and fetal well being. The incidence of specific malignant neoplasms in pregnant women parallels that of nongravid women of reproductive age [43]. The most frequent malignant neoplasms associated with pregnancy are cervical and breast cancer, malignant melanoma and Hodgkin lymphoma [44].

Effect of cancer treatment during pregnancy on its outcome

The majority of the information on the effects of *in utero* exposure to chemotherapy comes from retrospective case reports and series. The available data suggest that the risk of pregnancy loss and malformation depend on the timing of chemotherapy exposure (pregnancy trimester) and the type of chemotherapeutic agents used. Fetuses exposed to chemotherapy *in utero* in the second and third trimesters can be carried to term, born without evidence of congenital abnormalities and develop normally. However, this conclusion comes from small case series. Clearly, all ongoing prospective collection of data on the children born to women undergoing therapy for cancer is necessary [45].

Since most cytotoxic agents used today reach the fetus in significant concentrations after maternal administration and these agents are known to be mutagenic to somatic cells, significant concerns have been raised regarding the adverse effects of these treatments on fetuses exposed *in utero*. As with gamete exposure, most existing data on the mutagenic effects of chemotherapeutic agents come from animal studies with very little information on the effect of individual drugs in humans, as most reports arise from exposures to multiple agents administered in combination for common malignancies [45].

The potential teratogenic effect of cancer treatment during pregnancy depends upon the developmental stage of the fetus at the time of exposure. These developmental stages can be divided into the peri-implantation period, the embryonic period, which is the period of major organogenesis (third- to eighth-week post-conception), and the fetal period (ninth completed gestational week to term) [46]. During the early postimplantation–predifferentiation period (first 2 weeks post-conception), the conceptus is

Table 2. Tests for ovarian reserve.

Ovarian reserve test	Characteristics	Ref.
Biochemical ovarian reserve tests		
Serum follicle-stimulating hormone	Longest established test for estimating ovarian reserve; FSH level obtained on day 3 of the menstrual cycle; levels below 10 mIU/ml are indicative of adequate ovarian reserve; levels between 10 and 15 mIU/ml are indicative of reduced ovarian reserve; levels above 20 mIU/ml are associated with almost no chance of pregnancy	[71]
Serum estradiol	Condensed follicular development with early follicular recruitment is a sign of ovarian aging and poor ovarian reserve; day 3 estradiol level > 80 pg/ml indicate disrupted folliculogenesis	[72,73]
	Some deny a value for estradiol measurement in determining ovarian reserve	[74]
Inhibin B	Assays are still not widely available (considered as research rather than standard clinical practice); regarded as a direct measure of ovarian reserve, as it is mainly secreted by the granulosa cells of preantral follicles	[75–78]
	Low levels of both inhibin A and inhibin B are typical in women with premature ovarian failure and postmenopausal women	[77]
	A fall in the inhibin B concentration suggested as an earlier marker for limited ovarian reserve than an elevated FSH concentration	[78]
Anti-Müllerian hormone	Experimental rather than standard clinical practice; reflects the health of granulosa cells; decreases with age in postmenopausal women	[79–81]
Clomiphene citrate challenge test	Clomiphene citrate 100 mg/day is given on cycle days 5–9 and measurement of FSH concentrations on days 3 and 10	[82,83]
	In women with a normal ovarian reserve, the increase in estradiol and inhibin production by the developing follicles should be able to overcome the estrogen antagonist effect of clomiphene on the hypothalamic–pituitary axis and suppress FSH levels back into the normal range by day 10; an exaggerated FSH response and/or an elevated basal FSH value are considered to be signs of diminished ovarian reserve; some believe that this test does not add more information compared with day 3 FSH level	
GnRH agonist stimulation test	Experimental rather than standard clinical practice; evaluates the estradiol serum concentration change from cycle day 2 to 3 after administration of a GnRH agonist, which causes a temporary increase in the pituitary secretion of FSH and LH, which, as a consequence, stimulates ovarian estradiol production; available data are mainly from patients receiving assisted-reproduction treatment; relatively expensive; unproven value in differentiating between normal and diminished ovarian reserve	[84–86]
Human menopausal gonadotropin test	Experimental rather than standard clinical practice; looks at basal values of FSH, E2 and inhibin with hormonal and ultrasound parameters after 5 days of stimulation with human menopausal gonadotropin; relatively expensive; unproven value in differentiating between normal and diminished ovarian reserve	[87]
Biophysical ovarian reserve tests		
Antral follicles by vaginal sonography	An antral follicle count of less than five usually signifies a poorer prognosis	[88,89]
Ultrasound measurement of ovarian volume	A model has been proposed using the ovarian volume to predict reproductive age; the main limitation is the lack of data on age-dependent ovarian volume measurements in the general population	[90]
Invasive reserve test		
Ovarian biopsy	Experimental rather than standard clinical practice; invasive; expensive; contradictory evidence on the value of the antral follicle count in predicting ovarian reserve	[91]

E2: Estradiol; FSH: Follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone; LH: Luteinizing hormone.

mostly resistant to teratogenic insult [47]. Any embryonic damage during the first 4 weeks of gestation most likely leads to the death of the conceptus [48]. By the tenth week of gestation (post conception), organogenesis is complete (except CNS and gonads). During organogenesis (third to tenth week post conception), damage to any developing organs is likely to lead to major malformations while exposure to cytotoxic agents beyond this period (the second and third trimester) is not associated with teratogenic

effects. However, exposure during this period can lead to intrauterine growth restriction, prematurity and stillbirth [49,50]. It is important to point out here that disturbance of fetal development later in gestation may manifest only later in development. In particular, impairment of neurologic maturation may not be apparent at delivery and manifests early in life [51].

In humans, the teratogenic risk of cancer treatment appears to be significantly lower than commonly thought. The incidence of major malformations in fetuses exposed to chemotherapy during the first trimester is estimated to be 10–20% [52]. Malformations were reported in all organ systems, without a particular pattern. A review of 139 cases (82 articles) of women exposed to chemotherapy during the first trimester of pregnancy reported a total of 24 (17%) infants born with malformations after single-agent exposure and 25% after combination-agent exposure [53,54]. Malformations are more commonly associated with antimetabolites. The incidence of fetal malformations declined to only 6% when the antimetabolite folate antagonists were not included. In 1985, the National Cancer Institute started a registry for *in utero* exposure to chemotherapeutic agents. Out of the first 210 children monitored, there were 29 abnormal outcomes. More than 90% of those cases (27 cases) resulted from first-trimester exposure [55].

Pregnancy following cancer treatment

When discussing pregnancy following cancer treatment, three important questions arise:

- Can pregnancy can be achieved following cancer treatment?
- If pregnancy can be achieved, when would be the best time to try to conceive?
- What is the pregnancy outcome of conceptions achieved following cancer treatment?

The answer to the first question usually comes after determining the extent of damage to the fertility, as judged by how much ovarian reserve is left. However, it is important to realize that regular menses and normal reproductive hormonal levels after chemotherapy are not certain indicators of whether the ovarian follicular reserve has survived the treatment damage. On the contrary, complete cessation of menstruation and amenorrhea following cancer treatment sometimes does not indicate a 'permanent' gonadal damage and there is potential for return of ovarian function. So, follow-up tests to evaluate ovarian reserve are mandatory before definitive diagnosis of ovarian failure.

When pregnancy can be attempted is a matter of debate. Some recommend that patients who recover from ovarian failure after high-dose chemotherapy or radiotherapy treatments should not delay childbearing for too many years due to the risk of premature ovarian failure. These patients should try to conceive after a disease-free interval of a few years, but not less than 6–12 months after treatment, because of the possible toxicity of the treatment for growing oocytes [56,57]. In support of this, Fenig and colleagues report an increase in low birth weight and spontaneous abortions, especially if conception occurred less than a year after radiation exposure [58]. They advise delaying pregnancy for a year after the completion of radiotherapy. Another benefit would be an adequate period of time before pregnancy is attempted during which an absent relapse of the primary tumor makes it confirmed.

Regarding the third question of the outcome of conceptions achieved following cancer treatment, radiation of the uterus can result in increased risk of adverse obstetric outcomes, as discussed earlier, including higher risk of miscarriage and placental problems, and intrauterine growth restriction. This is mainly believed to be due to the effect on the uterine muscle and uterine blood flow. Conversely, studies that have monitored pregnancies in women exposed to chemotherapy before conception have not registered increased rates of miscarriage or congenital abnormalities in comparison with the general population. Because 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 as a result of dominant–lethal mutations at a very early stage [57].

Effect of cancer treatment on male reproduction

As discussed earlier, different stages of female reproduction are affected by cancer and its treatment, the same applies to reproduction in the male, including puberty, fertility and andropause. The two major advantages that men have regarding fertility preservation include the almost lifelong capacity to replenish their gamete production (sperm formation), as well as the much more successful and easier approaches for male gamete preservation (sperm freezing) than female gamete preservation (oocyte freezing).

Surgery

Surgical interventions such as bladder-neck or prostate resection, bilateral retroperitoneal lymphadenectomy or extensive pelvic surgery, can result in ejaculatory problems as a result of retrograde flow of semen into the urinary bladder. Modified nerve-sparing surgical improvements have reduced this adverse outcome without compromising the efficacy of the procedure with 70–80% of men with radical prostatectomy or radical cystoprostatectomy maintaining sexual function [59]. It is also important to mention here that sperm retrieval from centrifuged post-retrograde ejaculation urine samples followed by intrauterine insemination and assisted reproduction (*in vitro* fertilization and intrauterine cytoplasmic sperm injection) provide viable and very effective options for achieving pregnancy in these situations.

Chemotherapy

As discussed earlier, in the section on chemotherapy-induced female fertility damage, cytotoxic chemotherapy can cause gonadal injury and the nature and extent of the damage depends on the drug administered, the dosage received and the age of the patient [4]. Since cytotoxic treatment targets rapidly dividing cells, it is not surprising that spermatogenesis can be impaired after cancer treatment. However, the exact mechanism of the damage is uncertain, although it appears to involve depletion of the proliferating germ cell pool by killing cells not only at the stage of differentiating spermatogonia but also stem cells themselves. In addition, stem spermatogonia that do survive fail to

differentiate further [60]. TABLE 3 summarizes the various damaging effects of different cancer therapies (chemotherapy and radiotherapy) on spermatogenesis.

Radiotherapy

Ionizing radiation has adverse effects on gonadal function in men of all ages. The degree and persistence of the damage depend on the dose, radiation field and radiation schedule [61]. Very low doses of irradiation (<1.2 Gy), can affect sperm production. However, hormonal function (androgen production) is affected less, since Leydig cells that produce androgens are more resistant to damage from radiotherapy than the cells of germinal epithelium. Moreover, Leydig cells can resist damage by radiation doses of more than 15–25-times the dose of radiation that would affect sperm production (function is usually preserved up to 20 Gy in prepubertal boys and 30 Gy in sexually mature men). These boys were found to progress through puberty with normal testosterone levels despite a severe impairment of spermatogenesis [62]. Doses of more than 4 Gy can cause permanent damage to spermatogenesis [63].

When reversible gonadal damage is caused, sperm counts are typically at their lowest 4–6 months after treatment is completed and a return to pretreatment levels usually occurs in 10–24 months. However, longer periods are required for recovery after higher doses [64]. Irreversible gonadal damage occurs in a large proportion (~80%) of men following TBI as a conditioning regimen for stem cell transplantation [65].

It is important to mention here that, in many cases, men who regain spermatogenesis after cancer treatment have low sperm counts and motility and an increased rate of chromosomal abnormalities [66]. These effects appear to be dose-dependent, with an apparent threshold [67], and persist for up to 3 years after radiotherapy, so that contraception for a period of 1–3 years is recommended after testicular irradiation. This is important to avoid the risk (at least the theoretical risk) of chromosomally abnormal offspring.

Evaluating the effect of cancer treatment on male fertility (testicular reserve tests)

The strategy of measuring hormonal levels (sex hormones and gonadotropins) as in the functional tests for ovarian reserve does not apply to men. The testicular endocrine function (androgen levels) as a functional test for testicular fertility potential (sperm production) may not apply mainly because androgen production by Leydig cells is more resistant to cancer treatment (as explained earlier) than spermatogenesis. However, direct assessment of gonadal fertility potential is much easier in men than women as the sperm parameters in the ejaculated semen can be assessed.

Evaluation of the gonadal testicular function in male patients includes clinical assessment of pubertal progression, biochemical analysis of plasma gonadotropins and sex steroids and, most important of all, a semen analysis for fertility potential. Testicular enlargement is the first sign of puberty in boys, followed by penis enlargement and the development of pubic hair. Many patients will have preserved Leydig cell function after gonadotoxic treatment and will, therefore, develop healthy secondary sexual characteristics. However, their testes might be of reduced size and consistency, with a loss of tubular space suggestive of diminished sperm production [68]. Men

Table 3. Various damaging effects of different chemotherapeutic agents on spermatogenesis.

Cancer treatment	Effect on sperm production
Radiation (2.5 Gy to testis), chlorambucil (1.4 g/m^2), cyclophosphamide (19 g/m^2), procarbazine (4 g/m^2), melphalan (140 mg/m^2), cisplatin (500 mg/m^2)	Prolonged azoospermia
BCNU (1 g/m^2), CCNU (500 mg/m^2)	Azoospermia in adulthood after treatment before puberty
Busulfan (600 mg/ m^2), ifosfamide (42 g/m^2), BCNU (300 mg/m^2), nitrogen mustard, actinomycin D	Azoospermia likely, but always given with other highly sterilizing agents
Carboplatin (2 g/m^2), doxorubicin (adriamycin), (770 mg/m^2), thiotepa (400 mg/m^2), cytosine arabinoside (1 g/m^2), vinblastine (50 g/m^2), vincristine (8 g/m^2)	Prolonged azoospermia not often observed at indicated dose; can be additive with above agents in causing prolonged azoospermia but causes only temporary reductions in sperm count when not combined with above agents
Amsacrine, bleomycin, dacarbazine, daunorubicin, epirubicin, etoposide, fludarabine, fluorouracil, 6-mercaptopurine, methotrexate, mitoxantrone, thioguanine	Only temporary reductions in sperm count at doses used in conventional regimens, but additive effects are possible
Prednisone	Unlikely to affect sperm production
Interferon-α	Unlikely to affect sperm production
Examples of new agents: oxaliplatin, irinotecan, monoclonal antibodies (trastuzumab, bevacizumab, cetuximab), tyrosine kinase inhibitors (erlotinib, imatinib), taxanes	Effect on sperm production is unknown

Modified from [9].
BCNU: Carmustine; CCNU: Lomustine.

with mildly compromised Leydig cell function have been found to have normal plasma testosterone levels but with slightly increased amounts of luteinizing hormone [69]. Inhibin B is secreted mainly from Sertoli cells in men and might be reduced after gonadotoxic chemotherapy, indicating reduced sperm production [70].

Conclusion

The recent advances and success of cancer therapy, particularly for childhood cancer and patients who had cancer during their reproductive age, tremendously increased the demand for selecting the most fertility-friendly approaches for cancer treatment. Cancer itself and different modalities of cancer treatment, including chemotherapy and radiotherapy, are known to have significant deleterious effects on human fertility, both in men and women. Reasonable, evidence-based recommendations regarding the effect of cancer treatment on human fertility are needed to counsel patients during the journey of cancer diagnosis, treatment and follow-up, including the various options for fertility preservation.

Expert commentary

There is a tremendous demand for the provision of reproductive care for survivors of cancer treatment including fertility options, management of pregnancy and other needs such as contraception and sexual dysfunction. Such demand is without doubt increasing everyday with more successful outcomes of cancer treatment and availability of new effective modalities to satisfy fertility and reproductive needs. Collaborative team work between reproductive endocrinology specialists with expertise in caring for survivors of cancer treatment and oncology specialists aware of the recent advances in fertility preservation is highly desirable in order to provide care for cancer victims throughout their journey of cancer management.

Five-year view

There is no doubt that the increasing number of cancer survivors will prompt the establishment of health centers that will specialize in providing care to meet the reproductive demands for cancer survivors. More research is needed to find out the best reproduction-friendly treatment regimens without jeopardizing the chance of curing cancer. Prospective follow-up studies and registries for the reproductive outcomes following cancer treatment are expected. Moreover, new technologies for fertility preservation are expected to flourish with refined protocols and technologies that will hopefully lead to reasonably successful outcomes. More focus and attention by general practitioners and specialists in reproductive endocrinology and oncology on reproductive potentials following cancer treatment will help provide better healthcare to cancer patients. This should lead to better counseling and selection of cancer treatment options with improved consideration of reproductive outcomes. This is particularly true in light of the successful technology of fertility preservation including the established (e.g., sperm and embryo cryopreservation) as well as the emerging new technologies (e.g., ovarian tissue banking and oocyte cryopreservation).

Key issues

- As most childhood cancers will probably be cured and cancer is not infrequent during the reproductive lifespan of men and women; the number of adults who desire parenthood following cancer treatment is significantly high. This is particularly true for the high desire for parenthood in young patients exposed to cancer treatment.
- Cancer and its treatment modalities (e.g., surgery, chemotherapy and radiotherapy) have significant short- and long-term adverse effects on human reproduction, both in men and women.
- Those major concerns extend to possible adverse effects of cancer treatment on gametes and the outcome of future pregnancies.
- Several factors determine the type and extent of reproductive adverse effects imposed by cancer treatment, in particular, the type of cancer, the nature of the treatment agent and the patients' age.
- Although cancer has been reported to complicate approximately 0.02–0.1% of all pregnancies, such incidence is expected to rise with the concomitant increasing age of childbearing. Cancer during gestation poses a very difficult challenge to the pregnant patient, her fetus, relatives and medical staff.
- Collaborative teamwork between reproductive endocrinologists interested in care of the reproductive needs of cancer survivors and their oncology specialists is highly desirable for proper counseling throughout the journey of cancer treatment.

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