

Fertility and Pregnancy Outcome after Treatment for Cancer in Childhood or Adolescence

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ABSTRACT

Successful therapy for children and adolescents with cancer includes the use of ionizing irradiation and/or chemotherapeutic agents. These may produce DNA damage, resulting in cell death, or the damage may be sublethal. These effects may be expressed in the gonads as sterilization or germ cell DNA damage. Sterilization may be acute, or identified by the occurrence of premature menopause. DNA damage may be identified by an increased risk for chromosomal syndromes, single gene

defects or major congenital malformations in the offspring. Management of pediatric and adolescent cancer patients must include recognition of the potential for germ cell injury, counseling of patients regarding strategies for germ cell preservation, and long-term follow-up of the offspring of pediatric and adolescent cancer survivors to determine their increased risk, if any, for adverse pregnancy outcome, genetic disease and cancer. *The Oncologist* 1997;2:171-179

INTRODUCTION

The treatment of children and adolescents with cancer has become very successful. Almost 70% will survive for five years after diagnosis [1], with most five-year survivors expected to survive for many additional years. One of the issues of greatest concern to these survivors is the effect of their cancer and its treatment on their fertility and the health of their offspring. This review will consider the effects of treatment on germ cell survival, fertility, and health of offspring, but will not discuss the effects of radiation therapy or chemotherapy on gonadal hormone production or the role of hormone replacement therapy in the management of men and women with treatment-induced gonadal hormone insufficiency.

FERTILITY AFTER CHILDHOOD CANCER

Germ Cell Survival

Germ cell survival may be adversely affected by radiation therapy and chemotherapy. Ovarian damage results in both sterilization and loss of hormone production because ovarian hormonal production is closely related to the presence of ova and maturation of the primary follicle. These functions are not as intimately related in the testis. As a result, men may have normal androgen production in the presence of azoospermia.

Ovary

The number of oocytes in the ovary reaches a peak of 6.8×10^6 at five months of gestation. At birth there are approximately 2×10^6 primordial follicles present. This number decreases to 0.7×10^6 by six months of age, and to 0.3×10^6 by seven years of age [2]. The nonrenewable nature of oocytes renders the ovary uniquely susceptible to damage by radiation therapy and chemotherapeutic agents.

All women who receive total-body irradiation prior to bone marrow transplantation develop amenorrhea. Recovery of normal ovarian function occurred in only nine of 144 patients and was highly correlated with age at irradiation of less than 25 years [3].

The frequency of ovarian failure following abdominal radiation therapy is related to both the age of the woman at the time of irradiation and the radiation therapy dose received by the ovaries.

Whole-abdomen irradiation produces severe ovarian damage. Seventy-one percent of women in one series failed to enter puberty, and 26% had premature menopause following whole-abdominal radiation therapy doses of 2,000 to 3,000 cGy [4]. Others reported similar results in women treated with whole-abdomen irradiation [5] or craniospinal irradiation [6, 7] during childhood.

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The frequency of ovarian failure is correlated with the treatment volume. Ovarian failure occurred in none of the 34 women who received abdominal irradiation to a volume which did not include both ovaries, 14% of 35 women whose ovaries were at the edge of the abdominal treatment volume, and 68% of 25 women whose ovaries were entirely within the treatment volume [8]. These reports corroborated a study of ovarian histology which identified severe ovarian damage in children who had received abdominal irradiation, with or without chemotherapy [9].

Ovarian failure is correlated, in addition, with the radiation therapy dose. Ovarian failure occurred in 80% of five women who received 125 to 249 roentgens, 69% of 35 women who received 250 to 374 roentgens, 87% of 26 women who received 375 to 499 roentgens, 94% of 36 women who received 500 to 624 roentgens, and 100% of 72 women treated with 625 to 749 roentgens to both ovaries. The frequency of ovarian failure was lower among women less than 40 years of age who received radiation therapy doses less than 624 roentgens [10]. These data are similar to the estimate for the LD₅₀ of 600 cGy for the oocyte [11].

Ovarian function may be preserved by limiting the ovarian radiation dose. This can be accomplished in selected patients using midline oophorectomy [12, 13], lateral ovarian transposition [14], or heterotopic ovarian autotransplantation [15]. With midline oophorectomy, the ovarian doses received from pelvic irradiation can be limited to 220 to 550 cGy when the treatment dose is 4,400 cGy [12], and in women who are less than 25 years of age at the time of treatment, ovarian failure is infrequent (Table 1) [12, 16, 17]. One of these procedures should be considered prior to irradiation of any female child or adolescent who will receive pelvic irradiation.

Ovarian function was evaluated in women following treatment with combination chemotherapy (Table 2) [18-21]. These studies, performed following treatment with the combination of nitrogen mustard, vincristine, procarbazine and prednisone (MOPP); the combination of nitrogen mustard, vinblastine, procarbazine, and prednisone (MVPP); or the combination of chlorambucil, vinblastine, procarbazine and prednisone (ChIVPP) demonstrated the sensitivity of the older patient to the gonadal toxicity of such therapy (Table 3) [22-25], whether three or six cycles were administered (Table 4) [26]. Younger women had a lower frequency of amenorrhea following treatment with one of these combinations.

Ovarian function was evaluated in women treated with drug combinations which did not include procarbazine. Ovarian function was normal in all of six women treated for non-Hodgkin's lymphoma with a cyclophosphamide-containing drug combination [27]. Others reported that pubertal progression was adversely affected in 5.8% of 17 patients treated before puberty, compared with 33.3% of 18 patients treated during puberty

or after menarche. However, the administration of cyclophosphamide did not correlate with the abnormal pubertal progression observed in these patients [28]. *Cis*-platinum administration resulted in amenorrhea in 14% of seven patients [29].

Table 1. Relationship between ovarian radiation dose and the occurrence of amenorrhea

Radiation dose (cGy)	Amenorrhea
0 - 100	16% (1/6)
101 - 200	14% (1/7)
201 - 300	12% (1/8)
301 - 400	25% (1/4)
401 - 500	44% (4/9)
501 - 600	50% (3/6)
601 - 700	25% (1/4)

Table 2. Frequency of amenorrhea following treatment with combination chemotherapy

Patient age	Regimen	Frequency of amenorrhea
All ages	MVPP	63% (20/32)
All ages	MOPP	39% (17/44)
All ages	ChIVPP	19% (6/32)
All ages	ChIVPP/EVA	80% (16/20)

Table 3. Relationship between age at treatment and frequency of amenorrhea following treatment with combination chemotherapy

Patient age	Regimen	Frequency of amenorrhea
<30 years	MVPP	52% (17/33)
30 - 51 years	MVPP	86% (31/36)
<25 years	MOPP	20% (3/15)
>25 years	MOPP	89% (8/9)
<30 years	MOPP	0% (0/10)
30 - 40 years	MOPP	50% (5/10)

Table 4. Relationship among age at treatment, number of cycles, and frequency of amenorrhea following treatment with combination chemotherapy

Patient age	Number of cycles	Regimen	Frequency of amenorrhea
16 - 30 years	3	MOPP	3% (1/31)
	6	MOPP	9% (1/11)
31 - 45 years	3	MOPP	61% (11/18)
	6	MOPP	62% (5/8)

Chemotherapy with doxorubicin, cyclophosphamide, and high-dose methotrexate produced irregular menses in 20% of five women, and persistent amenorrhea in 20% of five women treated for soft-tissue sarcomas [30]. Therapy with high-dose methotrexate (250 mg/kg/dose), with or without vincristine, did not cause ovarian failure in any of four women evaluated after the completion of therapy [31]. Treatment with nitrosourea, with or without procarbazine, produced ovarian damage in young women treated with craniospinal irradiation for malignant brain tumors [32].

Women who received high-dose (50 mg/kg/day \times 4 days) cyclophosphamide prior to bone marrow transplantation for aplastic anemia all developed amenorrhea following transplantation. In one series, 36 of 43 had recovery of normal ovarian function 3-42 months after transplantation [3].

Loss of ovarian function following chemotherapy administration to post-menarcheal patients is associated with significant changes in libido and sexual function [33]. Recovery of ovarian function is unlikely if menstrual periods do not return within three months after cessation of treatment [34].

The presence of apparently normal ovarian function at the completion of chemotherapy should not be interpreted as evidence that no ovarian injury has occurred. Premature menopause is well documented in childhood cancer survivors, especially those women treated with both an alkylating agent and abdominal irradiation [35]. When the pelvis is excluded from the treatment volume and treatment does not include combination chemotherapy, premature menopause is infrequent [36].

Testis

Testicular function may be damaged by surgery, irradiation, and/or chemotherapy. Retrograde ejaculation is a frequent complication of bilateral retroperitoneal lymph node dissection performed on males with testicular neoplasms [37, 38], and impotence may occur following extensive pelvic dissections as may be performed to remove a rhabdomyosarcoma of the prostate [39].

One of the first studies of the effects of testicular irradiation on spermatogenesis was conducted using inmate volunteers from the Oregon State Penitentiary who underwent vasectomy at the completion of the radiation experiments. Complete recovery of spermatogenesis was observed 9-18 months after treatment in those treated with 100 cGy, by 30 months in those treated with 200 or 300 cGy, and after 60 or more months in those treated with 400 or 600 cGy [40, 41].

Men treated with whole-abdomen irradiation may develop gonadal dysfunction. Five of ten men were azoospermic, and two were severely oligospermic when evaluated at ages 17-36 years following treatment with whole-abdomen irradiation for Wilms tumor at ages 1-11 years, with the penis and scrotum

either excluded from the treatment volume, or shielded with 3 mm of lead. The testicular radiation doses varied from 796-983 cGy [42]. Others reported azoospermia in 100% of 10 men 2-40 months after radiation therapy doses of 140-300 cGy to both testes [43]. Similarly, azoospermia was demonstrated in 100% of ten men following testicular radiation therapy doses of 118-228 cGy. Recovery of spermatogenesis occurred after 44-77 weeks in 50% of the men, although three of the five with recovery had sperm counts below $20 \times 10^6/\text{ml}$ [44]. Oligo- or azoospermia was reported in 33% of 18 men evaluated 6-70 months after receiving testicular radiation doses of 28-135 cGy [45]. In another report, none of five men who received testicular radiation doses of less than 20 cGy became azoospermic. By contrast, two who received testicular radiation doses of 55-70 cGy developed temporary oligospermia, with recovery to sperm counts greater than $20 \times 10^6/\text{ml}$ 18-24 months after treatment [46].

Administration of higher doses, such as the 2,400 cGy used for the treatment of testicular relapse of acute lymphoblastic leukemia, results in both sterilization and Leydig cell dysfunction [47]. Craniospinal irradiation produced primary germ cell damage in 17% of 23 children with acute lymphoblastic leukemia [48], but in none of four children with medulloblastoma [49]. With adequate shielding, gonadal failure following radiation therapy to a volume that does not include the testis is infrequent [50].

Combination chemotherapy which includes an alkylating agent and procarbazine causes severe damage to the testicular germinal epithelium (Table 5) [19-21, 51-60]. Azoospermia was present in all men by the start of the third cycle of MVPP chemotherapy [56], and less than 20% of men had recovery of spermatogenesis when evaluated 37-48 months after treatment, suggesting that recovery of spermatogenesis in this population of patients was infrequent [55]. Azoospermia occurred less frequently following treatment with two, rather than six, cycles of MOPP (Table 6) [61], and elevation of the basal follicle stimulatory hormone (FSH) level, reflecting impaired spermatogenesis, was less frequent among patients receiving two courses of vincristine, procarbazine, prednisone, Adriamycin (OPPA), than among those who received two courses of OPPA in combination with two or more courses of cyclophosphamide, vincristine, procarbazine and prednisone (COPP) [62].

Most studies suggest that procarbazine contributes significantly to the testicular toxicity of combination chemotherapy regimens. The combination of doxorubicin, bleomycin, vinblastine and DTIC frequently produced oligo- or azoospermia during the course of treatment. However, recovery of spermatogenesis occurred after treatment was completed in contrast with the experience reported following treatment with MOPP [57].

Table 5. Frequency of azoospermia following completion of combination chemotherapy

Treatment regimen	Frequency of azoospermia
MOPP	75% (42/56)
M(O/V)PP, COPP	87% (5/6)
MVPP	86% (132/154)
COPP	100% (106/106)
ChIVPP	100% (11/11)
ChIVPP/EAV	95% (21/22)
ABVD	0% (0/13)

Table 6. Relationship between number of chemotherapy cycles and the frequency of azoospermia after combination chemotherapy

Treatment regimen	Number of cycles	Frequency of azoospermia
MOPP	2	0% (0/7)

An early report suggested that the prepubertal testis was less sensitive to damage by MOPP chemotherapy than the postpubertal testis [54]. Several groups of investigators reported that damage to the prepubertal testis could not be identified until the patient entered puberty if the frequency of testicular damage was estimated by the presence of an elevated serum FSH level [51, 63-66]. None of these studies reported that prepubertal males were at lower risk for chemotherapy-induced testicular damage than were postpubertal patients.

Treatment for nonseminomatous germ-cell tumors of the testis usually includes the combination of cisplatin, vinblastine, and bleomycin. Oligospermia or azoospermia was reported in most men following treatment with this chemotherapy regimen, with azoospermia still present in 25%-30% of men 24-94 months after completion of treatment [67-69]. Interpretation of these results, as well as those in men with Hodgkin's disease, is complicated by the high frequency of oligo- or azoospermia in these patients prior to initiation of treatment (outlined below).

Testicular function was evaluated in patients following treatment with combination chemotherapy for acute lymphoblastic leukemia during childhood. Basal serum FSH and luteinizing hormone (LH) levels were normal in 32 prepubertal boys evaluated, whereas 37.5% of eight early-pubertal, and 50% of four late-pubertal subjects had raised basal serum FSH levels [70]. The factors which influenced the severity of testicular damage were the total dose of cyclophosphamide, administration of a cumulative dose of cytosine arabinoside which exceeded 1 gm/M², and the length of time between the

cessation of treatment and testicular biopsy [71]. Blatt *et al.* reported normal testicular function in 14 boys treated for ALL with therapy which did not include either cyclophosphamide or intravenous cytosine arabinoside, emphasizing the importance of the agents employed in determining the gonadal toxicity of a combination chemotherapy program [72].

Three of the four men treated with high-dose methotrexate for osteosarcoma had normal sperm counts, whereas the fourth was severely oligospermic when first evaluated after cessation of treatment [31]. Treatment of men with doxorubicin, cyclophosphamide, and high-dose methotrexate for soft-tissue sarcoma produced azoospermia in 100% of eight men following chemotherapy and proximal radiotherapy, 25% of eight men following chemotherapy and distal radiotherapy, and 20% of five men treated with chemotherapy only. Recovery of spermatogenesis was documented in men treated with chemotherapy only or chemotherapy and distal radiation, whereas azoospermia persisted in those men treated with chemotherapy and proximal radiotherapy [73]. Similar results have been reported in male survivors of non-Hodgkin's lymphoma, in whom pelvic radiation therapy and cumulative cyclophosphamide dose greater than 9.5 gm/M² were independent determinants of failure to recover spermatogenesis [74], and in survivors of Ewing's and soft-tissue sarcoma, in whom treatment with a cumulative cyclophosphamide dose greater than 7.5 gm/M² was correlated with persistent oligo- or azoospermia [75].

FERTILITY

The fertility of survivors of childhood cancer, when evaluated in aggregate, is impaired. The adjusted relative fertility of survivors compared with that of their siblings was 0.85 (95% confidence interval (CI)—0.78-0.92). The adjusted relative fertility of male survivors (0.76, 95% CI—0.68-0.86) was slightly lower than that of female survivors (0.93, 95% CI—0.83-1.04). The most significant differences in the relative fertility rates were demonstrated in male survivors who had been treated with alkylating agents, with or without infradiaphragmatic irradiation [76].

Fertility may be impaired by factors other than the absence of sperm and ova. Conception requires delivery of sperm to the uterine cervix and patency of the Fallopian tubes for fertilization to occur, as well as appropriate conditions in the uterus for implantation. Retrograde ejaculation occurs with a significant frequency in men who undergo bilateral retroperitoneal lymph node dissection. Uterine structure may be affected by abdominal irradiation. A recent study demonstrated that uterine length was significantly less in ten women with ovarian failure who had been treated with whole-abdomen irradiation. Endometrial thickness did not increase in response to hormone replacement therapy in three women who underwent weekly

ultrasound examination. No flow was detectable in five women with Doppler ultrasound through either uterine artery or through one uterine artery in three additional women [77]. These data are pertinent when considering the feasibility of assisted reproduction for these survivors.

HEALTH OF OFFSPRING

Most chemotherapeutic agents are mutagenic, with the potential to cause germ cell chromosomal injury. Possible results of such injury include an increase in the frequency of genetic diseases and congenital anomalies in the offspring of successfully treated childhood and adolescent cancer patients.

Several early studies of the offspring of patients treated for diverse types of childhood cancer identified no effect of previous treatment on pregnancy outcome and no increase in the frequency of congenital anomalies in the offspring [78-80]. However, a study of offspring of patients treated for Wilms tumor demonstrated that the birthweight of children born to women who had received abdominal irradiation was significantly lower than that of children born to women who had not received such irradiation [81], a finding which was confirmed in several subsequent studies [82-84]. The abnormalities of uterine structure and blood flow reported following abdominal irradiation may explain this clinical finding.

Prior studies of offspring of childhood cancer survivors were limited by the size of the population of offspring and the number of former patients who had been exposed to mutagenic therapy. Several recent studies which attempted to address some of these limitations did not identify an increased frequency of major congenital malformations [80, 85-91], genetic disease [80] or childhood cancer [91-93] in the offspring of former pediatric cancer patients, including those conceived after bone marrow transplantation [94].

In general, the studies of pregnancy outcome following treatment with chemotherapeutic agents are reassuring with respect to the possible increased occurrence of congenital malformations or genetic diseases in the offspring. However, the number of exposed patients available for study is still small, and the follow-up of those offspring who have been identified is short, precluding definitive statements regarding the risk of cancer in the offspring.

PATIENT MANAGEMENT

Patients who will receive therapy with the potential to limit or abolish fertility need sensitive, informed management. Important aspects of management include considerations of gonadal protection, germ cell storage, and assisted fertilization.

Protection of the ovary using oral contraceptive agents and luteinizing, hormone-releasing hormone agonists was evaluated in women treated with MVPP. Although one

study demonstrated that permanent amenorrhea did not occur in six women aged 18-31 years who received an oral contraceptive during the period of treatment with MVPP [95], another was unable to demonstrate a protective effect of oral contraceptive administration on the ovarian function of women treated with MVPP [18]. Amenorrhea occurred in all eight women, aged 17-34 years, treated with a luteinizing hormone releasing hormone (LHRH) agonist (Buserelin) and three of ten MVPP-treated control women. Four of the Buserelin-treated women had recovery of ovarian function after therapy with MVPP was completed [96].

Buserelin administration was evaluated for protection of the testis. No protective effect, as estimated by post-therapy sperm count, was evident in 20 Buserelin-treated men, when compared with 10 control men [96]. Similarly, no protective effect of treatment with another LHRH agonist, D-Trp⁶-Pro⁹-N-ethylamide-LHRH (LH-RHa), on spermatogenesis was demonstrated in six men following treatment with MOPP [97].

Men with previously untreated Hodgkin's disease and testicular carcinoma frequently have semen with low numbers of inadequately mobile sperm [98-103]. Although artificial insemination by husband (AIH) has been successful utilizing frozen semen specimens from patients whose pretreatment samples had adequate numbers ($>20 \times 10^6/\text{ml}$) of motile sperm [99-102], fertilization is possible with lower sperm concentrations using gamete intrafallopian tube transfer or in vitro fertilization. Thus, sperm banking should be considered for any male who is not azoospermic prior to therapy and whose therapy may result in azoospermia [104].

Retrograde ejaculation may occasionally be treated successfully with sympathomimetic agents [105]. Recently, several reports have been published detailing successful fertilization using spermatozoa recovered following sexual activity from urine of men with retrograde ejaculation [106-109].

Assisted reproduction technology has extended the possibility of pregnancy to women with treatment-induced ovarian failure. Although less likely to successfully implant, frozen embryos have implanted successfully after transfer [110], and there are several reports of successful initiation and progression of pregnancy in postmenopausal women given exogenous hormone replacement and embryos produced from donor oocytes and their male partner's sperm [111-113].

Recent laboratory investigations have demonstrated that spermatogenesis may be reconstituted in the mouse from frozen spermatogonial stem cells [114-116], and that fertility could be restored by reimplantation of frozen-thawed primordial follicles or ovarian cortical slices [117, 118]. These techniques may allow reconstitution of fertility in humans utilizing the stored tissues of the patient obtained prior to initiation of cancer treatment.

SUMMARY

Gonadal damage is not infrequent in survivors of childhood and adolescent cancer. Surgical removal of the ovaries from radiation therapy treatment volumes should be performed when possible. Careful attention must be paid to radiation therapy technique, especially the use of effective shielding of the testes and ovaries from the radiation beam, when such use will not adversely impact the likelihood of local tumor control. Gamete banking offers the potential for later reproduction using assisted reproduction technology, when sterilization is an

unavoidable sequela of successful treatment. Counseling of survivors should include discussions of the possibility of immediate sterilization or premature menopause as the result of treatment. Young women must assess the risk of premature menopause when contemplating postponement of pregnancy to allow completion of graduate education or career development. Adolescent and young adult survivors need to be aware that sterilization is not a generic outcome of cancer therapy, and that precautions to prevent pregnancy must still be taken if pregnancy is not the desired outcome of sexual activity.

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