REVIEW ARTICLE

The Effect of Chemotherapy and Radiotherapy on Fertility

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ABSTRACT

Improvements in cancer treatment have led to increasing numbers of cancer survivors who may desire to have children. Both chemotherapy and radiotherapy can have long-term consequences on reproductive function. Chemotherapeutic agents, especially alkylating agents, are gonadotoxic. Cranial irradiation may cause hypothalamic-pituitary dysfunction and disturb the hormonal regulation of menstruation and fertility. Abdominal or pelvic irradiation has direct toxic effects on the gonads. Female cancer survivors are at risk of premature ovarian failure and adverse pregnancy outcomes. Male survivors are also at risk of subfertility or infertility. This article reviews the effects of chemotherapy and radiotherapy on fertility, pregnancy, and neonatal outcomes of cancer patients.

Key Words: *Chemoradiotherapy; Fertility preservation; Neoplasms; Pregnancy; Radiation injuries*

中文摘要

化療和放療對生育的影響

鄺麗雲

隨著癌症治療不斷的改善，越來越多癌症康復者可能希望有下一代。可惜化療和放療往往會對生殖器官有長遠的影響。化療藥物，尤其是烷化劑，對生殖功能造成損傷。而全腦照射會引致下視丘及腦下垂體功能異常，從而干擾負責調控月經及生育的荷爾蒙環境。腹部或盆腔放療對性器官有直接的毒性。女性癌症康復者會有卵巢早衰的危險並引致不良妊娠。男性癌症康復者也可能經歷生育力低下或不育的風險。本文探討化療和放療對癌症康復者在生育、妊娠及新生兒方面的影響。

INTRODUCTION

Fertility is often an issue or concern for children and younger adults treated for malignancy, as both radiotherapy and chemotherapy can have long-term effects on the gonads. With the increasing success of combined treatment in many paediatric cancers, approximately 78% of all patients diagnosed before 15 years of age survive for five years and the majority are now expected to survive into adulthood.[1]

Several malignant conditions affect younger adults including melanoma, cervical cancer, germ cell tumours, leukaemia and lymphoma, ovarian cancer, and breast cancer. Malignancy is estimated to occur in one in every 49 women under the age of 40 years in western countries.[2] According to the Hong Kong

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Cancer Registry, the incidence of cancer in males under the age of 40 years was 259 per 100,000 in 2009 and the corresponding incidence in females was 346 per 100,000.[3] In females, fertility problems after cancer treatment can manifest as amenorrhoea, oligomenorrhoea, subfertility, infertility, or adverse pregnancy outcomes. In males, both sperm quantity (decreased sperm count, oligospermia, azoospermia), and quality (impaired sperm motility, morphology and DNA integrity) can be affected. There may also be structural and functional problems, such as abnormal uterine and vaginal growth in young girls and abnormal ejaculation or erectile dysfunction in males after radiotherapy. Fertility issues may also impact on survivors' quality of life and self-esteem. This article reviews the effects of chemotherapy and radiotherapy on the fertility, pregnancy, and neonatal outcomes of cancer patients.

CHEMOTHERAPY

Several classes of chemotherapeutic agents are gonadotoxic (Table 1[4]). The impact of combination chemotherapy on germ cells is dependent on the type and dosage of drugs used. Alkylating agents are the most gonadotoxic chemotherapeutic drugs because this class of drugs induces DNA damage and is cell cycle–independent. Alkylating agents cause dose-dependent, direct destruction of oocytes and follicular depletion, and may bring about cortical fibrosis and ovarian blood vessel damage.[5,6] The reported rate of premature ovarian failure after various diseases and chemotherapeutic protocols differs enormously and depends mainly on the chemotherapeutic protocol used and the age of the woman. About 50% of women over 25 years old and 20% of women under 25 years old treated with MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) for lymphoma would develop premature ovarian failure.[7] Platinum agents are female-specific mutagens.[8] These agents may cause chromosomal aberrations leading to dyskaryosis — such as deletions, ring formations and DNA rearrangements — resulting in embryotoxicity and embryonic demise. It has been estimated that alkylating agents pose the highest risk of ovarian failure with an odds ratio of almost 4, while platinum derivatives have an estimated odds ratio of 1.77 for risk of ovarian failure. The other drug families do not cause a significant increase in ovarian failure rates.[5,9]

Male germ cells are also sensitive to damage by alkylating agents. The threshold dose of cyclophosphamide in relation to infertility has been estimated to be between 7.5 g/m^2 and 9 g/m^2, and in postpubertal patients 300 mg/kg, equivalent to 10 g/m^2.[10,11] A cisplatin dose of 600 mg/m^2 is likely to cause prolonged azoospermia.[12,13] Chemotherapy-induced Leydig cell failure resulting in androgen insufficiency and requiring testosterone replacement therapy is rare.[14]

Germ cell toxicity is also a significant late toxicity of haematopoietic stem cell transplantation which will include high-dose chemotherapy, with or without total body irradiation as conditioning. Germ cell failure with raised serum levels of follicle-stimulating hormone (FSH) decreased gonadal growth and delayed puberty has been observed among patients after transplantation.[15]

The Need for Contraception after Treatment

The first trimester is the period of embryogenesis and organogenesis (4-13 weeks). Exposure of a pregnant woman to chemotherapy in the first trimester is associated with increased risk of fetal anomalies, miscarriage, and intrauterine fetal demise. Doll et al[16] reported that the incidence of fetal malformations with first-trimester chemotherapy exposure with a variety of agents ranged from 14 to 19%. However, exposure in the second or third trimester was associated with an incidence of foetal malformations of only 1.3%. In the general population, the incidence of major congenital malformations has been reported as approximately 3% of all births.

Table 1. Gonadotoxic chemotherapeutic agents.[4]

High risk (prolonged azoospermia or premature ovarian failure)	Intermediate risk	Low risk
Alkylating agents:	Cisplatin / carboplatin	Methotrexate
Cyclophosphamide	Adriamycin	Fluorouracil
Melphalan	Taxoids (docetaxel and paclitaxel)	Vincristine
Busulfan		Bleomycin
Other nitrogen mustard analogues		Actinomycin D
Chlorambucil		
Procarbazine		

Pregnancy occurring within several months after cytotoxic treatment has been shown to be associated with increased rates of fetal demise and fetal malformation. No increase in miscarriage or congenital anomalies was detected in studies reporting on neonates born more than two years after chemotherapy.[5,6] Contraception is recommended for the first two years after chemotherapy.[4] This is to prevent fertilisation of ova that may have been exposed to chemotherapy during the period of folliculogenesis and growth, as the growth of ovarian follicles in humans from primordial to metaphase II stage can take three to nine months. Another consideration in terms of contraception use is uncertain disease control, as most instances of recurrence are detected within the first two years after treatment and patients may have frequent radiological examinations during this period.

There are data from experimental animals which indicate high levels of mutagenic effects in offspring from matings during or soon after treatment of the male with chemotherapy or radiation.[17] Damage to sperm DNA for up to two years after completion of therapy has been reported in patients undergoing radiation therapy and chemotherapy for testicular cancer and systemic therapy for Hodgkin's lymphoma.[17,18] Due to the potential genetic risk of mutagens on germ cells, it is recommended that male patients complete semen cryopreservation prior to the initiation of chemotherapy and that they practise reliable contraception from the time of initiation of treatment for up to two years.[17,18]

Preserving Fertility after Chemotherapy
Non-gonadotoxic Cancer Therapy
Optimal cancer treatments which could directly target only malignant cells would have no side-effects on the gonads. Improved cancer treatment protocols and the increasing availability of molecular target therapy may contribute to future progress in this direction without diminishing the efficacy of cancer treatment.

Cryopreservation of Gametes or Embryo
The American Society of Clinical Oncology issued recommendations on fertility preservation for cancer patients in 2006.[19] At present, sperm banking and embryo cryopreservation are considered standard practice. All pubertal boys with testis volumes of above 10 to 12 ml are encouraged to donate a semen sample prior to cancer therapy. It is reasonable to obtain two to three ejaculates per patient because semen quality may be reduced. Alternatively, electro-ejaculation,

penile vibratory stimulation, obtaining spermatozoa in a urine sample or testicular sperm extraction from a biopsy can be used as a source to retrieve spermatozoa for boys unable to ejaculate. With advances in assisted reproduction techniques, in particular intracytoplasmic sperm injection, the problems of low sperm numbers and poor motility can be circumvented and the efficacy of sperm cryobanking improved.

For women, in-vitro fertilisation and embryo cryopreservation are the only non-investigational, ubiquitously agreed upon, and clinically established methods of preserving fertility. However, this may require postponing chemotherapy and is frequently not applicable to young and single women. In the past two decades, cryopreservation of unfertilised ova has gained popularity and there has been increased success, owing to the use of the vitrification method.[4] However, this approach involves hormonal stimulation which may not be desirable for hormone sensitive cancers, such as breast cancer.

Cryopreservation of Gonadal Materials
For prepubertal boys and girls, a potential alternative strategy for preserving fertility involves cryopreservation of immature gonadal tissue. The gonadal tissue can be re-transplanted to the patient after treatment. However, the best timing and optimal amount of gonadal tissue collected and the technology of cryobanking are complex issues that need to be resolved. Also, as there may be cancer cell contamination in the gonadal tissue, there is the possibility of reseeding malignant cells in cured cancer patients.[20,21]

Administration of Gonadotropin-releasing Hormone Agonistic Analogues
Gonadotropin-releasing hormone agonistic analogues (GnRH-a) have been suggested as chemoprotective agents. It is hypothesised that suppression of pituitary gonadotropin production, with subsequent reduction in ovarian follicular cell division and growth, render the follicles less vulnerable to cytotoxic agents.[22] To date, the evidence for the use of GnRH-a is controversial. Prospective studies and a meta-analysis concluded that the addition of GnRH-a to chemotherapy can significantly preserve ovarian function and fertility in premenopausal women facing gonadotoxic chemotherapy.[16,23] However, results from recently published well-conducted randomised trials are mixed and conflicting.[24,25] Many trials used ongoing menses and biomarkers as surrogates for ovarian function. The

value of the strategy for fertility preservation is unclear because of the lack of rigorous data from any study showing that actual fertility outcomes are improved with GnRH-a treatment throughout chemotherapy.

None of these methods is ideal and none guarantees future fertility in all survivors. A combination of various modalities for a specific individual may increase the odds of preservation of future fertility.

RADIOTHERAPY

Radiotherapy can affect fertility by causing hormonal dysfunction or direct damage to the gonads.[26]

Effect of Cranial Irradiation

Cranial irradiation can disrupt the hypothalamic-pituitary axis and cause dysregulation of the secretion of gonadotropin-releasing hormone, FSH, luteinising hormone (LH), oestradiol, progesterone, and prolactin. Disruption in hormonal balance may manifest as amenorrhoea or early menopause in females and infertility in both sexes. Bath et al[27] assessed hypothalamic-pituitary-ovarian function in 12 female survivors who had prophylactic cranial irradiation (PCI) of 18 to 24 Gy for acute lymphoblastic leukaemia and compared with healthy controls. The median age at diagnosis was 4.7 years and at assessment was 20.8 years. Although all 12 patients treated with PCI achieved adult sexual development and menarche, they had decreased LH secretion, an attenuated LH surge, and shorter luteal phases compared with controls. Short luteal phases have been associated with incipient ovarian failure and early pregnancy loss. This highlights that a regular menstrual cycle does not always mean normal fertility. A recent report from the Childhood Cancer Survivor Study also showed that female childhood cancer survivors who received 22 to 27 Gy hypothalamic/pituitary irradiation had a significantly reduced chance of pregnancy compared with those who received no cranial irradiation.[28]

Males who have cranial irradiation may also have delayed puberty and decreased testosterone production. Some studies have also shown that cranial irradiation can induce precocious puberty in both sexes, which may be due to cortical disinhibition of the hypothalamus.[29]

In adults treated for brain tumours, cranial irradiation can also induce endocrinopathies. Pai et al[30] found that after a median follow-up of 5.5 years, the 5-year and 10-year actuarial rates of hyperprolactinaemia were 72% and 87% respectively, and the 5-year and 10-year rates of hypogonadism were 29% and 36% respectively, after correcting for hyperprolactinaemia. The median time to development of hyperprolactinaemia and hypogonadism was 2.5 years and 4 years, respectively.

Effect of Abdominal or Pelvic Irradiation
Ovarian Dysfunction

Ionising radiation can cause direct DNA damage to ovarian follicles, leading to follicular atrophy and decreased ovarian follicular reserve. This can hasten the natural decline of follicle numbers, leading to impaired ovarian hormone production, uterine dysfunction due to inadequate oestrogen exposure and early menopause. Primordial follicles are considered more radio-resistant than maturing follicles. Radiation dose, age at the time of radiation exposure, and extent of the radiation treatment field are significant determinants of ovarian failure. Wallace et al[31] found the LD50 (i.e. the dose required to kill 50% of the total oocytes) to be 2 Gy. Subsequent mathematical modelling by Wallace et al[32] predicted that the effective sterilising dose (ESD) or the dose of fractionated radiotherapy at which ovarian failure would occur immediately after treatment in 97.5% of patients decreased with increasing age at treatment. The estimated ESD was 20.3 Gy at birth, 18.4 Gy at 10 years, 16.5 Gy at 20 years, and 14.3 Gy at 30 years.[32] In a report from the Childhood Cancer Survivor Study, 5149 female childhood cancer survivors were compared with 1441 female siblings who were aged 15-44 years.[33] The relative risk for survivors of ever being pregnant was 0.81. Those who received a hypothalamic/pituitary radiation dose of 30 Gy or more, or an ovarian/uterine radiation dose of greater than 5 Gy were less likely to have ever been pregnant. Those who had a high dose of alkylating agents or who were treated with lomustine or cyclophosphamide were less likely to have ever been pregnant also.[33]

Uterine Dysfunction

Females who have had pelvic irradiation have been reported to have an increased risk of pregnancy-related complications, including spontaneous miscarriage, preterm labour and delivery, low-birth-weight infants, and placental abnormalities.[34,35] These findings have been attributed to reduced uterine volume, impaired uterine distensibility due to myometrial fibrosis, uterine vasculature damage, and endometrial injury.[36,37] The degree of uterine damage depends on the total radiation dose, site of irradiation, and patient age at the time of treatment. The prepubertal uterus is more

vulnerable than the adult uterus to the effect of pelvic irradiation, with doses of 14 to 30 Gy likely to cause uterine dysfunction.[38] Children who have had total body irradiation as conditioning for bone marrow transplantation are also at risk of developing vaginal occlusion as a result of pelvic radiation and graft-versus-host disease.[39]

A report by Signorello et al[40] from the Childhood Cancer Survivor Study showed that offspring of patients treated with high-dose radiotherapy (>5 Gy) to the uterus were at increased risk of preterm delivery, low birth weight, and small gestational age compared to offspring of patients who had not received radiotherapy. This increased risk was apparent at low uterine doses, starting at 50 cGy for preterm birth and at 250 cGy for low birth weight.[40]

The literature indicates that patients who have had previous abdominal or pelvic irradiation need intensive obstetric monitoring during pregnancy, as they have an increased risk of adverse pregnancy and neonatal outcomes. Delivery by caesarean section may present the best option for these women and should be considered.

Testicular Failure

Male infertility can result from the disease itself (best documented in patients with testicular cancer and Hodgkin's lymphoma), anatomical problems (e.g. retrograde ejaculation or anejaculation), primary or secondary hormonal insufficiency, or damage or depletion of the germinal stem cells.

The germinal epithelium is very sensitive to radiation damage. A dose, as low as 0.1 Gy, can lead to short-term cessation of spermatogenesis. Doses of 2 to 3 Gy can cause long-term azoospermia. Doses of higher than 6 Gy will lead to permanent infertility. Table 2 shows the time to recovery of spermatogenesis after various radiation doses to the testis.[41] Following total body irradiation of 10 to 13 Gy, azoospermia was found in 85% of men and oligozoospermia in the remainder.[14] Irradiation can cause damage to Leydig cells also. The

Table 2. Recovery of spermatogenesis in males after graded doses of radiation to the testes.[41]

Radiation dose (Gy)	Time to recovery of sperm concentration
<1	9-18 months
2-3	30 months
≥4	>5 years

doses required are much higher than the doses needed to cause germ cell failure. Leydig cell damage has been shown to be dose-dependent and inversely related to the age at treatment.[42] Essentially, the evidence suggests that all boys who are pubertal or younger and receive 24 Gy for testicular leukaemia are at high risk of delayed sexual maturation associated with decreased testosterone levels, and that they require androgen replacement therapy.[42] The majority of males who receive 20 Gy or less as fractionated testicular irradiation appear to retain the ability to produce normal amounts of testosterone. A report from the Childhood Cancer Survivor Group showed that compared with siblings, young male cancer survivors are approximately half as likely to achieve a pregnancy five years or more after diagnosis.[43] A radiation dose to the testes of more than 7.5 Gy and use of alkylating agents were the major risk factors noted in the report.[43]

Radiation therapy for malignancies in lower abdominal sites may lead to unavoidable gonadal irradiation. However, the exposures are usually fractionated and the total gonadal dose is much less than 0.6 Gy. Such exposures are insufficient to cause permanent sterility, but raise the possibility of radiation-induced genetic damage in germ cells. So far, there is no evidence of an increased incidence of genetic defects in children of cancer survivors who have been exposed to mutagenic chemotherapy and radiotherapy doses to the gonads.[44,45] Some experimental studies have suggested that radiation-damaged spermatogonia are self-destructive, but any evidence for this phenomenon in the ovary is non-existent.[46]

Measures to Preserve Fertility after Radiotherapy

For females undergoing radiotherapy to the pelvis, ovarian transposition to relocate the ovaries outside the pelvic radiation fields can be considered. Improvement in radiotherapy techniques, such as intensity-modulated radiotherapy, use of appropriate shielding, and proton therapy may also help to reduce radiation exposure to the ovaries.

CONCLUSIONS

Chemotherapy and radiotherapy have significant effects on fertility. Fertility issues should be discussed in paediatric and adult patients as appropriate before treatment and referral to fertility specialists should be considered. Available options for preserving fertility should be discussed and a combination of methods

may be considered. However, considerations regarding fertility preservation should not compromise timely commencement of life-saving treatment for malignancy. Psychological counselling is recommended when a man or woman is distressed about potential infertility to reduce anxiety and depression. A multidisciplinary approach is recommended in the management of these problems.

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