A review of the incidence and survival of childhood and adolescent cancer and the effects of treatment on future fertility and endocrine development

M H Botha, MMed (O&G), PhD
Unit for Gynaecological Oncology, Department of Obstetrics and Gynaecology, Stellenbosch University and Tygerberg Academic Hospital, Tygerberg, Western Cape

T F Kruger, MB ChB, MPharmMed (Clin Pharm), MMed (O&G), FCOG (SA), FRCOG (Lond), MD
Unit for Reproductive Biology, Department of Obstetrics and Gynaecology, Stellenbosch University and Tygerberg Academic Hospital

Cancer is not uncommon in children. The reproductive system is an important site for late effects of cancer treatment, and normal pubertal development depends on an undamaged hypothalamic-pituitary-gonadal axis. Fertility compromise can occur due to chemotherapy, radiotherapy to the hypothalamic-pituitary-gonadal axis, or surgery. Cryopreservation techniques of germ cells are improving and may offer hope for fertility preservation.

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Cancer is not an uncommon diagnosis in children. The incidence of childhood cancer (generally referring to children up to the age of 15) is 110 - 130 per million children per annum.[1] It is estimated that the cumulative risk of a child being diagnosed with cancer is slightly higher in boys (1:444) compared with girls (1:594).[2] In South Africa accurate figures for childhood cancer are not available. The reported incidence is around 70 - 80 per million. However, it is estimated that one in 600 children will suffer from cancer before they turn 16. Many of these cancers are diagnosed late or may not be diagnosed at all.[3]

The prognosis for patients with cancer diagnosed under the age of 15 has improved dramatically over the past 30 years. More than 80% survive longer than 5 years, and more than 70% will be long-term survivors. Information from cancer statistics during the 1970s to 1980s indicate that in the USA, the cure rate of all childhood cancers combined was between 70% and 90% (Table 1).[4] The estimated 5-year survival of children of both sexes improved form 50.4% in 1973 to 79.2% in 1990.[5]

Neuroblastomas and Wilms' tumours occur most commonly in infants less than 5 years old, while Hodgkin's lymphoma and bone tumours usually present in the teenage years and early adult life. Leukaemia may occur at all ages.

Older children and young adults have historically not been studied to the same extent as young children with regard to cancer incidence. The age range for adolescence for the purpose of scientific reporting has been set at 15 - 19 years.[6] More recently the concept of 'young adult oncology' has referred to a larger group of young people between the ages of 15 and 29 years.[7] This group is at an important developmental phase, particularly with regard to establishment of normal hormonal and sexual function. The spectrum of cancers affecting this group differs from that in younger children and adults and is summarised in Table 2.

Tumours of the male and female genital tracts become more common in the young adult group. Testicular cancer is the commonest form of solid malignancy among young adult males, and the frequency increases with age from 15 to 29 years.[8] Cure rates for men with seminomas exceed 90%, but non-seminomatous tumours have a poorer outcome. In young women 18% of total malignancies are of gynaecological origin.[9] Carcinoma of the cervix becomes more frequent, while germ cell tumours, particularly dysgerminomas, represent the most common ovarian malignancies.

It is estimated that 1 in 570 adults are cancer survivors and that this may increase to 1 in every 250.[5] The increased cure rate means that

Table 1. Incidence and survival figures for common childhood malignancies[69]

	Incidence/100 000/year	Cure rate (%)
ALL/non-Hodgkin's lymphoma	5.0 - 6.0	78 - 80
Hodgkin's lymphoma	0.4	>90
Brain tumours	4.0	Depends on type
Wilms' tumours	0.9	80

ALL = acute lymphoblastic leukaemia.

Table 2. The relative frequencies (%) of cancers in adolescents and young adults aged 15 - 29 years[69]

	Age (yrs)		
	15 - 19	20 - 24	25 - 29
Lymphoma	26	22	16
Leukaemia	12	7	4
Central nervous system	10	7	5
Endocrine system	9	12	11
Skin	8	14	18
Male genital	8	13	11
Female genital	8	8	12
Bone and joint	8	3	1
Soft tissue	5	3	2
Digestive system	2	3	5
Oropharynx	2	3	2
Respiratory system	2	2	2
Urinary system	2	2	2
Breast	0	2	8
Other	2	2	1

many more patients with a history of cancer will reach adulthood and want to have children. The reproductive system is an important site for late side-effects of cancer treatment, and normal pubertal development depends on an undamaged hypothalamic-pituitary-gonadal axis. Practitioners should be aware of the potential harm to the endocrine and reproductive systems after life-saving but potentially toxic chemo- and/or radiotherapy. Fertility can also be compromised by chemotherapy, radiotherapy of the hypothalamic-pituitary-gonadal axis or surgery. Chemotherapy and radiotherapy may also be used in patients with non-malignant auto-immune diseases such as systemic lupus erythematosus and rheumatoid arthritis, as well as certain haematological diseases.[10]

The effects of chemotherapy on the ovary

In females the production of sex hormones requires the presence of germ cells. Young women will experience endocrine function loss more often than men after chemo- and radiotherapy in childhood and adolescence. Unlike men, women have a fixed number of germ cells that gradually diminish with age. At puberty, between 200 000 and 400 000 follicles are present which may eventually mature, but only 400 - 500 mature oocytes are produced in a normal reproductive lifespan.[11] At the age of menopause only a few hundred follicles are left.[12] Anti-cancer therapy may increase the rate of follicular loss and therefore lead to premature ovarian failure. Premature menopause is one of the common toxic side-effects of cancer treatment.[13] Chemotherapy may affect the ovary to cause amenorrhoea in 40 - 68% of cases, depending on various factors.[14]

Mechanisms of damage to ovarian function

The pharmacological action of chemotherapy is mainly aimed at disrupting the process of DNA synthesis and cell replication. In general the alkylating agents interact with DNA, preventing replication and/or transcription. Anti-tumour antibiotics such as actinomycin D work on the same principle. Other agents may damage the structure of DNA directly, while adriamycin acts by damaging the plasma membrane. The plant-based chemotherapy agents such as the taxanes disrupt the function of tubulin, which is critical in the normal mitotic process.

Specific chemotherapy agents, particularly the alkylating ones such as cyclophosphamide and chlorambucil, may cause permanent DNA damage in ovarian follicles. Other chemotherapy agents are less harmful, and include 5-fluorouracil, methotrexate, etoposide and adriamycin.[15] There are various mechanisms of damage to the ovaries. The damage may be directly to the primordial follicles with death of follicular cells. Human and animal studies have shown that chemotherapy can damage ovarian pre-granulosa cells,[16] with increased apoptosis during oocyte and follicle loss.[17] Vascular effects associated with antineoplastic agents have been reported, and recognised mechanisms for such toxicity include drug-induced endovascular damage.[18] In a descriptive study Meirow and co-workers studied the histological features of ovarian tissue from 17 women exposed to chemotherapy and compared them with 18 patients who were not exposed.[19] The pathologists were blinded for patient characteristics. They found injury to blood vessels and focal fibrosis of the ovarian cortex in ovaries of patients previously exposed to chemotherapy. Blood supply for the ovarian cortex is by an end-artery system and the cortex is a fairly poorly oxygenised tissue. After chemotherapy there is prominent thickening and narrowing of the vessels, and neo-vascularisation with abnormal blood vessels to the ovarian cortex is seen on microscopy. There is also cortical fibrosis. Direct damage to the follicles can also be seen after chemotherapy.

Mature follicles are more vulnerable to chemotherapy damage.[20] Certain endocrine mechanisms may play a role in the damage to larger follicles. Anti-Müllerian hormone (AMH) is mainly secreted by growing follicles and AMH levels drop significantly during therapy.[21] A drop in AMH may cause raised recruitment and make more follicles vulnerable to damage due to chemotherpy.

AMH may be used as a marker of ovarian reserve. Serum AMH levels can be measured to assess sub-clinical ovarian damage in patients treated with chemotherapy.[22] A possible mechanism to protect ovarian function may be to administer anti-Müllerian hormone during treatment with chemotherapy to reduce recruitment of follicles.

Age at treatment

One of the most important clinical factors that influence the risk for permanent ovarian damage is age at treatment. The risk for ovarian failure increases with age (Table 3).[23-26] This is because the number of primordial follicles is far higher at a younger age.

Amenorrhoea due to chemotherapy is more common in women who were over the age of 30 years at the time of treatment (50

Table 3. The effect of age on the rate of premature ovarian failure after cyclophosphamide chemotherapy[8]

Age (yrs)	Premature ovarian failure (%)
<20	13
20 - 30	50
>30	100

- 89%) compared with younger women, where normal menses was preserved in 48 - 100% of cases.[27-29] Chemotherapy-related amenorrhoea may be transient. However, if the condition is present for more than 1 year after treatment, less than 11% of women over the age of 40 years and only 12 - 15% of women younger than 40 will experience a return to menses.[30]

Treatment for young people with cancer

The most common forms of malignancies affecting young people and the treatment for these malignancies are summarised in Table 4. It is clear that multi-agent chemotherapy regimens and radiation may contribute to reproductive failure. It is often difficult to determine the individual effect of specific therapies on fertility outcome.

Haematological malignancies

There are a significant number of reports in the literature about the effects of chemotherapy on fertility and hormonal function after treatment for haematological malignancies in younger women. Treatment for Hodgkin's lymphoma with MVPP (mechlorethamine, vinblastine, procarbazine and prednisolone), MOPP (mechlorethamine, vincristine, procarbazine and prednisolone) or ChIVPP (chlorambucil, vinblastine, procarbazine and prednisolone) resulted in permanent ovarian failure in 19 - 63% of cases.[23-27] Treatment for acute lymphoblastic leukaemia (ALL), however, had less long-term risk for permanent amenorrhoea.[31,32] Conditioning with chemotherapy before bone marrow transplantation is usually associated with transient amenorrhoea. Cyclophosphamide doses of 200 mg/kg caused amenorrhoea in all women on treatment, but all recovered normal ovarian function after bone marrow transplantation.[33] Doses higher than 200 mg/kg may cause premature ovarian failure.[34] Multi-agent combination chemotherapy regimens may have synergistic toxicity, and the specific contribution of each agent is often difficult to determine.

Breast cancer

In the USA breast cancer is the most common cancer in women of reproductive age (<40 years of age), and approximately 13% of all breast cancer diagnoses are made in women younger than 45.[35] Alkylating agents (e.g. cyclophosphamide) are often included in the treatment plans for breast cancer. The higher the cumulative dose of cyclophosphamide, the higher the risk of premature menopause. In cases treated with CMF (cyclophosphamide, methotrexate and 5-flurouracil) the incidence of amenorrhoea was 61% in patients younger than 40 years and 95% in patients older than 40 years.[26] A slightly higher incidence of amenorrhoea was found with a regimen containing FEC (fluorouracil, epirubicine and cyclophosphamide) compared with CMF (51% v. 42.6%).[36] Anthracycline-based regimens had a lower incidence of amenorrhoea.[15] There is very little evidence with regard to taxanes and the risk of subsequent amenorrhoea, but there does not appear to be an increased overall risk when it is added to chemotherapy regimens.[37]

Pregnancy after chemotherapy

Maltaris *et al.* summarised the obstetric outcome in patients with previous epithelial ovarian carcinoma after receiving fertility-preserving treatment.[37] Not all of the patients received chemotherapy. A total of eight studies were included in the review, and 113 pregnancies were described out of the total of 282 patients. The number of term deliveries was 87. In this group the number of reported relapses of ovarian carcinoma was 33 and that of disease-related deaths 16.

In a study reported by Newlands *et al.*, cyclophosphamide therapy for choriocarcinoma was associated with a reduction in the fertility rate when compared with treatment with methotrexate only;[38] 79% of the total number of patients desiring pregnancy had at least one live birth after cyclophosphamide, compared with 86% in those who received methotrexate only.

Radiotherapy damage to hormone production and fertility in women

The extent of radiotherapy damage to ovarian function and reproduction is determined by the total dose of radiation, the fractionation schedule, and the age of the patient at the time of treatment.[13,39] The human oocyte is exquisitely sensitive to the damaging effects of radiation, and the estimated median lethal dose (LD_{50}) is less than 4 Gy.[13] A descriptive study by Wallace *et al.* found that 37 of 38 females developed ovarian failure after whole-abdominal irradiation in childhood of 20 - 30 Gy; 71% had primary amenorrhoea, i.e. never had normal pubertal development, and premature menopause occurred in the rest at a median age of 23.5 years.[39] Total-body irradiation (TBI) is sometimes used alone or in combination with cyclophosphamide as conditioning for bone marrow transplantation. This treatment is often associated with infertility, and only a small number of patients (9 out of 144) had normal ovarian function after TBI at a dose of 9 - 16 Gy combined with cyclophosphamide 120 mg/kg before bone marrow transplantation. The effect of age at treatment was also demonstrated in this study, with a greater probability of recovery of ovarian function observed in younger girls.[33]

The uterus may be damaged by radiotherapy, and reduced uterine volume and decreased elasticity of the myometrium can be found in girls who received pelvic or abdominal irradiation or TBI

Table 4. Treatment of childhood cancers[14]

	Chemotherapy	Cranial radiation therapy	Gonadal radiation therapy
Acute lymphoblastic leukaemia	+	±	±
Non-Hodgkin's lymphoma	+	±	±
Hodgkin's lymphoma	+	-	±
Brain tumours	±	±	±
Wilms' tumour	+	-	±

before puberty.[40,41] Even though successful pregnancies following radiotherapy have been reported, there is an increased incidence of miscarriage, intra-uterine growth restriction and premature delivery.[31] It is difficult to measure uterine damage after exposure to radiotherapy, but endometrial sampling may help in the assessment of endometrial function. Exact prediction of eventual reproductive outcome, however, is very difficult.

It is clear from Table 5 that the risk of premature ovarian failure is higher if the patient receives treatment at an older age.

Table 5. The effect of radiation on ovarian function[69]

Dose (Gy)	Ovary
0.6	No deleterious effect
1.5	No effect in <40 yrs Some risk of POF in >40 yrs
5	60% sterile <40 yrs 100% sterile >40 yrs
8	70% sterile <40 yrs 100% sterile >40 yrs
>8	100% sterile

POF = premature ovarian failure.

Ovarian trans-position outside the field of radiotherapy may reduce the dose to the ovary. Howell and Shalet described how lateral transposition of the ovaries to the para-colic gutters may reduce the radiotherapy dose by up to 95%.[42] This may protect the sensitive follicles from direct dose-related damage. Other reports, however, were less optimistic and found that ovarian transposition may compromise blood supply, and there was mixed success with this technique due to scattered radiation and vascular compromise.[43] Ovarian transposition may have a place in cases where the pelvic dose of radiotherapy is not high enough to be damaging to the other organs in the reproductive tract.

Cranial irradiation may cause hypo-pituitarism in doses over 30 Gy.[44,45] Up to 60% of patients experienced a gonadotropin deficiency 4 years after treatment with cranial irradiation.[45] Effects on other pituitary hormones such as growth hormones have also been reported.[46] In a report by Nygaard *et al.*, a cranial radiation dose of between 18 and 24 Gy was identified as a possible risk factor for a significantly lower first birth rate compared with women without any radiation.[47] The presence of a regular menstrual cycle may not be an adequate indication of hypothalamic-pituitary function, and sub-fertile women who received cranial radiation need careful hormonal assessment.

Chemotherapy and testicular function

In men endocrine and exocrine functions of the gonads are separated. The average age of spermarche is 13.4 years. The alkylating agents are gonadotoxic, with procarbazine particularly harmful. This is a very useful drug used in the treatment of Hodgkin's lymphoma, where repeated courses of alkylating agents are often needed. The Sertoli and germ cells are more chemosensitive than the Leydig cells; a patient with normal testosterone production may therefore have azoospermia.[48] Azoospermia is likely if the volumes of the post-pubertal testes are less than 10 ml each as measured by the Prader orchidometer.

It is clear that in multi-agent chemotherapy regimens there may be synergistic toxicity of individual agents, and it is often very difficult to determine the specific contribution of each agent. Certain agents have been identified as particularly gonadotoxic to the testes, including the alkalating agents procarbazine, cisplatinum and vinblastine.[49-56] Cyclophosphamide may cause azoospermia in up to 13% and oligozoospermia in 30% of patients treated with a total dose of 560 - 840 mg/kg.[53] Ifosfamide is sometimes used for the treatment of sarcomas, and a dose of between 84 and 126 mg/m^2 was associated with impaired spermatogenesis.[57] Newer combinations such as the ABVD combination (adriamycin, bleomycin, vinblastine and decarbazine) have been shown to be less gonadotoxic, with full testicular recovery after 18 months of treatment in nearly all patients.[55] The testicular seminiferous epithelium that is responsible for spermatogenesis is more sensitive to the effects of chemotherapy; however, the Leydig cells are more resistant to damage and in certain cases, although secondary sexual characteristics may develop normally, there may be severe impairment of sperm production.[48,58] In higher cumulative doses Leydig cells may also be damaged,[59] but this rarely occurs in clinical practice.

Radiotherapy and testicular function

Radiotherapy may damage the hypothalamic-pituitary axis if the dose is more than 30 Gy to the cranial region. Radiotherapy may also damage the testes; the damage may be reversible if the dose is between 20 and 200 cGy, but irreversible azoospermia will develop over 400 cGy. Low production of testosterone will only occur when the dose goes above 1 500 cGy.

Pubertal development is usually normal after treatment with TBI in preparation for bone marrow transplantation.[60] It was found that these boys had slightly higher levels of follicle-stimulating hormone and that mean testicular volume was lower than normal at an average of 10.5 ml. Luteinising hormone (LH) was elevated, which may indicate subtle hormonal dysfunction of the Leydig cells.[60] Other reported studies found no change in LH levels after preparation for bone marrow transplantation.[61,62]

Conclusion

'First do no harm' is an important precept of Hippocrates (around 460 - 377 BC). Non-maleficence, which is the ethical principle that flows from this, is fundamental to medical ethics. Beneficence refers to actions that promote the wellbeing of others. In the management of serious disease such as cancer there is often a conflict between these two moral imperatives. The obligation not to harm others is usually more stringent than the obligation to help others. In an effort to cure cancer (an act of beneficence) the treatment itself may at the same time also cause significant harm. Many treatments have serious, harmful late effects including an effect on future fertility and hormone production. Every young patient deserves safe and effective oncological treatment but with the least long-

term negative effects. A multi-disciplinary team approach involving oncologist, surgeon and counsellor should include a reproductive health specialist if fertility may be compromised by cancer therapy. Clinicians should consider the long-term side-effects of treatment before mapping out a treatment plan, and use fertility-sparing techniques where appropriate.

It is important to consider collecting a semen sample before the initiation of chemotherapy.[58] Cryopreservation of sperm is a well-known technique and has excellent outcomes. If pre-pubertal boys cannot produce a sample through masturbation, testicular biopsies are a viable alternative.

In certain clinical situations the ovaries of a young woman will be exposed to high doses of toxic cancer therapy. If surgical transposition will be of no benefit due to systemic chemotherapy, an option may be to remove ovarian tissue for the period of therapy. Preservation of ovarian tissue before cancer treatment and later transplantation of the tissue (when toxic treatment is finished) may restore hormonal function and sometimes even fertility. The self-evident candidates for ovarian tissue or oocyte cryopreservation are young women and girls with haematological cancer who need aggressive chemotherapy regimens.

There are indications that, with improving technical ability, slow-freezing of oocytes is becoming more efficient with increases in survival rates of individual oocytes, better fertilisation rates and ultimately an improvement in pregnancy rates.[63] More recently, vitrification (ultra-rapid cooling technique) of human oocytes has been described, and the success rate after vitrification seems to be improving.[64]

Despite the experimental nature of ovarian tissue cryopreservation, ovarian tissue harvesting and banking has been offered to many patients in clinical practice over the past two decades.[65-67] Case reports of successful pregnancy from cryopreserved ovarian tissue give hope that this technique may become part of clinical practice.[68]

Cryotherapy techniques offer real hope to boys and girls who need gonadotoxic therapy, and ovarian tissue, testicular tissue, sperm and ova may be harvested and stored before treatment is started.

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