Subfertility following treatment for childhood cancer

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The majority of children with cancer can now expect to be cured. Recent advances in assisted reproduction have focused attention on the long-term fertility outcome for these survivors. This article summarizes the current state of our knowledge about who is at risk of subfertility after childhood cancer and discusses possibilities of fertility preservation that are currently being researched.

Subfertility is a well recognized adverse event for a minority of young adults successfully treated for childhood cancer. Cancer in childhood is rare, with about 1400 new cases per year in the UK, and a cumulative risk of 1 in 650 by the age of 15 years. Continued therapeutic advances, and management in specialist paediatric centres, means that the majority of children can realistically hope for long-term survival. With 65% overall survival rate, the prevalence of long-term survivors in the young adult population has been estimated to be 1 in 1000. Consequently, questions regarding their ability to achieve normal reproductive potential are assuming greater importance. The impact of radiotherapy and chemotherapy on reproductive function has been widely investigated and a number of gonadotoxic agents have been implicated. This article identifies the long-term survivors who may be at risk of subfertility.

EPIDEMIOLOGY OF CHILDHOOD CANCER

Childhood cancers exhibit greater diversity in terms of anatomical site and histological type than adult cancers, where carcinomas of the breast, lung and gut predominate (*Figure 1*). Approximately one third of all cancers in childhood are leukaemias, of which 80% are acute lymphoblastic leukaemia (ALL), followed by brain and spinal tumours which accounts for about 25% of cases. Embryonal tumours (neuroblastoma, retinoblastoma, Wilms' tumour and hepatoblastoma) make up 15% of cases, and lymphomas 11% (both Hodgkin's and non-Hodgkin's).

The remainder comprises bone (osteosarcoma and Ewing's sarcoma) and soft tissue tumours (rhabdomyosarcoma), and a variety of rare tumours. Leukaemia and embryonal tumours are more common in children under 5 years of age in contrast to Hodgkin's disease and osteosarcomas, which peak in puberty and early adulthood. Childhood cancers are 30% more common in boys than girls (Stiller, 1997). The reproductive potential of these children depends not on the underlying diagnosis but on the nature of the treatment they have received.

REPRODUCTIVE FUNCTION

Males

The testes have two main functions: testosterone production and spermatogenesis. Testosterone production occurs in the Leydig cells and is essential for the development of secondary sexual characteristics and spermatogenesis. Spermatogenesis occurs in the seminiferous tubules supported by the Sertoli cells, which also secrete a regulatory hormone, inhibin B.

Production of sperm and sex steroids are stimulated by the anterior pituitary hormones, follicle-stimulating hormone (FSH) and luteinizing

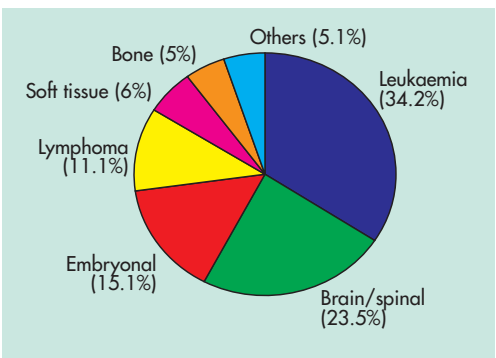

Figure 1. Distribution of the major childhood cancers. From Stiller (1997).

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hormone (LH) respectively. In turn, testosterone and inhibin B exert a negative feedback influence on FSH and LH release (*Figure 2*). Maturation of germ cells to spermatozoa takes about 70 days, and spermatogenesis itself begins in puberty with mature sperm detected at Tanner stage III (Kulin et al, 1989; Griffen and Wilson, 1992; Morris, 1996; Hayes et al, 1998).

Assessment of testicular function: The male reproductive tract is highly susceptible to the toxic effects of chemotherapy and radiation, which may disrupt the endocrine axis or damage the testes directly. Assessment of testicular maturation and function involves pubertal staging, plasma hormone analysis and semen analysis (*Table 1*). Pubertal staging provides clinical information about both of the testicular functions.

The development of normal secondary sexual characteristics would suggest intact Leydig cell function with normal steroidogenesis, while testicular volumes are an important indicator of spermatogenesis. Testicular volume of <12 ml, determined using the Prader orchidometer, is strongly suggestive of impaired spermatogenesis. Hormone analysis involves measurement of plasma FSH, LH and sex steroids; however, in prepubertal children this is an unreliable predictor of gonadal damage because the prepubertal hypothalamic–pituitary–testicular axis is quiescent. In post-pubertal boys elevated LH and diminished testosterone levels would indicate Leydig cell dysfunction, while elevated FSH and diminished inhibin B would support germ cell failure (*Table 1*). Following pubertal staging and hormone analysis, semen analysis is necessary to confirm spermatogenesis. Sperm count and quality following cancer treatment are very variable and semen analysis can provide useful information about the likelihood of natural fertility or whether assisted reproduction may be required.

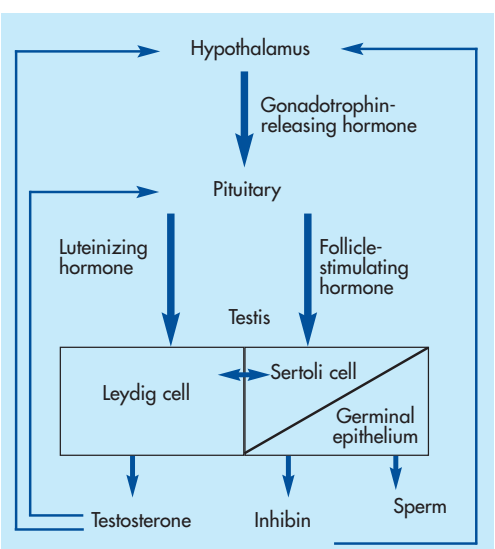

Figure 2. Schematic representation of the hormonal control of the testis. The hypothalamic–pituitary–testicular axis regulates production of sperm and testosterone within the testis, which in turn exerts a negative feedback control mechanism.

Females

The process of gametogenesis is considerably different in the ovary compared to the testis. Numbers of primordial ovarian follicles are highest at birth and begin an exponential atretic process to menopause. Follicular development involves a two-stage process:

1. A gonadotrophin-independent phase of primordial priming, beginning in utero and continuing throughout the reproductive years
2. From puberty onwards the gonadotrophin-dependent phase begins to allow further development of the follicle with monthly ovulation of a mature oocyte (Carr, 1979; Zeleznik, 1996).

Assessment of ovarian function: Assessment of ovarian function in females involves documentation of menstrual history, pubertal staging and plasma hormone analysis (*Table 2*). The development of secondary sexual characteristics, normal gonadotrophin levels and regular menses would support normal ovarian function. However, apparently normal ovarian function does not imply fertility, as some females may have sustained uterine damage as a consequence of their treatment. On the other hand, irregular menses does not preclude pregnancy.

WHO IS AT RISK OF SUBFERTILITY?

Cytotoxic agents may induce azoospermia and impair Leydig cell function in males, and cause parafollicular agenesis and premature ovarian

TABLE 1.
Assessment of male reproductive function

Assessment of testicular function	Pubertal staging	Testicular volume (Prader orchidometer)
	Hormone levels	FSH/LH/testosterone/inhibin B
	Semen analysis	
Testicular damage	Leydig cell dysfunction	Reduced testosterone
		Elevated LH
	Germinal cell dysfunction	Reduced testicular volume
		Elevated FSH
		Low inhibin B
		Impaired spermatogenesis

FSH = follicle-stimulating hormone; LH = luteinizing hormone

TABLE 2.
Assessment of female reproductive function

Assessment of female reproduction	Menstrual history	
	Pubertal staging	
	Hormone levels	Follicle-stimulating hormone/luteinizing hormone/inhibin B
		Oestrogen/progesterone
	Ultrasound	Ovarian follicles
		Uterine assessment
Ovarian damage	Ovarian failure prepubertally	Delayed puberty
		Primary amenorrhoea
	Ovarian failure during or post puberty	Arrested puberty
		Secondary amenorrhoea
		Menopausal symptoms
	Hormone analysis	Elevated follicle-stimulating hormone
		Reduced oestradiol

failure in females. The degree of gonadal damage depends on the total dose of the drug received, and the age at time of treatment.

Males

Chemotherapy: Chemotherapy-induced testicular damage has been recognized for many years and was first identified by Spitz in 1948, when azoospermia was observed in men at autopsy following treatment with nitrogen mustard. Since then a number of gonadotoxic agents have been identified as producing long-lasting or permanent damage including cisplatin, procarbazine, vinblastine and the alkylating agents, such as chlorambucil and cyclophosphamide (*Table 3*) (Shalet et al, 1981; Watson et al, 1985; Wallace et al, 1989a, 1991; Mackie et al, 1996; Papadakis et al, 1999). Cytotoxic chemotherapy has a greater propensity for germinal epithelium with relative sparing of Leydig cell function.

TABLE 3.
Gonadotoxic chemotherapy agents

Alkylating agents	Cyclophosphamide
	Ifosfamide
	Nitrosoureas, e.g. carmustine (N,N′-bis(2-chloroethyl)-N-nitrosourea; BCNU), lamustine (N-2-chloroethyl)-N′chlorohexyl-N-nitrosourea; CCNU)
	Chlorambucil
	Melphalan
	Busulphan
Vinca-alkaloids	Vinblastine
Antimetabolites	Cytarabine
Others	Cisplatin
	Procarbazine

Most chemotherapeutic agents are delivered as part of a multi-agent regimen, making it difficult to determine the individual contribution of each potentially gonadotoxic agent. Some combinations of cytotoxic drugs may have a synergistic deleterious effect. The impact of chemotherapy on testicular function has been widely studied in the treatment of Hodgkin's disease. Treatment of Hodgkin's disease with the first combination chemotherapy regimen MOPP (six courses of mustine, vincristine, procarbazine and prednisolone) has been reported in a number of studies to result in permanent azoospermia in more than 90% of patients (Viviani et al, 1985; Heikens et al, 1996; Mackie et al, 1996; Papadakis et al, 1999). Alternative treatment of childhood Hodgkin's disease involving six to eight courses of ChlVPP (chlorambucil, vinblastine, prednisolone and procarbazine) produces similar results in males treated before and after puberty (Mackie et al, 1996).

The incriminating agents in these regimens are mustine and procarbazine, and chlorambucil and procarbazine respectively. Other chemotherapy regimens have also been studied, including COPP (cyclophosphamide, vincristine, procarbazine and prednisolone) and ABVD (adriamycin, bleomycin vinblastine and dacarbazine). Six courses of COPP, which includes the gonadotoxic agents procarbazine and cyclophosphamide, causes even greater damage to germinal epithelia, with reports of 100% azoospermia, together with subtle Leydig

cell dysfunction in one quarter of patients (Charak et al, 1990; Bramswig et al, 1990). The ABVD combination, which does not contain alkylating agents or procarbazine, was developed as a non cross-resistant regimen, which has been shown to be significantly less gonadotoxic, resulting in azoospermia in 33% of patients (Viviani et al, 1985; Kulkarni et al, 1997). While the survival rate from this regimen is comparable to MOPP, its effectiveness compared to ChlVPP may be reduced. Furthermore, this regimen is not without other side effects, as adriamycin may be associated with significant dose-dependent cardiac morbidity in later life (Hale and Lewis, 1994).

Unwanted side effects of chemotherapy for Hodgkin's disease are dependent upon the chemotherapy regimen and number of cycles. In an attempt to reduce the late sequelae following treatment for Hodgkin's disease hybrid protocols, combining two regimens (three cycles of ABVD and three cycles of ChlVPP), have been introduced. Although combination chemotherapy will expose the child to a wider variety of drugs, it is expected that the reduction in dose of any individual agent will reduce the unwanted side effects. In support of this, studies have shown that fertility is preserved in approximately 50% of men following three cycles of MOPP, in contrast to almost universal azoospermia following six cycles (da Cunha et al, 1984; Viviani et al, 1996).

Cis-platinum, in combination with other agents, for the treatment of osteosarcoma has been reported to damage germinal epithelia significantly, and further studies in testicular cancer patients report azoospermia or severe oligospermia in almost half of patients receiving doses of >600 mg/m^2 (Wallace et al, 1989a; Petersen et al, 1994). Patients undergoing bone marrow transplant receive preconditioning with high dose chemotherapy including the alkylating agents, melphalan and nitrosoureas, which invariably induce azoospermia (Chatterjee et al, 1994). In addition to radiotherapy, adjuvant chemotherapy with procarbazine and nitrosoureas has improved the survival of children with brain tumours at the cost of further morbidity to reproductive function (Ahmed et al, 1983).

Management of leukaemia, the commonest childhood malignancy, is continually evolving. Previous regimens included high doses of cytarabine and cyclophosphamide, which resulted in a 50% reduction in the seminiferous tubular fertility index (percentage of tubules containing identifiable spermatogonia), compared with age-matched controls (Lendon et al, 1978). However, germ cell damage may be reversible in some patients as reported by Wallace et al (1991). Current treatment of ALL in the UK lasts for 3 years and includes cytarabine (total dose: 2 g/m^2 or 4 g/m^2) and cyclophosphamide (total dose: 1.2 g/m^2 or 2.4 g/m^2), which although unlikely to be sterilizing, requires long-term follow-up and fertility assessment to be certain.

Radiotherapy: The degree and permanency of testicular damage depends on the field of treatment, total and fractionated dose of radiotherapy administered, and is inversely related to the age at time of treatment. Immature sperm cells are very sensitive to radiotherapy and doses as low as 0.1–1.1 Gy have been shown to damage dividing spermatogonia and disrupt cell morphology resulting in oligospermia (Howell and Shalet, 1998). Patients receiving greater than 1.2 Gy are likely to be rendered azoospermic (Speiser et al, 1973). Recovery of spermatogenesis from surviving germ cells is unpredictable and may occur more than 5 years after treatment (Howell and Shalet, 1998).

Leydig cells are more resistant to gonadotoxic treatments, resulting in preservation of testosterone production and development of secondary sexual characteristics, even when patients are azoospermic. Leydig cell damage is directly related to the dose and inversely related to the age of the child. Testicular irradiation with doses of greater than 20 Gy is associated with Leydig cell dysfunction in most prepubertal boys, while doses of greater than 30 Gy are required to damage Leydig cell function in adolescent boys and young adults, and these patients will require androgen replacement therapy (*Table 4*) (Giwercman et al, 1991; Shalet et al, 1989).

Females

Chemotherapy: Females are generally less susceptible to the deleterious effects of chemotherapy, however, ovarian failure and uterine dysfunction are well established consequences of certain treatment regimens. As with males, the alkylating agents are the most cytotoxic. Standard Hodgkin's disease treatment with MVPP (mustine, vinblastine, procarbazine and prednisolone) or ChlVPP (chlorambucil, vinblastine, prednisolone and procarbazine) result in ovarian dysfunction in 38–57% of patients, however, follow up is required to determine whether these patients progress to ovarian failure (Mackie et al, 1996; Whitehead et al, 1983).

In addition to dose dependence, gonadal toxicity in females demonstrates age dependence, with treatment after 35 years of age resulting in

a higher prevalence of ovarian failure. Predicting the likelihood of preserved reproductive function in females treated for childhood cancer can be difficult. In prepubertal females treated with six or more courses of ChlVPP, elevated gonadotrophin levels were observed in 50% of patients, indicating ovarian damage and emphasizing the importance of long-term follow-up (Whitehead et al, 1983; Mackie et al, 1996). It is expected that the hybrid regimen (three cycles of ABVD and three cycles of ChlVPP) will decrease the prevalence of ovarian dysfunction.

The larger number of surviving primordial follicles available after treatment may explain the apparent resistance of the prepubertal ovary and relative protection afforded to younger females. The impact of chemotherapy on ovarian function and subsequent recovery is often unpredictable. Recovery is reported in a proportion of women with secondary amenorrhoea, but premature menopause may occur and these patients should be followed up long term (Byrne et al, 1997).

Radiotherapy: Damage to the ovary may be a consequence of total body, abdominal or pelvic irradiation, and the degree of impairment is related to dose and age at time of treatment. Wallace et al (1989b) have shown that the LD50, the lethal dose required to kill 50% of the oocytes, is less than 4 Gy. In a large study by Doll and Smith (1968), ovarian failure was reported in 97% of patients (2068 women, 91% of whom were over 40 years old) when treated with 5–10.5 Gy. Significantly higher doses (20 Gy) are required to destroy the fixed pool of oocytes and induce ovarian failure in young women (*Table 4*) (Wallace et al, 1989c).

Follicle function and sex steroid production are interdependent such that damage to either structure results in failure of both functions, unlike in the testes where there is relative preservation of sex steroid production even when spermatogenesis fails. Hormone replacement therapy is necessary to relieve the symptoms of oestrogen deficiency such as vaginal dryness, hot flushes and irritability, and protect against cardiovascular disease and osteoporosis (Mulder, 1999).

In addition to the deleterious effects on the ovary, the uterus must also be considered, the function of which may be compromised following chemotherapy and radiotherapy. Reduced uterine volume and decreased elasticity of uterine musculature, possibly as a consequence of impaired vascularization, are found in girls receiving pelvic, abdominal and total body irradiation prepubertally (Wallace et al, 1989c; Critchley et al, 1992). Disruption of uterine architecture may compromise implantation and continuation of pregnancy.

Although successful pregnancies following radiotherapy are reported, the incidence of spontaneous abortion, premature delivery and intrauterine growth retardation is significantly increased (Li et al, 1987; Green et al, 1989). Interestingly, studies exploring the role of physiological exogenous sex steroid replacement therapy have shown an increase in uterine volume and endometrial thickness, in women with premature ovarian failure, following total body irradiation for childhood ALL (Bath et al, 1999). This is encouraging for future fertility prospects and should be a useful tool for assessing uterine responsiveness when considering these women for assisted reproduction.

PSYCHOLOGICAL ASPECTS

In addition to the chemotherapy- and radiation-induced azoospermia and premature ovarian failure, the psychological impact of these

TABLE 4.
Radiotherapy-induced gonadal damage

Gender	Site	Effect	
Males	Cranial/total body irradiation	Endocrine axis disruption	
	Total body irradiation/pelvis/testes	Germinal epithelium	>1.2 Gy — azoospermia
			0.1–1.1 Gy — oligospermia
		Leydig cells	>20 Gy — prepubertal
			>30 Gy — post-pubertal
Females	Cranial/total body irradiation	Endocrine axis disruption	
	Total body irradiation/pelvis	Ovarian failure	Older women >5 Gy
		(LD50 = 4Gy)	Younger women >20 Gy
		Uterine damage	Decreased volume
			Decreased elasticity

LD50 = lethal dose required to kill 50% of oocytes

changes on sexuality and quality of life must also be considered. Hormone replacement therapy will be necessary, not only for cardiovascular protection and bone mineralization, but also to treat the loss of libido, hot flushes, irritability and vaginal dryness associated with oestrogen deficiency. Men also experience reduced libido and poor sexual performance, and breakdown of relationships is common. Counselling may be necessary to provide support for these young men and women who are faced with the emotional turmoil resulting from infertility.

FERTILITY PRESERVATION

Pioneering experiments in ewes, together with media interest in the report of a successful autologous ovarian graft in a previously oopherectomized female, have focussed attention upon the possibilities of harvesting germ cell tissue before sterilizing cancer therapies in females, much as 'sperm banking' has long been used for adult males (Gosden et al, 1994; Sanger et al, 1992). Epididymal aspiration and testicular biopsy are now established practice for obtaining the 'single' sperm necessary for intracytoplasmic sperm injection and successful reversal of male infertility resulting from azoospermia (Aboulghar et al, 1997). Such issues have inevitably raised questions from parents and oncologists about their possible application in children undergoing cancer therapies.

The authors support the view of the Royal College of Obstetricians and Gynaecologists Working Party (2000) which recommends that those centres wishing to develop expertise in ovarian cryopreservation should establish clear guidelines as to the type of patients who are likely to benefit from cryopreservation, and protocols of counselling, consent and storage. At the present time cryopreservation of testicular tissue should only be offered in the context of an ongoing research study.

TABLE 5.
Best assessment of risk of subfertility following current treatment for childhood cancer by disease

Risk of subfertility	Disease/treatment	
*Low	Acute lymphoblastic leukaemia	
	Wilms' tumour	
	Soft tissue sarcoma: stage 1	
	Germ cell tumours with gonadal preservation and no radiotherapy	
	Retinoblastoma	
	Brain tumour	Surgery only
		Cranial irradiation (<24 Gy)
Medium	Acute myeloblastic leukaemia	
	Hepatoblastoma	
	Osteosarcoma	
	Ewing's sarcoma	
	Soft tissue sarcoma	
	Neuroblastoma	
	Non-Hodgkin's lymphoma	
	Hodgkin's disease: 'hybrid' therapy	
	Brain tumour	Craniospinal radiotherapy
		Cranial irradiation (>24 Gy)
High	Total body irradiation	
	Localized radiotherapy: pelvic or testicular	
	Chemotherapy 'conditioning' for bone marrow transplant	
	Hodgkin's disease: alkylating agent based therapy	
	Soft tissue sarcoma: metastatic	

*Low risk is assessed at <20%, high risk as >80%. Medium risk is difficult to quantify. Males are more susceptible to subfertility following chemotherapy than females but females may be at risk of premature menopause

CONCLUSIONS

As treatment for childhood cancer has become increasingly successful and sustained remission has been achieved, adverse effects on reproductive function are assuming greater importance. Best assessment of risk of subfertility following current treatment of childhood cancer is shown by disease in *Table 5*. There is insufficient evidence to be definitive, therefore this is a best educated guide. The table may be used as a guideline on which to base fertility counselling at onset of treatment. It does not discriminate between central hypothalamic pituitary dysfunction and direct gonadal damage. Gonadal damage is usually manifest by elevated gonadotrophins (FSH). This is based on current knowledge of the cytotoxic agents and radiotherapy regimens responsible for the deleterious effects on gonadal function. It is hoped that clinical awareness will help paediatric oncologists to counsel patients and parents accordingly. HM

Conflict of interest: none.

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KEY POINTS

- The late effects of childhood cancer are related to the treatment received by the patient.
- The majority of children with cancer will be cured with normal reproductive potential.
- Those patients at high risk of subfertility as a result of their proposed treatment should be counselled appropriately and sexually mature competent males should be offered the opportunity to cryopreserve their sperm. Cryopreservation of ovarian cortical strips remains experimental but may become an option for some young women in the future.
- Assessment of gonadal function in all long-term survivors should be a routine part of their care.