

**Adult Haematology Long Term Follow-up Guideline –  
Endocrine Sequelae****Introduction**

Increases in the complexity and intensity of anti-cancer treatments, alongside improvements in supportive care, have led to remarkable improvements in overall survival of patients treated for haematological malignancy. As a result, there is a growing need for clinicians to be familiar with the potential for late consequences of available treatment modalities. The Society for Endocrinology has estimated that endocrine dysfunction/infertility accounts for up to 55% of significant on-going medical problems after cancer treatment. Increasing time from cancer treatment is a risk factor for developing endocrine dysfunction meaning that patients are at risk months or years after cytotoxic therapy has been completed.

This guideline will set out the recognised long term endocrine effects of chemotherapy, radiotherapy and peripheral blood stem cell transplantation (PBSCT) in adult patients treated for haematological malignancy; provide an outline of who, when and how to screen for endocrine dysfunction; and indicate when a referral to endocrinology should be made.

Fertility preservation must be addressed at the time of cancer diagnosis *prior* to commencing cancer treatment, in all but the most urgent situations. A separate guideline, covering fertility issues, is already available. [<http://nssg.oxford-haematology.org.uk/lymphoma/fertility-guidelines.pdf>]

Long term follow up is now reasonably well established in long term survivors of childhood cancer and many of the recommendations contained in this guideline are based on published experience from the paediatric setting.

**Aims**

- To provide an overview of the potential long term endocrine consequences of chemotherapy, radiotherapy and PBSCT in adult haematology patients
- To provide operational guidance on regular surveillance within the outpatient clinic setting
- To set out a strategy for appropriate investigation and referral of patients suspected to have endocrine dysfunction
- To offer guidance for on-going monitoring if/when a patient is discharged to primary care

**Thyroid Dysfunction**

Primary hypothyroidism is common when radiotherapy fields have included the thyroid gland (neck, mediastinal and mantle fields, total body irradiation [TBI]), occurring in approximately 50% of patients in most series. The usual onset is 2-5 years post irradiation, though new cases can emerge later. Fractionated TBI confers a lower risk than single dose TBI and the incidence following busulfan/cyclophosphamide conditioning is reported at 11%. Hypothyroidism is rare out with the transplant setting but may occur with high total cumulative doses of alkylating agents, and is a recognised side effect of some novel agents (e.g. tyrosine kinase inhibitors).

- Patients post PBSCT should have TSH measured at 6 and 12 months post-transplant, then annually thereafter. Other patients should have thyroid function tests where indicated by history or examination.
- Uncompensated primary hypothyroidism is characterised by an elevated thyroid stimulating hormone [TSH] and a low free thyroxine [freeT<sub>4</sub>]. Thyroid hormone replacement therapy should be instituted.
- In the context of compensated primary hypothyroidism (asymptomatic, raised TSH with normal freeT<sub>4</sub>) *thyroid hormone replacement therapy is supported by most endocrinologists, when the TSH is significantly elevated but may not be so for milder cases and this should be discussed for each individual patient case.*

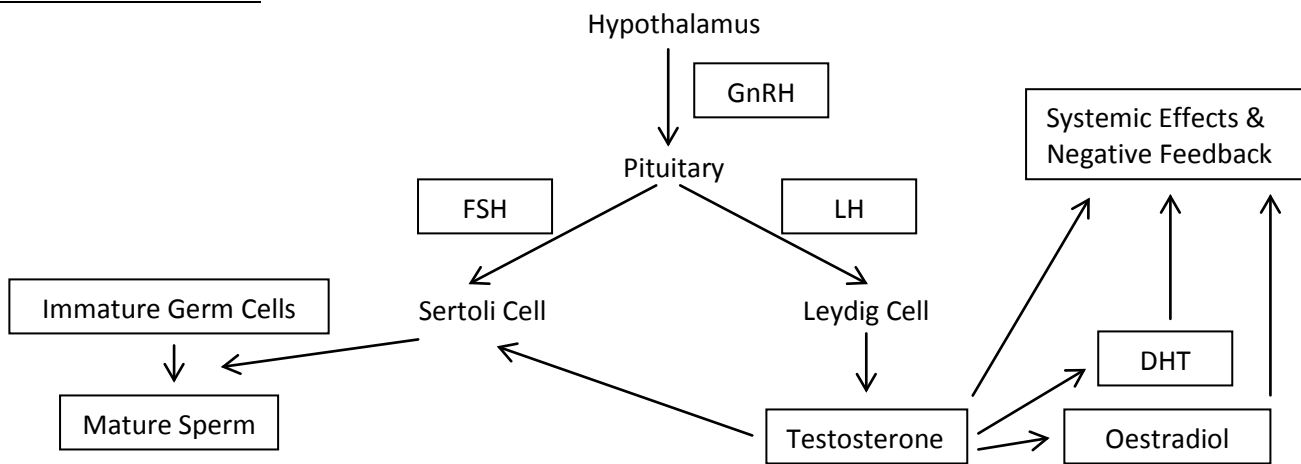
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- An increased risk of developing thyroid nodules and thyroid carcinoma has been observed following chemotherapy with and without radiotherapy treatment. The risk of thyroid cancer in patients whose radiotherapy field included the thyroid is 18 times higher than that of the general population. Ultrasound is the imaging modality of choice for investigation of a clinically suspected thyroid nodule/mass, followed by fine needle aspiration if needed

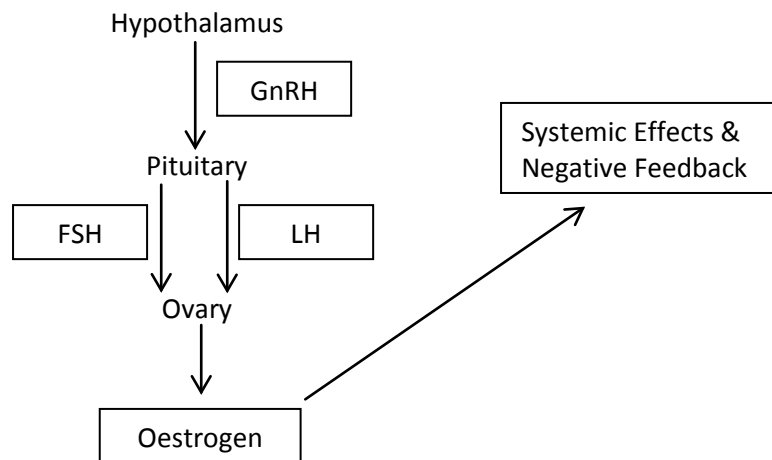
**Gonadal Dysfunction**

Treatment of cancer with chemotherapy, radiotherapy or surgery can have profound effects on germ cell survival. In women, ovarian hormone production is closely related to the presence of viable eggs and cyclical maturation of the primary follicle. As a result, infertility and early menopause are intrinsically linked. By contrast, in men, these functions are not so interdependent and normal androgen production can be maintained despite azoospermia. Fertility issues relating to adult patients with haematological malignancy are well set out in a separate guideline (ref) and will not be revisited here.

Normal Function - Men:



Normal Function - Women:



Effects of Cancer Treatment

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- Treatment with alkylating agents or radiotherapy commonly results in gonadal dysfunction in both men and women, which may be temporary or permanent. Increasing doses and combination therapy confer a higher risk. Procarbazine in combination with alkylating agents appears to be particularly toxic.
- In men a radiotherapy dose of 15Gy to the testes will affect Leydig cells and a much lower dose will impair spermatogenesis.
- In women, age at time of treatment is an important factor. Women are born with a finite complement of oocytes and menopause occurs when this supply is exhausted. Loss of primordial and growing follicles can result in interruption of the normal menstrual cycle during treatment. Younger women may have some oocyte reserve post treatment but this will be depleted in comparison to normal individuals and early menopause may result.
- Total body irradiation will usually prevent the return of normal gonadal function in both men and women.
- Annual evaluation of gonadal function is indicated in patients who have received alkylating agents (e.g. busulfan, cyclophosphamide, ifosfamide, melphalan, procarbazine, dacarbazine) or a relevant radiotherapy field (e.g. to para-aortic or iliac lymphadenopathy).
- Assessment should include history (menstrual cycle, menopausal symptoms, libido, sexual function) and examination (secondary sexual characteristics, testes).
- Initial investigations would include LH/FSH (♀&♂), oestradiol (♀), 9am testosterone (♂). For menstruating women, blood samples are best taken on day 3 of a 28 day cycle.
- *Referral to endocrinology would be appropriate where gonadotropin levels are above the normal range (see also hypogonadotropic hypogonadism below), testosterone or oestrogen are below the normal range or if a woman becomes oligo- or anovulatory (manifested as oligo- or amenorrhoea).*
- Early ovarian failure will result in loss of hormone production and HRT should be considered for symptomatic benefit and to maintain bone mineral density. In male, testosterone replacement is also recommended provided there are no contraindications.
- The psychological impact of gonadal failure should not be underestimated.

See also Appendix 1 for a list of chemotherapy agents / doses implicated in hypogonadism.

### Diabetes Mellitus

- The risk of persistent diabetes mellitus post-HSCT has been reported in retrospective studies to be between 7-13%.
- High dose steroids are a cornerstone of many combination chemotherapy regimes used in haematological practice and can lead to both short- and long-term problems with glucose tolerance.
- There are no formal guidelines for monitoring for diabetes in patients who have received treatment for haematological malignancy.
- *Patients with symptoms such as polydipsia, polyuria or visual disturbance should be investigated with fasting blood glucose and HbA1c measurement.*
- Appropriate lifestyle interventions should be encouraged. The diabetes mellitus is usually followed up in primary care.

### Bone Mineral Density

- High cumulative doses of steroids, high cumulative doses of methotrexate, cranial irradiation and HSCT are risk factors for deficits in bone mineral density.
- Up to 50% of HSCT recipients will have osteopaenia or osteoporosis, as assessed by DEXA scanning post-transplant and the risk is higher in patients with chronic graft versus host disease (GVHD).
- Bone mineral densitometry is recommended within 12 months post-transplant for women and men who have had prolonged exposure to corticosteroids or calcineurin inhibitors by the European Group for Blood and Marrow Transplantation (EBMT), and American Society for Bone Marrow Transplantation (ASBMT).

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- If normal bone mineral density is documented at 12 months post- transplant, a repeat DEXA scan is recommended at 2 years.
- *Prophylaxis with calcium and vitamin D supplementation should be considered in any at risk patient. Recommended regimes comprise an elemental calcium intake of 1000-1500mg/day plus Vitamin D 1000 IU/day. This regime may change if the patient is already Vitamin D deficient.*
- In established osteoporosis, bisphosphonates are the mainstay of treatment.

### Metabolic Syndrome

Clinical understanding of metabolic syndrome is an evolving field but most diagnostic definitions include central obesity with two or more of; hypertension, atherogenic dyslipidaemia and abnormal glucose metabolism. Impaired glucose tolerance, hypertension, high triglycerides and obesity are well described in long term survivors of childhood cancer and a high frequency of cardiovascular risk factors is recognised in haemopoietic stem cell transplant (HSCT) recipients.

- Cardiovascular mortality is significantly increased following high dose treatments for haematological malignancy.
- Total body irradiation and exposure to high dose steroids are risk factors for the development of clinical features of the metabolic syndrome, but other chemotherapy agents may play a less well defined role.
- Long term follow-up of HSCT patients should include rigorous attention to obesity, blood pressure control, glucose tolerance and lipid metabolism.

### Primary Adrenal Failure

- Persistence of adrenal suppression following treatment with exogenous steroids is related to dose intensity and prolonged exposure but function usually recovers gradually and primary adrenal failure is rare, unless the exposure is particularly prolonged.
- Slow tapering of dose and appropriate dose increases at times of physiological stress are important in patients with prolonged exposure.
- *Adrenal axis testing with 9am cortisol and a short Synacthen test should be considered in patients with unexplained weight loss, postural hypotension, hyponatraemia and hyperkalaemia.*

### Hypothalamic-Pituitary Axis

Hypothalamic Factor	Inhibitory (-) or Stimulatory (+)	Pituitary Hormone
Growth Hormone Releasing Hormone	+	Growth Hormone [GH]
Somatostatin	-	Growth Hormone
Dopamine	-	Prolactin
Gonadotropin Releasing Hormone [GnRH]	+	Luteinising Hormone [LH] & Follicle Stimulating Hormone [FSH]
Thyrotropin Releasing Hormone [TRH]	+	Thyroid Stimulating Hormone [TSH]
Somatostatin	-	Thyroid Stimulating Hormone
Corticotropin Releasing Hormone [CRH]	+	Adrenocorticotropin [ACTH]
Anti-diuretic hormone [ADH]	+	Adrenocorticotropin

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Cranial irradiation can affect any of the 6 anterior pituitary hormones and their hypothalamic regulatory factors. Routine follow-up of patients with a history of cranial radiotherapy should include a record of all manifestations related with each pituitary hormone deficit (these patients should have routine follow-up by endocrinologists).

**Growth Hormone Deficiency**

Growth Hormone deficiency is particularly important in children and young adults and it is sensitive to the lowest doses of radiation exposure. Precocious puberty can also occur in pre-pubertal children receiving moderate doses of radiotherapy to the brain and this can further compromise radiation-associated growth hormone deficiency. Such cases require specialist assessment and management by paediatric endocrinologists.

- Specialist paediatric follow-up should be continued until growth is complete.
- GH replacement should be managed by an endocrinologist.

**Hyperprolactinaemia**

High doses of cranial irradiation or surgery disrupting the pituitary stalk can lead to loss of the negative regulation of prolactin by dopamine. Hyperprolactinaemia may result in galactorrhoea and hypogonadism (irregular menses, hot flushes, loss of libido, infertility and osteoporosis in women and loss of libido, impotence, infertility, osteoporosis in men).

- Sensitive symptoms may not always be disclosed by patients and those at risk should be asked direct questions sympathetically.
- Serum prolactin levels should be checked in patients with indicative symptoms or signs and an endocrine referral made if levels are found to be above the reference range.

**Hypogonadotropic Hypogonadism**

Failure of the hypothalamic-pituitary axis to produce gonadotropins may occur secondary to cranial irradiation or, rarely, following high dose treatment with alkylating agents.

- Patients at risk are those who have had high doses of cranial irradiation and it is *only rarely/not* seen as a consequence of treatment with cytotoxic chemotherapy alone (unlike hypergonadotropic hypogonadism – see above).
- Patients with symptoms or signs of gonadal failure should be investigated with serum LH, FSH, oestradiol (women) and 9.00 am testosterone (men). Ideally, women would have bloods taken on day 3 of a 28 day menstrual cycle.
- Hypogonadotropic hypogonadism is characterised by low or “inappropriately normal” serum concentrations of LH & FSH with resultant failure of production of sex hormones. Such patients should be referred to endocrinology.

**Central Hypothyroidism**

Hypothalamic toxicity can reduce production of thyrotropin releasing hormone. In addition, the secretory dynamics of TSH can be disrupted with a blunted pituitary response to stimulation by TRH. Symptoms may develop insidiously and *a low or low-normal or even slightly above normal serum TSH may lead to confusion*. Central hypothyroidism can occur alongside primary failure of the thyroid gland causing mixed hypothyroidism when both the hypothalamus/pituitary and thyroid gland have been affected.

- Symptoms and signs of hypothyroidism (e.g. skin dryness, weight gain, muscle weakness, drowsiness, constipation, oedema, cold intolerance) may be very non-specific.
- Patients presenting with symptoms and signs of hypothyroidism who have had cranial irradiation, *should be investigated with serum free T<sub>4</sub> even where serum TSH is not elevated*.

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- Mixed hypothyroidism has been described in 10-35% of patients following TBI conditioning for PBSCT.

### **Adrenal-corticotropin Deficiency**

Adrenocorticotrophic hormone [ACTH] deficiency (secondary adrenal insufficiency) is uncommon and there may not be a dose-dependent relationship to therapy: it has been described following doses of cranial irradiation <24Gy and reported in a small number of patients receiving chemotherapy alone.

- ACTH deficiency is an uncommon consequence of cancer treatment, but should be suspected in at risk patients, particularly if GH deficiency or central hypothyroidism has occurred.
- Symptoms and signs include light-headedness, weight loss, low energy levels, nausea, muscle weakness, orthostatic hypotension, hypoglycaemia, hyponatraemia and hyperkalaemia.
- *Lying and standing blood pressure readings, measurement of 9.00 am plasma ACTH, 9.00 am serum cortisol, plasma renin activity, aldosterone and electrolytes should be undertaken in suspected cases and abnormal results discussed with an endocrinologist. Dynamic assessment of the ACTH reserve is also needed.*
- Partial deficiency of ACTH may cause only subtle symptoms but intercurrent illness can precipitate a life-threatening Addisonian Crisis.

**Appendix 1**

**List of Chemotherapy Agents Implicated In Gonadal Failure**

<u>Drug</u>	<u>Toxic dose (if known)</u>
Busulfan	600mg/m <sup>2</sup>
Cisplatin	
Cyclophosphamide	♂ 9.5g/m <sup>2</sup> (or 200mg/m <sup>2</sup> pre-BMT) ♀ 7.5g/m <sup>2</sup> or <7.5g/m <sup>2</sup> with 60g/m <sup>2</sup> ifosfamide
Cytarabine	
Dacarbazine	
Ifosfamide	60g/m <sup>2</sup> + cyclophosphamide 7.5g/m <sup>2</sup>
Melphalan	
Procarbazine	

**References**

National Cancer Institute at the National Institutes of Health. Late Effects of Treatment for Childhood Cancer (PDQ®)

<http://www.cancer.gov/cancertopics/pdq/treatment/lateeffects/HealthProfessional>

..

Rizzo JD, Wingard JR, Tichelli A, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2006;12(2):138-151.

..

How I treat late effects in adults after allogeneic stem cell transplantation. Bipin N. Savani, Michelle L. Griffith, Shubhada Jagasia and Stephanie J. Lee. Blood March 17, 2011 vol. 117 no. 11 3002-3009

..

Children’s Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent and young adult cancers, Version 3.0. Arcadia, CA: Children's Oncology Group; October 2008

..

Guidance on Cancer Services – Improving Outcomes in Haematological Cancers – The Manual (2003) <http://www.nice.org.uk/nicemedia/live/10891/28786/28786.pdf>

..

Support Care Cancer. 2008 Apr;16(4):339-45. Adult life after surviving lymphoma in childhood. von der Weid NX.

..

Curr Opin Pediatr. 2007 Aug;19(4):480-7. Long-term endocrine sequelae of childhood cancer. Rutter MM, Rose SR.

..

Thyroid dysfunction among long-term survivors of bone marrow transplantation The American Journal of Medicine, Volume 73, Issue 5, November 1982, Pages 688-694 Charles A. Sklar, Tae H. Kim, Norma K.C. Ramsay

..

Hancock SL, Cox RS, McDougall IR: Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 325 (9): 599-605, 1991.

..

Nature Reviews Clinical Oncology 6, 219-228 (April 2009) Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy Francesco Torino, Salvatore Maria Corsello, Raffaele Longo, Agnese Barnabel & Giampietro Gasparini

..

Sanders JE, Hoffmeister PA, Woolfrey AE, et al.: Thyroid function following hematopoietic cell transplantation in children: 30 years' experience. Blood 113 (2): 306-8, 2009.

..

Mackie EJ, Radford M, Shalet SM: Gonadal function following chemotherapy for childhood Hodgkin's disease. Med Pediatr Oncol 27 (2): 74-8, 1996.

..

Papadakis V, Vlachopapadopoulou E, Van Syckle K, et al.: Gonadal function in young patients successfully treated for Hodgkin disease. Med Pediatr Oncol 32 (5): 366-72, 1999.

..



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Sanders JE, Buckner CD, Leonard JM, et al.: Late effects on gonadal function of cyclophosphamide, total-body irradiation, and marrow transplantation. *Transplantation* 36 (3): 252-5, 1983.

..

Late cardiovascular events after allogeneic hematopoietic stem cell transplantation: a retrospective multicenter study of the Late Effects Working Party of the European Group for Blood and Marrow Transplantation

André Tichelli et al *haematologica* August 1, 2008 vol. 93 no. 8 1203-1210

..

Surapolchai P, Hongeng S, Mahachoklertwattana P, et al.: Impaired glucose tolerance and insulin resistance in survivors of childhood acute lymphoblastic leukemia: prevalence and risk factors. *J Pediatr Hematol Oncol* 32 (5): 383-9, 2010.

..

Shalitin S, Phillip M, Stein J, et al.: Endocrine dysfunction and parameters of the metabolic syndrome after bone marrow transplantation during childhood and adolescence. *Bone Marrow Transplant* 37 (12): 1109-17, 2006.

..

Oudin C, Simeoni MC, Sirvent N, et al.: Prevalence and risk factors of the metabolic syndrome in adult survivors of childhood leukemia. *Blood* 117 (17): 4442-8, 2011.

..

Yao S, McCarthy PL, Dunford LM, et al. High prevalence of early-onset osteopenia/osteoporosis after allogeneic stem cell transplantation and improvement after bisphosphonate therapy. *Bone Marrow Transplant*. 2008;41(4):393-398.

..

Sklar C, Mertens A, Walter A, et al.: Final height after treatment for childhood acute lymphoblastic leukemia: comparison of no cranial irradiation with 1800 and 2400 centigrays of cranial irradiation. *J Pediatr* 123 (1): 59-64, 1993.

..

Schriock EA, Schell MJ, Carter M, et al.: Abnormal growth patterns and adult short stature in 115 long-term survivors of childhood leukemia. *J Clin Oncol* 9 (3): 400-5, 1991.

..

Constine LS, Rubin P, Woolf PD, et al.: Hyperprolactinemia and hypothyroidism following cytotoxic therapy for central nervous system malignancies. *J Clin Oncol* 5 (11): 1841-51, 1987.

..

Rose SR, Danish RK, Kearney NS, et al.: ACTH deficiency in childhood cancer survivors. *Pediatr Blood Cancer* 45 (6): 808-13, 2005.

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**Review**

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