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The impact of childhood cancer and its treatment on puberty and subsequent hypothalamic pituitary and gonadal function, in both boys and girls

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Childhood cancer survivors (CCS) are at an increased risk of endocrine disorders. Disorders of the hypothalamic-pituitary-gonadal (HPG) axis are a particular concern because of their impact on pubertal development and future fertility and may be of central (hypothalamic or pituitary damage) or primary (gonadal) origin. Hypogonadism may present as pubertal disorders during adolescence and subsequent infertility in adulthood but should be anticipated to ensure appropriate surveillance is in place to address these issues at an appropriate age. Those at risk of HPG axis dysfunction include those with tumours primarily affecting the hypothalamus, pituitary or gonads themselves or due to their treatment with surgery, radiotherapy and chemotherapy. CCS who have had cranial irradiation of more than 30 Gy are at risk of gonadotrophin deficiency. Those who have had gonadotoxic chemotherapy, especially alkylating agents or radiotherapy to the gonads are at risk of primary gonadal failure. HSCT survivors who have had chemotherapy and total body irradiation are at risk of primary gonadal failure but may also have gonadotrophin deficiency. Understanding those at risk is essential to appropriate counselling and long-term follow-up. This chapter gives an overview on the impact of childhood cancer and its treatment on puberty, gonadal function and fertility in childhood cancer survivors.

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Abbreviations

ACTH	Adrenocorticotropic hormone
AFC	Antral follicle count
ALL	Acute Lymphoblastic Leukaemia
AMH	Anti-Mullerian Hormone
CAR-T	chimeric antigen receptor T-cell
CCS	childhood cancer survivors
CED	Cyclophosphamide Equivalent Dose
CNS	Central Nervous System
CPP	Central precocious puberty
CSI	Craniospinal irradiation
CT	Chemotherapy
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DNA	Deoxyribonucleic Acid
e.g.	For example
FSH	Follicle stimulating hormone
GCT	Germ cell tumour
GH	Growth Hormone
GHD	Growth Hormone Deficiency
GnRH	Gonadotrophin Releasing Hormone
Gy	Grey
HH	Hypogonadotrophic Hypogonadism
HP	Hypothalamic Pituitary
HPG	Hypothalamic-pituitary-gonadal
HSCT	Haematopoietic Stem Cell Transplantation
HRT	Hormone Replacement therapy
i.e	In other words
IU	International Units
LH	luteinising hormone
OS	Overall Survival
PFS	Progression free survival
POI	Primary Ovarian Insufficiency
RT	Radiotherapy
TBI	Total Body Irradiation
TSH	Thyroid-stimulating hormone
US	United States

Introduction

The potential impact of childhood cancer and its treatment on puberty and fertility is a significant concern for childhood cancer survivors (CCS) and their carers. Understanding those at risk of damage to the hypothalamic-pituitary-gonadal (HPG) axis is an essential pre-requisite to appropriate counselling to families and long-term follow-up, in order to identify those who would be eligible for fertility preservation at the time of diagnosis prior to treatment and those who should have specific follow-up to monitor pubertal progress. This will ensure any evidence of pubertal abnormalities (early or delayed) is identified appropriately, and addressed in a timely fashion.

Improved survival after childhood cancer treatment, which now exceeds 80% in Western Europe and the United States (US) [1,2], has produced an increasing cohort of survivors. There is an estimated

400 000 CCS in the US in 2011 and the numbers are expected to continue increasing worldwide over time. The prevalence of any chronic condition among 5-year survivors ranged from 66% (ages 5–19 years) to 88% (ages 40–49 years) [3] and endocrine dysfunction is recognised to occur in an estimated 50% of survivors [4]. Long-term endocrine effects are determined by a range of factors including the original disease, and its site, the age of presentation, the modality of treatment received: radiotherapy, surgery, chemotherapy, or more recent immunotherapies and the time since treatment.

Improving outcomes and risk stratification have allowed reductions in the use of some treatments with long term toxicities. Particularly, the potential to risk stratify based on clinical or genetic criteria which can mean where the evidence indicates, low risk patients are exposed to less toxic treatments [5] although high risk patients still receive the optimal treatment required to cure their disease. More recently, the development of new cancer therapies, both adaptations of previous therapies such as in proton radiotherapy and novel immunotherapies, using monoclonal antibodies and chimeric antigen receptor T cell (CAR-T) have the potential to significantly change the spectrum of late effects occurring in CCS [5].

The impact of childhood cancer and its treatment on puberty is via damage to the HPG-axis. Puberty encompasses the pubertal growth spurt, development of secondary sexual characteristics and increasing bone mineral density to achieve adult maturity in terms of final adult height, sexual development and potential for fertility and requires the co-ordinated function of the HPG axis. Damage due to an oncological diagnosis or its treatment that alters the control or function of the HPG axis therefore presents with aberrations in timing or progression of puberty with impact on growth, sexual development, bone health and fertility.

Damage to the HPG axis in CCS can be due to either a central (hypothalamic-pituitary (HP)) or primary (gonadal) insult or in some cases both. Central hypogonadism occurs when there is damage to the hypothalamus or pituitary due to tumour, surgery or cranial irradiation which affects luteinising hormone (LH) or follicle stimulating hormone (FSH) production leading to either early (precocious), or reduced or absent production with consequent effects on stimulation of gonadal function. Primary hypogonadism occurs when tumour, surgery, radiotherapy or chemotherapy damage the testicles or ovaries. Both can occur together, for instance after Haematopoietic Stem Cell Transplantation (HSCT), particularly with additional preceding cranial irradiation when pituitary exposure to radiotherapy affects gonadotrophin production, but gonadal damage occurs due to chemotherapy and total body irradiation (TBI).

This chapter will look at the impact of childhood cancer and its treatment on puberty, gonadal function and fertility, reviewing documented sequelae of historical and recent treatment strategies and also any changes in the risk of HPG axis damage with the use of newer treatment modalities.

Prevalence of HPG axis dysfunction

The reported prevalence of gonadal disorders among CCS varies considerably due to heterogeneity of patient characteristics in study cohorts such as the age of treatment exposure, gender, primary diagnosis, treatment regimens and follow-up time.

Disorders of the hypothalamus and pituitary can include both central precocious puberty (CPP) and delayed puberty. Rivarola et al. reported CPP as the presenting symptom in 26% of children with suprasellar or pineal lesions [6]. CPP is reported between 11.9% and 15.2% of CCS [7,8] and gonadotrophin deficiency 10.8% [9] of central nervous system (CNS) tumours in general. Gan et al. reported the presence of CPP in 26% and gonadal deficiency in 20.4% of CCS treated with 48–55 Gy of cranial radiotherapy for low-grade glioma involving the optic pathway, hypothalamus, and suprasellar region after a median of 8.3 years follow up [10]. Among non-pituitary/suprasellar childhood brain tumour survivors, Brignardello et al. reported an overall 6.3% incidence of hypogonadotrophic hypogonadism (HH) in a mixed cohort of primary diagnosis [11]. Clement et al. reported HH in 4.2% of CCS diagnosed aged 12 years or older after a median follow up of 6.6 years [12]. In the St Jude's cohort of adult CCS, 10.8% were shown to have HH after a median period of 27.3 years post cranial irradiation for haematological or solid malignancies, with an increased risk among those who had >22 Gy [9].

Variable prevalence of primary gonadal failure is reported. Green et al. reported acute ovarian failure in 6.3% of CCS, and the risk of premature menopause was 13.2 times higher than their siblings

(8% vs. 0.8%) [13]. The St. Jude Lifetime Cohort Study with 921 female CCS at median age of 31.7 years reported a 10.9% prevalence of primary ovarian insufficiency (POI) 24 years after the initial diagnosis, but this was likely an underestimate as participants taking oral contraceptives to prevent pregnancies or regulate menstrual cycles or for the treatment of polycystic ovarian syndrome were assumed not to have POI [14]. In the general population, azoospermia occurs in approximately 1% and in 10–15% of infertile males [15]. Studies with non-selective cohort of adult male CCS survivors reported azoospermia in 17.8–42·9% [16–20]. A Swedish study reported a 6.7 fold increase in the odds of hypogonadism (defined as testosterone <10 nmol/L and/or LH > 10 IU/L) in male CCS compared to age-matched controls [21].

The prevalence of primary gonadal failure is much higher in CCS treated with specific therapies with high risk of gonadotoxicity. Data more specific for patients who have received alkylating agents reported gonadal failure in 11% of males and 44% of females treated for childhood lymphoma [22,23]. In CCS treated with HSCT, pubertal failure/arrest have been reported in 57% of prepubertal/peripubertal children, ovarian failure in 65–84% of adult females [24] and testicular failure with azoospermia in 48–85% of adult males [25,26].

Aetiology of HPG axis dysfunction in CCS

HPG axis function can be affected either by tumours involving the hypothalamus, pituitary, gonads or related structures or by a range of oncology treatments (surgery, radiotherapy or chemotherapy) that can damage HP function. This will impact on pubertal timing, pubertal progress to adult maturity and future fertility potential.

Hypothalamic-pituitary damage causing central hypogonadism

Tumour factors

The significance of the actual site of the primary cancer diagnosis, such as hypothalamic involvement of the tumour in the suprasellar region, has been shown as a much stronger independent predictor of CPP and HH than patient and treatment factors [10].

Both CPP and pubertal delay or arrest due to central hypogonadism can be the first clinical sign of a CNS tumour in the HP region. CPP was the initial presenting features in 8 out of 45 cases of optic pathway gliomas or astrocytomas from a case series of 100 children with CNS lesions [27]. Optic pathway gliomas such as astrocytomas are one of the most common groups of tumours to cause CPP, because of their proximity to the HP axis [27,28]. These tumours may be located at the HP region and disrupt hormonal regulation due to mass effect and/or hydrocephalus secondary to ventricular system obstruction.

The same tumour types of the sellar/suprasellar region and/or their treatment with neurosurgery and radiotherapy may also present as or evolve into HH in children [10]. For example, delayed onset puberty was the first clinical sign in 19% of craniopharyngioma survivors [29]. In a cohort of CCS, Gan et al. showed that CCS with CPP were at a higher risk of developing central hypogonadism than those without CPP (37.5% vs 14.6% respectively) [10].

Rarely gonadotropin independent precocious puberty in childhood may occur as a result of HCG secreting tumours (e.g. choriocarcinoma of the liver, hepatoblastoma), and germ cell tumours of the sellar/suprasellar region and mediastinum or sex hormone secreting tumours such as adrenocortical tumours, ovarian tumours (e.g. teratomas, dysgerminomas) and testicular tumours (e.g. sertoli cell tumour, Leydig cell adenomas) [30].

Treatment factors

Photon radiotherapy. Cranial radiotherapy is a key treatment modality of CNS tumours. CNS tumours are the most common paediatric solid tumour, and 20% of solid tumours present in children and adolescents under 15 years of age. Table 1 summarises current standard treatment options for CNS tumours. Radiotherapy involving the whole brain and HP axis leads to evolving pituitary dysfunction, and its

Table 1
Current treatment options for CNS tumours involving Radiotherapy (RT) (adapted from Huynh et al 2018 [60]).

Tumour	Primary treatment	
Glioma	Surgery mainstay of treatment followed by close surveillance If complete resection OS 80–100%; 10–15 disease free years	Treatment dependent on tumour grade. Adjuvant RT for disease progression as improves PFS but not overall survival Chemotherapy and repeat surgery
High grade Astrocytoma	Surgery & RT	Poor prognosis. Temozolamide not shown to improve survival in adolescents
Medulloblastoma	Combination of maximal safe resection surgery, RT and adjuvant chemotherapy (vincristine, cisplatin, cyclophosphamide)	RT: cranio-spinal with posterior fossa boost Standard risk 23.5 Gy, high risk 36 Gy. RT postponed/avoided for children <3 years due to higher risk of toxicities
Atypical teratoid/rhabdoid tumour (ATRT)	Combination of maximal safe resection surgery, high dose and IT chemotherapy and high dose RT	Prognosis poor Presentations frequently < 3 years when use of RT controversial
Intracranial ependymoma	Maximal safe resection surgery and post-operative RT 54–59.4 Gy	Focal irradiation with CSI for neuraxial spread Results less good when chemotherapy for younger patients to avoid RT
Germ Cell Tumours (GCT)	a. Germinomas: CSI or RT to ventricular system and tumour bed boost b. Non- germinomatous GCT: RT (54 Gy) and platinum-based CT	a. Pre-radiation CT further improvement. b. Less favourable prognosis. RT alone OS 20–45% increases to 70–80% with added CT
Chordomas and Chondrosarcomas	Skull base chordomas: surgery and postoperative RT	Slowly growing malignant tumour, poor prognosis without treatment. Chemotherapy not effective
Meningiomas	Usually benign: Surgical excision Adjuvant RT if incomplete resection If atypical, anaplastic, or disseminated: surgery and adjuvant RT	If unresectable radical RT
Sarcomas	Brain metastasis: combined surgery, CT and RT	RT use varies in different centres/countries

Key: CT = chemotherapy, CSI = craniospinal irradiation, GCT = germ cell tumour, OS = overall survival, PFS = progression free survival, RT = radiotherapy.

impact is known to be dose and schedule dependent [31]. Gonadotropin deficiency has been reported in 30% of children given high-dose cranial irradiation (>30 Gy), with increasing prevalence with time since irradiation [32].

Practice has changed over recent decades with regards to prophylactic low-dose CNS-directed radiotherapy (18–24Gy) previously used in children with acute lymphoblastic leukaemia (ALL), but now only for patients with evidence of CNS disease [33]. However cranial radiotherapy is standard treatment for brain tumours in children over 2 years and adolescents for the foreseeable future (doses up to 60 Gy), either alone or in combination with chemotherapy [34–36]. Cranial irradiation is given to children over 2 years to treat head and neck disease, such as nasopharyngeal tumours (doses up to 60 Gy), and TBI (10–14Gy) as part of conditioning in conjunction with chemotherapy before HSCT for malignant conditions [37].

Therapeutic radiation is divided into several fractions delivered over several days or weeks. Cranial irradiation can cause CPP more commonly in girls than boys treated with low doses (18–24 Gy), but CPP occurs equally in boys and girls treated with intermediate doses (25–30 Gy). This sexual dimorphism of the effect of cranial radiotherapy treatment reflects the inherent differences in the control of the onset of puberty as girls go into normal puberty at a younger age and more easily and idiopathic gonadotrophin dependent precocious puberty is more common in girls [38] whereas boys start puberty later with a higher prevalence of constitutionally delayed puberty [39]. The development of radiation-induced hypopituitarism depends on the biological effective dose delivered to the HP axis which is determined by the total dose, fraction size, and radiotherapy schedule [40–44]. Gonadotropin deficiency can subsequently occur after initial CPP even after low-dose irradiation in female survivors

of ALL at a mean of 20·8 years. The risk, specific hormone deficiency and speed of development of increases with increasing biological effective dose increases [45] and any effects of radiotherapy are cumulative [46–49]. Anterior pituitary hormones are lost in a predictable hierarchy; growth hormone (GH) is the most commonly affected anterior pituitary hormone, followed by the gonadotropins, FSH and LH, and then adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH) less predictably [31]. GH deficiency can occur after low-dose radiation (18–24 Gy) suggesting that the hypothalamus is more sensitive to radiation damage [3,50–53], whereas higher doses (>30 Gy) are needed to damage the anterior pituitary and cause the development of multiple pituitary hormone deficiencies.

The time to develop pituitary hormone deficiency also decreases with increasing bioequivalent radiation dose to the HP axis and the progressive accumulation of HP dysfunction with time indicates either delayed radiotherapy effects or secondary pituitary atrophy after hypothalamic damage [43,45,54]. There is some indication of an effect of age at irradiation on the evolution of pituitary deficiency, although data are limited, and relate to differing prevalence of growth hormone deficiency (GHD) and ACTH deficiency after irradiation in childhood and adulthood [16,55].

The toxic effects of radiotherapy to the HP region in children are age and gender dependant. Younger age at radiation exposure was also associated with earlier onset of puberty in both gender but with sexual dimorphism as previously described [56,57]. Other patient factors reported to increase the risk of central hypogonadism in CCS includes being male, white race and obese [9].

Proton therapy. Development of new treatment modalities are aimed at reducing potential long-term toxicities whilst maintaining optimal disease control and aiming for cure. The use of proton therapy is increasing rapidly in recent years. Proton therapy allows energy to be deposited in a well-defined peak localised to the tumour with minimal exit dose and therefore should reduce radiation exposure to large volumes of normal tissue and reduce unwanted long-term treatment-related toxicities. Data are now emerging to allow comparison of outcomes of proton with photon therapy. Eaton et al. reported lower prevalence of sex hormone deficiency (3% vs 19%) but no significant difference in precocious puberty (18% vs 16%) in childhood medulloblastoma survivors treated with proton therapy compared with conventional photon therapy [58]. Yock also reported a prevalence of 3% of sex steroid deficiency in 58 patients with medulloblastoma treated with protons median craniospinal irradiation (CSI) dose 23.4 Gy, and 54 Gy boost dose, median follow-up 7 years [59]. A recent review of the published literature of 74 papers of proton therapy in paediatric patients concluded that survival and tumour control outcomes were comparable to photon therapy but with reduced incidence of severe acute and late toxicities, including endocrine sequelae, with the caution that numbers were not large, cohorts were often mixed and longer term follow up was needed [60].

Immunotherapies. Oncological treatments are evolving all the time, to improve oncological outcomes and minimise toxicities. There have been exciting advances in the use of immunotherapies. Monoclonal antibodies, check point inhibitors, bi-specific T-cell engagers and CD19 chimeric antigen T cell have now been approved for children's cancer therapy but as yet there is limited experience in children, but increasing experience in adult practice. Recent trials reported the incidence of hypophysitis in 0–5% of adult patients treated by anti-CTLA4 immune check point inhibitors (e.g. ipilimumab) 6–12 weeks after initiation of therapy for different tumour types and the risk seems to be dose-dependent. Magnetic resonance imaging reveals findings of an enlarged pituitary gland with thickening of the stalk. Hypopituitarism is indicated by abnormal levels of ACTH, cortisol, TSH and free T4, GH, prolactin, IGF-I, FSH, LH, and testosterone (in males). Hypogonadotropic hypogonadism has been reported in 83–87% of male patients with hypophysitis treated with anti CTLA4 [61]. Potential long-term endocrine toxicities of these new treatments in children are currently unknown and need further evaluation.

Hypothalamic-pituitary-gonadal damage causing primary hypogonadism

Primary gonadal failure in CCS may be a direct consequence of the tumour itself (e.g. ovarian or testicular tumours) or its treatment with surgery, chemotherapy and radiotherapy. The risk is

associated with the cancer type, treatment modality and dose, age at diagnosis and treatment, gender, and background genetic factors. Gender is a key factor with different risk factors for females and males.

Female primary hypogonadism (ovarian failure)

A recognised definition of female primary gonadal failure/premature ovarian insufficiency is: primary amenorrhoea or the absence of menstrual cycles for ≥4 months and 2 sequential elevated FSH levels in the postmenopausal range under the age of 40 years [62].

Females have a non-replenishable pool of germ cells from birth and the number of primordial follicles reduces with age. The age of natural menopause in the general population ranges from 40 to 58 years, which is influenced by ethnicity, parity and lifestyle choices such as smoking [63]. The pool of germ cells can be further reduced in CCS who have received radiotherapy to the abdomen, pelvis and spine, and/or certain chemotherapy agents, particularly alkylating agents, which deplete the oocyte pool leading to a reduction in ovarian reserve [64]. In addition, there is also genetic variability in chemotherapy induced gonadal impairment among female CCS as the level of residual ovarian reserve is influenced by the size of the original pool (see Fig. 1). The impact of genetic variation on ovarian reserve is currently being addressed by international collaborative research [65].

Effects from ovarian tumour and surgery. Ovarian tumours are rare in childhood and constitute around 1–2% of childhood malignancies [66], with two thirds of these being germ cell tumours [67]. Others include surface epithelial stromal tumours, sex cord–stromal tumours, and miscellaneous tumours (i.e., gonadoblastoma, malignant lymphoma and leukaemia, small cell carcinoma, and soft-tissue tumours). Benign teratomas are treated with complete surgical resection alone. Treatment for ovarian germ cell tumours usually consists of unilateral adnexectomy followed by chemotherapy. Bilateral disease is uncommon and no surgical interventions are performed if the contralateral ovary appears macroscopically normal to avoid the risk of extra adhesions and impairment of ovarian reserve [68]. Normal gonadal function as indicated by menstrual regularity have been shown in data from young adult women who have undergone unilateral salpingo-oophorectomy during childhood for ovarian pathologies [69].

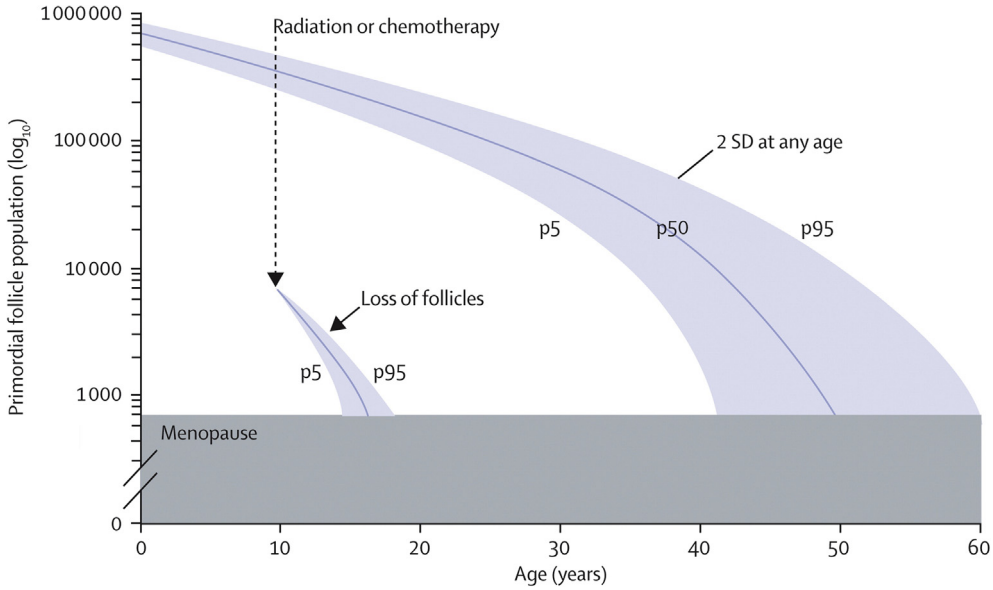

Fig. 1. Decline of ovarian follicular reserve in women undergoing chemotherapy (De Vos M *et al* Lancet 2010;376:911–21, with license to reproduce from publisher).

Effects from chemotherapy. A recent systematic review reported an overall risk of gonadal failure in mixed cohorts of chemotherapy-treated only female CCS as 0–19% [70]. Chow et al. reported reduced likelihood of pregnancy (HR 0·87, 95% CI: 0·81–0·94) and having a live birth (HR 0·82, CI:0·76–0·89) female CCS compared with sibling controls [71]. Chemotherapeutic agents, specifically alkylating agents (e.g. busulfan, cyclophosphamide, ifosphamide, lomustine, and procarbazine), commonly used in the treatment of Hodgkin's lymphoma and conditioning pre HSCT, are gonadotoxic in a dose-dependent manner. The exact mechanism of chemotherapy-induced ovarian failure is unclear. It has been proposed that gonadal toxic chemotherapy causes damage to the deoxyribonucleic acid (DNA) of the underdeveloped oocytes and pre-granulosa cells of the primordial follicles in a dose-dependent fashion, resulting in depletion in the number of primordial follicles, cortical fibrosis and subsequent ovarian atrophy [72].

Treatment factors. Gonadal toxicity is dependent on the type and cumulative dose of alkylating agents used, although a clear dosage threshold could not be safely define [71,73] The cyclophosphamide equivalent dose (CED) uses grams of cyclophosphamide (Table 2) as a reference to convert doses of commonly used alkylators to equipotent values provides a common quantitative measurement to allow comparison of gonadotoxic outcomes [74].

Premature menopause was more frequently present in survivors of Hodgkin's lymphoma who have received procarbazine, and the risk increases in a dose-dependent manner [70]. In CCS treated with HSCT survivors, a much greater risk of ovarian failure (68% vs 29%) has been shown in survivors who have received busulfan during conditioning compared with those without [75]. Childhood HSCT survivors treated with reduced intensity regimens containing fludarabine and melphalan compared to patients conditioned with a myeloablative regimen containing busulfan and cyclophosphamide took significantly longer to develop biochemical features of ovarian insufficiency from the onset of puberty in females [76]. The Childhood Cancer Survivors Study study reported Procarbazine at any age and cyclophosphamide aged 13–20 years as independent risk factor for ovarian failure [77]. Platinum compounds (e.g. cisplatin and carboplatin), taxanes and anthracyclines follow alkylating agents in terms of gonadal toxicity. Antimetabolite group, such as methotrexate and 5-fluorouracil, and vinca alkaloids (vincristine and vinblastine) have minimal or no gonadal toxic effects [74,77].

However, as chemotherapy drugs are usually administered in combinations, the accumulative effects of drugs with minimal or moderate gonadal toxicity may still induce a significant degree of ovarian damage when they are given for a longer period of time and/or at higher doses. The addition of busulfan (16 mg/kg) to low or high doses of cyclophosphamide (120 and 200 mg/kg, respectively) caused permanent ovarian damage to almost everyone [78–80]. In addition, patients who had received adjunct radiotherapy affecting gonads such as CSI radiation for CNS tumours and TBI conditioning pre-HSCT further increases the risk of gonadal failure.

Table 2
Cyclophosphamide Equivalent Doses of Alkylating agents.

Alkylating agents	Cyclophosphamide Equivalent Doses (CED)
Cyclophosphamide	1.000
Ifosfamide	0.224
Procarbazine	0.857
Busulfan	8.823
Chlorambucil	14.286
Carmustine	15.000
Lomustine	16.000
Melphalan	40.000
Thiotepa	50.000
Chlormethine	100.000

CED can be calculated using the following formula: CED (mg/m^2) = 1.0 (cumulative cyclophosphamide dose [mg/m^2]) + 0.244 (cumulative ifosfamide dose [mg/m^2]) + 0.857 (cumulative procarbazine dose [mg/m^2]) + 14.286 (cumulative chlorambucil dose [mg/m^2]) + 15.0 (cumulative carmustine dose [mg/m^2]) + 16.0 (cumulative lomustine dose [mg/m^2]) + 40 (cumulative melphalan dose [mg/m^2]) + 50 (cumulative thiotepa dose [mg/m^2]) + 100 cumulative chlormethine dose [mg/m^2]) + 8.823 (cumulative busulfan dose [mg/m^2]).

Patient factors. A systematic review of 5607 chemotherapy-treated female childhood and young cancer survivors diagnosed between 1945 and 2012 with follow up time of 0.3–48.4 years have demonstrated that the use of alkylating agents and older age at treatment as the most influential risk factors for ovarian failure [70]. The age of menopause for the whole group of cancer survivors was on average younger in comparison to the general population of median age at 44 years. Median ages of menopause were reported at 33.5 years in survivors of Hodgkin's lymphoma and as low as 14.4 years in haematological malignancies treated with HSCT exposed to conditioning regimens containing either busulfan or other alkylating agents [70].

The risk of ovarian failure is higher in patients who had received treatment at an older age [13,81] and more advanced stages of puberty [75]. Ovarian failure is almost universal in patients who have received HSCT in young adulthood, whereas, those treated before the onset of puberty have a better chance of subsequent ovarian recovery and achievement of spontaneous menarche [82,83]. Younger patients may be protected because of the larger number of non-growing follicles or higher resistance of these follicles to vascular damage and cortical fibrosis induced by chemotherapy in the preadolescent females.

Effects from radiotherapy. Acute ovarian failure was reported in 70–85% of the girls who were exposed to dose- and age-dependent abdominal-pelvic irradiation [77]. A meta-analysis of >2000 female CCS from 14 studies in the associations between radiotherapy and risk of reproductive health impairment for female CCS reported significant association between infertility, low anti-Mullerian hormone (AMH) levels (<1 ng/mL), stillbirth and low birth weight [84].

Radiotherapy works by directly inducing breaks in DNA strands, which can lead to apoptosis in the targeted radiation field and any peripheral tissue subjected to scatter. It was suggested that ovarian damage was a result of treatment-induced apoptosis, mitochondrial DNA damage, and damage in blood vessels, neovascularization and focal fibrosis. The timing of long-term endocrine effects secondary to radiation depends on the period of time it takes cells to duplicate. Therefore, radiation-induced hypogonadism may be delayed for many years after completion of treatment [85].

Treatment factors. Increased risk of POI is reported in females treated with radiotherapy at the lower abdomen, pelvis and spine with its severity associated with the field of exposure, total radiation dose, fractionation schedule and age of treatment. The proximity of the ovaries to the radiation field remains a significant risk factor for ovarian failure. In a heterogeneous cohort of CCS, POI was reported in 68% of patients who had both ovaries within abdominal radiotherapy fields, 14% whose ovaries were at the edge of the treatment field, and in none of 122 patients with one or both ovaries outside of an abdominal treatment field [86]. An ovarian radiation of >10 Gy was associated with a significant risk (OR 55; 95% CI 22.3–157.8) for acute POI defined as delayed/absent menarche or secondary amenorrhoea in the first 5 years after treatment in CCS [77].

The risk of POI is influenced by the dose and fractionation schedule of the radiation treatment. It has been estimated that 50% of human primordial follicles can be destroyed by less than 2 Gy [87]. Fractionated radiotherapy reduces ovarian damage and female CCS treated with 12 Gy fractionated TBI were shown to be five times more likely to have a spontaneous recovery of the ovarian function than girls receiving single dose of TBI [88]. Threshold radiation doses for POI were estimates at 20.3 Gy in infants, 18.4 Gy in children up to 10 years and 16.5 Gy in young people up to 20 years via a mathematical model [89].

However, there is no agreed safe threshold for the risk of POI in clinical practice as many cancer schedules include a combination of radiotherapy and chemotherapy. The additive effects of gonadal toxic chemotherapy are likely to further decrease the threshold dose of radiation induced ovarian failure. Females treated with abdominal/pelvic radiation for Wilms' tumour, Hodgkin's disease, neuroblastoma [90] or CSI for ALL [91] in combination with alkylating agents have a much greater risk of delayed or absent puberty. Ovarian failure was reported in almost 100% of female CCS who had undergone HSCT conditioned with TBI after puberty but in 50% of female CCS who had undergone HSCT before the age of 10 years [7].

In addition to ovarian damage, radiation also impacts the uterus. Uterine exposure to radiation during pelvic, spinal, abdominal, or total-body irradiation causes irreversible damage to the

endometrium, myometrium, and vascular structures, resulting in adverse reproductive and obstetrical outcomes. Childhood HSCT survivors conditioned with TBI compared with chemotherapy experience more deleterious influence on the uterus. The prepubertal uterus is more sensitive to radiation [92], and restoration of normal uterine growth remains inadequate in most HSCT survivors despite sex hormone replacement therapy (HRT) during puberty and achievement of withdrawal vaginal bleeding.

Patient factors. As with the effects of chemotherapy, female CCS who were exposed to radiotherapy at an older age have a higher risk of ovarian failure probably due to their lower follicular reserve [77]. Almost all patients who had undergone TBI-based HSCT over the age of 10 years experienced ovarian failure whereas only 50% of girls under 10 years of age are at risk [81].

Male primary hypogonadism (testicular failure)

A recognised definition of primary gonadal failure in males is: low testosterone levels with elevated LH and FSH levels, or failure to develop signs of puberty by the age of 14 years or arrested pubertal development for at least 6 months with elevated LH and FSH levels [93].

Unlike primary gonadal failure in females when both failed hormonal production and infertility occur together, gonadal damage in males can result in differing effects on spermatogenesis and steroidogenesis. The germinal epithelium of the seminiferous tubules, responsible for spermatogenesis, is highly sensitive to irradiation damage and chemotherapy toxicity regardless of age. Leydig cells have greater resistance to toxicity from chemo therapy and/or radiotherapy than Sertoli cells. Therefore, male CCS may maintain testosterone production enabling normal spontaneous pubertal development, despite evidence of germ cell failure with elevated FSH, low inhibin B, reduced testicular volume and azoospermia. Impaired spermatogenesis may be reversible or permanent, depending on the combinations of treatment and other patient factors. With greater gonadal toxicity, both spermatogenesis and steroidogenesis may be damaged.

Effects from testicular tumours and surgery. Testicular germ cell tumours make up 0.5% of paediatric malignancies [94]. Histological types are usually pure yolk sac tumours, or benign teratoma in pre-adolescents and embryonal carcinoma and mixed non-seminomatous germ cell tumours in adolescents and young adults. Surgical excision with orchiectomy is the standard initial step in treatment followed by chemotherapy. Radical orchiectomy is the traditional approach to all testicular malignancy. Whilst unilateral radical orchiectomy preserves contralateral testicular function, Leydig cell dysfunction and hypogonadism may still develop prematurely [95]. Survivors of germ cell tumours are at risk of androgen deficiency into adulthood. Data from long terms survivors of testicular cancer showed that hypogonadism occurs in an estimated 10–15% of patients after unilateral orchiectomy, resulting in the need for androgen replacement [95].

Effects from chemotherapy

Treatment effect. Similar to the effects on ovaries, toxicity of alkylating agents to the male testes is also dose dependent. Reduced fertility and azoospermia have been reported in CCS treated with CED of between 4 and 7.5 g/m^2 [71,74,93]. In a study of 171 male survivors of childhood lymphoma survivors, Servitzoglou demonstrated rise in FSH according to the number of MOPP (mechlorethamine, Oncovin, procarbazine, and prednisone) or OPPA (Oncovin, procarbazine, and prednisone, and Adriamycin) courses received by the patient, which is independent of age, or pubertal status at diagnosis [96]. The same study reported threshold dose of CED 6.3 g/m2 for gonadal toxicity, defined as FSH levels of >10 IU/L in >75% of the study cohort [96]. Green et al. reported azoospermia in 25% and oligospermia in 28% of 214 adult male CCS who had received alkylating agent chemotherapy with CED of 8480 and 10 830 mg/m^2 respectively, without radiotherapy. CED was negatively correlated with sperm concentration, but it was not possible to establish a completely safe lowest dose threshold for fertility as azoospermia and oligospermia have been reported In 11% of this cohort exposure to CED of <4000 mg/m^2 [74]. It has been shown that male CCS had a decreased likelihood of siring a pregnancy (HR 0·63, 95% CI: 0·58–0·68) or a live birth (HR 0·63, 95% CI:0·58–0·69) compared with siblings [71].

Leydig cells are not as sensitive as the germ cell to gonadotoxic effects, and therefore testosterone production and pubertal progression are not necessarily compromised by doses of alkylating agents that may induce sterility. Testosterone production is often maintained unless dose exposures exceed 20 g/m^2 [74], although subclinical Leydig cell damage has been recognised. For example, Howell et al. reported normal mean testosterone but significantly higher LH levels in 209 male survivors of Hodgkin's disease treated with MVPP (mechlorethamine, vinblastine, procarbazine and prednisone) compared with healthy controls, although subsequent decline in LH levels suggested recovery overtime [97].

In non-radiotherapy treated male HSCT survivors, the risk of delayed puberty is uncommon. Panasiuk et al. reported spontaneous puberty occurred in all male HSCT survivors treated with reduced intensity regimens containing fludarabine and melphalan compared with 89% of those who had myeloablative regimen of busulfan and cyclophosphamide at conditioning [76].

Patient factors. Unlike the impact on ovarian function, gonadal toxicity from alkylating agents in males was found to be independent of the diagnosis, age or pubertal status at diagnosis and assessment [74,98].

Effects from radiotherapy

Treatment factors. The effects of radiotherapy on the testes depend on the dose and field of exposure, as well as age of the patient. Subclinical Leydig cell dysfunction can occur in testes irradiated with 12 Gy while more substantial dysfunction is reported after exposed to 24 Gy [93]. In terms of spermatogenesis, transient impairment has been observed after low single fraction doses of 2–4 Gy of spermatogenesis whilst higher doses have been associated with more permanent long term damage [99].

In ALL, testicular involvement at initial diagnosis is rare and is usually treated with chemotherapy only. Testicular involvement in relapsed leukaemia is treated with orchiectomy and/or local radiotherapy. Patients with unilateral disease may be given prophylactic radiotherapy of 15 Gy to the unaffected side after orchiectomy, whereas those with bilateral disease treated with high dose local irradiation of 24 Gy in 12 fractions [100,101]. Unfortunately, Leydig cell failure has been reported to be almost universal in childhood ALL survivors with local radiotherapy of 24Gy for bilateral testicular disease [16], hence radiotherapy avoiding strategies should be considered to preserve testicular function. A recent study by Barredo et al. reported no differences in treatment outcomes and 5 year survival in children with isolated testicular B-ALL relapse in remission after induction phase treated with intensive chemotherapy only compared with those who received additional testicular irradiation [102]. However, the need for testicular irradiation in patient with other forms of ALL or early relapse remain to be addressed.

Various previous studies have shown spontaneous pubertal initiation and progression in HSCT treated leukaemia survivors without testicular disease, conditioned with alkylating chemotherapy and hyper-fractionated TBI during the prepubertal period [28,103,104]. However, it is important to be aware of a older cohort of survivors who received 4 Gy radiotherapy boost to the scrotum pre-transplantation as prophylaxis in addition to the routine 12–14.4 Gy TBI from historical protocols [105] who may be at a higher risk due to accumulative toxicity.

Patient factors. In contrast to females, the gonads of younger male CCS are more radiosensitive and vulnerable to testicular damage [16]. A higher rate of subsequent gonadal failure is reported in male CCS who received gonadotoxic radiation in the pre-pubertal and peri-pubertal age ranges than post pubertal or adult males. Leydig cell function is affected in prepubertal boys who have received testicular irradiation of doses >20 Gy whereas higher doses of >30 Gy causes the same effects in older boys [85].

Recovery of gonadal function post treatment

It has been shown that gonadal function may already be compromised at diagnosis in both genders [106,107] and is then further decreased by childhood cancer treatment. The cause of these reduced reproductive hormone levels is unclear, and may be due to stress, down regulation by endocrine

substances or cytokines produced by some tumours and metabolic conditions or malnutrition. Nevertheless, recovery have been shown in about half of the children with gonadal impairment over time [108].

In females CCS, ovarian function is preserved or recovers intermittently after treatment completion, as seen in 10–14% of HSCT survivors [78] where spontaneous pubertal progression and menarche can occur. However, progressive loss of ovarian function and premature menopause is common [109]. Ongoing monitoring is therefore required and patients should be advised not to postpone family planning over other lifestyle choices. Less than 3% of HSCT survivors achieve pregnancy and those who are successful have a high risk of adverse outcomes such as foetal loss, premature delivery and low birth weight [78,109].

In males CCS, recovery of gonadal function has also been reported in mixed cohorts of primary diagnosis long (>15 years) after discontinuation of treatment as indicated by normalisation of inhibin B levels. However, this recovery does not occur in survivors who had already reached critically low inhibin B levels after discontinuation of treatment such as survivors treated with high dose alkylating agents or TBI [110]. In CCS treated with HSCT, the chances of recovery are associated with the conditioning regimens [22,23]. For example, the rate of successful pregnancies in female partners of male patients post HSCT treated with cyclophosphamide only was significantly higher compared to those treated with busulphan/cyclophosphamide or TBI [78].

HPG damage causing combined central and primary hypogonadism

Myeloablative conditioning regimens with combined alkylating agents and TBI for HSCT can cause primary hypogonadism as described in the previous sections. TBI not only increases the risk of gonadal damage, but also raises the potential for central HP damage, particularly if an additional cranial irradiation boost is given. HSCT protocols have evolved with time in favour of reduced intensity chemotherapy conditioning without TBI in lower risk conditions. A multinational multicentre randomised control trial is currently taking place to evaluate outcomes of non-TBI conditioning in childhood ALL [111].

Endocrine management of CCS

CCS identified with significant risk of HPG axis damage, need counselling at the time of diagnosis and oncology treatment planning of their risk of pubertal or fertility issues in the future. Long-term multi-disciplinary follow-up with an experienced team involving endocrinology, fertility specialists and appropriate counsellors is required [4].

Fertility preservation for those at risk of primary gonadal failure

CCS at risk of primary gonadal failure described in the previous sections should be considered for fertility preservation before gonadotoxic therapy. Detailed approaches of the current options in fertility preservation in CCS are beyond the scope of this review and therefore only briefly summarised here.

In females, ovarian transposition is performed in patients with tumours requiring abdominal and pelvic radiotherapy to preserve ovarian function. However, the procedure can fail to protect the ovaries in 10–14% of cases [112]. The use of oral contraceptives or gonadotropin-releasing hormone (GnRH) analogues to suppress ovarian function during chemotherapy to induce a pseudo-prepubertal state has been proposed as a strategy to preserve fertility in cancer patients. Outcomes from trials with adult cancer survivors have been conflicting and there is lack of data in CCS [112]. In terms of cryopreservation, storage of ovarian tissue with primordial follicles is the only suitable fertility preservation method in pre and post-pubertal female prior gonadal toxic therapy such as TBI, and high-dose alkylating agents [113]. Such treatment is still under development and only available in specialised centres under ethically approved research protocols. Successful pregnancies from autograft of cryopreserved ovarian tissue obtained from childhood have been documented in HSCT survivors treated for non-malignant haematological diagnoses [114,115]. In cancer survivors, there are concerns regarding the potential risk of reseeding tumour cells following auto transplantation of ovarian tissues.

In males with testicular tumours, while malignant yolk sac tumours can only be treated by radical orchidectomy, testicular sparing surgery are advocated in small well-defined teratomas with favourable prognostic factors to preserve testicular function [116]. In adolescent males undergoing gonadal toxic cancer therapy, sperm cryopreservation is currently the best option to preserve future fertility. However, patients often experience difficulties in providing semen samples via masturbation due to their young age and illness, and artificial methods such as penile vibratory stimulation or electroejaculation requires general anaesthesia [117], and samples obtained are usually of suboptimal quality [118]. In vitro maturation of germ cells to sperm remains experimental. In pre-pubertal males who lack mature spermatozoa, experimental protocols on testicular cryopreservation are being studied but with no outcome data in humans yet. Auto grafting of biopsied tissue has been successful in animals but the risk of re-introduction of malignant cells precludes this option in leukaemias, with some suggestion that other tumour types may also be risky [117].

Presentation of hypothalamic-pituitary-gonadal problems in childhood cancer survivors

HPG axis damage may be identified during follow-up by aberrations in the timing or progress of puberty.

- Early Puberty: signs of puberty presenting before 8 years in girls and 9 years in boys.
- Delayed or Absent Puberty: girls who have not reached breast stage 2 by 13 years and boys who have not achieved testicular volumes of 4 mls by 14 years. As those at risk of HPG dysfunction should be known, it is preferable to anticipate delayed puberty to allow endocrine intervention and pubertal progression at an appropriate age.
- Arrested Puberty: this is more difficult to define but failure of progression of puberty at a reasonable rate.
- Post-pubertal failure in the HPG axis: secondary amenorrhoea and symptoms of oestrogen deficiency in females, but in males, symptoms of testosterone deficiency are more difficult to identify.
- Abnormal consonance of puberty when the normal sequence of puberty has not happened: in girls this may be evidence of androgens without oestrogenisation and in boys, evidence of androgens without evidence of testicular development.

These presentations may be *de novo* as part of the presenting signs and symptoms of the cancer itself or they may develop during or after treatment of the cancer diagnosis, and in many individuals they could be late effects of treatment occurring some years after treatment. They may be in isolation or with other signs and symptoms of endocrine deficiency.

As a general rule, investigation and clinical management of early or late puberty in CCS follow the same principles as in non-CCS individuals [4,119,120], but there are some specific features of clinical assessment and timing and response to interventions to bear in mind in CCS.

CCS presenting with early puberty

Evaluation of CPP in CCS

As previously described, early puberty is evident in girls under 8 years, and boys under 9 years with secondary sexual characteristics. Assessing puberty in boys using testicular volumes is unreliable if there is concomitant testicular damage (after chemotherapy or testicular irradiation). LH levels may rise if CPP is occurring but may also reflect an emerging primary gonadal failure.

Tall stature and rapid growth usually accompany CPP, but in CCS with CPP a growth spurt may be absent as growth may be affected by other factors such as concomitant GHD, or poor spinal growth after CSI. Therefore, growth rate may be normal for age (but not stage of puberty) or indeed slow.

Standard investigations usually include a bone age X-ray, and endocrine investigations (basal LH/FSH, sex steroids, GnRH test in suspected cases of CPP) and pelvic ultrasound scan in girls. Cranial imaging should be considered for those CCS not undergoing routine cranial imaging as part of their oncology surveillance.

Management of CPP in CSS

If gonadotrophin dependent precocious puberty is identified in CCS, it is managed in the same way as in idiopathic CPP with GnRH analogues [4]. The aims of treatment are to improve growth outcomes and manage psychosocial concerns for young children experiencing the emotional rollercoaster of puberty early. There are data supporting the use of GnRH analogues to improve adult height in idiopathic CPP [121–124] and in CCS [8,27]. However, in CCS there are potentially many other factors adversely impacting on growth and so patients and their carers need to be warned that adult height may still be compromised compared with a child with idiopathic CPP. Loss of final height is particularly likely in CCS treated with CSI due to loss of pubertal spinal growth spurt [125,126] and this is more marked in those who were treated at a younger age and at higher doses [127]. A final height loss of between −0.86 and −1.06 SDS has been reported in CCS treated with cranial irradiation and TBI respectively [128]. CCS with medulloblastoma treated with CSI are one of the groups most at risk of GHD, and despite GH replacement, showed a compromised median height of SDS -1.9 and spinal height SDS of −2 [126].

It may also be appropriate to consider GnRH analogue treatment for those with an early but not precocious puberty, i.e. to hold puberty at a later age than usual in idiopathic CPP, if puberty is progressing rapidly [27,129] or if other adverse factors are at play such as associated GHD when there is evidence that final height may be improved by GnRH analogues [27,130]. If there is on-going oncology treatment and puberty is progressing, there may be a rationale to delay puberty to allow time for growth and puberty after completion of oncology treatment, but there is currently no evidence that delaying puberty at a normal age improves adult height in CCS.

After treatment for CPP in CCS is completed, on-going pubertal surveillance is required as there remains a risk of future HH.

CCS presenting with delayed, arrested or absent puberty

Evaluation of delayed, arrested or absent puberty in CCS

A key aim of long-term follow-up of CCS is to ensure optimal growth and pubertal development and well-being. Table 3 summarises those CCS at risk of hypogonadism who should have careful monitoring of growth and puberty during their treatment and subsequent follow-up [4]. In CCS who are at risk of HPG dysfunction, it is important to anticipate that delayed puberty is likely to occur and initiate treatment at an appropriate age in line with their peer group rather than waiting for obvious physical signs of delayed puberty to become too apparent. However clinical assessment may be more difficult, particularly in boys as testicular volume is not useful to stage puberty if there is primary gonadal damage which will compromise testicular growth. Growth rate may also be misleading if other factors are adversely affecting normal growth.

Fig. 2 summarises the diagnostic pathway to evaluate CCS at risk of hypogonadism and differentiate between primary and central hypogonadism.

Endocrine screening (raised circulating FSH, LH) as part of routine surveillance should identify those with a primary gonadal problem at an appropriate peri-pubertal age. Those CCS who have had both gonadotoxic treatment and HP damage as in HSCT particularly if they have had preceding cranial irradiation may have co-existing gonadotrophin deficiency, in which case basal LH, FSH will not be raised despite primary gonadal dysfunction. Additional investigations of gonadal function are described below.

Those at risk of HH could of course also have constitutional delay in growth and puberty (CDGP), which also occurs as in non-CCS and indeed may be more prevalent following serious ill health. The differentiation between CDGP and HH is always challenging but clearly in the CCS cohorts their medical history is key in identifying those at risk (see Table 3) of central HP axis problems due to tumour location, surgery or cranial irradiation > 30Gy. Other pituitary hormones are likely to be affected in these circumstances, particularly GH facilitating the recognition of gonadotrophin deficiency at an appropriate age. Post pubertal decline in sex steroid levels with low LH, FSH levels would also suggest HH.

Table 3
Risk factors of Hypogonadism in Childhood Cancer Survivors.

Hypogonadism	Patient factors	Disease & Treatment factors
CENTRAL	• Gender (Male > Females) • Prepubertal • Younger age	• Hypothalamic/pituitary/Suprasellar tumours • Cranial Irradiation >22–30 Gy • Longer time post treatment
PRIMARY Both genders	• Genetics fertility background • Smoking • Obesity	• HSCT with TBI (single >fractionated) • HSCT with myeloablative (e.g. TBI/Busulfan/cyclphophamide) > reduced intensity (e.g. Fludarabine/Melphalan) chemotherapy conditioning
Ovarian failure (females)	• Older age (>12y) • Post Pubertal	• Bilateral ovarian tumours • Alkylating agents: no safe threshold dose, surveillance recommended if MOPP >3 cycles; busulfan > 600 mg/m2; cyclophosphamide > 7.5 g/m^2; cyclophosphamide for HSCT; ifosfamide >60 g/m^2 • Radiotherapy no safe threshold dose, ovarian failure reported in 50% after <2Gy to abdomen/pelvis/spine, surveillence recommended if RT to ovaries prepubertal: 10–15 Gy, pubertal: 5–10 Gy
Leydig Cell Dysfunction (males)	• Younger age • Pre-pubertal	• Testicular cancer treated with unilateral orchiectomy • Radiotherapy: subclinical <12 Gy, significant >20 Gy prepubertal, 30 Gy post pubertal at treatment • Alkylating agents: usually subclinical, significant if CED > 20 g/m2, Surveillance recommended if treated with MOPP, Cyclophosphamide (≥20 g/m^2), Cyclophosphamide for HSCT, Ifosfamide (≥60 g/m^2)
Germ Cell Dysfunction (males)	• Younger age • Pre-pubertal	• Testicular cancer treated with unilateral orchiectomy • Bilateral testicular tumours with orchiectomy • Alkylating agents: CED > 5 g/m^2, surveillance recommended if treated with MOPP 3 cycles or more Busulfan (≥600 mg/m^2), Cyclophosphamide (≥7.5 g/m^2) Cyclophosphamide for HSCT Ifosfamide (≥60 g/m^2) • Radiotherapy to testes: >2–3Gy

Key: CED = cyclophosphamide Equivalent dose, HSCT= Haematopoietic Stem Cell Transplantation, MOPP = mustargen (chlormethine, nitrogen mustard), oncovin (vincristine), procarbazine, prednisone. TBI = total body irradiation.

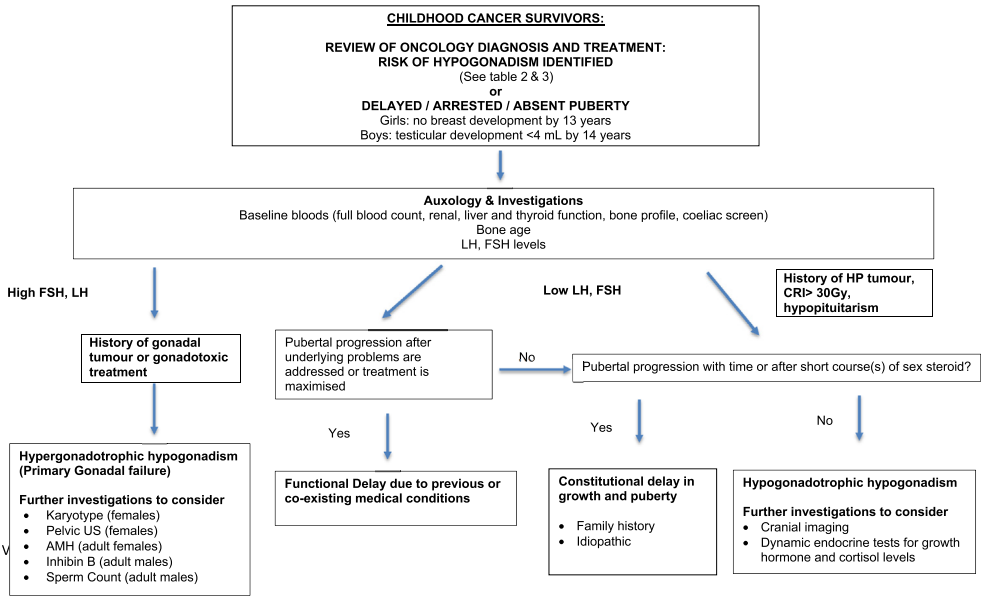

Fig. 2. Evaluation of potential hypogonadism in childhood cancer survivors at risk of HPG axis insufficiency.

Further investigation to assess gonadal function and reproductive capacity in CCS

The assessment of gonadal function in CCS should start with auxological measurements of weight, height and height velocity, and pubertal staging by clinical examination. Gonadal reserve may be predicted by biochemical markers such as FSH, AMH, inhibin B. Further information on prediction of reproductive capacity may be evaluated by radiological examinations for example Antral follicle count (AFC) and total ovarian volume via trans-vaginal ultrasound scans in females; and semen analysis in males.

Gonadotropins

In central hypogonadism, pulsatile release of FSH/LH from the anterior pituitary is absent or diminished leading to low sex hormone concentrations. Persistently raised FSH levels indicate the presence of gonadal failure and it is recommended as a screening tool in girls at risk for POI from the age of 12 years [73]. However, FSH level may be in the normal range normal in pre-pubertal children that may later develop gonadal failure, and CCS with co-existing gonadal failure and HH.

AMH

AMH levels is one of the best endocrine markers for age-dependent decline in ovarian reserve in the general population which correlates with AFC and is hence a marker of longitudinal decline in ovarian follicle reserve and predictor of menopause. AMH concentrations are relatively stable throughout the menstrual cycle and are unaffected by contraception treatment. However, interpretation is difficult in children and adolescents due to the lack of age and pubertal related reference data [119].

In female CCS, there is uncertainty in the use of AMH profiles in the prediction of fertility capacity and premature menopause and a very low AMH does not exclude spontaneous pregnancy in young CCS up to 25 years of age. There is also concerns that AMH levels may also be influenced by other factors other than AFC such as the diseases and general health status of the patients [62]. AMH is therefore not currently recommended as a screening tool for POI in CCS.

Inhibin B

In boys, inhibin B, secreted by Sertoli cells, demonstrates the presence of testicular tissue and is often used as a marker of spermatogenesis in adults. Various studies have evaluated the use of inhibin B in screening for gonadal damage in male CCS with conflicting outcomes. Inhibin B concentrations have been shown to correlate independently with sperm concentration in males treated for childhood Hodgkin's lymphoma with combination chemotherapy [131]. However, data from the St Jude's CCS cohort showed that neither serum inhibin B nor FSH is a suitable surrogate for determination of sperm concentration in a semen sample [132].

Semen analysis

The latest World Health Organization definition for semen analysis defined the lower fifth centiles as following: semen volume 1.5 ml, total sperm number 39 million per ejaculate, sperm concentration 15 million per ml, vitality 58% live; progressive motility 32%; total (progressive & non-progressive) motility 40% morphologically normal forms 4.0% [133]. Previous data have demonstrated that viable sperm can be collected from adolescent and young adult males who are newly diagnosed with a variety of cancers and should be collected before beginning therapy. However, significant reductions in semen quality have been shown after gonadotoxic therapy [118,134]. Poor sperm quality have also been shown in some patients with Hodgkin lymphoma even prior to therapy [134].

Pelvic and abdominal ultrasound

Pelvic ultrasound scanning is useful to examine pelvic anatomy and maturity, and signs of ovarian follicles to gonadotrophin stimulation in females. The prepubertal uterus has a tubular configuration with mean ovarian volume <1 cm^3 whist in puberty, the uterus becomes pear-shaped (fundus-to-cervix ratio 2:1 to 3:1) with visible endometrial lining and ovarian volume > 2 ml. Ovarian volume is used as an indirect measure of ovarian reserve and AFC reflect the remaining follicle pool. Reduced ovarian volume and AFC have been described in CCS even with normal menstrual cycles [88]. Data from

larger cohort study with 564 CCS demonstrated reduced ovarian reserve in specific subgroups of CCS, in particular the those aged over 35 years [135].

Management of delayed/absent puberty

Both central or primary cause of delayed puberty due to hypogonadism in CCS are currently managed with sex steroids induction/replacement as per standard protocols for patients with non-cancer diagnosis, outlined below [4].

HRT in females should start no later than the age of 12–13 years. Oestrogen therapy is usually started at a low dose of oral or transdermal preparation with gradual escalation to full adult dose over 3 years, and the addition of progesterone at the onset of uterine breakthrough bleeding or at least 2 years after starting oestrogen [120]. HRT via transdermal patches is recommended due to its better metabolic risk profile and also the higher risk of vascular events reported associated with oral preparations [136]. However, care should be taken in counselling about contraception, as although reduced fertility or infertility is very likely, it cannot be assumed and most HRT regimens do not provide contraception. Therefore, the standard oral contraceptive pills may be preferable to HRT in survivors who also require contraception in addition to sex hormone replacement. A back-to-back regimen of 9 week on 1 week off (instead of the standard 3 weeks on 1 week off) regimen is commonly used to reduce the length of time without oestrogen replacement, or additional oestrogen can be prescribed in the week off OCP. However, such decisions about oestrogen replacement must take into consideration of the potential increased risk of thrombotic events in CCS, particularly those who were treated with CSI [137]. Although there is not yet specific evidence related to CCS, aspirin is increasingly being considered as stroke prevention in adult CCS in long term follow up [138].

In males, pubertal induction is usually initiated around the ages of 12–14 years, using a low dose of monthly intramuscular or daily topical testosterone with a gradual dose titration to full adult dose over 3 years [120].

There is increasing interest in inducing puberty with gonadotrophins for those with HH [139], but as yet no experience in CCS.

Summary and conclusions

Pubertal disorders, both CPP and delayed or absent puberty and gonadal failure in adulthood are common in CCS. A clear understanding of the risk factors for hypogonadism in CCS is essential to inform appropriate counselling and optimisation of long-term health in CCS. CNS tumours and/or their treatment with neurosurgery and/or radiotherapy to the HP region may result in CPP or LH/FSH deficiency. In terms of primary hypogonadism, female CCS, treated with alkylating agents, radiotherapy to the pelvis and at an older age during treatment are of the highest risk of develop POI. In males, impaired germ cell function and therefore oligo- or azoospermia occurs after exposure to much lower doses of alkylating agents and/or testicular radiation than Leydig cell damage and as a result steroid hormone production may be maintained. Delayed puberty and hypogonadism in CCS are treated with sex hormone replacement as per standard protocols for non-CCS, but anticipation of primary hypogonadism allows options for fertility preservation for CCS, although these may be limited and still experimental. Gonadal dysfunction in CCS may evolve over time and lifelong surveillance of high risk groups is essential.

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Practice Points

- CCS are at a high risk of gonadal dysfunction which often manifest as pubertal disorders during childhood or fertility problems in adult life. Gonadal function in CCS may evolve with time and lifelong monitoring is essential.
- Additional factors in clinical assessment of CCS need to be recognised. Growth velocity is not a reliable indicator if there is concomitant GHD or loss of spinal height after CSI. Testicular volume is not a reliable indicator of pubertal progress in boys who have had gonadotoxic treatment.
- Gonadal dysfunction in CCS may result from the primary malignancy itself and/or its treatment such as surgery, radiotherapy and/or chemotherapy.
- CPP can occur after low dose cranial irradiation, and is more common in girls at a lower dose (18–24Gy) but is equal at an intermediate dose (25–30Gy).
- Central hypogonadism can be caused by damage to HP region due to tumour effect, surgery and/or cranial radiotherapy >22–30Gy.
- POI is likely in female CCS treated with alkylating agents, radiotherapy to the pelvis and at an older age/post pubertal at the time of treatment
- Primary testicular damage depends on treatment exposure in male CCS: germ cell function can be impaired by alkylating agents of >5 g/m^2 and testicular radiation>2–3Gy, whereas Leydig cell dysfunction is usually subclinical unless there is exposure to very high doses of alkylating agent of 20 g/m^2 and testicular radiation of 20–30Gy.
- CPP and delayed puberty due to hypogonadism in CCS are treated as per standard protocols for non-CCS.

Research Agenda

- New cancer therapies will need long-term follow-up of CCS to identify potential endocrine late-effects and options for fertility preservation in CCS are a rapidly developing field.

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