Reproductive Complications in Childhood Cancer Survivors

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KEYWORDS

• Infertility • Gonadal failure • Late effects • Childhood cancer survivor
• Premature ovarian failure • Radiation effects • Fertility preservation

KEY POINTS

- Male and female childhood cancer survivors (CCSs) may be at risk for gonadal insufficiency, resulting in pubertal delay or pubertal arrest, reduced bone mass, sexual impairment, and infertility.
- Best practice for CCSs should include consultation on the risk for gonadotoxicity, infertility, future obstetric risk, and sexuality, because this greatly influences their quality of survival.
- CCSs at risk for gonadal dysfunction should be screened according to the recent recommendations and be referred upon indication to a (pediatric) endocrinologist, andrologist, gynecologist, or fertility specialist with experience in CCSs.

INTRODUCTION

Gonadal dysfunction and infertility after cancer treatment is of major concern to childhood cancer survivors (CCSs) and their parents.[1] Uncertainty about fertility or being diagnosed with infertility has a negative impact on quality of survival.[2] This article reviews determinants of gonadal damage and their impact on fertility and pregnancies. It

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also provides specific recommendations for screening and treatment of gonadal function to enable timely treatment of gonadal insufficiency and its effects, such as stunted linear growth, delayed pubertal development, effects on bone health, and sexual functioning. Options for fertility preservation are discussed.

FEMALE GONADAL TOXICITY, FERTILITY, AND REPRODUCTIVE COMPLICATIONS

Definition

Premature ovarian insufficiency (POI) is a clinical condition that develops under the age of 40 years and is characterized by the absence of menstrual cycles for greater than or equal to 4 months and 2 sequential elevated follicle-stimulating hormone (FSH) levels in the postmenopausal range.[3]

Risk Factors

Overall, female CCSs have an estimated nonsurgical cumulative risk of developing POI of approximately 8%.[4] A large nationwide retrospective cohort study demonstrated that a majority of CCSs did not show signs of reduced ovarian reserve; however, specific subgroups of CCSs are at high risk.[5] CCSs at high risk for POI are those who have been treated with alkylating agents or radiotherapy to a field, including the ovaries (**Box 1**, **Fig. 1**).

The human ovary is sensitive to cytotoxic agents.[6] Commonly used alkylating and similar DNA interstrand cross-linking agents in pediatric oncology are the alkylating agents (busulfan, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine [nitrogen mustard], melphalan, and thiotepa), the triazenes (procarbazine, dacarbazine, and temozolomide), the nitrosoureas (carmustine [BCNU] and lomustine [CCNU]), and platinum agents (carboplatin and cisplatin). A dose-dependent relation for developing POI has been shown for alkylating agents. For use of a single drug, a high level of evidence has been found for busulfan and melphalan; however, for other single agents, the level of evidence is much lower,[6] which is due mainly to the fact that in most studies patients are treated with combination therapy, making it difficult to determine the independent absolute risk of a single alkylating agent. To combine and compare cumulative dosages of different alkylating agents for survivor outcomes, such as POI, the cyclophosphamide equivalent dose (CED) has been shown useful.[7] International consensus is that a high risk for infertility is likely when the CED is greater than or equal to 6000 mg/m^2 to 8000 mg/m^2, and a lower risk after CED is 6000 mg/m^2 to 8000 mg/m^2.

Radiation exposure is another acknowledged risk factor for damaging the ovarian tissue and the uterus.[6] The magnitude of the radiation effect is related to dose, fractionation, and age at time of radiation exposure. A mathematical model has been developed in which threshold doses for POI are calculated for infants (20.3 Gy), children up to 10 years of age (18.4 Gy), and adolescents up to 20 years of age (16.5 Gy), illustrating that the older the patient, the lower the dose needed to deplete the nongrowing follicle pool and thus cause POI.[4] POI has been described after treatment with ^{131}I-meta-iodobenzylguanidine MIBG and surgery for neuroblastoma.[8] In CCSs who were treated with ^{131}I for differentiated thyroid carcinoma, transient effects on female gonadal function have been reported.[9] The effect of ^{131}I and ^{131}I-MIBG on the human ovary should be investigated further. Interindividual variability in susceptibility to therapy-related gonadal impairment suggests a role for genetic variation. This issue is being addressed in the PanCareLIFE study, Europe's largest clinical cohort to study the impact of treatment regimens on the quality of life of CCSs.[10]

Box 1
Harmonized recommendations for premature ovarian insufficiency surveillance in survivors of childhood, adolescent, and young adult cancer

General recommendation

Survivors treated with 1 or more potentially gonadotoxic treatments,[a] and their providers, should be aware of the risk of POI and its implications for future fertility (level A and level C evidence).

Who needs surveillance?

Counselling regarding the risk of POI and its implications for future fertility is recommended for survivors treated with

- Alkylating agents in general (level A evidence)
- Cyclophosphamide and procarbazine (level C evidence)
- Radiotherapy, potentially exposing the ovaries (level A evidence)

Which surveillance modality should be used for prepubertal and peripubertal survivors?

Monitoring of growth (height) and pubertal development and progression (Tanner stage) is recommended for pre-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy, potentially exposing the ovaries (expert opinion/no literature search).[a,b]

FSH and estradiol are recommended for evaluation of POI in prepubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy, potentially exposing the ovaries,[a] who fail to initiate or progress through puberty (expert opinion/no literature search).[c,d]

Which surveillance modality should be used for postpubertal survivors?

A detailed history and physical examination with specific attention for POI symptoms (eg, amenorrhea and irregular cycles) are recommended for postpubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy, potentially exposing the ovaries (expert opinion/no literature search).[a]

FSH and estradiol are recommended for evaluation of POI in postpubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy, potentially exposing the ovaries,[a] who present with menstrual cycle dysfunction suggesting POI or who desire assessment about potential for future fertility. Hormone replacement therapy should be discontinued prior to laboratory evaluation when applicable (expert opinion/no studies).[d,e]

AMH is not recommended as the primary surveillance modality for evaluation of POI in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy, potentially exposing the ovaries,[a] who desire assessment about potential future fertility (expert opinion/no studies).

AMH may be reasonable in conjunction with FSH and estradiol for identification of POI in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy, potentially exposing the ovaries,[a] aged >25 years who present with menstrual cycle dysfunction suggesting POI or who desire assessment about potential for future fertility (expert opinion/no studies).

When should prepubertal and peripubertal survivors be referred?

Referral to pediatric endocrinology/gynecology is recommended for any survivor who has

- No signs of puberty by 13 years of age
- Primary amenorrhea by 16 years of age
- Failure of pubertal progression[f] (expert opinion/no literature search)

When should postpubertal survivors be referred?

Referral to gynecology/reproductive medicine/endocrinology (according to local referral pathways) is recommended for postpubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries[a] who present with menstrual cycle dysfunction suggesting POI (expert opinion/no literature search).

What should be done when abnormalities are identified in prepubertal, peripubertal, and postpubertal survivors?

◀ Consideration of sex steroid replacement therapy is recommended for prepubertal, peripubertal, and postpubertal survivors diagnosed with POI by referral to gynecology/endocrinology (expert opinion/no literature search).

What should be done when potential for future fertility is questioned?

Referral to gynecology/reproductive medicine/endocrinology according to local referral pathways) is recommended for postpubertal female CCSs treated with potentially gonadotoxic chemotherapy and/or ovarian irradiation[a] without signs and symptoms of POI who desire assessment about potential for future fertility (expert opinion/no literature search).

Abbreviations: level A, high level of evidence; level B, moderate/low level of evidence; level C, very low level of evidence.[a] Treatments with evidence of causing POI include alkylating agents in general (level A evidence), cyclophosphamide, procarbazine (level C evidence), and radiotherapy to a field that includes the ovaries (level A evidence).[b] At least annually, with increasing frequency as clinically indicated based on growth and pubertal progression.[c] At least for girls of 11 years of age and older, and for girls with primary amenorrhea (age 16).[d] If amenorrhea, measure FSH and estradiol randomly; if oligomenorrhea, measure during early follicular phase (day 2–5).[e] This assessment should be performed after ending oral contraceptive pill/sex steroid replacement therapy use, ideally after 2 months without oral contraceptive pills.[f] The absence of initiation of puberty (Tanner stage 2 breast development) in girls 13 years or older or failure to progress in pubertal stage for $\geq$12 months.

From van Dorp W, Mulder RL, Kremer LC et al. Recommendations for premature ovarian insufficiency surveillance for female survivors of childhood, adolescent, and young adult cancer: A report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. Journal of Clinical Oncology 2016; 34:3440–3450; with permission.

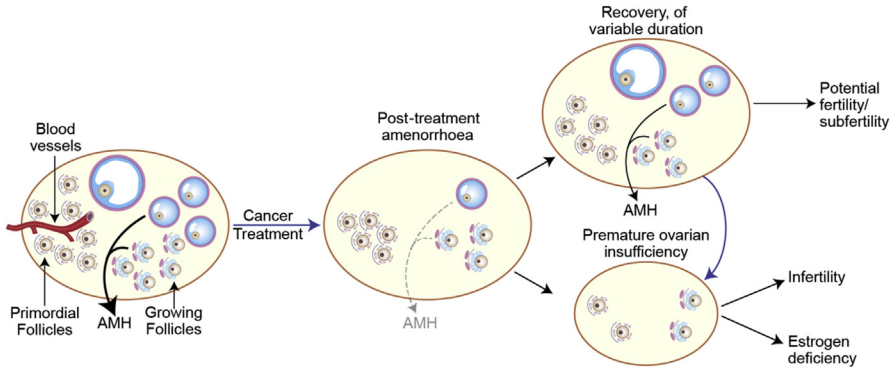

Fig. 1. Representation of the effects of gonadotoxic treatment on the ovary. Illustration of the key effects of cancer treatment on the ovary, highlighting the variable recovery after treatment such that some patients have permanent POI with infertility and estrogen deficiency, but others show recovery allowing fertility, although their reproductive life span may be shortened. (*From* Jayasinghe YL, Wallace WHB, Anderson RA. Ovarian function, fertility and reproductive lifespan in cancer patients. Expert Review of Endocrinology and Metabolism 2018; 13:125–136; with permission.)

Consequences of ovarian damage may be decreased production of estrogen (and to a lesser extent androgen), resulting in pubertal delay or failure, primary or secondary amenorrhea, osteoporosis, cardiovascular disorders, psychosocial problems, infertility, and sexual health issues. Radiation to the uterus has been associated with miscarriage, premature delivery, placental abnormalities and stillbirth.[4,11]

Screening for Premature Ovarian Insufficiency

In young prepubertal and peripubertal CCSs, clinical assessment for POI is advised by measurement of height, plotted in a growth chart in relation to target height, and calculating height velocity, in conjunction with clinical examination of pubertal stage. Determination of the FSH concentration is the recommended screening tool in girls at risk for POI age 12 or up[6] (see **Box 1**). The serum antimüllerian hormone (AMH) concentration is an endocrine marker for age-dependent decline in ovarian reserve.[12] A validated normative model for AMH from birth to senescence has been made, describing a transition period in early adulthood, after which AMH reflects the progressive loss of the nongrowing follicle pool.[13] For women and girls under 24 years of age, the interpretation of AMH as indirect marker of ovarian reserve remains speculative, which makes the value of AMH in predicting early menopause in CCSs uncertain.[14] Also, a very low AMH in young adolescent CCSs does not exclude spontaneous pregnancy. Furthermore, AMH concentrations seem to be influenced not only by treatment but also by the general disease state.[15] For all these reasons, AMH currently has not been recommended as screening tool for POI in CCSs[3] (see **Box 1**). Measuring AMH concentrations may be considered, however, after finding an increased FSH concentration, because the combination of an increased FSH with undetectable AMH has been related to ovarian insufficiency.

It is strongly advised to refer CCSs with signs of gonadal failure after treatment of childhood cancer to a pediatric endocrinologist for estrogen and progestogen treatment and, upon request, also to a fertility specialist for fertility counseling (see **Box 1**). A pediatric endocrinologist induces puberty with gradual administration of sex steroids, aiming to mimic the timing and key milestones of normal puberty. The need for puberty induction should be anticipated in girls who have been exposed to high-risk therapy.[4,6] For adult CCSs, an endocrinologist or gynecologist considers hormone replacement for optimization of bone mineralization or relieve of symptoms, such as hot flushes, joint pain, and tiredness. Hormone replacement generally is recommended until the age of natural menopause.[4]

Fertility Preservation in Female Childhood Cancer Survivors

CCSs who have been exposed to cytotoxic drugs, radiation therapy including the ovaries in the radiation field or to surgery near the ovaries radiotherapy, or surgery, including the ovaries, deserve counseling regarding the available fertility preservation methods that may apply to them.[6,16,17] It is important that the attending physician actively counsels and informs the survivor whether there are questions about fertility, pregnancy, or sexuality during the long-term follow-up visits. In a questionnaire among 484 survivors, fewer than half of the women reported to have received information about their treatment's impact on fertility, and only 14% reported that they received information about fertility preservation.[18]

Counseling CCSs at risk for POI includes first providing information on established and experimental options for preservation of gonadal function after cancer treatment.[19]

Autotransplantation of previously cryopreserved ovarian cortex tissue in CCSs can be done for fertility restoration or endocrine replacement. After reimplantation of ovarian tissue, ovarian activity is restored in more than 95% of cases. The mean duration of ovarian function after reimplantation is 4 years to 5 years, but the function can persist for up to 7 years, depending on the follicular density at the time of ovarian-tissue cryopreservation.[20] The first successful pregnancy after replacement of cryopreserved ovarian tissue was reported in 2004.[21] At present, more than 130 live births have been described, with a pregnancy rate of 29% to 41% and a live birth rate of 23% to 36%.[17,20]

Also, successful puberty induction has been described in two 13-year-old girls with hypergonadotropic hypogonadism.[22,23] Although these reports are of scientific and clinical importance because they prove that follicular growth may be activated in prepubertally cryopreserved ovarian tissue, they also open the discussion upon the subject if this procedure is beneficial for an adolescent or not.[24] Tissue replacement for puberty induction has many disadvantages, such as escalation of estrogen dose, early exposure to progesterone, the fact that it has only temporary effect (loss of valuable tissue), and the potential risk of malignant contamination.[17,24] For all these reasons, endocrine substitution therapy is recommended by exogenous hormonal replacement therapy over tissue replacement.

For postpubertal CCSs at risk for developing POI who did not receive prior fertility preservation methods, oocyte cryopreservation is a feasible fertility preservation technique. This may be offered to selected female CCSs at risk for POI, if hormonal treatment intervention is allowed from an oncological perspective.[25]

For CCSs with full-blown POI and no egg cell reserve, currently, no techniques are possible to restore fertility. For these survivors, however, it is important to stress that replacement of estrogen may influence growth of the uterus, enabling possible future pregnancy by donor oocytes.[26,27] The latter may not hold for CCSs who have been treated with radiotherapy to a field, including the uterus, such as in survivors with ovarian failure secondary to total body irradiation of 20 Gy to 30 Gy in which hormone replacement therapy did not seem to increase uterine size, blood flow, or endometrial thickness.[28]

Female fertility outcomes and reproductive complications

The overall reduction in the likelihood of pregnancy in female CCSs aged under 40 compared with the general population has been reported to be 38%.[29] In a large Swedish cohort of CCSs, the hazard ratio (HR) for having a first live birth in CCSs was significantly lower than in healthy controls,[30] although it was lower only for CCSs with malignancy of the eye, central nervous system (CNS) tumors, or leukemia. Women surviving childhood cancer have a lower HR for having a first live birth compared with women diagnosed with cancer in adolescence (HR 0.47 vs 0.89, respectively).[30] CCSs who have received abdominal or cranial radiotherapy take significantly longer to become pregnant than their siblings.[31]

Uterine radiotherapy with doses greater than 5 Gy (relative risk 2.48; 95% CI, 1.54–4.01) significantly increases the risk of infertility.[31] As a consequence of radiation exposure to the uterus or lack of sex steroids, female CCSs may be at increased risk for miscarriage, fetal growth restrictions, perinatal deaths, preterm births, delivery of small-for-gestational-age infants, preeclampsia, and abnormal placentation.[3,28]

The fact that survivors of CNS tumors have the lowest HRs for the chance to become pregnant (HR 0.53 and HR 0.62 for male CCSs and female CCSs, respectively[30]) not only may be the consequence of pituitary damage resulting in hypogonadism or a toxic effect of chemotherapy on the gonads but also may be a reflection of the

fact that achieving pregnancy requires an adequate neurocognitive development. Impaired cognitive impairment is in turn associated with lower educational level, higher unemployment, less independent living, and a higher risk of never getting married. All these factors may influence the chance for pregnancy.[32]

There seems to be no increased risk for congenital abnormalities in the offspring of CCSs.[33]

Referral and Treatment of Female Childhood Cancer Survivors with Gonadal Dysfunction

CCSs with gonadal insufficiency should be referred for treatment to the appropriate health care provider like a dedicated (onco-) endocrine and/or fertility expert.

Sex steroid hormone replacement therapy is indicated in all girls and women age less than 40 with hypogonadism to restore pubertal development and remediate or prevent the consequences of premature estrogen deficiency, such as loss of bone mass, loss of self-esteem, and decrease in sexual activity.[34] In postpubertal girls and women, replacement of estrogens has a positive influence on bone health and cardiovascular status.[35] There is insufficient evidence that androgen replacement therapy in women with POI has beneficial effect on sexual function, bone mineral density, or quality of life.[36]

For prepubertal female CCSs, timing and dosing of estrogen substitution are essential to enable a normal pubertal and bone development as well as a normal social development during the teenage years. CCSs less than 18 years of age should be referred to an experienced pediatric endocrinologist. Estrogen supplementation is given, with monitoring of Tanner stage in relation to age, growth velocity, and skeletal maturation at regular basis. This may be challenging in girls who have been exposed to gonadotoxic agents in combination with cranial radiation or a tumor in the sellar region resulting in hypopituitarism. In this case, simultaneous growth hormone (GH) deficiency, luteinizing hormone (LH)/FSH deficiency, and primary gonadal failure may be present, influencing growth velocity and bone maturation. It also makes interpretation of laboratory values, such as insulinlike growth factor 1, LH, and FSH, challenging.

The association between sex steroid replacement therapy and risk of developing breast cancer was evaluated by the Childhood Cancer Survivor Study, in which a lower of developing breast cancer was found for CCSs with POI and treatment with estrogen replacement than CCSs without POI.[37]

The timing, dosage, and route of estrogen replacement is the same as those recommended for non-CCSs.[38–40] There is some evidence that transdermal versus oral replacement therapy in female CCSs may be of advantage[35,41]; however, this evidence was considered insufficiently strong.[6,35] Treatment with estrogen needs to be combined with progestin for endometrial cycling.

In cases of simultaneous GH deficiency, it may be chosen to start GH replacement therapy first before estrogen replacement therapy, to ensure an adequate pubertal growth velocity. These choices should be made individually by the pediatric endocrinologist and should be discussed with the teen survivor, balancing the advantages of estrogen replacement and pubertal development versus delaying this and optimizing final height.

MALE GONADAL TOXICITY, FERTILITY, AND REPRODUCTIVE COMPLICATIONS

In male CCSs, primary gonadal failure due to Leydig cell failure is defined as having decreased androgen concentrations in combination with elevated LH and FSH levels or failure to develop signs of puberty by age 14 or no change in pubertal stage for at

least 6 months at the age at which progression would be expected in combination with elevated levels of LH and FSH.[42] Impaired spermatogenesis is the consequence of Sertoli cell failure and is defined as having azoospermia or oligozoospermia. Male gonadal function may be hampered by damage to the testes or due to hypothalamic-pituitary (HP) damage resulting in central hypogonadism (**Table 1**).

In the testes, 2 distinct cell types are present: the Sertoli cells, which are important for spermatogenesis, and the Leydig cells, which are responsible for steroidogenesis (testosterone production). Spermatogenesis can be impaired without manifest damage to steroidogenesis. Although survival of the germ cells is most crucial for future fertility, the Sertoli cells (somatic stem cells) play an important role for fertility, because they create the environment that is needed to support development and survival of the germ cells. If these germ cells are lost, no restoration of spermatogenesis occura.[43] In addition, decreased testosterone production may lead to sexual dysfunction or impaired spermatogenesis leading to subsequent impaired fertility. Leydig cell failure and Leydig cell dysfunction recently have been associated with impaired glucose tolerance, insulin resistance, increased abdominal/body fat, and decreased quality of life.[44]

Risk Factors for Male Gonadal Failure

The function of the Leydig cells, Sertoli cells, or testicular germ cells may be distorted as a consequence of surgery, chemotherapy, or radiation to a field involving the testes.[42] Damage to the testicular vessels, changes in pituitary hormone concentrations, growth factors, or the structure of the seminiferous tubule structure also may cause dysfunction of the Sertoli cells or Leydig cells. This also holds for interstitial effects on the Leydig cells, leading to alterations in hormones or growth factors that may have an impact on germ cells directly or indirectly (eg, testosterone deficiency) through effects on other somatic cell populations. Gonadal function also already may be hampered before the start of treatment.[45]

In a large CCSs study, the prevalence rates of Leydig cell failure and Leydig cell dysfunction were reported to be 6.9% and 14.7%, respectively, after a mean follow-up time of 22 years after cancer diagnosis.[44] Independent risk factors for Leydig cell failure included an age of 26 years or older at assessment, testicular radiotherapy at any dose, and alkylating agents at CED greater than or equal to 4000 mg/m^2.[44]

In male CCSs treated for leukemia with alkylating agents, long-term depletion of the spermatogonial pool was seen whereas survivors without alkylating agents remained within normative reference values for prepubertal boys.[46] Spermatogenesis in male CCSs was described to be impaired after treatment with busulfan, cyclophosphamide, mechlorethamine (nitrogen mustard), ifosfamide, fludarabine/melphalan, and procarbazine.[42] Treatment with cyclophosphamide with a CED greater than or equal to 5 g/m^2 has been reported to induce impaired spermatogenesis.[47]

Although possible recovery of gonadal function in male CCSs has been reported even long after discontinuation of cancer treatment,[48] recent data demonstrated an increasing risk for Leydig cell failure, with increasing age at follow-up indicating that there may be an association with longer follow-up time and Leydig cell function.[44] Recovery or further decline of male gonadal function in time should be studied further in prospective cohorts.

Radiotherapy, including total body irradiation to a field, including the testes, has been associated with an increased risk for androgen deficiency.[42] The threshold for Leydig cell damage has been shown to be 12 Gy; however, spermatogenesis can already be impaired even after exposure to a radiation dose greater than 2 Gy.[32]

Table 1
Cancer treatments and risk factors associated with male adverse reproductive outcomes

	Reproductive Outcome		
Treatment	**Impaired Spermatogenesis**	**Testosterone Deficiency**	**Sexual Dysfunction**
Chemotherapy			
Alkylating agents	CED[a] >5 g/m^2	Possible, CED >20 g/m^2 or combinations	Possible, secondary to testosterone deficiency
Radiation			
Testicular	Low risk <12 Gy [c] High risk >12 Gy	Moderate risk >12 Gy High risk >20 Gy	Possible, secondary to testosterone deficiency
Pelvis, spine, lower extremities	Scatter or incidental dose to testes ≥2–3 Gy	Unlikely	Spinal field T11 and below, radiation field that includes genitourinary organs
Hypothalamus, pituitary, optic pathway	≥30 Gy	≥30 Gy	Possible, secondary to testosterone deficiency
Surgery			
Orchiectomy-unilateral[b]	Testicular cancer—possible reduced spermatogenesis	Testicular cancer—possible premature hormonal aging	Unlikely
Pelvic	Unlikely	Unlikely	Retroperitoneal lymph node dissection, Prostatectomy, Rectal surgery
Spinal	Unlikely	Unlikely	T11 and below
HP, optic pathway	Possible, tumor invasion of hypothalamus	Possible, tumor invasion of hypothalamus	Possible, secondary to testosterone deficiency

[a] An established unit for quantifying therapeutic exposure to different alkylating agents based on hematologic toxicity; for specific calculations, see Green and colleagues.[7]
[b] Data derived from studies with survivors of testicular cancer.
[c] Some evidence suggests that spermatogenesis may be impaired after radiation to the testes of 5 Gy. The risk for impaired spermatogenesis increases with increasing radiation dose.

Adapted from Kenney LB, Antal Z, Ginsberg JP, et al. Improving Male Reproductive Health After Childhood, Adolescent, and Young Adult Cancer: Progress and Future Directions for Survivorship Research. J Clin Oncol. 2018;36(21):2160-2168. https://doi.org/10.1200/JCO.2017.76.3839; with permission.

Impaired spermatogenesis may be reversible or permanent, depending on the combinations of treatment and on the cumulative dose of chemotherapy given. When counseling CCSs with impaired gonadal function, the survivor must be informed that infertility in male CCSs may be the result of a combination of factors, such as impaired spermatogenesis, androgen insufficiency, HP function, and sexual dysfunction. Each of these factors, in turn, can be a result of direct toxic effects of the given therapy or can be a consequence of psychosocial effects of having had cancer as a child.

Screening for Male Gonadal Failure

Different recommendations for screening of male gonadal failure exist. Due to discrepancies within the existing recommendations, the International Guideline Harmonization Group (IGHG) has formed a collaborative for recommendations on whom and how to screen for testicular insufficiency after treatment of childhood cancer.[42,49] Consensus was found to recommend that all CCSs treated with 1 or more potentially gonadotoxic agents should be advised and counseled about the risk of impaired spermatogenesis and its implications for future fertility.[42]

The assessment of gonadal failure in male CCSs should consist at least of a detailed history of the survivor, including physical examination, monitoring of height, body mass index, Tanner stage, and testicular volume in prepubertal and peripubertal boys. In older boys and adolescents, attention should be paid to the sexual history (onset of puberty, libido, presence of erections, and sexual activity).

For prepubertal boys at risk for gonadal insufficiency, it has been recommended to monitor height and pubertal development and progression (Tanner stage, including testicular volume); in postpubertal men, early morning serum testosterone and LH/FSH concentrations can be measured to monitor for gonadal insufficiency.[42] Semen analysis generally is considered the gold standard to evaluate male fertility and it should be offered to all postpubertal male CCSs when information on fertility is requested.

Inhibin B is secreted by the Sertoli cells. Therefore, it has been evaluated for use in screening for gonadal damage in male CCSs. In male CCSs treated for childhood Hodgkin lymphoma with combination chemotherapy (Adriamycin/epirubicin, bleomycin, vinblastine, and dacarbazine) with or without mechlorethamine, vincristine, prednisone, and procarbazine (MOPP), inhibin B concentrations were correlated independently with sperm concentration.[50] In prepubertal boys, it was found to be a potential marker, when used in combination with FSH, for semen quality. Even in this study, however, semen analysis still was suggested as the gold standard.[50] Two other studies that investigated the diagnostic value of inhibin B and FSH concentrations for detecting azoospermia and oligospermia showed that measurements of FSH, inhibin B concentrations, and using the inhibin-FSH ratio all show fairly diagnostic value for detecting azoospermia.[51,52] With these studies in mind, it has been concluded that inhibin B measurements may be useful but are not as reliable as the gold standard, and, therefore, should not be recommended as the standard screening tool.

The accuracy of FSH as a predictor of azoospermia in adult CCSs remains controversial, with conflicting results. Strong supporting evidence was found for the use of serum FSH as a surrogate biomarker for azoospermia in adult CCSs, with an optimal FSH threshold of 10.4 IU/L to detect azoospermia (specificity of 81% and sensitivity of 83%).[53] The IGHG recommended that if survivors require assessment of fertility, semen analysis is preferred to determination of FSH or inhibin B serum concentrations.[42]

Treatment of Male Gonadal Failure

Consequences of androgen (testosterone) deficiency in male CCSs can be pubertal delay or pubertal arrest, gynecomastia, reduced bone mass, lethargy, fatigue, diminished muscle mass, abdominal obesity, and sexual impairment. A recent study associated Leydig cell failure in CCSs with diabetes mellitus and all-cause mortality.[44] Timely diagnosis of androgen deficiency is important because most of the consequences of androgen deficiency may be overcome with testosterone replacement therapy.

Also, considering that sexual health has been shown to be important for overall health and quality of life, awareness and screening for sexual impairment in CCSs deserve attention. Sexual impairment may be present not only in CCSs with gonadal failure but also after surgery or radiation involving the lower spinal cord, prostate, distal colon, or rectum, due to disruption of the innervation required for erection and ejaculation.[32] These CCSs may be referred to an (andro-) urology department for specific techniques to improve sexual function.

Fertility Preservation in Boys Treated for Childhood Cancer

There are several experimental and established techniques for preservation of male fertility.[42] For pubertal and postpubertal male CCSs at potential risk of infertility due to treatment with alkylating agents, radiotherapy to volumes exposing the testes, hematopoietic stem cell transplantation, cisplatin, or orchiectomy or cranial radiotherapy, it has been recommended by the IGHG to offer semen cryopreservation before start of gonadotoxic therapy. Also, in male CCSs with high risk of recurrent disease and subsequent high risk of impairing further testicular function, sperm banking may be offered. In postpubertal male CCSs, sperm may be banked by cryopreservation after masturbation, or, if masturbation is not possible and there is a high risk of infertility, alternative techniques, such as vibration, electroejaculation, and microsurgical epididymal sperm aspiration or testicular sperm cell extraction, have been described.[54,55] In prepubertal boys, no proved fertility preservation option is available. The IGHG moderately recommends offering testicular tissue harvesting for cryopreservation in a research setting to prepubertal childhood, adolescent, and young adult (CAYA) cancer patients with high risk for infertility. In theory, this can be autotransplanted at the time the CCS is ready for it, after screening for residual malignant cells. Research is done by different groups to expand the spermatogonial stem cells in vitro.[32] Although the research in this field is active, there currently is no treatment possible for male CCSs with azoospermia after cancer treatment, except for pregnancy using donor sperm.

Male Fertility Outcomes

Male CCSs have been shown to have a reduced chance of siring a pregnancy than siblings (HR 0.56; 95% CI, −0.49–0.63), with increased risk for males after exposure to more than 7.5-Gy radiotherapy to both testes and higher cumulative doses of alkylating chemotherapy (CED >4000 mg/m^2).[56]

Referral and Treatment of Male Childhood Cancer Survivors with Gonadal Dysfunction

The most optimal timing to start testosterone supplementation in CCS boys depends on the decline in serum testosterone concentration, the growth height velocity, and bone age in combination with the development of and wish for secondary sexual characteristics. Testosterone may be administered orally, intramuscularly, or topically. The

goal of sex steroid replacement in male CCSs is to obtain adequate pubertal development in combination with optimization of final height, accrual of bone and muscle mass, and satisfaction upon secondary sexual characteristics and sexual functioning. In CCSs with central hypogonadism and no previous exposure to gonadotoxic drugs, stimulation of the testes for pubertal induction may be done using HCG. In this situation, during the virilization phase, the testes enlarge, which may give the developing teenager more self-confidence and improve body satisfaction. Disadvantages of HCG versus testosterone replacement therapy are the manner of administration and the cost effectiveness; HCG is more expensive and should be administered twice weekly subcutaneously. These advantages and disadvantages should be discussed with the teen survivor by an experienced pediatric endocrinologist. There seems to be no difference in effect of treatment with HCG versus testosterone replacement therapy on virilization (in case of sufficient testes) or fertility outcome.

CENTRAL HYPOGONADISM (FEMALE AND MALE)

Central hypogonadism results from inadequate or failing pulsatile release of gonadotropin-releasing hormone from the hypothalamus and/or inadequate FSH/LH secretion from the anterior pituitary. The most common causes for this condition are either a tumor in the sellar or suprasellar hypothalamic region or radiation exposure to a field that includes the HP region.[57] In rare cases, combined primary gonadal insufficiency and central hypogonadism exist due to the combination of treatment with gonadotoxic chemotherapy and damage to the HP region.

Central hypogonadism, or hypogonadotropic hypogonadism, leads to pubertal delay or arrest in peripubertal and postpubertal CCSs as well to signs and symptoms of sex steroid deficiency in adolescents, including all the possible consequences, as discussed previously. When there has been no exposure to gonadotoxic treatments, fertility may not be impaired because the gonads can be stimulated by FSH, human chorionic gonadotropin (HCG), or a combination treatment.[58] This should be counseled with the survivor, because the survivor may not be aware of the differences between hyperpogonadotropic (primary) and hypogonadotropic (central) hypogonadism with regard to fertility outcome.

Central hypogonadism may be diagnosed after cranial radiation, including the HP region, with greater than 22 Gy to 30 Gy, in survivors with tumors in the sellar or suprasellar region, such as craniopharyngeoma or germinoma, or after neurosurgery in the HP region, such as in patients with low-grade glioma.[59] The overall incidence of hypogonadotropic hypogonadism in CCSs was reported to be 6.3%.[60] In a Dutch cohort of 481 childhood brain tumor survivors age 12 years or older, 4.2% were found to have hypogonadotropic hypogonadism after a median onset of 4.5 years.[61] In 748 children followed for a median period of 27.3 years after cranial irradiation, the prevalence of LH/FSH deficiency was found to be 10.8% and was associated significantly with male sex and obesity.[59] Strikingly, hypogonadism was not treated in 78.5% of individuals, and presence of hypogonadism could be associated with hypertension, dyslipidemia, low bone mineral density, slow walking, abdominal obesity, low energy expenditure, and muscle weakness. These results emphasize the need for adequate screening and timely treatment of androgen deficiency.

PSYCHOLOGICAL CONSEQUENCES

Worries and uncertainty about gonadal or sexual dysfunction and fertility may have a great impact on CCSs. Dealing with infertility, even if it has been anticipated, needs time and professional guidance. For this reason, psychological support must be

present and offered to the survivor and is part of the expert oncofertility team and/or late effects clinic team.[1]

SUMMARY

Male and female CCSs may be at risk for gonadal insufficiency, resulting in pubertal delay or pubertal arrest, reduced bone mass, lethargy, fatigue, and sexual impairment. In addition, male CCSs may present with gynecomastia, diminished muscle mass, and abdominal obesity and female CCSs with hot flushes and sweating. Best practice is that all CCSs should be informed about their risk for gonadal toxicity, infertility, future obstetric risk, and reduced sexuality, because this greatly influences their quality of survival. Consultation about fertility preservation options and alternative family planning should be done for CCSs at high risk before transition toward adult survivorship clinics and repeated at appropriate time intervals based on international established guidelines for fertility preservation.

CCSs at risk should be screened according to recent recommendations and be referred on indication to a pediatric endocrinologist, andrologist, gynecologist, or fertility specialist with experience in CCSs. Before and during pregnancy, risk factors for premature delivery should be considered and discussed with obstetric medicine care experts.

DISCLOSURE

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