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Reduced male fertility in childhood cancer survivors

Sun Hee Lee, MD[1],
Choong Ho Shin, MD, PhD[2]

[1]Department of Pediatrics, Gachon University Gil Medical Center, Incheon, [2]Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea

With advances in cancer treatment, more pediatric cancer patients have increased their life expectancy. Because cancer-related therapy causes various physical and psychological problems, many male survivors experience later problems with thyroid and sexual functions, and with growth. As outcomes have improved, more survivors need to maintain their reproductive function to maximize their long-term quality of life. Cancer and cancer-related treatment can impair fertility by damage to the testes, to the hypothalamic-pituitary-gonadal axis, or to the genitourinary organs. Prior radiation therapy to the testes, the use of alkylating agents, and central hypogonadism further impair fertility in male survivors of childhood cancer. Following any course of chemotherapy, peripubertal maturation, any testicular volume changes, and symptoms of androgen deficiency should be monitored systematically. If patients request fertility testing, spermatogenesis status can be evaluated either directly by semen analysis or indirectly by determination of the levels of testosterone/gonadotropins and by monitoring any changes in testicular volume. According to the patient's condition, semen cryopreservation, hormonal therapy, or assisted reproduction technologies should be provided.

Keywords: Infertility, Chemotherapy, Radiotherapy, Male, Survivor

Introduction

According to the nationwide statistics of the National Cancer Center, the 5-year event-free survival rate of Korean boys and adolescents with cancer between 2001 and 2005 was about 70%[1)]. Two out of three survivors experienced later effects and 43% had delayed endocrine effects, including thyroid (22%), sexual (22%), growth (17%), and metabolic (6%) dysfunctions[2)]. As outcomes have improved, more survivors need to maintain their reproductive function to maximize long-term quality of life[3)].

Spermatogenesis depends on the proliferation and maturation of germ cells derived from spermatogonial stem cells in the seminiferous tubules, which comprise both germinal and Sertoli cells. Spermatogenesis is regulated through endocrine interactions between the hypothalamic-pituitary axis and Sertoli cells. Follicle stimulating hormone (FSH) stimulates the Sertoli cells to secrete androgen-binding protein, facilitating germ cell differentiation by binding to testosterone.

Cancer and cancer-related treatments can impair male fertility by damage to the testes, to the hypothalamic-pituitary-gonadal axis, or to the genitourinary organs[4,5)]. Recognizing treatment-associated reproductive risks and educating survivors and providers are very important for improving the health and quality of life of male survivors of childhood cancer. This article reviews the late effects of pediatric cancer therapies on fertility and fertility preservation options.

Risk factors

Reduced fertility is common among adult survivors of cancer who received some form of

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Address for correspondence:
Choong Ho Shin, MD, PhD
Department of Pediatrics, Seoul National University Children's Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea
Tel: +82-2-2072-3570
Fax: +82-2-743-3455
E-mail: chshinpd@snu.ac.kr

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chemotherapeutic agents, testicular radiation, or experienced damage to the hypothalamus or pituitary glands. In 2009, the Childhood Cancer Survivor Study (CCSS) reported that radiation therapy to the testes of more than 7.5 Gy, a cumulative alkylating agent dose score of ≥2, treatment with procarbazine, or treatment with high doses of cyclophosphamide were the major factors decreasing the likelihood of a cancer survivor achieving a pregnancy, as measured by the hazard ratio (HR)[6].

1. Chemotherapy–induced gonadal failure

If chemotherapeutic agents do not kill stem spermatogonia, spermatogenesis recovers within 12 weeks after the cessation of therapy[7,8]. However radiation or chemotherapy drugs (e.g., alkylating agents) that kill stem cells can induce azoospermia that lasts much longer than 12 weeks[5]. Spermatogenesis can be impaired by agents that alkylate DNA (e.g., cyclophosphamide, mechlorethamine, ifosfamide, procarbazine, busulfan, melphalan, and the nitrosoureas BCNU [carmustine] and CCNU [lomustine]) that cross-link DNA (e.g., cisplatin). The CCSS reported that survivors aged 15–44 years who were not surgically sterile were less likely to sire a pregnancy than siblings. For example, treatment with cyclophosphamide (parenteral >9.2 g/m^2, oral >10.637 g/m^2) produced HR of 0.42 with a 95% confidence interval (CI) of –0.31 to 0.57; procarbazine treatment (4.2–7.0 g/m^2) produced HR of 0.48 with 95% CI of –0.26 to 0.87[6].

The cumulative dose of a cytotoxic agent determines the duration and magnitude of impaired spermatogenesis. Prolonged azoospermia is associated with the total cumulative dose of cyclophosphamide (single agent[9], ≥19 g/m^2; combination with other drugs[10], >7.5 g/m^2), procarbazine[11] (≥4 g/m^2), melphalan[12] (≥140 mg/m^2), cisplatin[13] (≥500 mg/m^2), busulfan[14] (≥600 mg/m^2), and chlorambucil[15] (≥1.4 g/m^2). In addition, treatments with adriamycin, vinblastin, or cytosine arabinoside have additive effects with the above agents in causing prolonged azoospermia, but cause only temporary reductions in sperm count when not so combined[5]. Whether the prepubertal testis is less sensitive than the postpubertal testis to damage by chemotherapy is not known. The CCSS reported that only very young boys (<4 years of age at diagnosis) were more likely to sire a pregnancy later in life than those who were 15–20 years of age at diagnosis[6]. Although the prepubertal testis does not show complete spermatogenesis, there is evidence that cytotoxic treatment given to prepubertal boys affects their later fertility[10,16]. The Children's Oncology Group suggests that having a prepubertal status at diagnosis is not protective against germ cell toxicity of alkylating agents[17].

2. Radiation–induced gonadal failure

Testicular germ cells are very sensitive to radiation and germinal cell depletion is dose dependent. Thus, a direct radiation dose as low as 0.15 Gy can cause a significant depression in the sperm count and temporary azoospermia can occur after a dose of 0.3 Gy[18,19]. Higher doses cause a more rapid onset of oligospermia and azoospermia by a direct effect on the later stages as well as earlier stages of spermatogenesis[19]. Differentiating cells are damaged by doses as low as 1 Gy, which reduce the numbers of spermatogonia and preleptotene spermatocytes[18]. Irradiation with much higher doses (2–3 Gy) kills spermatocytes with a resultant decrease in spermatid numbers. Spermatids show no overt damage, but after 4–6 Gy irradiation the resultant spermatozoa are significantly decreased in number, signifying that some spermatid damage must have occurred[19]. During the first 50–60 days after low-dose irradiation (1.5–2 Gy), sperm production remains above 50% of control values and then drops dramatically with resultant temporary oligo/azoospermia[19]. A single testicular dose of radiation exceeding 4–6 Gy can result in permanent azoospermia[16,18,20]. Fractionated irradiation of the testes can be more harmful; thus, fractionated doses greater than 0.35 Gy cause aspermia with the time taken for recovery increasing with dose, and with doses of more than 2 Gy, aspermia may be permanent[21].

3. Comparison between post– and prepubertal males

By appropriately expressing chemotherapy doses on a per meter squared basis and calculating radiation doses to the gonad, the doses of a variety of chemotherapy and radiotherapy regimens that can produce permanent azoospermia in survivors of childhood and adolescent cancers after they reach puberty appear to be the same as those for adults[22]. Radiosensitivity is much lower in Leydig cells than in spermatogenic cells. Radiosensitivity is higher in prepubertal boys than adult men, so the testicular irradiation dose inducing Leydig cell dysfunction is >20 Gy in prepubertal subjects [2493061] and this dose is known to be higher after puberty[23]. The CCSS showed that the likelihood of survivors siring a pregnancy decreased after radiation administered to the testes exceeded 7.5 Gy (HR, 0.12; 95% CI, –0.02 to 0.64)[6].

4. Radiation–induced gonadotropin deficiency

Gonadotropin deficiency can develop when the hypothalamus and pituitary gland are damaged by surgery, tumors, or cranial radiation. Because radiation-induced gonadotropin deficiency is dependent on irradiation dose and target tumor location, conventional fractionated cranial irradiation (30–50 Gy) induces gonadotropin deficiency in 60% of pituitary tumor survivors after 10 years and in >20% of patients with nonpituitary brain tumors[4]. The severity of gonadotropin deficiency varies from subclinical to severe, when it can diminish the levels of circulating sex hormones. Radiation-induced gonadotropin deficiency also has a wide clinical spectrum from subclinical to severe forms. Clinically significant gonadotropin deficiency is usually a late complication with

a cumulative incidence of 20–50% on long-term follow-up, regardless of whether radiation was administered in childhood or during adulthood[4].

Assessment

Assessment of male reproductive function starts from the assessment of pubertal development. For survivors exposed to alkylating agents (higher cumulative doses or combinations of alkylators) or radiation (≥ 20 Gy to the testes and pelvis; ≥ 30 Gy to the cranium) before the onset of puberty, the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer (COG-LTFU Guidelines) recommend annual assessment of pubertal development until sexual maturity using Tanner staging, with testicular volume determined using a Prader orchidometer[17]. If patients request fertility testing, spermatogenesis status is evaluated either directly by semen analysis or indirectly by determination of the levels of gonadotropins and testicular volume changes. Men with an abnormal semen analysis should be counseled that it is nearly impossible to predict whether or not an individual's testicular function will recover after treatment, or over what period of time the recovery will or will not occur. Therefore, contraception should be used if paternity is not desired[17].

1. Semen analysis

Semen analysis is the initial investigation of fertility potential in cancer survivors. This test provides information about the functional status of the germinal epithelium, epididymis, and accessory sex glands. The World Health Organization (WHO) manual has established new reference values for semen characteristics in its 5th edition, which are lower than those reported previously[24,25]. Although semen analysis provides useful descriptive data including sperm count, motility, vitality, and morphology, parameters above the lower reference limits do not guarantee fertility, nor do values outside those limits necessarily imply male infertility or pathology[26]. An abnormal semen analysis is suggestive of testicular germ cell damage, but azoospermia may also be secondary to ejaculatory dysfunction or hormone deficiencies in survivors at risk for those complications[17]. When the ejaculate volume is less than 1.0 mL, the physician should perform a postejaculatory urinalysis to rule out retrograde ejaculation[27].

2. Endocrine evaluation

The initial hormonal evaluation should consist of measurements of serum FSH, luteinizing hormone (LH), and testosterone levels as indicated clinically. Men with primary testicular failure typically show low circulating testosterone levels. When the hypothalamus-pituitary axis is intact, serum FSH and LH levels are elevated after puberty. However, if this axis is damaged by radiation, FSH and LH levels do not increase and remain within normal or low normal range.

Although serum inhibin B is known to be a marker of germ cell function, the levels of inhibin B alone or inhibin B in combination with FSH do not reflect normal spermatogenesis in patients who have undergone cancer treatment in childhood[28]. Therefore, the COG-LTFU guidelines do not recommend screening for inhibin B routinely[17].

3. Testicular volume change

Approximately 85% of the testicular mass consists of germinal tissue, so a reduced germinal cell mass is associated with reduced testicular size and a soft consistency[29]. Azoospermic and severely oligoasthenozoospermic survivors of cancer had significantly smaller mean testicular volume and higher basal FSH levels than other survivors, but small testicles (sum of both testicular volume ≤20 mL) and/or abnormally high basal FSH levels (> 10 mIU/mL) were present in only half of the azoospermic survivors[30].

Treatment of reduced fertility

Male patients with hypogonadotropic hypogonadism usually require therapy with gonadotropin releasing hormone and human menopausal gonadotropin (or FSH) to induce spermatogenesis[31].

Cryopreservation of sperm before cancer therapy is a successful method for fertility preservation in postpubertal men[32]. Recent advances in sperm storage and in assisted reproductive technology, such as *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), can allow men to achieve successful pregnancies using cryopreserved spermatozoa[33]. Such cryopreserved gametes showed a 36.4% successful pregnancy rate with intrauterine insemination and a 50.0% pregnancy rate with IVF and ICSI[34].

Fertility preservation for prepubertal male patients requires much more research because their spermarche has not yet started. One potential new fertility preservation technique is the cryopreservation of testicular tissue containing spermatogonial stem cells, but it is still experimental. Harvesting spermatogonial stem cells from preserved testicular tissue for *in vitro* maturation and testicular tissue grafting might be an option, but several hurdles remain[16].

Men with oligospermia can achieve fatherhood using IVF and ICSI because these techniques require only a minimal amount of spermatozoa for fertilization. In addition, new techniques for harvesting mature spermatozoa from testicular tissue, such as microsurgical epididymal sperm aspiration, testicular sperm extraction, and microscopic testicular sperm extraction (mTESE), have been applied to men with azoospermia for achieving fertilization using ICSI[35]. When applying mTESE and ICSI to men with azoospermia after chemotherapy, the sperm retrieval rate was 37% and the fertilization rate was 57.1%[36].

Conclusions

With the development of new cancer treatments, more pediatric cancer patients can increase their life expectancy. Chemotherapy causes a variety of physical and psychological problems. With the increasing age of patients, reproductive problems including reduced fertility occur in male survivors of childhood cancer treated with alkylating agents, testicular radiation, or cranial radiation. At the end of chemotherapy, pubertal maturation, any testicular volume changes, and symptoms of androgen deficiency should be systematically monitored. If survivors reach 14 years of age or androgen deficiency is suspected, circulating testosterone and gonadotropin levels should be measured. If patients request fertility testing, spermatogenesis status can be evaluated either directly by semen analysis or indirectly by determination of the levels of testosterone and gonadotropins and by monitoring any changes in testicular volume. According to the patient's condition, semen cryopreservation, hormonal therapy, or assisted reproductive technologies such as IVF or ICSI should be provided. With these advances, we hope to develop better ways for preserving male fertility and thereby improve the health and quality of life of cancer survivors.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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