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Review

Fertility in childhood cancer survivors following cranial irradiation for primary central nervous system and skull base tumors

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ABSTRACT

Recent advances in pediatric cancer treatment have improved disease control and survival outcomes for childhood cancers survivors, including those treated for primary central nervous system and skull base malignancies. Future research in this population will focus on identifying risk factors for infertility, novel screening techniques and recommendations, and quality-of-life outcomes improvement. The purpose of this review is to define the infertility complications observed in pediatric cancer survivors who receive cranial irradiation for central nervous system and skull base malignancies.

In the United States, there were approximately 379,000 cancer survivors of child and adolescent cancer as of January 2010 [1]. With advances in multimodality therapy, 5-year survival rates have increased to about 83% [2,3] and children with primary central nervous system (CNS) malignancies represent approximately 14% of long-term survivors. Cancer survivors are at increased risk for post-treatment toxicities and chronic conditions compromising neurologic/neurosensory, cardiovascular, pulmonary, endocrinologic, or reproductive function [4]. Infertility is a major treatment-related toxicity, which is the result of a disease or dysfunction of the reproductive tract preventing conception of a child or the ability to carry a pregnancy to delivery [4]. Failed conception after at least 1 year of unprotected intercourse should prompt evaluation, unless physical findings and medical history dictate earlier intervention [5,6]. Childhood cancer survivors with CNS and skull base tumors may be less likely to conceive [7,8]. Successful fertility requires functional testes, ovaries, and genitourinary organs as well as a functional hypothalamic–pituitary–gonadal (HPG) axis, all of which can be affected by the initial tumor involvement, treatment, and the psychogenic effects of therapy. Risk of infertility depends on direct effects of treatments received: surgical, chemotherapeutic, and radiotherapeutic [9,10]. This review specifically summarizes frequently unidentified fertility concerns and outcomes of cancer survivors who have received cranial irradiation.

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Frequency of infertility following childhood cancer treatment

The Childhood Cancer Survivor Study (CCSS) reported outcomes of young male and female survivors treated for various malignancies, identifying risk factors for procreating. The relative risk (RR) for female survivors of becoming pregnant was 0.81 (95% CI, 0.73–0.90) [7]. After adjustment for confounding factors, the likelihood of pregnancy was decreased for hypothalamic–pituitary doses above 30 Gy (RR, 0.61; 95% CI, 0.44–0.83; $P = 0.002$). Male participants were less likely to sire a pregnancy (hazard ratio, 0.56; 95% CI, 0.49–0.63) [11] yet no effect on fertility after pituitary irradiation was observed after adjusting for confounding factors in males (RR, 0.25; 95% CI, 0.06–1.13; $P = 0.72$). Results from the CCSS cohort demonstrated that 64% of survivors with self-reported clinical infertility eventually conceived after 1 or more years of failed attempts at conception [5]. Infertility and pregnancy outcomes may be underestimated because there are no standards for laboratory study parameters to define infertility, patient desire, number of pregnancy attempts, time to conception, or successful utilization of infertility treatments [5].

The German Childhood Cancer Registry reported 1110 female and male childhood cancer survivors treated with cranial irradiation, chemotherapy, or both [12]. Depending on the pituitary irradiation dose, survivors reported fewer pregnancies with their partners, higher rates of infertility and permanent amenorrhea (Table 1) [12]. Those who had received cranial radiotherapy had a significantly shorter time to pregnancy than survivors exposed to pelvic radiotherapy or alkylating agents; this finding may be due to selection bias of a good prognosis group that received low-dose radiotherapy [5]. Higher cranial doses may produce

Table 1
Assessments of reproductive health in females treated for primary central nervous system and skull base tumors.

	Prepubertal	Pubertal	Postpubertal
History	– Complete history pertaining to visit – Any signs of pubertal onset – Psychosocial assessment – Medications	– Complete history pertaining to visit – Pubertal onset, temp – Menstrual cycle patterns (regular/irregular, primary vs secondary amenorrhea) – Sexual activity – Function (dryness, dyspareunia, libido) – Contraception/pregnancy – Psychosocial assessment – Medications	– Complete history pertaining to visit – Pubertal onset, temp – Menstrual cycle patterns (regular/irregular, primary vs secondary amenorrhea) – Sexual activity – Function (dryness, dyspareunia, libido) – Contraception – Pregnancy (low-birth weight, premature labor, spontaneous abortions, etc) – Psychosocial assessment – Medications
Physical examination	– Annual physical examination (sooner if clinically indicated) – Height/weight – Tanner staging	– Annual physical examination (sooner if clinically indicated) – Height/weight – Tanner staging	– Annual physical examination (sooner if clinically indicated) – Height/weight
Screening	At diagnosis – Obtain baseline sexual hormone studies prior to initiation of treatment in children diagnosed with CNS and skull base tumors (prolactin, LH, FSH, testosterone, estradiol, and GnRH stimulation test) – AMH At follow-up – Repeat LH, FSH, estradiol, GnRH Stimulation test, and AMH only as clinically indicated if evidence of accelerated growth and signs or early pubertal development – X-ray for bone age as clinically indicated in the setting of accelerated growth and early pubertal development	At diagnosis – Obtain baseline sexual hormone studies prior to initiation of treatment in children diagnosed with CNS and skull base tumors (prolactin, LH, FSH, testosterone, estradiol, and GnRH Stimulation test) – AMH At follow-up – Repeat LH, FSH, estradiol, GnRH stimulation test, and AMH at 13 years of age – Repeat LH, FSH, estradiol, GnRH Stimulation test, and AMH sooner or as clinically indicated if delayed puberty, irregular menses, primary or secondary menses, or clinical signs of secondary estrogen deficiency	At diagnosis – Obtain baseline sexual hormone studies prior to initiation of treatment in children diagnosed with CNS and skull base tumors (prolactin, LH, FSH, testosterone, estradiol, and GnRH Stimulation test) – AMH At follow-up – Repeat LH, FSH, estradiol, GnRH stimulation test, testosterone, and AMH at 13 years of age – Repeat LH, FSH, estradiol, GnRH Stimulation test, testosterone, and AMH sooner or as clinically indicated if delayed puberty, irregular menses, primary or secondary menses, or clinical signs of secondary estrogen deficiency. – Consider bone mineral density in patients diagnosed with hypogonadism
Precocious puberty	Tumor-related factors Tumor Involvement of the hypothalamus or pituitary glands Treatment-related factors Radiotherapy CSI Cranial, skull base, orbit/eye Nasopharynx Risk factor Cranial irradiation dose $\geqslant$18 Gy	Not applicable	Not applicable
Hypogonadism	Not applicable	Treatment-related factors Chemotherapy Alkylating agents, heavy metals, and nonclassical alkylators Radiotherapy CSI (any ovarian dose) Cranial ($\geqslant$30 Gy) Skull base, orbit/eye Nasopharynx Spine (lumbar, sacral, whole) Surgery Injury to HP axis	Treatment-related factors Chemotherapy Alkylating agents, heavy metals, and nonclassical alkylators Radiotherapy CSI Cranial ($\geqslant$30 Gy) Skull base, orbit/eye Nasopharynx Spine (lumbar, sacral, whole) Surgery Injury to HP axis

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