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SPECIAL ARTICLE

Oncofertility in Canada: the impact of cancer on fertility

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ABSTRACT

Background

Cancer can be a devastating diagnosis. In particular, malignancy and its indicated treatments have profoundly negative effects on the fertility of young cancer patients. Oncofertility has emerged as a new interdisciplinary field to address the issue of gonadotoxicity associated with cancer therapies and to facilitate fertility preservation. In Canada, these fertility issues are often inadequately addressed despite the availability of resources. The goal of this four-part series is to facilitate systemic improvements in fertility preservation for adolescent and young adult Canadians with a new diagnosis of cancer.

Methods

In this article, we review the gonadotoxic effects of cancer treatment on young men and women of reproductive age.

Results

The detrimental effects of cancer on fertility can be severe and may vary depending on the chemotherapy, radiotherapy, or surgical treatments involved.

Conclusions

Fertility preservation should be addressed in an effort to mitigate the gonadal damage that may come with cancer therapy.

KEY WORDS

Oncofertility, fertility preservation, cryopreservation, gonadotoxicity, young adult, adolescent

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1. INTRODUCTION

Cancer can be a devastating diagnosis. Its face changes, as do its implications from one type to the next, and from one individual to the next. Young men and women diagnosed with various forms of this disease are often left to deal with the long-term medical and emotional consequences. In particular, malignancy and its indicated treatments have demonstrated profoundly negative impacts on fertility. Moreover, the overwhelming diagnosis and the quick decisions for treatment are often accompanied by an equally short window in which fertility preservation must be addressed and managed in an effort to mitigate the gonadal damage that may come with cancer therapy[1].

Improvements in cancer diagnosis and treatment and, hence, survival rates have also led to valiant efforts in fertility preservation. Oncofertility had recently emerged as a "new interdisciplinary approach to address the reproductive future of young men, women, and children facing a life-preserving but fertility-threatening cancer diagnosis"[2]. Despite progress, the field is still in its infancy. It has all the necessary components to achieve remarkable success and to establish hope in young cancer survivors, and yet it is still lacking in collaborative efforts. The ideal construct would involve a proactive and multidisciplinary dialogue with the patient about fertility prognosis and fertility-sparing options, provision of readily accessible information and resources, and an established, efficient system of referral to fertility specialists[1]. The reality of the newly diagnosed cancer patient is that fertility issues are often inadequately addressed. Despite availability, most fertility centres in Canada receive a very low yield of referrals from among newly diagnosed cancer patients of reproductive age[3,4].

The goal of this four-part series is to facilitate improved education and communication concerning fertility preservation in adolescent and young adult Canadians with a new diagnosis of cancer.

In the subsequent three parts of the series, we will outline oncofertility options, describe the services currently available in Canada, point out potential challenges, and outline strategies to help maximize and facilitate fertility preservation in new young cancer patients.

2. CANCER IN YOUNG ADULTS AND ADOLESCENTS

In 2008, the annual number of new cancer cases was estimated at 12.7 million worldwide, including 5.6 million in the developed world and more than 1.6 million in North America[5], and the incidence rate has continued to rise, both from an international[5] and a Canadian standpoint[6,7]. The Canadian Cancer Society estimated that, in 2011, more than 84,000 women and 93,000 men would be newly diagnosed. Of those new patients, 4200 women and 2500 men would be in their reproductive years (20–39 years of age)[8]. An estimated 1 in 46 women and 1 in 69 men will develop cancer between birth and 39 years of age[9].

Concurrent with the increase in diagnoses of cancer, survival rates have improved thanks to better early detection and therapeutic management strategies[10]. Excluding Quebec, Canada's 5-year survival rates for all cancers have risen to 62% in 2004–2006 from 56% in 1992–1994[11,12]. Members of the younger reproductive population have shown even higher survival rates[13]: in the 15–44 age group, 81% are cancer-free after 5 years (2004–2006)[12].

3. THE IMPACT OF CANCER ON FERTILITY

The present understandings of ovarian physiology and the natural reproductive processes of aging have indicated that the reproductive potential of women is finite[14]. Of the 6–7 million primordial follicles presumably laid down early in utero, only 500,000 to 2 million remain at birth and 300,000 at puberty[15,16]. Over a woman's reproductive lifespan, 400–500 oocytes are released, and that already limited procreative potential is often lost completely by her early forties[17,18]. Most recently, White *et al.*[19] contradicted this notion of finite reproductive potential by isolating "ovarian stem cells" in reproductive-age women, showing that these cells are capable of meiotically producing haploid oocytes (*in vitro* and *in vivo* using mouse hosts). Their theory is beyond the scope of the present paper, and current knowledge holds that continuous oocyte atresia and deterioration in oocyte quality with age are apparent[20]. Moreover, other natural and iatrogenic factors (for example, genetic variation, resection of endometriomas, and so on) may also compound the picture of baseline "ovarian reserve"[21]. Cancer treatments most commonly affect fertility by destroying the presumably finite and vulnerable ovarian stores. However, the effects of disease and its therapy may also have destructive effects on other organs and endocrine components of the reproductive axis[22].

Production of sperm by men similarly depends on age, pubertal status, and stage of life. Men do not undergo the process of gametogenesis and germ-cell differentiation until puberty, but the process of male spermatogenesis is continuous thereafter. Spermatogenesis, its hormonal regulation, and the ultimate ability to expel sperm depends on a healthy germinal epithelium, supporting Leydig and Sertoli cells, a functional hypothalamic–pituitary–gonadal axis, and a pathway (ejaculatory system) for mature sperm cells[23]. Malignancy—and more commonly, gonadotoxic therapy—often leads to male infertility by quantitative or qualitative destruction of spermatogonial germ cells[24]. However, as in women, any other component of the reproductive pathway may be affected[14].

3.1 Effects in Women

Chemotherapy can have devastating effects on the ovaries. The exact mechanism is still unclear, but possibilities include increased rates of follicular apoptosis, ovarian cortical fibrosis, damage to ovarian vasculature, and premature activation with increased recruitment and destruction of follicles[25,26]. Anticancer medications may destroy the oocyte pool by interfering with processes specific to cell proliferation (cell-cycle specific), but may also act on cells not actively proliferating (non-cell-cycle specific). The latter actions tend to be more harmful[27]. The effects may be partial or complete and may in turn correlate with the patient's subsequent ovarian dysfunction[26].

The quantitative effects of chemotherapy on female fertility are variable and depend on both patient- and drug-specific factors. From the patient's standpoint, factors affecting ovarian reserve and age are the most important variables to consider[14,20,28,29]. The postpubertal ovaries tend to be much more susceptible to the gonadotoxic effects of chemotherapy, and this susceptibility becomes more pronounced with age[30]. For women undergoing alkylating agent induction in preparation for autologous bone marrow transplantation, Schimmer *et al.* found an average age of 30 years at onset of treatment for those who did not recover ovarian function compared with 19 years for those who did[31].

Cyclophosphamide-containing regimens (often used in breast cancer treatment) have highlighted the effect of age quite well. An estimated 80% or more of women more than 40 years of age develop amenorrhea when treated with regimens using cyclophosphamide at 5 g/m^2. A dose increase of at least 50% (and estimated by some to be as high as 200%) would be required to produce the same effect at an age of less than 20 years[14,32]. Moreover, similar regimens with a

greater than 80% risk of amenorrhea in the over-40 age group have a less than 20% risk in the under-30 age group[14,28]. The actual risk of reaching menopause within 1 year of a breast cancer diagnosis is estimated to increase from 5%–40% at age 40 to 20%–100% at age 50 with the use of cyclophosphamide chemotherapy[33]. A recent retrospective study of 620 women after they had received systemic chemotherapy alone in multiple non-gynecologic cancers identified significantly increased rates of acute ovarian failure and infertility with increasing age at diagnosis[34].

From a treatment-specific standpoint, drug type and dose administered are both important considerations[14,20,29]. Higher-dose chemotherapy regiments tend to have greater effects on ovarian function. Accordingly, an inverse relationship has been noted between chemotherapy dose and the surviving oocyte follicular pool[35].

In a study involving 214 age-controlled patients with Hodgkin lymphoma, the rate of amenorrhea was higher in patients who received either higher doses or more cycles of chemotherapy. Amenorrhea rates of 3.5% and 23.5% were observed with, respectively, 2 or 4 cycles of COPP (cyclophosphamide–vincristine–procarbazine–prednisone) with ABVD (doxorubicin–bleomycin–vinblastine–dacarbazine). Regular and escalated BEACOPP (bleomycin–etoposide–doxorubicin–cyclophosphamide–vincristine–procarbazine–prednisone) given for 4 cycles yielded amenorrhea rates of 11.8% and 40.4% in patients less than 30 years of age, and similar trends were noted for those 30 years of age and older[28,36].

Assessing risk of gonadal toxicity with individual chemotherapy agents constitutes a challenge, because those agents are often given in combination. Combination regimens that include alkylating agents (for example, cyclophosphamide, cisplatin, procarbazine, chlorambucil, busulfan), which act independently of the cell cycle, theoretically have the potential to affect greater numbers of gonadal cells, and they therefore carry the greatest risk of gonadal dysfunction[37]. They are often used in the treatment of breast cancer, lymphoma, and leukemia, and in preparation for bone marrow and stem-cell transplantation[14,38]. Walshe *et al.* reviewed almost 30 years of literature on the effects of various chemotherapy regiments in breast cancer patients. Alkylating-agent-based regimens resulted in amenorrhea in 18%–61% of younger women, generally 40 years of age and younger (61%–97% in older women)[39]. In another review, Minton *et al.* similarly noted cyclophosphamide-induced amenorrhea in 21%–71% of breast cancer patients under the age of 40 (49%–100% in those 40 years of age and older)[40].

The influence of taxanes, often used in combination chemotherapy (for example, with anthracyclines for breast cancer), is particularly difficult to elucidate. Some studies showed detrimental effects on menstrual status; others suggested that these agents confer no additional risk of amenorrhea[39,41,42]. More data in this area are needed.

Platinum derivatives and anthracyclines are of moderate risk. Low-risk agents include cytotoxic antibiotics (for example, actinomycin, doxorubicin, bleomycin)[39], antimetabolites (methotrexate, fluorouracil), and plant alkaloids (vincristine)[20,26,43].

Of note and to keep in mind, a significant deficiency in many of the studies examining the effects of gonadotoxic therapy (both chemotherapy and radiotherapy) on ovarian function has been the assumed representation of ovarian function by the presence or absence of amenorrhea[14,44,45]. Even in natural physiologic circumstances, fertility potential is lost an average of 10 years before menopausal amenorrhea[17,46]. More recent studies have used serum testing (for example, for follicle-stimulating hormone, estradiol, inhibin B, anti-Müllerian hormone) and imaging (for example, antral follicular count) as additional markers for immediate ovarian reserve[44,47]. However, those tests have not been shown to predict long-term ovarian function[48]. They act as short-term measures and as indirect estimates of the total follicular pool; they have no ability to assess oocyte quality[17,49].

Despite the chromosome-altering effects that chemotherapy can have on growing follicles, data indicating the short- and long-term effects on offspring are limited. The evidence thus far suggests no increased incidence of Down syndrome, Turner syndrome, or abnormal karyotype in children born to parents who have undergone chemotherapy treatment[50,51]. However, gross limitations in outcomes data and sample sizes still warrant caution in achieving pregnancy after oocyte exposure to gonadotoxic treatment.

Radiotherapy is similarly detrimental to the female reproductive system. Again, the effects are particularly noted with oocyte and gonadal function[27]. As in the case of chemotherapy, treatment-specific and patient-specific factors should both be considered. Dose-specific damage has been noted, with the surviving oocyte pool having been shown to decline by 50% after less than 2 Gy direct radiation to the ovaries[52]. Comparatively, the much higher doses used in total-body irradiation (in preparation for bone marrow transplantation) have resulted in ovarian failure rates of 72%–100%[26].

Age and baseline ovarian reserve should also come into play, as previously mentioned. Levine *et al.*[14] described a greater than 80% risk of amenorrhea in women receiving whole-abdomen or pelvic radiation doses of 15 Gy or more (prepubertal), 10 Gy or more (postpubertal), and 6 Gy or more (adult). The predicted age at ovarian failure (after dose-specific radiotherapy to the ovaries) has also been demonstrated in a mathematical model[53]. However, with more recent variations in radiation protocols, the increasing use of fractionation, and greater limitations on irradiated fields, the quantitative effects on the ovaries and on fertility have been more difficult to compare[26,54].

As in the case of chemotherapy, additional concerns arise about the possibility of genetic abnormalities in offspring after radiation to the ovary and oocytes. Caution should once again be exercised, animal data having suggested that genetic damage is a possibility. However, no conclusive evidence has thus far demonstrated increased risk to human offspring[55].

Radiotherapy may cause additional damage to the female reproductive system[56]. Detrimental effects on the uterine vasculature, impaired growth, and damage to the endometrium have been noted with pelvic radiotherapy doses of 14–30 Gy, particularly when administered to the prepubertal uterus[54,57]. This damage may, in turn, contribute to adverse pregnancy and neonatal outcomes, including increased rates of preterm labour; spontaneous abortion; fetal growth restriction; and placental growth, function, and implantation abnormalities[57,58]. Hawkins *et al.* found that, among 214 patients who had survived childhood abdominal tumours, first pregnancies resulted in spontaneous abortions in 22% of those who had undergone abdominal irradiation compared with 6% of those who had not ($p = 0.004$)[58]. Birth weight was also lower in successful pregnancies in the irradiated group. Radiation of the pelvis might also lead to infertility because of sexual dysfunction from atrophic vaginal tissue changes and development of radiation fibrosis and stenosis[59].

The hypothalamic–pituitary–gonadal axis has also shown susceptibility to the effects of radiotherapy. Total-body or cranial radiation may alter hypothalamic or pituitary secretion of gonadotropin-releasing hormone, follicle-stimulating hormone, luteinizing hormone, or prolactin—all of which may lead to dysregulation or partial or complete absence of ovulation[57,60]. Cranial irradiation in doses higher than 35–40 Gy has previously resulted in complete impairment of hypothalamic and pituitary function[14]. Fortunately, these effects are treatable with exogenous hormone replacement[20,61,62].

Finally, direct detrimental effects on the reproductive system may be seen with ovarian, endometrial, or cervical cancers; malignancies affecting the lower reproductive tract (for example, vulvar melanoma); or metastasis of nonreproductive cancers to the reproductive organs. The approach to many of those cancers may involve surgical removal of the reproductive organs in addition to possible chemotherapy and radiotherapy[63,64]. Even with conservative surgical resection options for ovarian tumours, decreased ovarian reserve may be the result[65]—an unsurprising outcome of excisional procedures to the ovary[66].

3.2 Effects in Men

Cancer, both the disease and its treatment, may result in equally profound effects on male fertility. As with the gonadotoxic effect of chemotherapy in women, dose[67], duration of therapy, and combination with other drugs must be considered[23,68].

Chemotherapeutics tend to affect germ cells the most and to cause detrimental changes such as fibrosis and hyalinization in interstitial gonadal tissue. Although Leydig cell function may also deteriorate somewhat, normal testosterone concentrations are typically maintained[24,69]. As in women, alkylating agents tend to be the most gonadotoxic in men, establishing the highest risk for prolonged azoospermia. These agents are often used in treating testicular cancer, lymphoma, and leukemia, and in preparation for bone marrow and stem-cell transplantation[14,68]. In a review by Howell *et al.,* more than 90% of patients with Hodgkin lymphoma became azoospermic after any of the various procarbazine-containing chemotherapy regimens: MVPP (mustine–vinblastine–procarbazine–prednisolone), MOPP (mechlorethamine–vinblastine–procarbazine–prednisone), ChlVPP (chlorambucil–vinblastine–procarbazine–prednisolone), and COPP[70]. Cytotoxic antibiotics and platinum agents have a medium risk for toxicity and generally do not result in prolonged azoospermia. After treatment with platinum for testicular cancer, normal spermatogenesis is seen in 50% of men at 2 years and in 80% at 5 years[14,68,70]. Plant derivatives (vinca alkaloids) are low-risk when given alone, but high-risk for azoospermia when combined with alkylating or platinum agents[23,68].

Radiotherapy is similarly damaging to the male gonads and may be an important part of cancer treatment, particularly in Hodgkin lymphoma; in prostate, rectal, and bladder cancer; and in the preparation for bone marrow transplantation[23]. The detrimental effects on fertility are most commonly a result of damage to the germinal epithelium[70]. The effects may be temporary or permanent, and they increase with dose, degree of scatter radiation, proximity to the testes, fractionation[71], and increasing patient age[67,70]. Changes to spermatogonia have been noted with doses as small as 0.1 Gy[68]. Oligozoospermia and azoospermia often result after radiation doses of less than 0.8 Gy and more than 0.8 Gy respectively, with only partial recovery after doses of 1–1.5 Gy. Doses greater than 2 Gy often lead to permanent azoospermia[68,72]. External-beam radiation has resulted in a scattered dose to the testicles as high as 18.7% of the original dose; brachytherapy scatter is thought to be much lower[23]. Total body irradiation doses of 10–12 Gy or more administered in childhood (often before hematopoietic stem-cell transplantation) has resulted in gonadal failure or azoospermia in more than 72% of patients[73,74]. Supporting Leydig cells tend to be more resistant to radiation, with doses of 20 Gy or more often required for persistent hypogonadism[69,75]. Cranial irradiation may also lead to a dysfunctional hypothalamic–pituitary–gonadal axis and therefore interference with spermatogenesis. As in women, such dysfunction may occur at a dose of 35–40 Gy[14].

The surgical management of certain cancers may also have profound effects on male fertility if the operative field involves the reproductive tract. Surgery around the prostate often results in erectile dysfunction, removal of the gonads, or damage to other anatomic components of the male reproductive tract[76]. A retroperitoneal lymphadenectomy may be necessary in testicular cancer, often leading to ejaculatory dysfunction[68,69], although new nerve-sparing techniques have managed to preserve function in 98% of patients[76].

Cancerous processes may themselves also contribute to subsequent infertility. Higher pretreatment rates of azoospermia and gonadal dysfunction have been noted both with hematologic malignancies and with testicular cancer[68,77]. Hodgkin lymphoma may have an indirect negative effect on fertility through disease-related cytokines[23]. The baseline azoospermia level in the general population is estimated at 1%[78]. Before treatment for Hodgkin lymphoma, abnormal semen parameters have varied from 7% to 80%[75,79–81]. In the largest retrospective study to date (n = 474), abnormal parameters were particularly increased (17% of subjects had poor semen quality, and 6% had azoospermia) in association with B symptoms (systemic symptoms including fever, night sweats, and weight loss)[80]. Other described mechanisms of injury have included hormone and metabolic derangements because of stress, malnutrition, and possibly endocrine substances produced by the tumours themselves[75,82].

4. SUMMARY

The quantitative impact of any given cancer on a young patient's fertility may be difficult to define, but detrimental effects have consistently been demonstrated. The damage may be secondary to a variety of treatments—including chemotherapy, radiotherapy, and surgery—or, less commonly, to the malignancy itself. Early and effective communication of this information to adolescent and young adult Canadians with a new diagnosis of cancer could be an important step in facilitating their fertility preservation.

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6. CONFLICT OF INTEREST DISCLOSURES

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