

Advanced practice nurses: Improving access to fertility preservation for oncology patients

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ABSTRACT

Cancer therapies such as chemotherapy, radiation therapy and surgery may place the future fertility of both children and young adults at risk. Oncofertility is a rapidly evolving area that involves increasing access to fertility preservation (FP) information and services. This manuscript aims to: a) highlight the fertility risks associated with cancer therapy and its psychosocial impact, b) describe FP options, c) discuss the unique challenges of FP in distinct cancer populations, and d) illustrate the pivotal role of APNs in oncofertility counselling and education.

Cancer survival rates are steadily increasing and have now exceeded 80% and 90% for childhood cancers and adult lymphoma, testicular and breast cancers (Johnson et al., 2013; Rodriguez-Wallberg & Oktay, 2014). Survivors, however, face many challenges after their cancer is cured including fertility issues that occur in approximately 15% to 30% of patients (Johnson et al., 2013). Not only does this affect the patient's

ability to procreate, but it also causes significant psychosocial distress in those affected (Kort, Eisenberg, Millheiser, & Westphal, 2014).

Cancer therapies such as chemotherapy, radiation therapy and surgery may place the future fertility of both children and young adults at risk. Oncofertility is a rapidly evolving area that involves increasing access to fertility preservation (FP) information and services. Both Canadian and American fertility guidelines have been developed in response to this (Loren et al., 2013; Roberts, Tallon, & Holzer, 2014). FP options exist for post-pubertal and pre-pubertal males and females prior to treatment. However, there is variation in the utilization of these techniques (Medicine, 2013b). Increasingly, survivors who were unable to preserve their fertility before treatment now have the opportunity to pursue FP after treatment.

The Canadian Nurses Association (CNA) argues that Advanced Practice Nurses (APN) have the education, clinical expertise, leadership skills and understanding of organizations, health policy and decision making to play an important role in client and system outcomes (2007). APNs in cancer care settings are qualified to facilitate access to FP services and to educate the broader health care team. This manuscript aims to: a) highlight the fertility risks associated with cancer therapy and its psychosocial impact, b) describe FP options, c) discuss the unique challenges of FP in distinct cancer populations, and d) illustrate the pivotal role of APNs in oncofertility counselling and education; particularly in established hospital-based programs located in downtown Toronto, Canada.

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PSYCHOSOCIAL IMPACT IN YOUNG ADULTS

Adolescents and young adults (AYA) are defined by the National Cancer Institute (NCI) (2015) as individuals who are 15 to 39 years of age. More than 2,000 AYA are diagnosed with cancer annually in Canada (Nagel & Neal, 2008; Yee, Buckett, Campbell, Yanofsky, & Barr, 2012). A cancer diagnosis and the treatment process can negatively impact a young person's quality of life. AYA with cancer are often undergoing key developmental tasks that are disrupted with a cancer diagnosis, such as developing meaningful relationships and pursuing higher education or a career (Fernandez et al., 2011). These interruptions can result in increasing levels of distress, anxiety, and depression in young patients (Fernandez et al., 2011).

Fertility is an important consideration for young adult cancer survivors (Rodriguez-Wallberg & Oktay, 2014). Survivors are at increased risk for experiencing emotional distress and reduced quality of life if they become infertile from cancer therapy (Loren et al., 2013). Evidence shows that cancer survivors who receive specialized counselling about reproductive concerns prior to cancer therapy have been found to have greater long-term quality of life (Vadaparampil, Hutchins, & Quinn, 2013).

This demonstrates the importance of having fertility discussions with AYAs prior to initiating cancer treatment. Moreover, to fulfill the requirements of informed consent, the risks of infertility should be discussed (Loren et al., 2013).

THE EFFECT OF CANCER THERAPIES ON FERTILITY

The effect of cancer treatment on fertility is dependent on multiple factors including the tumour pathology, location and presence/location of metastases. Patient age, gender and pre-treatment gonadal function are also relevant factors. Most importantly, however, remains treatment modalities and doses (Rodriguez-Wallberg & Oktay, 2014).

Direct, indirect and scatter radiotherapy can affect reproductive organs. The following radiation practices are considered high-risk threats to fertility: total body irradiation (TBI); testicular radiation and pelvic or whole abdominal radiation in females (Rodriguez-Wallberg & Oktay, 2010). Craniospinal radiotherapy ($\geq 2,500$ cGy) may also affect fertility, as a result of its effect on the hypothalamic pituitary axis. Commonly, multimodality treatments are used, which may cause a synergistic effect on both the tumour and, unfortunately, on fertility (Table 1).

In males, spermatogonia give rise to spermatozoa. However, spermatogonia are very sensitive to radiation regardless of age. As long as spermatogonia are not depleted and a population of these germ cells remain, regeneration of spermatozoa may continue (Rodriguez-Wallberg & Oktay, 2014). Leydig cells, located within the testis and produce testosterone, appear more sensitive to pre-pubertal radiation; conversely in adults, Leydig function and testosterone production continues despite azoospermia (complete absence of sperm) (Rodriguez-Wallberg & Oktay, 2014).

In females, ovarian germ cells undergo rapid mitotic division in utero producing oogonia which transform into oocyte. Oocyte numbers peak at five months gestation and then start to decrease in utero and continue to decrease throughout life until complete oocyte depletion is reached at menopause.

Cancer and/or its treatment can affect fertility. The type of cancer itself can directly result in impaired fertility related to

the need for orchiectomy or oophorectomy, while gonadotoxic therapy can result in impaired spermatogenesis and decreased numbers of primordial oocytes. Gonadotropin deficiency can also result from CNS-directed radiotherapy. Functional and anatomical abnormalities of the genitourinary organs can result from spinal/pelvic surgery or radiation. In males, damage or depletion of germinal stem cells can result in decreased number of sperm, abnormal sperm motility and/or morphology or decreased DNA integrity (Wallace, Anderson, & Irvine, 2005). In females, primordial follicles including oocytes and granulosa cells are extremely sensitive to alkylating agents (Rodriguez-Wallberg, 2012; Wallace et al., 2005). These effects on ovarian function can result in acute (immediate) ovarian failure or premature ovarian failure (POF), also called early menopause. Reported incidence of POF following chemotherapy varies widely from 30%–70% for premenopausal women; however, the rate increases to 90%–100% for those undergoing myeloablative haematopoietic stem-cell transplantation due to high doses of alkylating agents and total body irradiation (Blumenfeld, 2014).

Additional fertility challenges may also exist for females who have had uterine irradiation. These women may develop impaired uterine blood flow and injury to the endometrium. This can lead to fibrosis, reduced elasticity, and small uterine volumes (Barton et al., 2013; Green et al., 2002). Those who become pregnant following pelvic radiation have increased unfavourable pregnancy outcomes including spontaneous abortion, preterm delivery and low birth weight infants (Green et al., 2009; Green et al., 2002; Wo & Viswanathan, 2009).

FERTILITY PRESERVATION MODALITIES

Sperm banking

The cryopreservation of sperm is a proven and relatively inexpensive means of FP that, unfortunately, is not routinely offered to all oncology patients (Ogle et al., 2008). The practice of offering sperm cryopreservation to young adults facing gonadotoxic therapy is supported by FP clinical guidelines; ASCO, APHON & CFSA (Fernbach et al., 2014; Loren et al., 2013; Roberts et al., 2014). Other options such as testicular

Low Risk	Intermediate Risk	High Risk
<ul style="list-style-type: none"> • Protocols containing nonalkylating agents ABVD, COP, multiagent therapies for leukemia • Anthracyclines & cytarabine • Multiagent protocols using VCR • Radioactive iodine 	<ul style="list-style-type: none"> • BEP (2-4 cycles), Cisplatin (> 400 mg/m²), carboplatin (> 2 g/m²) • Testicular radiation due to scatter (1–6 Gy*) • FOLFOX4 • Abdominal/pelvic radiation (10–15 Gy* in prepubertal girls, & 5–10 Gy* in post pubertal girls) 	<ul style="list-style-type: none"> • Any alkylating agent + TBI • Any alkylating agent +pelvic/testicular radiation • Total cyclophosphamide > 7.5 g/m² • Procarbazine containing protocols MOPP > 3 cycles, BEACOPP > 6 cycles • Protocols with BCNU or Temozolamide & Cranial Radiation • Testicular (> 6 Gy*) or pelvic/whole abdominal radiation (> 15 Gy* in prepubertal, or > 10 Gy* in post pubertal girls) • TBI • Cranial radiation (> 40 Gy*)
Adapted from Loren et al., 2013 *Gy x 100 = cGy		

sperm extraction (TESE) and electroejaculation do exist for those who are unable to produce a sperm sample through masturbation (Fernbach et al., 2014; Nahata, Cohen, & Yu, 2012; Rodriguez-Wallberg & Oktay, 2014).

Testicular tissue preservation

Testicular tissue preservation is an experimental technology that is the only FP option for prepubescent boys. This procedure involves an open biopsy of the testes and is offered in many countries as part of a clinical trial. The Assisted Human Reproduction Act (Government of Canada, 2004) prohibits the acquisition of reproductive tissues from minors in Canada for any reason other than the minor's future use of the tissues to conceive a child. Therefore, the tissue cryopreserved for Canadian children may not be used in clinical research or by any person other than the minor.

Research is currently being conducted to use cryopreserved tissue to help restore fertility for cancer survivors through two methods: 1) re-implantation of the testicular tissue back into the testicle with hope of restoring spermatogenesis, 2) in vitro stimulation of the tissue into mature sperm that will be used via intracytoplasmic sperm injection (ICSI) technology to achieve an in vitro fertilization (IVF) pregnancy (Ginsberg, 2011). It is anticipated that, in the future, these technologies will be more established and accessible to cancer survivors.

Oocyte/embryo cryopreservation

Women have the option of cryopreserving oocytes or embryos prior to cancer treatment if there is time to do so. Oocyte cryopreservation is useful when they are unpartnered or desire reproductive autonomy, and if they object to embryo cryopreservation for religious or other reasons (Roberts et al., 2014). While this option was previously considered experimental, recent advances in cryotechnology, specifically vitrification have led to it becoming standard practice for the purpose of FP (Roberts et al., 2014). Embryo cryopreservation is available to women who have a partner and/or sperm available to them.

To retrieve mature oocytes (required for both procedures), controlled ovarian hyperstimulation with gonadotropins is required and this takes approximately two weeks from the start of a menstrual period. Random start (for example in the late follicular or luteal phase) of stimulation medication is also possible, but should be reserved for those with time constraints.

Leydig cells	Located within the testis and produce testosterone, appear more sensitive to pre pubertal radiation; conversely in adults, Leydig function and testosterone production continues despite azoospermia
Azoospermia	Complete absence of sperm
Tanner stage III	The Tanner stage is a scale of physical development in children, adolescents and adults. In stage Tanner stage III, male patients have sufficiently progressed through puberty and are able to produce mature sperm (usually between the ages of 13 and 14)

Ovarian tissue cryopreservation

Ovarian tissue cryopreservation (OTC) is an experimental technology that offers an FP option for prepubescent girls and women who, for any reason, are unable to undergo oocyte or embryo cryopreservation (Ginsberg, 2011). Ovarian tissue is acquired during a laparoscopic surgical intervention; cortical strips of ovarian tissue, which are rich primordial follicles, are cryopreserved for future use.

The use of these tissues in fertility treatment through re-transplantation or in vitro culture and maturation of gametes remains a developing technology (Rodriguez-Wallberg & Oktay, 2014). The re-implantation of cryopreserved ovarian tissue has achieved resumption of ovarian function in menopausal survivors resulting in a small number of spontaneous and IVF pregnancies (Levine, Canada, & Stern, 2010). However, the re-transplantation of ovarian tissue from patients with hematological or ovarian cancers is not recommended due to the high risk of retransmission of malignant cells (Levine et al., 2010). Another option for the use of cryopreserved ovarian tissue is the maturation of primordial oocytes in the laboratory. The oocyte then would be fertilized in vitro and the embryo transferred into the uterus of the survivor or gestational surrogate (Knight et al., 2015).

Oophoropexy

Oophoropexy is the surgical relocation of the ovaries outside of the radiation field. This practice has been shown to reduce the risk of ovarian failure by about 50%. Failure of this procedure is related to scatter radiation and damage to the blood vessels supplying the ovaries (Rodriguez-Wallberg & Oktay, 2014). Oophoropexy is supported as an FP intervention for females undergoing pelvic radiation by several clinical guidelines including APHON, and ASCO (Fernbach et al., 2014; Loren et al., 2013).

Gonadotropin-releasing hormone agonists (GnRHa)

GnRHa medications have been historically prescribed to suppress ovarian function in women receiving gonadal toxic chemotherapy. The theory suggests that simulating the pre-pubertal state is protective for the ovaries, but the literature supporting the use of ovarian suppression with GnRHa medication for FP in women undergoing cancer therapy remains conflicted. Clinical practice guidelines developed by ASCO (Loren et al., 2013) do not support GnRHa use for FP while the Canadian Fertility and Andrology Society (CFAS) guidelines support their use (Loren et al., 2013; Roberts et al., 2014). Women and girls undergoing gonadotoxic therapies should be counselled about this option, but informed about this controversy so that an informed decision can be made.

PEDIATRIC CONSIDERATIONS

Special challenges exist for young children and peri-pubertal adolescents facing potentially gonadotoxic therapies. Children are not in a position developmentally to either understand or consent to any forms of treatment, let alone FP procedures. A sensitive approach to the physical and emotional maturity of the child needs to be taken when discussing these issues.

Many barriers exist to sperm banking including: clinician discomfort with broaching the subject, parental/patient discomfort, the lack of appropriate patient educational materials, and the financial cost associated with cryopreservation (Medicine, 2013a). In addition, religious, cultural, and relationship sensitivities can make FP conversations difficult (Wright, Coad, Morgan, Stark, & Cable, 2014). Several studies have shown that childhood cancer survivors feel regret when they have no fertility options after completing treatment, suggesting the importance of overcoming barriers, when possible, to ensure that patients and families understand the effects of treatment on fertility and FP options (Loren et al., 2013).

Logistically, mature sperm can normally be found when patients have sufficiently progressed through puberty (Tanner stage III); with sperm production being only effective around the ages of 13 to 14 (Guerin, 2005). Pre-pubertal patients are not physically mature enough to produce mature spermatozoa and oocytes. For females, there is an added stress because procedures are more invasive and often require treatment delays (Crawshaw, 2013). The current ASCO (Loren et al., 2013) guidelines suggest that established methods of FP should be offered to post-pubertal adolescents with patient assent and parental/guardian consent. It may be possible in some circumstances for peri-pubertal girls who are not yet menarcheal to also undergo ovarian stimulation for mature oocyte cryopreservation (Medicine, 2013b). For pre-pubertal children, investigational methods that are available should be presented and the children referred to specialty centres with ethically approved research protocols (Loren et al., 2013; Rodriguez-Wallberg & Oktay, 2014).

ADULT CONSIDERATIONS

Although discussions about fertility and FP are of great importance to young people with cancer, challenges to FP have also been identified in young adults (Loren et al., 2013). Some of the challenges include: (1) cost of fertility treatment(s), and (2) delaying cancer treatment to undergo preservation processes.

The cost of FP often prevents both male and female patients with a cancer diagnosis from undergoing fertility treatments (Yee et al., 2012). The cost of sperm banking is approximately \$300 upfront with an annual storage fee of \$240 (Hospital, 2012). The cost for females to undergo one IVF cycle is approximately \$5,000 to \$8,000 including the cost of hormone medications necessary for this process (Hospital, 2012). Fertile Future, a Canadian advocacy agency, has an FP reimbursement program that provides some financial support for eligible young people with cancer called Power of Hope.

Time is critical for young adults considering FP prior to cancer therapy and attempts are most effective before treatment is initiated (Loren et al., 2013; Yee et al., 2012). For women, FP can take two to four weeks with established techniques (Loren et al., 2013). It is, therefore, critical that women are referred to a fertility clinic in a timely manner. Time is less of an issue for males and they are often able to sperm bank within 24 hours of receiving their cancer treatment plan.

CANCER SURVIVORS

The effects of cancer treatment on fertility can remain a source of distress for cancer survivors. It is difficult, particularly in women, to precisely predict fertility impairment. Younger adults have reported feelings of loss, compromised self-esteem, self-image, and identity from the threat of impaired fertility (Tschudin & Bitzer, 2009).

Menstruation is not a sensitive measure of fertility and patients require additional testing for fertility assessment (Barton et al., 2013). Measures of anti-mullerian hormone (AMH) can be used to track ovarian reserve in addition to routine hormones (LH, FSH, estradiol) and antral follicle count. There is still an opportunity for women at risk for POF to preserve oocytes or embryos once their therapy is complete in case she goes into ovarian failure prior to conceiving. Oocyte and embryo cryopreservation is carried out similarly whether done before or after cancer treatment. It is important to note, that pregnancy may be a possibility for women in POF provided they use previously cryopreserved gametes or donor oocytes to conceive and are given hormones to support the pregnancy early in the first trimester. Once a woman is in POF it is no longer possible to preserve her fertility.

Pregnancy is often discouraged in the first two years after chemotherapy. This is related to the recurrence risk and to prevent fertilization of ova that may have been exposed to therapy (Blumenfeld, 2014; Green et al., 2002; Meistrich & Byrne, 2002). Estrogen receptor positive breast cancers are generally treated with endocrine therapy. This is typically prescribed for five years or longer and may have teratogenic effects on a fetus. Consequently, patients are faced with either further delaying childbearing until endocrine therapy is complete or interrupting their treatment in order to conceive, which may compromise their disease outcome.

For males, complete azoospermia is often not achieved until about 18 weeks following radiotherapy or two months following gonadotoxic chemotherapy (Meistrich, 2013). Sperm production then ceases for the duration of treatment. After treatment, the highest chance for sperm count recovery is within the first two years; however it can take up to five years. Recovery beyond five years is rare (Meistrich, 2013). Although sperm recovery can take time, it is usually progressive. Males who have been treated with gonadotoxic therapy can have semen analysis performed post treatment to determine if their sperm production has recovered. Azoospermia should not be diagnosed then until five years post therapy.

It has been found that when the testis contains less than three to four million sperm, the sperm do not survive epididymal transit and reach the ejaculate (Meistrich, 2013). Patients who demonstrate prolonged azoospermia may be candidates for microdissection testicular sperm extraction (TESE) to retrieve sperm produced in the testis, but are not making it to the ejaculate. Studies have shown that 37% of azoospermic patients have sperm retrieved with TESE (Hsiao et al., 2011). This is more likely in patients treated without alkylating agents.

THE ROLE OF APN'S IN EDUCATION

Although nurses and physicians have positive attitudes towards FP, conversations around preservation options and referrals to fertility clinics are inconsistently taking place in oncology care settings (King et al., 2008; Yee, Buckett, et al., 2012). Knowledge gaps prevent providers from consistently addressing this topic with their patients (King et al., 2008; Yee, Buckett, et al., 2012). The major gaps include: lack of knowledge on FP options, being unaware of fertility clinic locations, time constraints, and physician behaviours (King et al., 2008; Yee, Buckett, et al., 2012). Oncology nurses can play a key role in the care of AYA patients, as they are able to identify patient concerns such as fertility, and can further collaborate with the medical team to address this area of need (Vadaparamil et al., 2013). In order to initiate conversations and provide interventions around fertility, nurses have indicated that training through continuing education sessions must be provided at their centres (King et al., 2008).

At a large tertiary adult cancer centre in Toronto, an AYA Program has been launched. The program focuses on supporting young adult patients around their unique needs—including fertility. Presentations on FP have been delivered by the APN to the nursing staff across all disease sites. The goal of these presentations is to enhance provider knowledge on fertility risks, preservation options and the referral process to a fertility clinic. In addition, AYA toolkits which include resources specific to young adults with cancer have been implemented in the clinics and on the inpatient units. Fertility brochures and referral forms have been added to these kits, so that health care providers can easily access fertility information and services for their patients. A price list from a local fertility clinic and information on the Power of Hope program are also included to help patients plan and prepare for their appointment with a fertility specialist. Furthermore, the APN has consultations with young adult patients where they are provided with additional information on fertility preservation options before and after treatment. Fertility clinic referrals are also facilitated by the APN based on the patient's need. Approximately 100 consultations were completed in the first year of the program.

Fertility pathways have also been developed in collaboration with an APN from a local fertility clinic to guide the primary care team when making referrals to this service. The goal of these interventions is to build healthcare provider capacity by providing them with the knowledge, tools and support that will enable them to facilitate conversations and interventions around FP.

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In a pediatric tertiary care centre also in Toronto, a dedicated APN role was created in FP to address the educational needs of patients and professionals for both experimental and proven options. This pilot position was funded by the hospital foundation. The FP APN receives consultation requests from the primary teams, at which point she discusses the risks that the proposed treatment may have on future fertility with the patient and family. Options for FP are discussed as appropriate for the age and gender of the patient. If patients and families elect to pursue FP interventions the APN organizes the intervention with the appropriate teams: gynecology, urology, the treating team and the fertility centre. More than 60 consults have been completed by the APN in the first year of the program.

A secondary goal of the FP APN role is to create systems to support FP in the pediatric organization. Several interventions have been accomplished to date including: clinical practice guidelines for both male and female patients, an educational sperm banking pamphlet, and educational sessions with the multidisciplinary team to encourage FP discussion with families.

At the collaborating fertility clinic, an APN triages and prioritizes all female oncofertility referrals and patients are seen within a week, often within a day, by the APN in partnership with the staff physician. Male patients who are referred for sperm banking for oncology are booked within 48 hours, as well. The APN and staff physicians have also developed partnerships with oncology centres in Toronto and across the province and have delivered presentations on FP to a variety of HCP groups.

APNs: LEADING FERTILITY PRESERVATION PRACTICE

The effects of infertility can be devastating to both male and female survivors of cancer. FP methods do exist and should be offered in a routine and standardized way to those at risk. There are some barriers and opportunities to developing integrated FP programs at both pediatric and adult tertiary cancer centres. APNs are ideally positioned and have the skill set to enhance FP practices among oncology health care providers. APNs can (1) role model fertility practices recommended by clinical guidelines; (2) understand the risks that a cancer diagnosis and therapy pose on a patient's fertility; (3) have the experience to develop and educate staff on fertility; (4) counsel patients on their fertility risks and preservation options; and (5) conduct research on the effectiveness of their interventions. As a result, APNs can positively impact fertility practices in oncology programs and ultimately improve the quality of life of young people with cancer.

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