CURRENT ONCOLOGY

PRACTICE GUIDELINE

Fertility preservation in reproductive-age women facing gonadotoxic treatments

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ABSTRACT

Background Advancements in the treatments for cancer and autoimmune and other hematologic conditions continue to improve survival and cure rates. Despite those changes, various gonadotoxic agents and other treatments can still compromise the future fertility of many women. Progress in medical and surgical reproductive technologies has helped to offset the reproductive consequences of the use of gonadotoxic therapies, and allows for future fertility and normal pregnancy.

Methods A review of the literature was performed to outline the pathophysiology of gonadotoxicity from various treatments. The success of fertility preservation, fertility sparing, and cryopreservation options are reviewed. Barriers and facilitators to referral and oncofertility treatment in Canada are also outlined.

Results According to the quality of the evidence, recommendations are made for fertility assessment, patient referral, cryopreservation, and other assisted reproductive technologies.

Conclusions To ensure ongoing fertility in women undergoing gonadotoxic treatments, assisted reproductive technologies can be combined with a multidisciplinary approach to patient assessment and referral.

Key Words Oncofertility, fertility preservation, cryopreservation, gonadotoxicity, young adults, adolescents

Curr Oncol. 2015 Aug;22(4):e294-e304 www.current-oncology.com

INTRODUCTION

This guideline is based on currently available evidence in what is often a rapidly advancing field of study. Recommendations might not reflect emerging evidence and are subject to change. Clinical guidelines are intended as an aid to—not a replacement for—clinical judgment. Clinical guidelines neither prevent clinicians from exercising their freedom in good clinical practice, nor relieve them of responsibility to make appropriate decisions based on their own knowledge and experience.

Reproductive Challenges for Young Women Undergoing Gonadotoxic Treatments

Modern cancer treatments for young women have improved cure rates, but more often than not the price paid for survival is the loss of reproductive function from gonadal toxicity. High-dose alkylating agents and ionizing radiation have well-recognized gonadotoxicity, inducing sterility in a high proportion of patients.

Breast cancer affects more than 24,000 Canadian women annually. Of those women, 15% are of reproductive age, making breast cancer the most common malignancy in that age group. Those women also represent the bulk of referrals to assisted reproductive technology facilities for fertility preservation[1]. Other cancers seen in young women include hematologic (lymphoma and leukemia), endometrial, and cervical cancers. Less commonly, patients with autoimmune disorders such as systemic lupus erythematosus and hematologic conditions will require chemotherapeutic agents for medical management. Gonadal function and fertility outcomes have improved greatly with the newer regimens, but patients and physicians alike have to be aware of the deleterious effects that such treatments have on reproduction.

Management of young woman with cancer presents several unique medical and social challenges. In general, these patients are ill-prepared for the diagnosis of cancer and the reality of their own mortality. With a limited understanding of assisted reproductive technologies or even basic fertility issues, patients are unlikely to seek medical advice about fertility preservation. Breast cancer patients less than 40 years of age are also confronted with more aggressive tumours and reduced disease-free survival[2–4].

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Combination chemotherapy regimens for breast cancer are delivering ever-increasing rates of 5-year survival in early-stage disease, and further reductions in mortality are achieved with the addition of adjuvant hormonal therapies for patients with estrogen receptor–positive tumours[5]. However, given the improved survival with tumours of all types and at all stages, the need for adequate fertility counselling and a multidisciplinary team approach for these patients has never been greater[6]. Patients facing potentially sterilizing chemotherapy and radiotherapy can now benefit from recent advances in cryopreservation techniques that allow for the banking of oocytes, embryos, and ovarian tissue without compromising survival.

In this Canadian Fertility and Andrology Society guideline, we outline the current understanding of the pathophysiology of gonadotoxicity from cancer treatments, the methods to minimize the resulting damage, and the use of medical and surgical reproductive technologies to allow for future fertility and pregnancy. Evidence is graded as outlined in the report of the Canadian Task Force on Preventive Health Care (Table I).

Chemotherapy

"Ovarian reserve" refers to the population of primordial follicles in the ovary; those follicles make up more than 90% of the follicular population at any given time. The ovarian pool of oocytes and their individual reproductive potential decline with age, as reflected in diminishing fecundity rates and pregnancy rates with medical fertility treatments[9–11]. Chemotherapeutic agents appear simply to accelerate that process[12]. The gonadotoxicity of combination chemotherapy treatments varies according to the specific agents used, their cumulative doses, the protocol used, and the reproductive potential of the patient at the time of treatment[13,14]. Cyclophosphamide and other alkylating agents are the most toxic to the ovary, producing a dose-dependent exponential decline in primordial follicle density[15,16]. Compared with other regimens, cyclophosphamide-containing protocols are 4 times more likely to result in ovarian failure, with almost 80% of failures occurring within the first year[13]. Protocols are classified into low, intermediate, or high risk of inducing ovarian failure, with the incidence of menopause ranging from less than 20% to more than 80%[17,18].

Quantifying the gonadotoxic effects of each chemotherapeutic regimen is difficult and, to date, poorly studied. Most existing clinical trials and population studies for chemotherapeutic agents report the incidence of premature ovarian failure and ovulatory dysfunction as the measure of fertility. Infertility and diminished ovarian reserve are typically associated with eumenorrhea and ovulatory cycles[19]. Destruction of pre-ovulatory follicles results in temporary amenorrhea for a period of 3–4 months; however, long-term ovarian function can be maintained by as little as 10% of the ovary, and so clinical measures of menstrual function are a poor benchmark for assessing ovarian damage[20]. In the absence of long term follow-up of fertility and pregnancy outcomes, the effects of cancer treatment on future reproductive function will be underestimated.

As expected, the incidences of acute ovarian failure, infertility, and early menopause in chemotherapy patients correlates with age[19]. Regardless of the type of chemotherapy agents administered, at least a fraction of ovarian reserve will be lost, even if that loss is not immediately apparent with clinical and laboratory evaluation. Most objective measures of ovarian reserve are altered by chemotherapy[21]. Low-risk treatments such as doxorubicin–bleomycin–vinblastine–dacarbazine for Hodgkin lymphoma appear to have minimal short-term effects on reproduction in women under 30 years of age, but clear effects in both menstrual function and ovarian reserve testing are seen in older age groups[22]. Even if a patient is deemed to be at low risk for premature menopause, a shorter reproductive life can be expected even if regular menstrual cycles resume[23,24].

Anecdotal experience suggests that cancer survivors with a history of chemotherapy have poor outcomes with medical fertility treatments. Youth is certainly a protective factor, but long-term follow-up of childhood cancer

TABLE I Quality of evidence assessment and classification of recommendations as defined by the Canadian Task Force on Preventive Health Care

Quality of evidence assessment[7]		Classification of recommendations[8]	
I	Evidence obtained from at least one properly randomized controlled trial	A	There is good evidence to recommend the clinical preventive action.
II-1	Evidence from well-designed controlled trials without randomization	B	There is fair evidence to recommend the clinical preventive action.
II-3	Evidence obtained from comparisons between times or places with or without the intervention (dramatic results in uncontrolled experiments—such as the results of treatment with penicillin in the 1940s—could also be included in the category)	D	There is fair evidence to recommend against the clinical preventive action.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E	There is good evidence to recommend against the clinical preventive action.
		L	There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors could influence decision-making.

patients demonstrates clear effects on ovarian reserve and reproductive potential later in life[25–31]. Fortunately, chemotherapeutic agents do not appear to have long-term effects on the genetic competency of surviving oocytes or on the future pregnancies themselves[32], but based on murine data, the risk of fetal malformation might be elevated for up to 6–12 months after exposure[33]. Overall, the most commonly used combination chemotherapies likely advance a woman's reproductive age by 10 years, with onset of menopause depending on the patient's ovarian reserve at the start of treatment[34].

Radiation Therapy

Like chemotherapy agents, ionizing radiation has an impact on the female reproductive tract that is related to age at exposure and effective dose (fractionation schedule)[35,36]. Abdominopelvic irradiation can lead to high rates of premature ovarian failure, with even less than 2 Gy causing loss of more than 50% of the primordial follicle pool[37,38]. By comparison, typical doses for gynecologic malignancies total 50 Gy. Hypothalamic–pituitary–gonadal function can be impaired by cranial irradiation, with the highest incidence of central hypogonadism occurring with doses above 30–40 Gy[39,40]. Other risk factors for premature ovarian failure include concurrent administration of alkylating agents, high-dose radiation, and the diagnosis of Hodgkin lymphoma[38].

Pelvic irradiation impairs fertility and is associated with poor pregnancy outcomes, including early and midtrimester loss, preterm birth, and low birthweight[41]. The pathophysiology appears to involve vascular, endometrial, and myometrial damage[31,42]. Exposure before completion of puberty impairs normal uterine development, with a resulting reduced adult uterine volume that is refractory to estrogen replacement therapy. The potential need for gestational surrogacy should be discussed in such cases.

GUIDELINES

Early Access to Care and Barriers to Referral

In 2006, the American Society of Clinical Oncology set out to provide guidance to oncologists about fertility preservation and concluded that the process of informed consent requires a discussion of future fertility issues and options for fertility preservation[17]. An algorithm was suggested, which includes provision of counselling from a structured group including the medical oncologist, a reproductive endocrinologist, and a psychologist. Ideally, a collaborative multidisciplinary team of this kind would satisfy the need for a patient-centred approach to determining a realistic likelihood of success given all the factors that can play into such a multifaceted issue. Recently, a collaborative group called the Cancer Knowledge Network (http://www.cancerkn.com) was established in Canada. The network endeavors to educate patients and professionals and to connect patients with their regional fertility preservation services.

Despite the American Society of Clinical Oncology recommendation, some cancer specialists do not routinely discuss fertility preservation, and nearly half never refer patients to a fertility specialist[43]. Many barriers have been identified, including a lack of knowledge about fertility preservation options[44] and available local resources[45,46], and the perception that assisted reproductive technologies are cost-prohibitive and of limited efficacy[47,48]. The constraints of time and concern about cancer treatment delay are also cited, but early involvement of the fertility specialist is critical for the provision of timely fertility preservation services[49,50]. In a direct comparison of patients undergoing fertility preservation treatments with those undergoing standard cancer treatment protocols, no statistical or clinical differences were observed between the groups with respect to time from initial diagnosis to chemotherapy initiation or time from definitive operation to chemotherapy ($p \leq 0.27$ and $p \leq 0.79$ respectively)[51]. The median time from referral to oocyte retrieval was 32 days (range: 13–66 days)[51], with a multidisciplinary team arranging *in vitro* fertilization (IVF) within 18 days from referral (median of 11 days for ovarian stimulation)[52]. Chemotherapy can actually start up to 3 weeks earlier if a fertility preservation referral is made before cancer surgery[53]. Collaborative efforts between the fertility specialist and the oncology team should aim to provide informed counselling about future infertility and the suitability of individualized fertility preservation treatments[54]. Such counselling requires early referral and timely consultation with a fertility specialist, with the provision of fertility preservation treatment in conjunction with the oncologic management schedule.

Recommendations

After a diagnosis of cancer or another medical condition requiring potentially sterilizing medical or surgical treatments in a reproductive-age woman, immediate referral to a reproductive endocrinology and infertility specialist is strongly suggested to provide patients with counselling about their fertility and fertility preservation management options (level II-B).

A multidisciplinary network to facilitate referrals to professionals with expertise in fertility preservation should be considered (level II-3B).

Assessment of the Young Cancer Patient

Before considering fertility preservation treatments, the patient must consider the individualized risk that the cancer treatment poses to future fertility. In the case of breast cancer, practitioners should be mindful of the 2-year period of observation after completion of chemotherapy and the lengthy delays that the use of adjuvant hormonal therapies implies. It is important that the oncology team be consulted before fertility preservation treatment is initiated. Careful coordination of the fertility preservation treatments might be required to allow for timely delivery of cancer treatment, with a clear understanding having been reached with the patient that cure takes precedence over fertility.

Ovarian reserve testing should be considered to help in developing the ovarian stimulation protocol and to provide a reasonable estimate of age-related prognosis. For many years, basal follicle-stimulating hormone (FSH) has been the standard evaluation of ovarian reserve and a simple means to screen patients for diminished response and poor outcome with IVF[55]. Antimüllerian hormone (AMH) is proving to be the most predictive for ovarian response

to exogenous gonadotropins and for pregnancy outcome, and also the most versatile in such patients[56–58]. Antimüllerian hormone is detectable at all ages and, unlike FSH, is stable throughout the menstrual cycle; it can therefore be assessed at the time of presentation. In combination with the patient's age, AMH can help to assess future fertility by quantifying the short-term chemotoxic effects on ovarian reserve[59], providing an estimated age of menopause[60,61] and assessing the patient's susceptibility to the gonadotoxic effects of chemotherapy[62,63].

Like FSH, AMH is a better predictor of oocyte numbers and ovarian response to gonadotropins than it is of successful pregnancy[64,65]. Complete transvaginal pelvic ultrasonography with antral follicle count is an essential part of basic fertility assessment in prospective patients[66]. In addition to providing further data about the patient's ovarian reserve[67,68], pre-treatment ultrasonography also evaluates for pelvic pathology and adnexal anatomy in preparation for controlled ovarian stimulation and oocyte harvest.

Recommendations

All or some combination of serum FSH, serum AMH, and antral follicle count should be performed before chemotherapy to assist in the selection of gonadotropin doses and to prognosticate the gonadotoxic effects of chemotherapy (level II-2B).

Follow-up serum FSH and AMH should be considered for assessing the gonadotoxic effects of chemotherapy (level II-2A).

Fertility Preservation Options

On the basis of a fertility assessment, the oncologic treatment plan, and the patient's reproductive needs, individualized fertility preservation plans can be formulated for most patients. The decision to proceed with fertility preservation treatments should take into account age, diagnosis, oncology treatment regimen, reproductive potential with and without treatment, and the patient's personal or social situation. More universally, gonadotropin-releasing hormone (GnRH) agonists administered concurrently with cytotoxic treatments in an effort to provide some level of protection are suitable for all ages. Assisted reproductive technologies have been used to generate oocytes and embryos for cryopreservation and future use. Creation of embryos requires sperm from a partner (or when there is no partner, donor sperm). Oocyte vitrification is proving to be an excellent option for women even when a partner is present because it provides the patient with reproductive autonomy. *In vitro* maturation is an investigational strategy available through a limited number of centres. Although also investigational, ovarian tissue cryopreservation is the most hopeful option for children and young adolescents who are otherwise limited by their reproductive immaturity.

GnRH Agonists

Reports of reduced amenorrhea rates in young women using adjuvant GnRH agonists prompted investigation of the chemoprotective properties of those agents in the ovary. Despite limited evidence for their efficacy, GnRH agonists are currently in routine use at some centres during chemotherapy. Proposed mechanisms of action include hypogonadotropism-induced ovarian quiescence, reduction of ovarian blood flow, and agonistic effects on ovarian GnRH receptors. Three small prospective randomized studies have assessed GnRH agonists, with two studies demonstrating a reduction in premature ovarian failure, one of which reported a reduction to 11.4% from 66.6%[69–71]. A meta-analysis also showed a protective effect; however, most studies used historical controls[72].

A potential concern with the use of GnRH agonists in breast cancer patients is that the resulting hypoestrogenic state could inadvertently arrest malignant cells in the resting (G0) phase, rendering them less susceptible to chemotherapy[73,74]. Larger studies are required to better evaluate the efficacy of GnRH agonists.

Recommendation: Before combination chemotherapy, GnRH agonists can be considered as a means of gonadal cytoprotection (level I-B).

Embryo Cryopreservation

Cryopreservation of embryos is a standard technique used by all IVF clinics for the banking of supernumerary embryos and for situations in which the transfer of fresh embryos is ill-advised, such as in severe cases of ovarian hyperstimulation syndrome (OHSS)[75]. As a method of fertility preservation, embryo cryopreservation has been available to cancer patients for many years. Foremost with this technique is the need for a male partner, unless the patient is prepared to use donor sperm. The patient's chance of a successful future pregnancy depends on the number of high-quality embryos obtained, which in turn depends on the number of IVF cycles and the time available to achieve adequate stimulation. In 2012, the clinical pregnancy rate for frozen embryo transfer by the 32 IVF facilities in Canada was 29.9%[76]. With all of the necessary resources at hand, many IVF facilities routinely cryopreserve embryos as a means of fertility preservation in patients with male partners or in those who wish to use donor sperm.

Recommendation: Embryo cryopreservation is a recommended method of fertility preservation (level I-A).

Oocyte Cryopreservation

For women without a male partner or women desiring reproductive autonomy, oocyte cryopreservation has become the standard approach. Historically, the technique has been beset by lower pregnancy rates than those associated with embryo cryopreservation; however, with recent advances in cryo-technology, the service is becoming more widely available[77]. The low pregnancy rates were related to several technical challenges encountered during the freeze–thaw process and the *in vitro* maturation of immature oocytes.

Mature oocytes provide the best chance for pregnancy, but have several characteristics that make them susceptible to cryo-damage. The oocyte's large size (low ratio of surface area to volume) and high water content make it vulnerable to ice crystal formation, rupture, and limited penetration of cryoprotectant solutions[78]. Because mature oocytes are arrested in metaphase II, the spindle apparatus is fully extended and prone to disassembly at lower temperature, with

subsequent chromosome dispersion and aneuploidy[79,80]. Despite the potential obstacles, clinical and neonatal outcomes to date attest to the safety of this technology[81]. The efficiency, feasibility, and safety of the technology have developed to the point that the American Society for Reproductive Medicine no long considers it experimental for the purpose of fertility preservation in women undergoing gonadotoxic therapies[82,83].

Vitrification has been integral to the improvements in and success of oocyte cryopreservation. The technique directly solidifies the oocyte and surrounding solution into a glasslike (vitreous) state, minimizing the formation of potentially disruptive intracellular and extracellular ice crystals. Meta-analyses support the superior thawing survival and clinical outcomes achieved with oocyte vitrification[84–86]. A recent randomized controlled trial demonstrated the clinical equivalency of vitrified and fresh oocytes in the setting of anonymous oocyte donation[87]. Other groups are also starting to report similar success, and the technique has quickly become the standard approach for both oocyte and embryo cryopreservation[88]. With refinements in technique and better clinical outcomes, oocyte cryopreservation is proving to be a simple and versatile method of fertility preservation that can provide women with reproductive autonomy.

Recommendation: Oocyte cryopreservation by vitrification is a recommended method of fertility preservation (level I-A).

Controlled Ovarian Stimulation in Cancer Patients

Using modern IVF protocols and appropriate doses of gonadotropins, oocyte and embryo yield and, ultimately, the number of future attempts for pregnancy can be maximized. In the case of breast cancer, a period of 4–6 weeks between surgery and chemotherapy is a common restriction, allowing for only 1 or 2 IVF cycle attempts, given that gonadotropins are traditionally initiated with menses.

Protocols using GnRH antagonists provide the most flexibility during ovarian stimulation. Treatments with GnRH antagonists are shorter, require less gonadotropin, and reduce the risk of OHSS[89–92]. Gonadotropins can be initiated with spontaneous menses, by truncation of the menstrual cycle with the administration of a GnRH antagonist shortly after ovulation[93], or randomly throughout the patient's cycle[94–98].

The dose of gonadotropins should be individualized to the patient based on age and ovarian reserve testing, with the goals of maximizing the number of high-grade embryos at the end of the process and of not compromising the patient's medical status before the start of cancer treatments. Data to suggest that these patients have different gonadotropin requirements or that the quality of the oocytes and embryos are compromised by their illness are minimal, but dosing decisions should be left to a physician with experience using gonadotropins in these patients[99]. In an attempt to minimize the patient's estrogen exposure after oocyte retrieval and her risk of early OHSS, GnRH agonists can be used with antagonist cycles for triggering final oocyte maturation[100–102]. Like oocyte donors, these patients are not at risk for the more clinically worrisome late OHSS because they are not conceiving. Given that inadequate induction of the luteinizing hormone surge is the principal risk of the technique, reserving the GnRH agonist "trigger" for patients with a hyper-response or supplementing with a small dose of human chorionic gonadotropin is also acceptable[101,103,104]. In such cases, GnRH antagonist protocols are preferred for several reasons, but are often the most practical option given that gonadotropins can be started quickly.

Long GnRH agonist protocols are still used for controlled ovarian stimulation, but have the well-recognized risk of inducing a luteal "flare" from the pituitary, with rescue of the corpus luteum and functional ovarian cysts leading to treatment delays[105].

Recommendations: Ovarian stimulation protocols using GnRH antagonists should be considered for embryo and oocyte cryopreservation (level II-3B).

To minimize the risk of OHSS, GnRH agonists are recommended for the induction of oocyte maturation when using GnRH antagonist cycles (level I-2A).

Use of Cytoprotective Agents During Ovarian Stimulation in Breast Cancer Patients

Many breast cancer tumour cells are estrogen receptor–positive and accordingly are susceptible to environments with estrogen excess[106,107]. Even tumours that are classified as receptor-negative will contain a small percentage of receptor-positive cells[92,108,109].

Serum estradiol levels reach supraphysiologic levels during controlled ovarian stimulation: typically 5000 pmol/mL and not uncommonly exceeding 10,000 pmol/mL (peak natural cycle levels are 750–1300 pmol/mL). Although no clinical data are currently available, high levels of estrogens could in theory stimulate subclinical disseminated disease[110], and so any therapy that antagonizes the effect is reasonable[111–113]. Two strategies are commonly used to minimize that estrogen exposure: recovering oocytes from an unstimulated IVF cycle, or administering cytoprotective agents in combination with gonadotropin stimulation.

Aromatase inhibitors have proved to be efficacious as an adjuvant therapy for the management of micrometastatic disease[111,114–116], and they have gained popularity as ovulation induction agents and adjuncts in IVF protocols[117]. More importantly for the breast cancer patient, they suppress estradiol production during IVF stimulation. Letrozole is the most potent of the aromatase inhibitors, suppressing greater than 96% of estradiol activity. With concurrent use of aromatase inhibitors, gonadotropins can be administered to maximize embryo yield while minimizing estradiol levels[118,119]. Ultrasound follicle tracking serves as the only measure for dosing adjustment and assessing the patient's risk for OHSS. Because the ovary remains hyperstimulated well beyond retrieval of the oocytes, sustained use of letrozole for at least another 7 days is recommended.

Recommendation: In women with breast cancer and other estrogen-sensitive diseases, aromatase inhibitors should be considered when administering gonadotropins (level II-3B).

Ovarian Cryopreservation and Transplantation

Any patient receiving chemotherapy or radiotherapy that targets the ovarian follicles can be considered a candidate for ovarian cryopreservation, assuming a low risk for ovarian metastasis[120]. Also, some patients might not have sufficient time to undergo ovarian stimulation for oocyte or embryo freezing, or might have an oncology plan that includes abdominal surgery.

Since the first experiments with ovarian transplantation in animals[121], steady advances have been made in humans, and other species have also been successfully transplanted with both autologous ovarian tissue and human xenografts[122]. With the knowledge gained from those experiments, trials in human transplantation were initiated. In the case of cancer patients, caution should be exercised to prevent the reintroduction of disease. Transmission of cancer has been demonstrated in the animal model[123,124], and metastatic seeding of the ovary commonly occurs with some cancers. In the case of *BRCA* mutation, the risk of ovarian cancer is significant; screening for the mutation should therefore be considered in all breast cancer patients before ovarian tissue harvest[125].

At an appropriate time after completion of the patient's cancer therapy, the tissue is thawed and transplanted either orthotopically or heterotopically within subcutaneous tissue or the pelvis[126–130]. The major barrier to the technology is delayed revascularization and the resulting ischemia and fibrosis, with subsequent loss of primordial follicles[121,131]. Grafts become hormonally active 3–4 months after transplantation, at which time oocyte harvesting can be attempted, with or without the aid of exogenous gonadotropins to stimulate follicle development. To date, more than 23 live births have been reported in humans; however, some could have originated from the contralateral *in situ* ovary, because only one ovary is typically harvested[132–138]. Several groups are currently experimenting with whole-ovary vitrification and transplantation as a means to improve efficiency and clinical outcomes[139–142]. Given the limited success of that technology to date, the potential for reseeding of metastatic disease, and the surgical risks, ovarian transplantation should still be considered investigational and limited to cases in which oophorectomy is planned. The procedure is further constrained by the limited number of individuals and facilities with expertise in the technique.

Recommendation: Ovarian tissue cryopreservation and transplantation is investigational and should be limited to cases of oophorectomy or other predetermined abdominal surgeries by surgeons with the necessary experience, and in connection with clinical research approved by a research ethics board (level II-3B).

Pregnancy After Cancer

No consensus has emerged about the best time to conceive after cancer treatments. Because most recurrences are diagnosed within the first 2 years, patients are commonly asked by their oncologists to wait. However, some studies suggest that early conception does not negatively affect survival[143,144]. Five-year survival is actually higher in breast cancer patients who achieve a pregnancy[145,146], although that observation could certainly be related to a "healthy patient" bias. Ultimately, decisions about the timing of pregnancy should be made in consultation with a cancer specialist.

Fertility-Sparing Surgical Options

The harmful effects of radiation on the ovaries can be minimized by ovarian transposition, a procedure in which the ovaries are surgically transposed to a location outside the radiation field[147]. Transposition can also be combined with gonadal shielding to further reduce the dose effect[148]. Using transposition, preservation of menstrual function have been reported to range from 65% to more than 88%[149–151]. The risks associated with the procedure include ovarian cysts, adhesions, pelvic pain, ovarian migration, premature ovarian failure, and tubal injury[20,152]. Some malignancies carry a small risk of metastatic disease to the ovary, and so transposition could facilitate the spread of disease[20,153,154]. Any benefit of transposition can be lost when adjuvant chemotherapy is used[155,156]. Other fertility-sparing surgical options include cervical conization or trachelectomy for select early-stage cervical cancer patients, and unilateral oophorectomy or cystectomy in select ovarian neoplasms[157,158].

Recommendation: When possible, fertility-sparing surgery should be considered if it does not compromise survival (level III-B).

Ethics Considerations

Standard treatments confer an overall net benefit to the patient, but when the treatments are experimental, the benefit must be carefully considered. The evolving field of oncofertility uses investigational procedures with the aim of improving outcomes. For such interventions, the guidance of an institutional review board is recommended, with formal protocols and associated consent forms clearly stating the proposed treatment as investigational.

The consent process for women of all ages should include a discussion of these topics:

- Risk to future fertility of cancer treatments
- Fertility preservation treatment options
- Risks of delaying cancer treatment
- Any investigational aspects of fertility preservation treatments
- Realistic likelihood of the success of fertility preservation options
- Potential risks of fertility preservation treatments
- Treatment costs
- Disposition of human reproductive material
- Posthumous reproduction
- Alternative fertility options (oocyte donation, adoption, gestational surrogacy)

SUMMARY

Recent strides in the technology of oocyte and embryo cryopreservation provide effective fertility preservation options through assisted reproductive technologies in Canada. A multidisciplinary approach and education of

oncology professionals will help to ensure that cancer patients receive the appropriate fertility preservation counselling and services.

ACKNOWLEDGMENTS

The authors thank the Canadian Fertility and Andrology Society clinical practice guideline committee.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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