Canadian Fertility & Andrology Society

Clinical Practice Guidelines

Fertility Preservation In Reproductive Age Woman Facing Gonadotoxic Treatments

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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 per year. Fifteen per cent of these women are of reproductive age, making it the most common malignancy in this age group and the representing the bulk of referrals to assisted reproductive technology (ART) facilities for fertility preservation[1]. Other cancers seen in young women include hematologic (lymphoma and leukemia), endometrial, and cervical. Less commonly, patients with autoimmune disorders like systemic lupus erythematosus (SLE) and hematologic conditions will require chemotherapeutic agents for medical management. Gonadal function and fertility outcomes have improved greatly with the newer regimens, however patients and physicians alike need to be aware of the deleterious effects that these treatments have on reproduction.

Management of the 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 on fertility preservation. Breast cancer patients under 40 years of age are also confronted with more aggressive tumor grades and reduced disease-free survival[2-4]. Combination chemotherapy regimens for breast cancer are delivering ever-increasing 5 year survival rates for early-stage disease, and further reductions in mortality are achieved with the addition of adjuvant hormonal therapies for patients with estrogen receptor positive tumors[5]. However, given the improved survival with all tumor types and stages, the need for adequate fertility counseling and a multidisciplinary team approach for these patients have never been greater[6]. Patients facing potentially sterilizing chemotherapy and radiotherapy can now benefit from recent advances in cryopreservation techniques which allow for the banking of oocytes, embryos, and ovarian tissue without compromising survival. With this CFAS guideline we outline the current understanding of the pathophysiology of gonadotoxicity from cancer treatments, the methods to minimize this 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 Preventative Health Care (Table1).[7, 8]

Table 1: Quality of evidence assessment and classification of recommendations as defined by the Canadian Task Force on Preventative 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-2 Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making

Quality of Evidence Assessment[7]	*Classification of Recommendations*[8]
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 may influence decision-making

Chemotherapy

Ovarian reserve represents the population of primordial follicles within the ovary, which make up more than 90% of the follicular population at any given time. The ovarian pool of oocytes and their individual reproductive potential declines with age, as reflected in diminishing fecundity rates and pregnancy rates with medical fertility treatments[9-11]. Chemotherapeutic agents appear simply to accelerate this process[12]. Gonadotoxicity of combination chemotherapeutic treatments vary according to the specific agents used, cumulative doses, protocol, and reproductive potential of the patient at the time of treatment[13,14]. Cyclophosphamide and other alkylating agents are the most toxic to the ovary, inflicting a dose-dependant exponential decline in primordial follicle density[15, 16]. Compared to other regimens, cyclophosphamide-containing protocols are four times more likely to result in ovarian failure, with almost 80% of cases 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 over 80%[17, 18].

Quantifying the gonadotoxic effects of each chemotherapeutic regimen is difficult and poorly studied to date. Most existing clinical trials and population studies for chemotherapeutic agents report the incidence of premature ovarian failure (POF) 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 to 4 months however long-term ovarian function can be maintained by as little as 10% of the ovary, so clinical measures of menstrual function are a poor assessment of 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 incidence of acute ovarian failure, infertility and early menopause in chemotherapy patients correlates with age[19]. Regardless of the type of chemotherapeutic agents administered, at least a fraction of ovarian reserve will be lost even if this is not immediately apparent with clinical and laboratory evaluation. Most objective measures of ovarian reserve are altered by chemotherapy[21]. Low risk treatments like ABVD (adriamycin, bleomycin, vinblastine

and dacarbazine) for Hodgkins lymphoma appear to have minimal short-term effects on reproduction in women under 30, however clear effects are seen in both menstrual function and ovarian reserve testing 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 would suggest 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 patients demonstrate 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 the future pregnancies themselves[32], but based on murine data the risk of fetal malformation may by elevated for up to 6 to 12 months after exposure[33]. Overall, the most commonly used combination chemotherapies likely advance a woman's reproductive age by 10 years, with the onset of menopause dependant on the patient's ovarian reserve at the start of treatment[34].

Radiation therapy

As with chemotherapeutic agents, the impact of ionizing radiation on the female reproductive tract relates to the age at exposure and effective dose (fractionation schedule)[35, 36]. Abdomino-pelvic irradiation can lead to high rates of premature ovarian failure, with even less than 2 Gy causing loss of over 50% of the primordial follicle pool (LD50)[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 POF include concurrent alkylating agent administration, high dose radiation and the diagnosis of Hodgkins lymphoma[38].

Pelvic radiation 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 prior to completion of puberty impairs normal uterine development, with a resulting reduced adult uterine volume which is refractory to estrogen replacement therapy. The potential need for gestational surrogacy should be discussed in these cases.

Early access to care and barriers to referral

In 2006, the American Society of Clinical Oncology (ASCO) set out to provide guidance to oncologists regarding 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 included provision of this counselling from a structured group which includes the medical oncologist, reproductive endocrinologist and psychologist. Ideally, such a collaborative multidisciplinary team would satisfy the need for a patient-centered approach to determining a realistic likelihood of success, given all the factors that can play into such a multifaceted issue. Recently, a collaborative group was established in Canada called the Cancer Knowledge Network which endeavors to educate patients and professionals, and to connect patients with their regional fertility preservation services (www.cancerkn.com).

Despite the ASCO recommendation, some cancer specialists do not routinely discuss fertility preservation, with nearly half never referring to a fertility specialist[43]. Many barriers have been identified, including a lack of knowledge of 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 for cancer treatment delay was also cited, however early involvement of the fertility specialist is critical for the provision of timely fertility preservation services[49, 50]. Directly comparing patients undergoing fertility preservation treatments to those with standard cancer treatment protocols, there were no statistical or clinical differences between the groups regarding time from initial diagnosis to chemotherapy initiation or in the time from definitive operation to chemotherapy (p=<0.27 and p=<0.79 respectively)[51]. The median time from referral to oocyte retrieval was 32 days (range 13-66 days)[51] with a multidisciplinary team functioning to provide IVF within 18 days from referral (median of 11 days for ovarian stimulation)[52]. Chemotherapy may 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 oncology team should aim to provide informed counseling regarding future infertility and the suitability of individualized fertility preservation treatments[54]. This 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 the diagnosis of cancer or other medical conditions requiring potentially sterilizing medical or surgical treatments in a reproductive-age woman, an immediate referral to a reproductive endocrinologists and infertility (REI) specialist is strongly suggested, to provide patients with counseling regarding their fertility and fertility preservation management options. (II-B)

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

Assessment of the young cancer patient

Prior to considering fertility preservation treatments the individualized risk that the cancer treatment poses to the patient's future fertility must be considered. In the case of breast cancer we should be mindful of the two year period of observation following completion of chemotherapy, and lengthy delays when adjuvant hormone therapies are employed. It is important that the oncology team is consulted prior to initiating fertility preservation treatment. Careful coordination of the fertility preservation treatments may be required to allow for timely delivery of the cancer treatment, with a clear understanding with the patient that her cure takes precedence over fertility.

Ovarian reserve testing should be considered to aid in the developing the ovarian stimulation protocol and to provide a reasonable estimate of her age-related prognosis. Basal follicle stimulating hormone (FSH) has been the standard evaluation of ovarian reserve for many years and a simple means to screen patients for diminished response and poor outcome from IVF[55]. Antimullerian hormone (AMH) is proving to be the most predictive for ovarian response to exogenous gonadotropins and pregnancy outcome and also the most versatile in these patients[56-58]. AMH is detectable at all ages, and unlike FSH, is stable throughout the menstrual cycle so can be performed at the time of presentation. In combination with the patient's age, AMH can help assess future fertility through the quanitfying of 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]. Similar to FSH, AMH is a better predictor of oocyte numbers and ovarian response to gonadotropins, than it is of successful pregnancy[64, 65]. A complete transvaginal pelvic ultrasound with antral follicle count (AFC) is an essential part of the basic fertility

assessment of these patients[66]. In addition to providing further data about the patient's ovarian reserve[67, 68], pre-treatment ultrasound also evaluates for pelvic pathology and adnexal anatomy in preparation for controlled ovarian stimulation and oocyte harvest.

Recommendations

Serum follicle stimulating hormone (FSH), antimullerian hormone (AMH) levels, and/or antral follicle count (AFC) should be performed prior to chemotherapy to assist in the selection of gonadotropin doses and to prognosticate gonadotoxic effects of chemotherapy. (II-2B)

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

Fertility preservation options

On the basis of a fertility assessment, 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/social situation. More universally, gonadotropin releasing hormone (GnRH) agonists are administered concurrently with cytotoxic treatments in an effort to provide some level of protection and 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 the use of 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 (IVM) is an investigational strategy available through a limited number of centers. Whilst also investigational, ovarian tissue cryopreservation serves as the most hopeful option for children and young adolescents who are otherwise limited by their reproductive immaturity.

Gonadotropin-releasing hormone (GnRH) agonists

Reports of reduced amenorrhea rates in young women using adjuvant gonadotropin-releasing hormone agonists (GnRHa) prompted the investigation of their chemoprotective properties in the ovary. Despite the limited evidence for their efficacy, these agents are currently used routinely by 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 addressed this question with two demonstrating a reduction in premature ovarian failure, one from 66.6% to 11.4%[69-71]. A meta-analysis also showed a protective effect, however most studies have used historical controls[72]. A potential concern with the use of GnRH agonists in breast cancer patients is that the resulting hypoestrogenic state may inadvertently arrest malignant cells in the resting (G0) phase, and render them less susceptible to chemotherapy[73, 74]. Larger studies are required to better evaluate the efficacy of these agents.

Recommendation

GnRH agonists can be considered as a means of gonadal cytoprotection prior to combination chemotherapy. (I-B)

Embryo cryopreservation

Cryopreservation of embryos is a standard technique employed 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 with severe cases of ovarian hyperstimulation syndrome[75].

As a method of fertility preservation, it has been available to cancer patients for many years. Foremost 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; in turn the number of IVF cycles performed, and the time available to achieve adequate stimulation. In 2012, the clinical pregnancy rate for frozen embryo transfer among the 33 IVF facilities in Canada was 34%[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 those that wish to use donor sperm.

Recommendation

Embryo cryopreservation is a recommended method of fertility preservation. (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 compared to embryo cryopreservation, but with recent advances in cryotechnology 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 cryodamage. The oocyte's large size (low surface area to volume ratio) and high water content also makes it vulnerable to ice crystal formation, rupture, and limited penetration of cryoprotectant solutions[78]. Since 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 (ASRM) 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 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 of oocyte vitrification[84-86].

A recent randomized controlled trial demonstrated clinical equivalency of vitrified oocytes to fresh 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 will provide women with reproductive autonomy.

Recommendation

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

Controlled ovarian stimulation of the cancer patients

By employing 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, we are commonly restricted to a period of four to six weeks between the time of surgery and chemotherapy, only allowing for one or two IVF cycle attempts since gonadotropins are traditionally initiated with menses.

GnRH antagonist protocols provide the most flexibility during ovarian stimulation. GnRH antagonist treatments are shorter, require less gonadotropin, and reduce the risk of ovarian hyperstimulation syndrome (OHSS)[89-92]. Gonadotropins can be initiated with spontaneous menses, through truncation of the menstrual cycle with the administration of a GnRH antagonist shortly following ovulation[93], or randomly throughout the patient cycle[94-98]. The dose of gonadotropins should be individualized to the patient based on age and ovarian reserve testing, with the goal of maximizing the number of high grade embryos at the end of the process, without compromising the patient's medical status prior to starting her cancer treatments. Minimal data exists to suggest that these patients have different gonadotropin requirements or that the quality of the oocytes and embryos are compromised by their illness, however dosing decisions should be left to a physician with experience using gonadotropins in these patients[99]. In an effort to minimize the patient's estrogen exposure after oocyte retrieval and her risk of early OHSS, GnRH agonists can be employed with antagonist cycles for triggering final oocyte maturation[100-102]. Similar to oocyte donors, these patients are not at risk for the more clinically worrisome late OHSS since they are not conceiving. Since an inadequate induction of the luteinizing hormone (LH) surge is the principle risk of this technique, it is also acceptable to reserve GnRH agonist "trigger" for patients with a hyperresponse, or to supplement with a small dose of hCG[101, 103, 104]. GnRH antagonist protocols are preferred in these cases 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 technique 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 utilizing GnRH antagonists should be considered for embryo and oocyte cryopreservation. (II-3B)

GnRH agonists are recommended for the induction of oocyte maturation when utilizing GnRH antagonist cycles in an effort to minimize the risk of ovarian hyperstimulation syndrome. (I-2A)

Use of cytoprotective agents during ovarian stimulation in breast cancer patients

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

Serum estradiol levels reach supraphysiologic levels during controlled ovarian stimulation, typically 5000 pmol/mL (peak natural cycle levels 750 to 1300 pmol/mL) and not uncommonly exceeding 10,000 pmol/mL. Although no clinical data currently exist, high levels of estrogens could in theory stimulate subclinical disseminated disease[110], so any therapy that antagonizes this effect is reasonable[111-113].

Two strategies are commonly employed to minimize this estrogen exposure: recovering oocytes from an unstimulated IVF cycle, or administering cytoprotective agents in combination with gonadotropin stimulation. Aromatase inhibitors have proven efficacious as an adjuvant therapy for the management of micrometastatic disease[111, 114-116]. 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 its 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. Since the ovary remains hyperstimulated well beyond retrieval of the oocytes, sustained use of letrozole for at least another seven days is recommended.

Recommendation

In women with breast cancer and other estrogen-sensitive diseases, aromatase inhibitors should be considered when administering gonadotropins. (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 that she is at low risk for ovarian metastasis[120]. Some patients may also not have sufficient time to undergo ovarian stimulation for oocyte or embryo freezing, or have abdominal surgery as part of their oncology plan.

Since the first experiments with ovarian transplantation in animals[121], steady advances have been made in humans. Since then, other species have been successfully transplanted with autologous ovarian tissue, as well as with human xenografts[122]. With the knowledge gained from these 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 occurs commonly with some cancers. In the case of BRCA, the risk of ovarian cancer is significant so screening for this mutation should 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 pelvis[126-130]. The major barrier for this technology is the delayed revascularization and resulting ischemia, fibrosis and subsequent loss of the primordial follicles[121, 131]. Grafts become hormonally active three to four 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 over 23 live births have been reported in humans, however some may have originated from the contralateral

in situ ovary since only one ovary is typically harvested[132-138]. Several groups are presently experimenting with whole ovary vitrification and transplantation as a means to improve efficiency and clinical outcomes[139-142]. With the limited success of this technology to date, the potential for reseeding of metastatic disease and surgical risks, ovarian transplantation should still be considered investigational and limited to cases where oophorectomy is planned. The procedure is further limited by the limited number of individuals and facilities with expertise in this 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 under a clinical research approved by a research ethics board. (II-3B)

Pregnancy after cancer

There is no consensus on the best time to conceive after cancer treatments. Since most recurrences occur in the first two years patients are commonly asked by their oncologist to wait. However, some studies suggest that early conception does not negatively impact survival[143, 144]. Five year survival is actually higher in breast cancer patients who achieve a pregnancy[145, 146], although this observation may certainly be accounted for by a healthy patient bias. Ultimately, the decision on timing of pregnancy should be determined in consultation with a cancer specialist.

Fertility sparing surgical options

The harmful effects of radiation on the ovaries can be minimized by ovarian transposition. The ovaries are surgically transposed to a location outside the radiation field[147]. This may also be combined with gonadal shielding to reduce the dose effect further[148]. Using this technique, reports on the preservation of menstrual function have ranged from 65% to over 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]. A small risk of metastatic disease to the ovary exists in some malignancies, so transposition could facilitate the spread of disease[20,153, 154]. Any benefits of transposition may be lost when adjuvant chemotherapy is employed[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

Fertility sparing surgery should be considered when possible if it does not compromise survival. (III-B)

Ethical considerations

Standard treatments confer an overall net benefit to the patient, but when experimental the benefit must be carefully considered. This evolving field of oncofertility is aimed at improving outcomes from investigational procedures. 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 the following:

1. Risk of cancer treatments on future fertility
2. Fertility preservation treatment options
3. Risks of delaying cancer treatment
4. Any investigational aspects of fertility preservation treatment
5. Realistic likelihood of success of the fertility preservation options
6. Potential risks of the fertility preservation treatment
7. Treatment costs
8. Disposition of human reproductive material
9. Posthumous reproduction
10. Alternative fertility options (oocyte donation, adoption, gestational surrogacy)

Summary

Recent strides in oocyte and embryo cryopreservation technology provide effective fertility preservation options through assisted reproductive technologies in Canada. A multidisciplinary approach and education of oncology professionals will help ensure that cancer patients receive the appropriate fertility preservation counselling and services.

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