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Fertility preservation for young cancer patients

Subfertility and gonadal failure are possible after childhood exposure to chemotherapy, making future reproductive function a growing survivorship issue that must be addressed.

ABSTRACT: Recent advances in cryopreservation are providing effective fertility preservation options for young Canadians requiring chemotherapy for cancer. Both female and male patients can opt to freeze gametes before undergoing treatment. Embryo, oocyte, and ovarian tissue freezing are possible for females, and sperm freezing is possible for males. The decision to proceed with fertility preservation is made by taking into account the patient's age, diagnosis, oncology treatment plan, fertility status, and personal/social situation. Management should include surveillance of ovarian reserve, counseling on fertility and sexual health, and provision of egg and embryo banking in cases where the patient's reproductive lifespan is likely to be significantly reduced. Barriers to fertility preservation include a lack of awareness and the high cost of these services. A multidisciplinary approach to care, education of oncology professionals and patients on issues related to reproduction, and better funding can help ensure that cancer patients receive timely counseling and appropriate fertility preservation services.

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Modern chemotherapeutic protocols are highly effective at destroying malignant cells, but also damage ovaries and testicles in the process, leading to infertility in a sizable percentage of patients. This is a challenging survivorship issue faced by fertility specialists and cancer specialists alike. Most young cancer survivors desire future pregnancy, and the psychological impact of infertility can be greater than the effects of the cancer itself, with overt PTSD seen in some cases.[1] Fertility preservation treatments can increase the likelihood of future pregnancy. More importantly, they can also provide patients with hope and a positive distraction during a very negative time in their lives. Young patients often have a limited understanding of their own reproduction and what options exist through modern assisted reproductive technology (ART), and are unlikely to seek advice on fertility preservation; therefore, referral to a fertility specialist with the ability to discuss and deliver these services is critical.

Ovarian reserve testing

Ovarian reserve (the pool of primordial follicles) and reproductive potential both decline as women age.[2] The reduction in natural fertility with age is mirrored by the lower pregnancy rates with medical fertility treatments such as in vitro fertilization (IVF). Chemotherapeutic agents accelerate the age-related loss of primordial follicles through an increase in recruitment of ovarian follicles (burnout theory), apoptosis of supporting granulosa cells, and disappearance of eggs.[3,4] The toxicity of chemotherapeutic treatments varies according to the specific agents administered, dose, and protocol, and the reproductive potential of the patient at the time of treatment.[5-8] Primordial follicles are not mitotically active, so they are still sensitive to alkylating agents (a mainstay of most combination chemotherapy), which are cell cycle-independent drugs that can cause direct DNA damage.

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The clinical measure of reproductive toxicity has traditionally been ovarian failure rates, which range from less than 20% to over 80%. Regardless of the type of chemotherapeutic agent administered, at least a portion of the ovarian reserve will be lost, even if this is not immediately apparent clinically.[9,10] Ovarian failure occurs when a woman's follicle population drops to a point where hormone fluxes are inadequate to maintain a normal menstrual cycle. In terms of the capacity to conceive with her own eggs, a patient is rendered sterile at this point.

Normal menstrual function can be sustained with less than 10% of ovarian mass, making ovarian failure a very late measure of reduced fertility. Even if a patient is deemed to be at minimal risk for premature ovarian failure, it is safe to assume that her reproductive lifespan will be shorter despite the resumption of regular menstrual cycles.[4,11-15] A survey of 2532 cancer survivors between the ages of 18 and 40 showed that infertility rates were higher than rates of acute ovarian failure, highlighting the fact that the impact on fertility can be underestimated if the focus is simply on menstrual disruption.[10] For breast cancer, which is the most common cancer in reproductive-age women, chemotherapy likely advances reproductive age by at least 10 years.

The decision to proceed with fertility preservation treatments requires taking into account the patient's age, diagnosis, oncology treatment plan, fertility status, and personal/social situation. Even if not undergoing gonadotoxic treatments, all reproductive-age women now have the option to improve on the prospects of future pregnancy through ART, and the decision-making process is largely the same, albeit less urgent. In the case of breast cancer, plans must account for the 2-year period of recurrence observation following completion of chemotherapy and the lengthy delays possible when adjuvant hormone therapies are employed. It is important that the oncology team be consulted prior to initiating fertility preservation treatment. Careful coordination of the fertility preservation protocol is required to allow for the timely delivery of the cancer treatment, with a clear understanding that cure takes precedence.

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Ovarian reserve testing is important for tailoring a woman's ovarian stimulation protocol and for providing a reasonable estimate of her likelihood of pregnancy in the future. All measures of ovarian reserve are affected by chemotherapy, and patients with a history of chemotherapy exposure appear to have a lower potential for pregnancy.[16] A cycle day 3 follicle-stimulating hormone serum level has been the standard way to evaluate ovarian reserve for many years, with anti-Müllerian hormone (AMH) level now proving to be a better predictor of reproductive outcomes and a more convenient option, as it can be performed at any time in the menstrual cycle. Unfortunately, AMH testing is not an insured service in BC, costing approximately $70. In combination with patient age, the AMH level is also useful for quantifying the effects of chemotherapy in individuals, for predicting response to ovarian stimulation, live birth rates, and for ovarian reserve surveillance.[17,18] A transvaginal pelvic ultrasound with antral follicle count is an essential part of the basic fertility assessment of these patients, and is as predictive as the AMH level for ovarian response to gonadotropins.[19]

In vitro fertilization and embryo freezing

The mainstay of fertility preservation in female patients is the freezing of egg and embryos generated through the IVF process.[20,21] It is important to minimize any delay of cancer treatments and to maximize the number of eggs without causing undue discomfort for the patient or complications such as ovarian hyperstimulation syndrome or ovarian torsion. With concurrent use of aromatase inhibitors, gonadotropins can be administered to maximize embryo yield while minimizing the normally elevated estrogen levels encountered during these

treatments, which can be particularly important for the breast cancer patient. IVF protocols are principally defined by the methods used to block the surge of luteinizing hormone. Inhibiting the ovulatory process allows for the precise timing of the egg retrieval procedure and prevents premature luteinization of the uterus to allow for transfer of fresh embryos. Gonadotropin-releasing hormone antagonist protocols provide the most flexibility for ovarian stimulation. These treatment cycles tend to be shorter, require less gonadotropin medication (which reduces costs), and can virtually eliminate the risk of ovarian hyperstimulation syndrome when a gonadotropin-releasing hormone agonist (GnRHa) is administered to trigger final maturation of eggs for harvest.[22] The ultimate goal is to maximize the number of eggs retrieved, while minimizing any risks and delay of cancer treatments.

Cryopreservation of embryos has remained the principal fertility preservation treatment for decades. It is employed by all IVF clinics for the banking of supernumerary embryos generated through IVF and for situations when pregnancy is ill-advised for medical reasons or is being delayed for social reasons. The likelihood of future pregnancy depends on the patient's age, the number of embryos obtained, and the number of IVF cycles performed. Of great importance is the growing body of evidence that demonstrates higher pregnancy rates and better perinatal outcomes when a frozen embryo transfer rather than a fresh embryo transfer is used.[18,23-27] A recent exciting advance in the technology is the use of embryo biopsy techniques for choosing embryos for use, by screening out aneuploidy (comprehensive chromosomal screening) and single gene defects (preimplantation genetic diagnosis).[28]

Oocyte and ovarian tissue freezing

For women wanting reproductive autonomy, or those without a male partner, oocyte cryopreservation has become the standard method of preserving fertility. Historically, the technique has been beset by lower pregnancy rates compared with embryo cryopreservation, but improvements have been seen with recent advances in vitrification, the flash-freezing technology now being offered by most Canadian IVF clinics. The poor outcomes of the past were related to several technical challenges inherent in freezing and thawing of oocytes, the largest human cells. Mature (meiosis II) eggs provide the best chance for pregnancy, but have several characteristics that make them susceptible to cryodamage, including large size (low surface area to volume ratio) and high water content, which makes the egg vulnerable to ice crystal formation, rupture, and limited permeability to cryoprotectant solutions. Recent studies have found pregnancy rates with frozen eggs approaching those of fresh.[29,30] Despite the potential obstacles, clinical and neonatal outcomes to date attest to the safety of this technology, and it is now recognized by the Canadian Fertility and Andrology Society as a standard of care.[31]

Reports of reduced amenorrhea rates in young women using adjuvant gonadotropin-releasing hormone agonists throughout chemotherapy have prompted research into the protective properties of GnRHa for the ovary. Proposed mechanisms of action include hypogonadotropism-induced ovarian quiescence, reduction of ovarian blood flow, and agonistic effects on ovarian receptors for gonadotropin-releasing hormone. Although not presently endorsed by the most recent guideline of the American Society of Clinical Oncology (2013) as a standard method of fertility preservation,[7] two large RCTs suggest that a reduction in the risk of premature menopause is approximately 50% in patients undergoing chemotherapy for breast cancer.[32,33] GnRHa administration prior to and during chemotherapy is presently used widely in BC.

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Since the first experiments with ovarian transplantation in animals, steady advances have been made in human subjects.[7] Patients receiving chemotherapy or radiotherapy that

targets the ovary can be considered candidates for ovarian tissue cryopreservation, particularly if they are undergoing abdominal surgery. At an appropriate time after completion of the patient's cancer therapy, the tissue is thawed and transplanted orthotopically or heterotopically within the pelvis. The major barrier for this technology is survival of the transplant. With fewer than 100 documented live births from transplanted ovarian tissue, the potential for reseeding of metastatic disease, and the surgical risks inherent in undergoing two procedures, ovarian transplantation is considered experimental and generally reserved for cases where oophorectomy is already planned.

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Sperm freezing

For men, fertility preservation typically involves cryopreservation of ejaculated sperm.[7] Rarely, surgical collection directly from the epididymis or testicle is required. The testicle is very sensitive to even low doses of systemic chemotherapeutic agents. Additionally, cancer patients commonly present with reduced sperm counts secondary to their illness. Reduction of spermatogenesis results from effects on the epithelium. Leydig function is typically unaffected, so testosterone deficiency is uncommon. Oligospermia and azoospermia rates range from 70% to 98% depending on the follow-up period. Spermatogenesis can recover at variable times, so long-term sperm testing is recommended.[34] Some patients are rendered azoospermic for life, and one study found cancer survivors were 50% more likely to be infertile.[34,35] Importantly, fetal malformation rates are elevated for up to 2 years following chemotherapy, so sperm should be banked prior to treatment for both fertility preservation and the health of any offspring.[36] The amount of sperm required for banking will depend on the clinical scenario, timeline to treatment, and availability of the patient.

Preserving fertility in children and adolescents

Cure rates for childhood cancers exceed 80% for most types. Despite the larger ovarian reserve of most young patients going into treatment, subfertility and gonadal failure are possible after childhood exposure to chemotherapy, making future reproductive function a growing survivorship issue for these patients as they transition into adulthood. The Childhood Cancer Survivor Study, which compared patients exposed to chemotherapy with randomly selected siblings, found a thirteenfold increase in the rate of ovarian failure in female cancer survivors.[37]

Children and adolescents with cancer are frightened, but their ability to understand the impact that medical treatments will have in future should not be discounted. They typically lack knowledge about their own reproduction and existing technologies for assisting with fertility, but do eventually want children.[1] Assuming that fertility preservation procedures are technically possible, all fertility preservation techniques are available to these patients. There are no legal restrictions in Canada to the application of assisted reproductive technology in pediatric cases, so long as the reproductive material is reserved for the patient.

Decisions on proceeding with treatment need to respect the patient's level of understanding of the medical issues, as well as the risks and benefits of the technologies. For girls, challenges with vaginal procedures can often be addressed with the use of transabdominal pelvic ultrasound for monitoring of ovarian stimulation and general anesthesia for harvesting of eggs. For boys, sperm recovery will depend on their stage of sexual development. Masturbation and exposure to pornography present ethical concerns, but for the most part is the only feasible approach. Obtaining appropriate consent is critical before employing invasive techniques such as testicular sperm retrieval and electroejaculation. As well, a fair estimate of the probability of obtaining mature sperm is needed.

In terms of reproductive health, transition to adulthood is poorly addressed by our medical system. Adequate management should include ovarian reserve surveillance, counseling on fertility and sexual health, and provision of egg and embryo

banking in cases where a woman's reproductive lifespan is likely to be significantly reduced. All patients must be made aware of the fact that pregnancy is possible in the vast majority of cases, irrespective of gonadal function, through the use of egg and sperm donation technologies. In the event of premature ovarian failure, patients should be counseled on the use of hormone replacement.

Barriers to services

Recent advances in cryopreservation are providing effective fertility preservation options for Canadians, yet barriers to services exist for cancer patients. A multidisciplinary approach to care and education of oncology professionals and patients on issues related to reproduction are both required. More work is needed to increase awareness in BC and to ensure that patients receive appropriate fertility preservation counseling and services in a timely manner. The high cost of these services must also be addressed. Presently, only Ontario and Quebec provide funding for egg, sperm, and embryo banking. Fertile Future, a national charity that is committed to making these treatments affordable for cancer patients, currently provides up to $3000 toward clinical costs for female patients and $350 for male patients. The pharmaceutical companies that manufacture gonadotropins used in IVF have been providing compassionate medications for many years. No area of our profession is more in need of public support and we will continue to lobby provincially and federally for these critical services.

Summary

While modern chemotherapeutic protocols are highly effective at destroying malignant cells, they also lead to infertility in a sizable percentage of patients. This is a challenging survivorship issue for fertility specialists and cancer specialists alike. Fertility preservation for males usually involves freezing sperm, and for females involves ovarian reserve surveillance and freezing of embryos, oocytes, or ovarian tissue. Young patients with cancer should be referred to a fertility specialist with the ability to discuss and deliver these services. BCMJ

Fertility preservation for cancer patients

- Breast cancer is the most common cancer in reproductive-age woman.
- Alkylating agents used in chemotherapy are gonadotoxic.
- The ability to have children in future is important to the majority of cancer patients.
- Options for fertility preservation include:
  - Embryo freezing (with partner sperm or donor sperm).
  - Oocyte freezing.
  - Ovarian tissue freezing (experimental).
  - Sperm freezing.
- Fertility preservation can generally be performed at little or no cost to the patient through the Fertile Future Foundation.

Competing interests

None declared.

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