

Fertility Preservation Options for Patients with Cancer

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DOI: 10.17925/EOH.2010.06.1.31

Abstract

Improving survival for many cancers that affect children and young adults, together with advances in fertility preservation, make a cancer-free future that includes a family a realistic possibility for patients who desire this option. Although it is difficult for many clinicians and patients to reconcile fears surrounding a life-threatening diagnosis with hope for long-term survival and even a future family, addressing this vital survivorship issue early in the course of diagnosis and treatment is imperative if the fullest range of fertility-preserving options is to be offered. Oncological therapies, including chemotherapy, radiation and surgery, pose various threats to fertility. Children, adolescents and young men and women with cancer have different options for maintaining their ability to have biological children. The current state of the science for fertility preservation in each of these demographic groups is discussed in this article. A multidisciplinary approach to the care of young cancer patients, a timely assessment of threats to fertility and opportunities for intervention provide young cancer patients with the best chance for a healthy future that includes biological offspring.

Keywords

Fertility preservation, oncofertility, cancer, chemotherapy, embryo cryopreservation

Disclosure: The authors have no conflicts of interest to declare.

Received: 10 November 2009 **Accepted:** 19 April 2010 **Citation:** *European Oncology*, 2010;6(1):31-4

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A discussion of a patient's desires for future fertility is a challenging topic to raise in the early stages of a cancer diagnosis. It is difficult for many clinicians and patients to reconcile fears surrounding a life-threatening diagnosis with hope for long-term survival and even a future family. Yet improved survival rates for many cancers that affect young patients and recent advances in fertility preservation, taken together, make planning for a cancer-free life that includes a family a reality. Both men and women have similar threats to fertility inherent to treatment for cancer, but the opportunities to intervene are quite different. The following is a review of the current state of the science of fertility preservation for cancer patients.

Men with Cancer

Fertility challenges in men with cancer are the most straightforward because of the relative ease of obtaining and cryopreserving sperm. This is not to say that significant threats to fertility do not exist. Treatments for cancer can cause direct damage to the germinal epithelium of the testis, disrupt the hypothalamic-pituitary-gonadal axis and cause psychological depression, which also affects fertility.¹ Testicular cancer, prostate cancer and the treatments prescribed for them, including orchiectomy and prostatectomy, can significantly decrease the production of sperm and cause erectile dysfunction. High-dose pelvic irradiation used to treat these malignancies, as well as rectal malignancies, may also permanently damage testicular and erectile function.² Radiation not directed towards the pelvis can also be toxic to sperm due to internal scatter, even at low doses.^{3,4} Spermatogenesis is a process that is extremely vulnerable to the

damaging effects of cytotoxic chemotherapy, and azoospermia or oligospermia frequently result.⁵⁻⁷

Cryopreservation of human sperm is an accepted technology in common use and there are reports of viable fertilisation with sperm stored this way for nearly 30 years. Unlike oocytes, sperm have no apparent loss of capacity for fertilisation after cryopreservation and subsequent thawing.⁸ This makes cryopreservation of sperm before treatment begins the best option for the preservation of male fertility. In cases of azoospermia caused by treatment or a pre-existing condition, a technique called onco-tese, which involves a testicular biopsy with isolation of sperm, can be utilised.⁹ To further substantiate the importance of pre-treatment counselling regarding fertility preservation before the initiation of therapy, there are reports of DNA damage to sperm for up to two years after completion of radiation and chemotherapy, making conception with these sperm suboptimal.^{10,11}

Young Women with Cancer

Of the cancers affecting young women, including leukaemia, lymphoma, ovarian cancer, cervical cancer and melanoma, the most common in this population is breast cancer. The American Cancer Society estimates that in 2009, 18,640 women under 45 years of age will be diagnosed with invasive breast cancer.¹² With improved treatments for breast cancer creating a large community of young survivors, quality of life issues, such as fertility, become more important. In a survey of 757 young breast cancer patients, Partridge et al. found that 57% had substantial concerns about future fertility and 29% reported that this

concern influenced their decisions for treatment.¹³ A successful strategy for fertility preservation must be made as part of the overall oncological treatment plan, and it is therefore important to address this with properly selected younger patients prior to treatment, rather than after treatment has commenced.

The greatest threat to fertility for breast cancer patients is conferred by the indication for systemic chemotherapy, and the decision to administer these treatments depends on the stage at diagnosis. Women with stage I disease and favourable tumour biology (oestrogen receptor [ER]-positive, progesterone receptor [PR]-positive, HER-2-negative) are typically treated with surgery as the primary modality. Once surgical treatment is completed, subsequent endocrine therapy and radiation therapy may also be necessary. Indirect evidence suggests that anti-oestrogen therapy can be delayed to allow for pregnancy after surgery and radiotherapy have been completed.^{14,15} The threat to fertility directly attributable to radiation therapy itself is likely quite modest, and the degree of damage to the ovaries is related to several factors, including age, dose of radiation and use of concurrent chemotherapy.¹⁶ The total dose of radiation to the pelvis needed to increase the risk of premature ovarian failure is in the order of 20Gy.^{17,18} Of the 50Gy delivered to the breast during standard whole-breast radiotherapy, only 2.1–7.6Gy reaches the pelvis via internal scatter, which is an order of magnitude less than the dose needed to induce premature ovarian failure.^{19,20} Because of this small but detectable exposure to radiation during treatment, pregnancy or harvesting of eggs for *in vitro* fertilisation should not occur concurrently with radiotherapy; either should be possible after treatment is completed.

Women with T1c and larger tumours, metastases to regional lymph nodes or with ER/PR-negative or Her2-neu-positive tumours are likely to receive chemotherapy, and thus face a more serious fertility threat. The impact of chemotherapy on fertility is dependent on the woman's baseline ovarian reserve and an initial work-up should include an ovarian function assessment with blood testing (follicle-stimulating hormone [FSH], leuteinising hormone [LH], estradiol) and/or an ultrasound-guided antral follicle count.²¹ There is also evidence that anti-Mullerian hormone (AMH) and inhibin B levels may correlate well with antral follicle count and be more consistent and valuable markers of ovarian reserve.²² Patients who will undergo treatment with an alkylating agent, including cyclophosphamide, run the highest risk of ovarian toxicity and menopause resultant from their therapy. In an analysis of more than 2,500 patients treated with multiple cycles of alkylating agents such as cyclophosphamide/methotrexate/5-fluorouracil (CMF), the risk of amenorrhoea was 40% for women under 40 years of age and 76% for women over 40 years of age.²³ Treatment with an anthracycline-based regimen, such as doxorubicin/cyclophosphamide (AC), utilises an anthracycline along with a lower dose of the alkylating agent and is associated with a lower risk of premature ovarian failure (POF).²⁴ The risk associated with the addition of taxanes is less defined. In a study by Tham et al., the incidence of permanent amenorrhoea with AC followed by a taxane (T) versus AC alone was increased only in women over 40 years of age. Younger women often resumed menstruation months after treatment was completed and this again demonstrates that age is one of the strongest predictors that a woman will experience chemotherapy-induced amenorrhoea.²⁵ The addition of trastuzumab to standard chemotherapy does not appear to have any additional effect on POF above that of the chemotherapy alone.²⁶

The options for fertility preservation for women diagnosed with breast cancer are varied and healthcare providers must take each patient and her tumour biology into account. Ovarian suppression by manipulation of the hypothalamic–pituitary–gonadal axis is one experimental approach. The Southwestern Oncology Group is conducting a randomised trial of the gonadotropin-releasing hormone (GnRH) agonist goserelin during treatment for hormone-receptor-negative breast cancer to evaluate its effect on preserving fertility. The British Ovarian Protection Trial in Oestrogen Non-responsive Pre-menopausal Breast Cancer Patients Receiving Adjuvant or Neoadjuvant Chemotherapy (OPTION) trial is similarly designed, but also includes hormone-receptor-positive women. Rechia et al. studied 100 women receiving one year of goserelin concurrent with their adjuvant treatment and, at a median follow-up of over six years, found that 67% recovered normal menses, including 100% of the women under 40 years of age.²⁷ Other smaller studies and animal models appear to support these findings, though more data are needed on utility and oncological safety before this treatment can be universally endorsed. Delaying the start of treatment to undergo one cycle of hormone stimulation and retrieval of oocytes is an option, although it may be less favourable for women with hormonally sensitive ER/PR-positive tumours. The use of exogenous oestrogens for fertility preservation may also have an indirect mitogenic effect on hormone-receptor-negative tumours, making hormone stimulation potentially oncologically unfavourable for these women as well.²⁸ A possible alternative is controlled ovarian stimulation (COS) with an aromatase inhibitor such as letrozole or anastrozole, given along with standard fertility medications. When given concurrently with gonadotropin injections, they can keep oestrogen at nearly physiological levels while potentially providing an oocyte and embryo yield comparable to those of standard ovarian stimulation protocols.^{29,30} Azim and colleagues have further demonstrated that there is no increased incidence of local breast cancer recurrence, or of decreased survival, in women having COS with the addition of letrozole compared with women who had no COS at a mean follow-up of 33 months.³¹

Another fertility preservation technique that does not require exposure to exogenous hormones is ovarian tissue retrieval. Once the ovarian tissue is retrieved, oocytes can be aspirated from the ovary and cryopreserved, or ovarian cortical tissue strips can be preserved.³² Ovarian cortical tissue can be used for subsequent re-transplantation, but this is currently considered suboptimal for cancer patients as it carries a risk of re-introducing cancer cells to the patient. Another option under development where the patient would not be exposed to whole pieces of re-transplanted ovarian tissue is a still experimental procedure called in follicle maturation (IFM). This procedure entails recovering immature follicles from cryopreserved ovarian tissue, growing and then maturing the oocytes *in vitro* and then using them for IVF. This procedure has thus far been successful in animal models and is showing promise in human tissue laboratory studies as well.^{33,34}

For women with heritable breast cancers, such as *BRCA1* and *BRCA2* mutation carriers, having future biological offspring through IVF poses additional issues, as any child would have a 50% chance of receiving the mutated gene. In May 2006, the UK Human Fertilisation and Embryology Authority approved the use of pre-implantation genetic screening for lower penetrance, late-onset cancer susceptibility syndromes such as hereditary breast cancer. Although most British women support its availability, few say they would personally have this done.³⁵ This technology has been used in Israel, where the rates of

genetically heritable breast cancer are much higher than in western nations, and the same technology may soon be available in Australia.

Third-party reproduction (parenthood through the use of gametes donated by a third party or through the use of uterine surrogacy) is an option for breast cancer survivors who cannot, for various reasons, perform any of the functions of a term pregnancy. Some potential advantages to third-party reproduction over adoption include the ability for at least one partner to share a genetic connection to the child and the possibility of sharing in the pregnancy experience. When, for personal or medical reasons, this is not a desired option, adoption remains an opportunity for non-biological parenting. A study examining the potential barriers to adoption for cancer survivors found that bias against adoption for these women was strongest for international adoption agencies, but also existed in domestic firms.³⁶ This work suggests that cancer survivors wishing to adopt should investigate both the attitudes and official policies of the agency and personnel assigned to them early in the process of adoption screening, when it is easiest to shift agencies if necessary.

Children with Cancer

Cancer remains a leading cause of death by disease in young children between one and 14 years of age. Haematological malignancies, sarcomas, lesions in the central nervous system, renal cancers and bone cancers are among the subtypes that strike young children.³⁷ An estimated 10,730 new cases were expected to occur among children from birth to 14 years of age in 2009, with 1,380 deaths predicted (about one-third of these from leukaemia). Despite these statistics, it is important to note that the mortality rates for childhood cancer have declined by 50% since 1975, and nearly 80% of children diagnosed with cancer now survive.¹² With improved treatments for most childhood cancers evolving over the past several years, the hope for a long, healthy and high-quality life after cancer is becoming a reality for many children. If that life is to include biological children, fertility preservation must be addressed as soon as feasible in the cancer treatment plan. One complicating issue is that of informed assent and the possibility that the parental decision made for a minor may not ultimately reflect the patient's wishes when she or he reaches the age of consent.³⁸

The majority of childhood cancers are treated with a combination of chemotherapy and radiation therapy. These treatments can dramatically affect the hypothalamic-pituitary-gonadal axis in addition to causing direct damage to the ovaries by effecting folliculogenesis or inducing premature ovarian failure.^{39,40} This toxic effect is generally dose-dependent and also damages the vulnerable germinal epithelium of the testes, permanently effecting spermatogenesis.^{41,42}

The options for fertility preservation for paediatric cancer patients are generally similar to those available for adults. A current exception is a lack of options for pre-pubertal boys, for whom no established

options for fertility preservation exist. The investigational technique of spermatogonia stem cell cryopreservation is being pursued as a possible option.³⁷ For post-pubertal boys and young men, cryopreservation of sperm is the most accepted method of fertility preservation when performed prior to the initiation of therapy. Semen can be collected via ejaculation or electro-ejaculatory assistance, or surgical sperm extraction can be performed.⁴³ For adolescent girls facing radiotherapy as part of their cancer treatment, oophoropexy to move the ovaries out of the direct line of the radiation delivery can be used to protect them.⁴⁴ Whole ovaries or gonadal tissue can be removed and cryopreserved and may be suitable for technologies such as *in vitro* follicle maturation in the future. As new techniques evolve and offer success, fertility preservation for children facing cancer will hopefully become a standard part of a comprehensive treatment plan.

Conclusion

As treatments for cancers affecting young men, young women and children improve, a large community of young survivors is forming and oncologists must help these patients to live their cancer-free futures to the fullest. Issues of consent, economic impact and ethical and moral implications need to be considered going forward as technological breakthroughs make fertility preservation after cancer a reality. While clinical practice and scientific discovery continue to progress, there is just cause for optimism that young patients with cancer can be offered viable options to preserve their fertility with minimal oncological consequences. As this becomes a reality, both the causes of and treatments for infertility in young cancer patients must be thoroughly examined to enable care-givers to be effective advocates for their patients regarding this vital survivorship issue. ■



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