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Oncofertility – An Emerging Discipline rather than a Special Consideration

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Abstract

Originally absent from the oncologist's consult, then placed in a 'quality of life' rubric, oncofertility should now be an essential part of a comprehensive cancer treatment plan in patients of reproductive age, including adolescents and young adults (AYAs). Oncofertility encompasses the endocrine health of the patient, as well as fertility management options. Thus, pubertal transitions in males and females, bone health, and menstrual health are all part of this discipline, enabling practitioners to work in interdisciplinary teams to solve problems in reproductive health. This review provides a summary of the essential considerations required for the assessment of reproductive risk and choice of fertility preservation options as well as considerations for developing oncofertility services for AYAs.

Keywords

oncofertility; fertility preservation; gonadotoxicity; oncofertility model of care; implementation; competency frameworks

What is Oncofertility Care?

As the survival rates for adolescents and young adults (AYAs) with cancer increase, there is an expectation that their reproductive health will be preserved whenever possible.

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Oncofertility is an umbrella term that includes care from both cancer and fertility health care providers (HCPs).^{1–4} It involves the discussion of risks to fertility and fertility preservation (FP) options, as well as the management of related complications such as pubertal delay, menstrual irregularities and bleeding, hormonal deficiency, and sexual dysfunction. Provision of information to and psychological support for the patient's partners and parents is integral to oncofertility care.⁵

Although many survivors will maintain their reproductive potential after successfully completing treatment for cancer, others experience temporary or permanent infertility as a result of their disease or treatment. The burden of infertility as a cancer complication is a potentially preventable problem.

How Does Cancer Treatment Cause Infertility?

Infertility occurs when cancer or cancer treatments damage gonadal tissue, gametes or sex hormones.^{6,7}

In males, cancer treatment may affect spermatogenesis or the production of LH/FSH in the pituitary or testosterone by the Leydig cells in the testes; all hormones essential for pubertal development and sexual function.⁸

The human ovary has a fixed number of primordial follicles which are at their maximum at 5 month's gestation.⁹ The follicles contain oocytes which are lost progressively with increasing age, resulting in menopause which, on average, occurs at around 50 years of age. Cancer treatment accelerates the follicle and oocyte depletion, leading to premature menopause.¹⁰

How Do We Predict the Gonadotoxic Risk of Treatment?

This requires clinicians to consider both pre treatment and treatment-related risk factors.

Pre-treatment factors include:

- Reproductive and obstetric health history
- History of sexually transmitted diseases or complications
- History of surgery or trauma to reproductive organs
- Family history of infertility
- Underlying medical conditions that could result in infertility

Unfortunately, cancer clinicians rarely consider or document pre-treatment factors.^{11–13} Moreover, there is no easy assessment of ovarian reserve, which makes the risk calculation imperfect, so post-treatment surveillance is an important part of the process.

Gonadotoxic risk can be stratified into four categories - no risk, low risk (less than 20%), intermediate risk (21–80%) and high risk (greater than 80%) by using fertility calculators,¹⁴ fertility risk tables⁶, Alkylating Agent Dose (AAD)¹⁵ or cyclophosphamide-equivalent dose calculators¹⁶ (CED), considering the following factors:

Cancer type and site

Cancers affecting the male and female reproductive organs or neuroendocrine axis (brain tumours or metastatic deposits) are likely to cause infertility by direct damage^{8–17}. Patients may have reduced fertility potential at diagnosis due to compromised general health factors.^{18–19}

Chemotherapy drugs and dose

Alkylating agents have an intermediate to high chance of causing infertility and this can be correlated to the cumulative dose prescribed (e.g. > 7.5gm of cyclophosphamide in females younger than 20 and > 5gm in older women).⁶ Platinum agents, anthracyclines and taxanes have an intermediate risk of infertility⁶ and 6 mercapturine, methotrexate, 5 fluorouracil, vincristine, bleomycin and actinomycin have a low or no risk⁶. High dose chemotherapy associated with haematopoietic stem cell transplantation causes severe and often permanent infertility in most cases.⁸

Novel therapy

There are many new agents and the data on reproductive risk is not comprehensive. Tyrosine kinase inhibitors^{20,21} are associated with infertility and further knowledge of others will develop over time, putting clinicians at present in a difficult situation with limited information.

Radiation therapy

Total body irradiation and cranio-spinal irradiation have a high risk of damage to the hypothalamic pituitary gonadal axis.¹⁷ Whole abdominal and pelvic radiation in females (> 15Gy in pre pubertal females, > 10 Gy in post pubertal females and > 6 Gy in adults) is associated with a high risk of infertility.⁶ The testis is highly sensitive to irradiation; a dose as low as 0.15 Gy causes reduced sperm production and doses of 0.5 Gy or above can cause azoospermia. Partial recovery from irradiation-induced azoospermia may occur; however, the time to recovery is proportional to the testicular dose.⁸

Surgery

Surgical procedures to male or female reproductive organs or the neuro-endocrine axis can result in infertility.

Combination treatment

The combination of chemotherapy with another treatment modality will also impact on patients overall reproductive risk.

A detailed history and knowledge of cancer treatment is essential for clinicians to make clear recommendations about a patients individual gonadotoxic risk.

Who Should Be Referred To A Fertility Specialist?

All patients of reproductive age who will have curative treatment should receive reliable information about the risk of reproductive harm and the potential options for FP.

International guidelines support referral to a specialist who can provide expert discussion and assessment. While there is agreement on intermediate and high risk patients receiving such consultation, there is no agreement about the role of experimental FP procedures in patients who have a low or unknown risk for infertility. Certainly patients requesting further discussion irrespective of risk should be referred for individualised assessment of risks and benefits. Paediatric FP can only be undertaken in settings where there is specialised governance and care often involves multidisciplinary teams of paediatric providers including clinical ethicists.²² Furthermore, young cancer patients may value discussions of contraception because they are often concerned about transmitting disease or treatments via intercourse. Allaying the latter and protecting against unintended pregnancies during or soon after treatment is necessary care for this population.²³

How Do We Assess Baseline Reproductive Function Prior To Fertility Preservation ?

In AYAs and older adult females, in addition to the reproductive history, ovarian function may be assessed by measuring follicular phase FSH, LH, estrogen and antral follicle count. Anti-Mullerian hormone (AMH), may be measured at any time of the cycle and is most useful in those over 25 years of age (Figure 1). These tests are not clinically useful in paediatric patients due to ovarian quiescence.

For male patients a testicular volume of 4mls and the ability to have an erection and masturbate correlates well with the ability to produce a semen sample and hormonal testing is not usually recommended (Figure 2).

What Types of Fertility Preservation Are Available?

FP is the umbrella term used for medical and surgical interventions which attempt to minimise the impact of cancer treatment on future fertility.²⁴ FP options depend on the patient's age, cancer type and available time before treatment.

Established Fertility Preservation Procedures in Females

Oocyte cryopreservation (OC) or embryo cryopreservation (EC) are both established methods of FP. Vitrification techniques have provided comparable success. OC requires ovarian stimulation and retrieval and the oocytes are frozen and thawed on the day of collection.^{5,7} Protocols are available which allow low estrogen stimulation and rapid mid-cycle stimulation making it suitable for patients with hormone-driven tumours and patients at different points in their menstrual cycle. However, at least 10–14 days are required, so planning for OC should occur during the diagnosis and staging period to reduce delays in starting cancer treatment. OC can be carried out in older post-pubertal patients but requires a degree of emotional maturity and so assessment should be carried out before starting OC in AYAs. EC involves the fertilisation of harvested oocytes. It is now considered unethical for a minor to have embryos created with donor sperm due to the success of OC, but EC may be considered in older patients in established relationships.

Ovarian transposition or oophoropexy may be used to protect ovarian function before a patient receives abdomino-pelvic radiation. This can be done in children and AYAs. This procedure aims to move the ovary out of the irradiation field, protecting it from direct radiation and irreversible damage.

Experimental Fertility Preservation in Females

Ovarian cortical tissue contains the majority of follicles and can be harvested in an attempt to preserve fertility.²⁵ Ovarian tissue cryopreservation (OTC) has developed into a highly promising strategy which, until recently, was being done under research governance, but is now considered standard of care in some centres due to an increase in pregnancies and live births.²⁶ It is an appropriate strategy in AYAs or older adults when there is not enough time or contraindications for OC/EC. OTC is the only option currently offered to prepubertal patients. One third to a whole ovary is removed and then processed by slicing into very fine pieces ($1 \times 1 \times 5$ mm) and cryopreserved. Tissue samples are tested by histology and molecular biological techniques to ensure that the frozen material is free of any cancer.²⁷ This tissue can be thawed and implanted after cancer treatment as an auto-graft or to a heterotopic site²⁸ so as to stimulate pubertal induction or hormonal regulation^{29,30} and allow natural or stimulated cycles.²⁷

In vitro maturation (IVM) involves the collection of immature oocytes from unstimulated ovaries or ovarian tissue followed by the maturation of oocytes in vitro.^{31–32} IVM allows for timely FP that does not require stimulatory cycles and will not result in the transfer of cancer cells.^{33,34} It would be invaluable in pre-pubertal females who cannot produce mature oocytes.⁶ IVM can also be combined with other FP procedures giving patients additional choices.

Established Fertility Preservation in Males

Sperm cryopreservation is a routine, highly reliable and well established approach for post-pubertal male patients.³⁵ With intracytoplasmic sperm injection (ICSI) conception is now possible for men with severe oligospermia or azoospermia. Fertility success rates in young men (14–30 years) who use their frozen sperm after overcoming their cancer are 36% using intrauterine insemination and 50% using IVF and ICSI.³⁶

In post-pubertal cancer patients who cannot ejaculate due to neurological or psychological problems electro-ejaculation is a safe and feasible procedure.³⁷

The extraction of spermatozoa from testicular tissue by microsurgical testicular sperm extraction (TESE)³⁸ can be carried out in post-pubertal males as young as 12 years of age³⁹ who cannot produce a sample by masturbation due to pain, neurological or psychological problems, but it requires a general anaesthetic.

Experimental Fertility Preservation in Males

Techniques for fertility preservation in pre-pubertal males are limited to tissue cryopreservation because the pre-pubertal testis does not produce mature spermatozoa. Maturation of spermatogonia from testicular tissue biopsy in pre-pubescent males for later

clinical use remains in the early phases of experimental research.⁴⁰ Recent studies have demonstrated that this is feasible in animal models and clinical application is hopeful in the future. As with ovarian tissue, testicular tissue is sent for histology prior to storage.

What Support Do Patients Require?

Psychological Support

Potential and actual infertility is one of the most distressing adverse consequences of successful cancer treatment⁴¹ in cancer survivors of all ages.^{42,43} It affects the future quality of life of patients and leads to psychological distress,⁴⁴ as well as being a predictor of stress in present and future relationships^{45,43}, and a factor in higher rates of divorce.^{46,47} Studies have demonstrated that patients fear rejection because of their impaired fertility status, and do not disclose their actual or suspected infertility to friends and/or new partners.^{48,49} Various studies demonstrate that not being given the opportunity to discuss reproductive concerns heightened psychological distress^{44,50,51}, however practical and psychological support has been shown to reduce fertility related psychological distress.⁴⁴

Decision Aids

Most patients and families wish to participate actively in decisions around their treatment. Patients⁵² and clinicians identify a need for tools which can support shared fertility decision-making.⁵³ FP decisions are complex requiring family and clinician understanding and good communication about the latest reproductive technologies and statutory requirements around storage and IVF. Furthermore, the decisions are value-laden with uncertain outcomes as there is no guarantee of future fertility. They are often rushed as decisions usually need to occur prior to cancer treatment, and occur at a time of vulnerability. These conditions are ripe for the development of decisional conflict (uncertainty around whether to accept or reject fertility options) and decisional regret (the belief that had their fertility choice been different their current situation would be better).^{54–57} The gold standard approach to facilitating complex decision-making when there is more than one reasonable choice and when personal values affect consideration of benefits and risks, is to use an evidence-based decision aid (DA).⁵⁸ These are evidence based tools, developed using International Patient Decision Aid Standards (IPDAS).⁵⁹ DAs enable the user to make reasoned decisions by providing unbiased information about all options, and actively engaging the user to consider which outcomes are in line with their own values (values clarification exercises). DAs have been shown to improve knowledge, facilitating faster decision-making, and reduce decisional conflict and regret.^{58,60} A number of DAs are available for both male and female patients in different formats; electronic or web-based,^{61–63} brochures^{60,64–67} or decision trees.⁶⁸ Two fertility DAs for the paediatric and AYA groups have been developed (one for women of reproductive age [16+ years]⁶⁹, and another for parents of children with cancer).⁵³ It is important that such tools are developed in collaboration with end-users and are evaluated appropriately. They can be updated widely and adaptable to a range of end-users in electronic form.

How Can We Reduce Barriers To Oncofertility Care?

Despite advances in FP and an increasing number of patients seeking FP, several clinician and patient barriers exist to providing oncofertility care.⁷⁰

Available data

There is still a lack of good quality data on the short and long term fertility effects of various chemotherapy regimens (with the exception of alkylating agents), especially for the new agents, combinations of chemotherapy and multimodality treatment;²¹ and accurate data on uptake, utilisation and equitable access. There is also the need to obtain data on complications of FP in cancer patients. While assisted reproductive treatment (ART) has low complication rates, the co-morbidity of a cancer diagnosis (e.g. pancytopenia requiring blood and platelet support, immunosuppression, thrombosis, presence of tumours) may result in more complications, therefore data are required to provide evidence-based guidelines on supportive care during FP.

Referral pathways and models of care

While some cancer centres have developed referral pathways and models of care, these are still limited to a few facilities. For children and adolescents these pathways are made more complex when the fertility specialists work in adult centres and patients have to be transferred to these facilities. The key components of an oncofertility service have not been defined yet, but information provision,^{71–74} age appropriate communication,^{75–78} financial support^{79–81}, and psychological support^{44,51,82} are all cited by patients as key components of oncofertility care.

Specialist advice and communication

Although an increasing number of HCPs are informing patients about the reproductive complications of cancer treatment, the rates of fertility discussion internationally are still very low⁸³. Some cancer specialists feel uncomfortable broaching the topic of sexual and reproductive health, especially when this is outside their realm of expertise.⁸⁴

When patients or parents receive information on oncofertility it is usually only from an oncologist and not from a fertility specialist, which means that patients may not have the most accurate information on FP. There is often also inadequate communication between oncologists and fertility specialists.⁸⁵ Given the competing demands of providing complicated and detailed information about fertility risk and FP options, there is a role for cancer specialists to work collaboratively with fertility specialists to achieve the best outcome for patients.^{7,86}

Access to Appropriate Care

FP consultations can be challenging because of the personal nature of the discussions and discomfort with having these discussions with clinicians they do not know well or having family members present.⁸⁷ Patients' reproductive health literacy and the influences of culture and religion also need to be considered. FP consultations should occur in age

appropriate environments that have staff who have expertise in communicating with patients of different ages.

As referral pathways are developed for paediatric and AYA oncofertility care, it is essential that services consider the implications for delivering services to minors which include mandatory child protection training of staff, access to resuscitation equipment, access to policies for medication in children, and consideration of appropriateness of resources for minors, especially those with content that may be considered pornographic. To overcome these issues, a family-centred approach can be taken by introducing specialised pathways of care within paediatric centres, but this can require significant organizational change.²²

Rural and culturally and linguistically diverse populations

Non-English speaking patients face additional barriers and FP information is less likely to be discussed with them.⁸⁸ Patients who are treated in rural cancer centres have additional barriers to accessing FP, as fertility centres are usually based in metropolitan locations.

Timing

Delays in referral to FP services and the time for treatment are often reasons why patients choose to start cancer treatment prior to FP.⁸⁹ As oncofertility models of care are developed, the integration of this care into standard practice will result in earlier discussions about fertility risk and FP, and earlier FP procedures. Earlier discussion will result in clinicians having an opportunity to do FP at the same time as staging and toxicity assessments, and potentially under the same general anesthetics as other procedures.

Follow up

The reproductive survivorship needs of cancer patients are well described, but oncofertility care in survivorship is not well integrated into standard care. Cancer survivors need reproductive care in many ways such as disclosure of the infertility risk of past treatment and discussion about FP procedures carried out already, and opportunities for FP in the survivorship period.⁹⁰ Discussions about sexual health, sexual dysfunction, preventative reproductive health (cervical smears and HPV vaccination) and management of hormonal insufficiency in male and female cancer survivors are important, and so is the assessment of reproductive potential following gonadotoxic treatment. A significant number of cancer patients will not have FP at diagnosis and the reproductive follow up after cancer treatment is complete may give a window of opportunity for FP. The timing and selection of these patient requires careful consideration to give them the opportunity to recover from cancer treatment and to minimize intervention on patients whose reproductive recovery is likely to be sustained (See Figures 1 and 2).

Costs

At present, the economic impact of FP consultations and FP procedures is a significant barrier, with few countries having FP integrated into public or private health care provision.^{79,80,81} The cost of psychological distress due to infertility and FP treatment is also not known. All the FP guidelines support fertility risk and FP options being discussed, but without public health care provision or insurance coverage these guidelines are an

impracticable recommendation for many patients, especially for those who are socio-economically disadvantaged.

Health literacy

Patients may have limited understanding about sex education and may feel too embarrassed to have conversations about sex and fertility in the presence of family members.⁹¹ Patients may not have the cognitive maturity to appreciate the multiple demands of an illness and the FP discussion may overwhelm AYA patients' independence and may necessitate reliance on parents or guardians. Conflict also arises over parents' ability to allow autonomous decision-making about future fertility.⁹² Some parental desires for future grandchildren may influence decision-making and may result in undue pressure to undertake FP procedures. Others may not allow their child time to think about options available. Studies have shown that, although most AYAs were pleased with their parents' involvement in the decision-making process, some preferred to have discussions without their parents being present.⁹³ For pre-pubertal patients, clinicians need to provide information and support in the survivorship period that is age appropriate and allows them to understand the reproductive choices that have been made and the future options for their reproductive health.

Training

In 2005, the Ethics Committee of the American Society for Reproductive Medicine extended physicians' duty to 'inform patients about options for fertility preservation and future reproduction prior to treatment'.⁹⁴ We now have 20 national and international guidelines on FP and specialist groups or medical associations that have made similar statements about oncofertility care in all age groups. However, despite these recommendations, HCPs report a lack of knowledge, skills and training associated with discussing FP.⁹⁵

It is also important to ensure that oncofertility care is a part of every cancer and fertility health care professional training for a diverse group of oncofertility care professionals including counsellors, doctors, nurses, psychologists and social workers, and to define the role of different cancer and fertility health care professionals so that we can improve the medical, practical and psychological support patients receive.^{82,96}

Ethical and legal issues

FP is complicated by moral, ethical and legal issues, which can be considerable barriers.^{97,98} Assent and consent for FP is complicated by the age of the patient, the timing of discussion occurring when patients have only just been told about a cancer diagnosis, the referral for FP being time sensitive, the difficulty of consenting patients who are unwell and parental third party consent.⁵⁴ The selection of patients for FP is based on gonadotoxic risk and also the chance of survival, and so wide variations exist between HCPs and patients about what degree of survival should qualify for FP.^{99,100}

What Are The Expected Future Oncofertility Developments?

In the last 10 years, oncofertility has evolved from a new word to a recognized field that has strong pre-clinical and clinical research outputs. Improved stimulatory protocols,¹⁰¹

laboratory and freezing techniques have been important factors in this success. The ongoing challenge for researchers has been to find a solution that provides patients with normal reproductive hormones, as well as a permanent fertility solution. The recent use of 3D bio-engineered mouse ovaries resulted in restoring both hormone function and fertility in mice without ovaries that went on to deliver pups.¹⁰² This is an exciting accomplishment that opens the door for future use in humans.

There has been an increased focus on new ovarian biomarkers that have applications for determining oocyte and embryo quality and provide information about a patient's ovarian potential before and after cancer treatments. Examples of these include Bone Morphogenetic Protein 15 (BMP15) and Growth Differentiation Factor 9 (GDF9) which are potential biomarkers of ovarian reserve.¹⁰³ Both proteins are produced exclusively by oocytes and are well established as regulators of oocyte quality. They have the potential to provide a more direct assessment of oocyte quantity and quality compared to current biomarkers of ovarian function⁷. The release of zinc in blastocyst development is also a potential novel biomarker that can be used to determine the quality of embryos post FP.¹⁰⁴

Conclusions

The oncofertility field has united with collaborative efforts across the world and the international consortium has grown with members from 39 countries, many now having their own consortia which are collaborating together on oncofertility initiatives.^{79,104–107} Twenty national and international FP guidelines are now available and both cancer and fertility HCPs have recognized the need for providing both verbal and written information and offering FP procedures to paediatric cancer patients, as well as AYA and older adult patients of reproductive age.

The current lack of evidence-based data for individual and combination treatment gonadotoxic risk, FP discussion and referral pathways, uptake and success of FP options highlights the need for oncofertility data collection. FP data will be extremely valuable in providing an insight into the magnitude of the problems in availability and use of fertility preservation services for pre-pubertal and reproductive age cancer patients, contributing to the international evidence base and assisting with future resource allocation, including development of policies about the storage of reproductive tissue specific to cancer patients.

It is very important that oncofertility care is thought of as a discipline rather than a special consideration and that oncofertility models of care and competency frameworks are developed to ensure that paediatric and AYA patients benefit from medical, psychological and practical age appropriate care while benefiting also from FP research and clinical trials.

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Abbreviation Table

AAD	Alkylating agent dose calculator
AFC	Antral Follicle Count
AMH	Anti-mullerian Hormone
ART	Assisted reproduction treatment
AYA	Adolescent and Young Adult
BMP15	Bone morphogenetic Protein 15
CED	Cyclophosphamide equivalent dose calculator
DA	Decision aid
EC	Embryo cryopreservation
FP	Fertility preservation
FSH	Follicle stimulating hormone
GDF9	Growth Differentiation Factor 9
HCPs	Health care providers
ICSI	Intracytoplasmic sperm injection
IPDAS	International Patient Decision Aids Standards
IVM	In-vitro maturation
LH	Luteinising hormone
OC	Oocyte cryopreservation
OTC	Ovarian tissue cryopreservation
TESE	Testicular sperm extraction

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Figure 1.
Considerations for Oncofertility Care in Female Patients at Diagnosis and Following Treatment

Figure 2.
Considerations for Oncofertility Care in Male Cancer Patients at Diagnosis and Post Treatment