The Winston Churchill Memorial Trust of Australia

Report by Dr. Antoinette Anazodo – 2015 Churchill Fellow

To identify gaps in the delivery of oncofertility (cancer and fertility) care in Australia

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Glossary and Definitions

AOFR - Australasian Oncofertility Registry.

Andrology - a branch of medicine concerned with male diseases and especially with those affecting the male reproductive system

Assisted Reproductive Technology (ART) - Methods used to achieve pregnancy by artificial or partially artificial means.

AYA – Adolescents and Young Adults, usually aged between 15-25 years old.

Azoospermia - absence of sperm in the semen.

Cancer - any type of malignant growth or tumor caused by abnormal and uncontrolled cell division.

Chemoradiation – chemotherapy followed by radiation to treat cancer

Egg - also known as an ovum, is the female reproductive cell or gamete.

Embryo – when an egg and sperm come together (fertilization) they form an embryo, which is the early stage of development of an animal.

Embryo cryopreservation – Eggs are collected from a female patient's ovaries and sperm is inserted into the egg (fertilization). The embryos are then frozen and stored.

Fertility - the ability to conceive a baby.

Fertility preservation – this is a way to help cancer patients keep their fertility after cancer treatment, in order to have their own biological children.

Fertilization – This is the fusion of an egg with a sperm, which leads to the development of an embryo.

Gonadal organs - defined as testes or ovaries.

Gonadal tissue or gonads – Glands that make sex hormones and reproductive cells; testes in the male, ovaries in the female.

Gynaecology - The medical practice dealing with the health of the female reproductive system (uterus, vagina, and ovaries).

Infertility - the inability to conceive after 1 year of intercourse without contraception.

Intracytoplasmic sperm injection (ICSI) - this is an in vitro fertilization procedure in which a single sperm is injected directly into an egg.

In Vitro Maturation (IVM) – This is a method of letting immature ovarian follicles mature in vitro (in a test tube). This method is new and used in a very small number of centres but babies have been born using this method.

IVF - In Vitro Fertilization techniques.

Neuroendocrine axis - the interaction between the nervous and endocrine systems mainly involving the hypothalamus, pituitary and gonads.

Obstetrics - The medical practice of looking after pregnant women during pregnancy and childbirth.

Oocyte cryopreservation - egg collection and frozen storage.

Oncofertility - Oncofertility bridges the disciplines of oncology and reproductive medicine in order to discover and apply new fertility preservation options for young patients facing fertility-threatening diseases or treatments.

Ovarian cryopreservation - the collection and frozen storage of tissue from the ovary.

Ovarian follicle count - Ovarian follicles are part of the female reproductive system, and are found in the ovary and decrease through reproductive life to zero at menopause. Each follicle contains a single egg. These eggs are developed only once every menstrual cycle (i.e. once a month in females) until menopause.

Ovarian tissue cryopreservation - A whole ovary or tissue from part of the ovary is collected frozen and then stored.

Ovarian transposition - surgical movement of the ovaries.

Ovary - The ovary is one of a pair of female reproductive organs that produce eggs and release hormones, including estradiol.

POF - premature ovarian failure.

Pre-pubertal testicular biopsy - the collection of immature testicular tissue in pre-pubertal male children, currently experimental.

Psychology - The study of the mind and of thought, feeling and behaviour.

Psychologist - This is a health professional that studies and treats psychological distress.

Psychological Distress - This is a term used to describe a range of symptoms and experiences that are commonly held to be troubling, confusing or out of the ordinary.

Quality of life - Fertility related well-being.

Reproductive health - The health of the reproductive system in its ability to produce gametes (eggs, sperm) and circulating steroid hormones (estradiol, testosterone) to ensure fertility and systemic effects of reproductive hormones.

Semen - This is a fluid produced by males that comes out of the penis by ejaculation. The semen contains sperm which can fertilize female eggs.

Sperm - The male reproductive cells that combine with female egg cells during fertilization.

Semen analysis - To examine semen to measure variables that impact on fertility like semen volume, sperm number, morphology (shape) and viability (motility or swimming speed and directionality)).

Sperm retrieval - the collection of sperm in post-pubertal men by epididymal or testicular biopsy when semen contains no or too few sperm or sperm cannot be collected by masturbation.

Sperm cryopreservation/banking - To collect sperm and then freeze and store for later use.

Spermatozoa - male reproductive cells.

Testicular sperm extraction (TESE) - This is the process of removing a small portion of tissue (biopsy) from the testicle under local anesthesia and extracting the viable sperm present in that tissue.

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It has been an honour to be a recipient of the Winston Churchill Fellowship in 2015, and a highlight of my professional career. I would like to express my sincere gratitude to the Trust for the opportunity the fellowship has afforded me, and to all the panel members who have generously given of their time. The fellowship provided an opportunity to explore and build links with international peers, and to examine a new specialty of medicine called 'Oncofertility.' Oncofertility is a discipline that brings together a large collaboration of multidisciplinary medical and allied health colleagues to ensure that all new and relapsed cancer patients have the opportunity to receive a reproductive consultation, management and support. My fellowship has introduced me to the broader Fellowship community, Australians from very different backgrounds, all with a passion for translational medical research in Australia. The fellowship has enabled national and international collaboration and partnerships that are currently resulting in significant benefits for this new specialty.

I would like to express my sincere thanks to my two referees, Professor Elizabeth Sullivan Associate Dean of Research, Faculty of Health, University of Technology, Sydney and Mr. Peter Orchard CEO of CanTeen Australia. Both my referees are acutely aware of the importance of this work for Australia and have been incredibly supportive.

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Executive Summary

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Improvements in cancer diagnosis and treatment in patients of a reproductive age, have led to significant improvements in survival rates, however a patient's fertility can be affected by both cancer and its treatment. As survival rates improve, there is an expectation by clinicians and patients that a patient's reproductive potential should be considered and protected. However, fertility preservation remains a major gap in acute cancer management with lifelong implications for cancer survivors. In Australia, oncofertility care is not integrated into standard clinical practice nationally and there are gaps in the clinical experience of both cancer and fertility personnel in terms of communication, psychological support and medical expertise for fertility preservation.

The objectives of my Churchill Fellowship was to:

1. Identify the role of oncofertility specialist programs in cancer centres;
2. Examine current models of oncofertility care and the feasibility of adapting a standardized model into the Australian context (for metropolitan, regional and rural centres).

Recommendations

- The impact of reproductive concerns on cancer patients requires a strategic focus by national cancer organisations to raise awareness and support for the implementation of approaches to address these concerns.
- Oncofertility Models of care need to be established to ensure that all cancer centres can implement the Australasian Oncofertility Charter Recommendations which include:
  - Health professionals working in cancer need to be appropriately skilled to provide patients, parents and partners with information on fertility preservation options and provide fertility related support during and after fertility preservation treatments.
  - Clear oncofertility referral pathways should be developed between each cancer centre and fertility/andrology centre to ensure that all patients have timely access to oncofertility services.
  - Development of models of care to ensure that Paediatric and AYA patients have an opportunity to receive experimental fertility preservation procedures in a framework that provides ethical and psychological support under a clinical trials protocol.
  - Patients in rural and regional locations need to be able to access fertility preservation consultation using telemedicine and the reproductive needs of those patients who require fertility preservation can be met by having satellite local sperm banking services for male patients and referral pathways into metropolitan fertility clinics for female patients who have decided to undergo this treatment prior to cancer treatment.
  - Fertility related psychological distress needs to be identified in cancer patients and supported by adequate referral to allied health professionals during fertility preservation, during cancer treatment and in the survivorship period.
  - An assessment of reproductive needs following successful cancer treatment needs to be included in the survivorship assessment.
- To address the current gap in knowledge, education programs should be developed and included in the core curriculum for training oncology medical, nursing and allied health staff. The aim would be to ensure that all staff in a cancer centre have basic knowledge on the gonadotoxic risk of cancer treatment including new novel immunotherapy as well as having information on current fertility preservation options and the pros and cons of oncofertility options in cancer patients of different ages.
- To address the current gap in communication skills which need to be be developed. The aim would be to ensure that all staff in a cancer centre have the communication skills to deal confidently with the practical, psychological and ethical elements of oncofertility consultations.
- A competency framework should be developed to ensure that the recommendations from thirteen international guidelines are implemented.

Background

Approximately 9,000 patients aged 0-44 years are diagnosed annually with cancer in Australia and 1,896 patients in New Zealand.[1, 2] Advances in cancer treatment have led to significant improvements in survival rates [1, 2] and clinicians are now turning their focus to the quality of survivorship. The loss of reproductive potential is one of the most distressing adverse consequences of successful cancer treatment, and can affect the quality of life of cancer survivors and lead to psychological distress.[3-5]

The human ovary contains a fixed pool of primordial oocytes which declines with age, culminating in menopause at an average age of 50 years.[6] Chemotherapy and radiotherapy may deplete the ovarian reserve and cause premature ovarian insufficiency (POI).[7] In males, spermatogenesis is extremely vulnerable to the damaging effects of chemotherapy and radiotherapy resulting in oligo/azoospermia. [7-9]

Although many survivors will maintain their reproductive potential (the ability to have a biological child), a cancer diagnosis or its treatment may cause damage to the ovaries, uterus, testes or neuroendocrine axis resulting in temporary or more commonly later onset of permanent infertility.[10-12] Some cancers will have a direct effect on the reproductive organs or the neuroendocrine axis because of the location of the cancer or surgical procedures in this area. Most patients will have a reduced fertility potential because of the severity of their illness or type of treatment (chemotherapy, bone marrow therapy or radiotherapy) and the dose or field of treatment.[13] Little is known about the extent to which new combination regimens or novel agents may result in an increased risk of infertility.[14]

Fertility preservation (FP) is the overarching term used for medical and surgical approaches to minimise the impact of cancer treatment on future fertility.[15] The burden of cancer-related infertility is unknown in Australia and New Zealand but this is an emerging health problem that can have an impact on a patient's quality of life and psychological wellbeing.[16-19] In addition, both male and female patients can have medical health problems such as fatigue, delayed puberty, hypogonadism, osteoporosis and cardiovascular disease as a result of early menopause.[20] With the development of FP strategies (oocyte, embryo, sperm, ovarian and testicular tissue cryopreservation) and oncofertility care (fertility management for cancer patients)[15, 21] ·an increasing number of patients of or before reproductive age are being referred for FP and may be able to plan a biological family post cancer treatment[22]

In 2006, the term ‘‘oncofertility’’ was introduced to describe a new subspecialty focused on the reproductive future for cancer survivors, who may face infertility (as a result of chemotherapy, radiation, or surgery).[23, 24] Oncofertility encompasses: (1) the science needed to develop new fertility preservation options for patients prior to the onset of cancer treatment; (2) the clinical specialties to integrate fertility preservation such as family planning, and hormonal management and (3) advances in oncofertility communication, education and service provisions.[24]

The discussion about the risk of infertility and fertility preservation are of great importance to patients with cancer.[25] International advocacy work has been conducted over the past decade in raising the awareness regarding discussing fertility issues in caring for and treating patients with cancer.[26] Clinical practice guidelines published by the Clinical Oncology Society of Australia;[27] the British Fertility Society, United Kingdom; and the American Society of Clinical Oncology, United States[28] have put the onus of responsibility on cancer health care providers to inform cancer patients about the potential fertility risks and the options for fertility preservation prior to cancer therapy and facilitating referrals.[26]

Fertility Preservation Options

FP options depend on a patient’s age, sex, time available prior to starting cancer treatment, whether the patient has a partner at the time, type of cancer, type of cancer treatment, and also the potential malignant involvement of gonadal tissue.

Options for female patients include embryo and oocyte cryopreservation, ovarian tissue cryopreservation and ovarian suppression with gonadotropin-releasing hormone (GnRH) agonists. [15, 29-33]Recent improvements in ovarian stimulation, oocyte and embryo freezing and ovarian tissue grafting have improved outcomes with the use of ART following FP.

Sperm cryopreservation is routinely used and is a highly reliable and well established approach for post pubertal male patients.[33-35] Post pubertal patients who are unable to produce sperm by masturbation either due to their immaturity, or psychological or medical factors, can have semen collected using alternative methods such as electro ejaculation or testicular sperm extraction (TSE).[36, 37] Men with cancer may present with subfertility at diagnosis even though gonadal or neuroendocrine tissue may not be involved. With intracytoplasmic sperm injection (ICSI), conception is now possible for men with severe oligospermia or those with azoospermia, where testicular spermatids can be extracted.

Currently, ovarian tissue cryopreservation is the only option available to pre-pubertal females cancer patients.[38] Clinicians are optimistic about the chance of pregnancy after re-grafting of ovarian tissue in adult patients but there is still the uncertainty surrounding the prospects for live birth after regrafting of tissue collected from a pre-pubertal girl. However, such tissue samples contain many primordial follicles and should yield mature oocytes when appropriately stimulated. Techniques for FP in pre-pubertal boys are limited to testicular tissue harvesting. It is hoped that in-vitro maturation techniques will provide an option for paediatric patients who have undergone testicular stem cell harvesting, however these remain experimental currently and unproven.[39, 40]

Current barriers for uptake of Fertility Preservation

Despite promising advances in technology in the past decade and an increasing number of patients seeking fertility preservation, several clinician and patient barriers exist in providing fertility preservation.

Available Information

There is a dearth of good quality data on the short and long term effects on fertility of various chemotherapy agents (with the exception of alkylating agents) especially for the new novel chemotherapy agents or combinations of chemotherapy or multimodality treatment.[41] A lack of current [41] and relevant information can be a potential barrier for patients receiving the specialty care they require.

Providing verbal information about the possible effects on fertility of cancer treatment at the time of receiving the cancer diagnosis is not ideal because at that time a patient's focus is on processing information associated with their cancer diagnosis.[42-44] However, studies also show that not being given the opportunity to discuss fertility preservation at any stage throughout the cancer trajectory causes heightened psychological distress.[45-47]

Unfortunately, less than 50% of cancer patients[43, 48-53] report being informed about potential risks to fertility associated with their cancer diagnosis, and less than 35% of cancer survivors recall discussing the possible risks of pregnancy during or after cancer treatment, or available fertility preservation options ,with a health care provider.[45, 54] One study found that fatherhood was important to young men, however only 60% recall having a discussion about fertility before treatment began, and 51% being offered sperm banking.[43, 54] recalled having a discussion about fertility before cancer treatment began, and 51% being offered sperm banking.[43, 54]

Some cancer specialists feel uncomfortable broaching the topic of sexual health, particularly if sexual and reproductive health is outside their realm of expertise.[55] Other studies have reported oncologists' non-referral relates to a deviation from their primary objective, which is to treat the patient's malignancy.[56] Concerns regarding delaying a patient's cancer treatment have also been documented as a concern and potential barrier for referral from cancer to reproductive specialist.[57] Health care professionals also report lack of knowledge, skills and training associated with discussing fertility preservation, as well as a lack of standardised guidelines available in Australia for referral.

Conversely, some cancer patients and their families may be focused solely on survival and may not consider the future impact of the cancer treatment on the patient's fertility. However, current studies report that parents, family members[28, 58] and young cancer patients[43, 45] would like to have discussions regarding their cancer and its implications on their reproductive health.

Health care professionals also report lack of knowledge, skills and training associated with discussing fertility preservation, as well as a lack of standardised guidelines for referral in Australia.[59-61]

Rural patients and Non-English speaking patients

Non-English speaking patients face additional barriers; fertility preservation information is mostly not discussed at the point of consultation by the cancer specialist. [52, 58, 62] Uptake for Assisted Reproductive Technology services are predominately utilised by affluent English speaking patients.[63-65]

Patients who are treated in rural cancer centres have additional barriers in accessing fertility preservation, as fertility and andrology centres are usually based in metropolitan or regional locations.[66-69] It is estimated that less than half of newly diagnosed male cancer patients, are offered sperm cryostorage services.[66-69] This means that patients have to be well enough to travel to these centres and additional delays occur as the work up prior to cancer treatment cannot be done concurrently with fertility preservation consultation and procedures. The use of telemedicine for fertility preservation consultation and the collection of semen samples locally for male patients, with samples being sent to these andrology or fertility centres, can improve access to fertility preservation for patients in rural areas.

Referral pathways

In Australia there are nationally agreed guidelines for fertility preservation, however we do not have state or national referral pathways and this results in some patients missing out on the opportunity for fertility preservation.[51, 70, 71] Referral pathways between clinics exist but they

are often ad hoc between certain clinicians. Unfortunately, many cancer specialists indicate that they are unaware of whom or where to refer a patient for fertility preservation services and this is a barrier for referral.[58, 62, 72] This is especially relevant for patients residing in rural and regional areas, where access to fertility preservation services is limited.

Specialist advice

Most cancer patients receive information about fertility preservation by cancer experts and not fertility and andrology specialists but unfortunately not all cancer doctors inform patients about the potential of losing their fertility [29, 73, 74] or do so on an ad hoc basis, even though they recognise the importance of providing this information.

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.'[28, 75]

Regrettably, there is inadequate communication between cancer and fertility specialists.[76] Specialist knowledge about fertility risks[76] to fertility of specific cancer treatments and fertility preservation options requires both cancer and fertility doctors to develop expertise in order to translate effective fertility preservation information in a timely manner to patients and their families. Given the competing demands of providing complicated and detailed information about fertility potential and the risk to fertility, based on cancer treatment, there is a role for cancer specialists to work collaboratively with reproductive and andrology specialists to achieve the best outcome for patients.[9, 77]

Institution-related barriers for comprehensive discussions with patients about the risk for fertility include the limited availability of educational materials about fertility preservation, lack of reproductive specialists for referral and time pressure.[42, 60, 78]

Timing

Timely referral and uptake of fertility preservation is important and so is early commencement of treatment with gonadotoxic agents. There is also controversial evidence arguing that sperm should not be cryostored after the start of treatment whereby mature sperm are exposed to mutagenic cytotoxic drugs. Delays in referral to fertility preservation services and length of fertility preservation treatment, are often reasons for why patients choose to start treatment prior to referral to fertility preservation experts.

Data

Although centres are beginning to collect national fertility preservation data through the Australasian Registry, to date there has been no Australian data published on the success and complication rates of fertility preservation in patients receiving gonadotoxic treatments, uptake in metropolitan, rural and regional cancer services, or differences in private or public cancer services.

Costs

Fertility preservation treatments are expensive; the upfront cost and the lack of Medicare and insurance coverage for some aspects of oncofertility care is often a reason for clinician's lack of referrals and patients not taking up referrals to a fertility or andrology specialist. Furthermore, the cost of storage of gametes (a mature sexual reproductive cell, such as a sperm or egg) or gonadal tissue (oocyte, embryo, semen and ovarian tissue) is expensive and this cost needs to be covered annually until patients use or discard the material. In Australia the average age at first birth is 30.7 years for women and 33 years for men and this means that gonadal tissue is likely to be stored for many years before being used to conceive by AYA cancer survivors.

Objectives of Scholarship

My Churchill fellowship has given me the opportunity to spend time in Children's Hospital of Orange Country, Northwestern University Campus (Northwestern University, Lurie Children's and the Northwestern Hospital) identifying the role of oncofertility specialist programs in both paediatric, AYA and adult cancer programs and examining current models of oncofertility care and the feasibility of adapting a standardized model into the Australian context (for metropolitan, regional and rural centres).

My fellowship has afforded me the opportunity to spend time in centres with established oncofertility programs in order to:

1. Evaluate the multidisciplinary roles of specialists required to run an oncofertility program and how successful models of care can be adapted into the Australian healthcare system;
2. Identify the barriers experienced by cancer and fertility multidisciplinary specialists and strategies employed to overcome these obstacles.

Key Highlights from the Fellowship and Recommendations

My fellowship started with a pre organized meeting organized on my behalf by the Oncofertility Think Tank. This meeting had representation from clinicians and allied health professionals from eighteen different cancer centres around America and the meeting was co-chaired by myself and Professor Sender. The objectives of the meeting were to discuss and brainstorm oncofertility care and review the success and improvements needed for patients across different ages.

The information from this meeting and my discussions from talking to clinicians throughout my fellowship has broaden my understanding regarding models of Oncofertility care.

Development of Oncofertility Services

In order for oncofertility care to become routine standard practice, models of care need to be developed to ensure that the new services meet the needs of cancer patients during and after cancer treatment. I was privileged to review different models of oncofertility care and the common elements for consideration included:

Workforce design

Cancer services are developing models of care that will allow the provision of oncofertility services and have the greatest impact on patient care. The development depends on local clinical need, funding availability, the type of service provision required for the population and the agreed referral pathways. Oncofertility services involve clinical teams within and outside of the cancer centre working together, this often involves a variety of public and privately funded services which are not co-located.

The timing of fertility preservation is very important especially for patients who are going to have oocyte or embryo cryopreservation that could lead to delays in treatment. Models of care need to ensure that cancer providers make early referrals and that once referred, patients are seen by fertility or andrology clinicians expediently. As clinicians are thinking more about fertility preservation, patients are being referred earlier. However, there is still the ongoing problem of patients only being referred once the diagnosis and staging are completed following multidisciplinary team discussions. If a referral is produced for all new suspected cancer patients, then the fertility preservation consultation and procedures can be done at the same time as cancer staging and toxicity assessment and this in turn would reduce any delays to a minimum.

Despite having 13 international guidelines we do not have recommendations about the medical supportive care needs of cancer patients and this is very important as cancer patients often present with acute medical problems which need to be considered carefully prior to and during fertility preservation procedures.

As expected, the overwhelming cancer diagnosis in itself causes significant psychological distress. Discussions regarding fertility preservation and subsequent procedures involved can intensify this distress. The model of oncofertility care may also exacerbate this distress as patients have to re-explain their cancer history multiple times to different health care professionals each time

they come for fertility assessments, bloods and procedures. Patients may also struggle with the environment of a fertility centre as they are surrounded by couples looking to start families and move on with their life while a cancer patient is worrying about their future. This is especially important for those in-patients who are transferred by hospital to the fertility clinic or younger patients who are easily identifiable as being different from other fertility patients. Many cancer patients report feeling uncomfortable in this environment and this may not only increase a patient's distress but becomes a deterrent for pursing fertility treatment.

As each centre develops their model of care there are a number of different options that can be considered which are discussed below.

The development of centralized oncofertility centres within cancer centres would allow seamless and timely collaboration between cancer, fertility and andrology specialists as well as dedicated facilities for cancer patients and the opportunity for research and access to clinical trials. These centres also ensure that health care professionals working in this area develop expertise as they look after a number of patients as well as making it easier to organize the timing of a patients staging and toxicity assessments around patient's fertility treatment. This would assist with reducing any delay in starting treatment. This model is likely to be more expensive as the infrastructure for a fertility centre with laboratories, embryologist, clinical space, procedure and theatre space is expensive. Cancer centres are unlikely to have the number of patients to make this a viable option and so there would have to be a centralized centre for a number of different cancer centres.

The other option would be for cancer and fertility specialists to agree on referral pathways and methods of transferring patients between cancer, fertility and andrology centres when patients need assessment and procedures. The benefits of this model is that these services already exist and they have very experienced staff and facilities already developed, which have accreditation, so starting these services would not require any additional funds. What is required is an investment of time to develop staff relationships, referral pathways and provide any additional training to both cancer and fertility staff about fertility preservation and the needs of cancer patients.

Lead clinician vs oncofertility team - All staff looking after cancer patients need to understand the oncofertility needs of these patients in the same way that cancer staff understand the supportive care or toxicity assessment needs of patients. Traditionally the patient's cancer clinician has been responsible for leading the oncofertility consultations, however there are successful examples of cancer centres having an oncofertility team which assumes this responsibility. This can be a multidisciplinary group of physicians, nurses or care coordinators.

This model allows the lead clinician to spend time discussing the cancer diagnosis, staging and work up without having to rush through and the introduce fertility preservation as a separate topic with a dedicated timeframe for discussion. AYA patients who may not have good reproductive health literacy and require more time to understand the information disseminated throughout the consultation and thus this model allows the additional time for patients. The additional time is also important for the parents of paediatric patients to assist with making difficult ethical decisions on behalf or with their child. This model has the advantage in that the oncofertility team leading the consultations are up to date with the latest information on FP strategies and have the skills to manage these consultations as well as being experts in oncological care. Lead clinicians may initially have some concerns about this model especially if they don't know the team or feel that they will be offering a type of treatment they don't approve of but building relationships over time and agreeing on criteria for oncofertility care has been very helpful.

Cancer vs fertility clinicians discussing fertility preservation – There are no studies looking at the difference in patient satisfaction, health literacy and uptake of fertility preservation services depending on whether the person who had the initial conversation was a cancer or fertility clinician. Certainly any patients who are interested in having fertility preservation after the cancer clinicians consultation will see an andrologist or fertility specialist.

Some centres do not have an oncofertility team but they have an organized referral pathway which means everyone has access to see a fertility/andrology specialist at diagnosis. The advantages of having the fertility expert leading this conversation is that they have the most up to date information about the different fertility preservation options and strategies and can speak directly to patients. Even if no fertility preservation has occurred, patients have found this consultation very useful and patients are in the system for later follow-up in the survivorship period. The disadvantage to this system is that it may lead to cancer clinicians not developing important skills in this area and as the number of cancer patients seeking fertility preservation increases, it will not be possible to sustain this model without adequate financial support for clinicians.

Different types of care coordination - Cancer centres have successfully developed care coordination by senior nursing. These nurses coordinate the care of patients while supporting their needs, thus ensuring that referrals and appointments take place. Senior nurses in care navigator positions who have expertise in oncofertility care and have demonstrated the importance of nurse driven care in developing these models. The advantage of this model structure is that nurse coordinators already have a good relationship with patients and are already organising tests and consultations so it would be easier for them to assume the role of providing fertility preservation education, resources and consultation.

Another example of care navigation is the role of care navigator established by the Northwestern Consortium. The current position is a non-medical professional who has an extensive understanding of oncofertility care and provides and assists patients from multiple clinical areas including, but not limited to, oncology, rheumatology, hematology and neurology with fertility preservation services. The care navigator triages the patient appropriately for fertility preservation services within a critical timeframe, support patients as they pursue fertility preservation services including psychosocial assessments, health education and coordination of services. The care navigator also serves as a resource for referring physicians, patients and the greater community regarding fertility preservation services both within the hospital but also at referring hospitals. The advantage of this model is that it allows health care professionals time to deal with other aspects of a patient's journey that require clinical and non- clinical skills and the service role will be cost saving to the oncofertility service. Health care professionals may need time to adjust to care coordination being driven by non-clinical team members, but it has proven to be a successful model.

Services have to ensure that all cancer patients have equitable access and therefore in Australia it is very important that patients in rural and regional centres are not disadvantaged and that patients from different cultural and religious groups are considered. Delivering services to remote communities is always a challenge but one way to reduce the barrier is to use telemedicine to provide oncofertility consultations with patients. These are easy to organize and allow patients to make decisions with the fertility team about their needs. Referral to metropolitan fertility or andrology centres can then be organized for those patients who decide to have fertility preservation. This model can also be used when patients are too unwell for a consultation with a fertility/andrology specialist but would like to discuss fertility preservation options and follow up.

Delivering oncofertility services for paediatric cancer patients has additional challenges that need to be considered. Some fertility preservation options are still experimental and need to be organized under the remit of a clinical research study. In addition to referral pathways and care navigation discussed earlier, fertility providers need to be able to provide services which are suitable for children who may be too unwell requiring surgical procedures. This would require both the staff who have the skills to care for children and a clinic environment suitable for children.

Governance and accountability – each service has to develop a service governance structure in addition to the model of care that ensures the safety of patients as well as ensuring best patient outcomes. The areas for consideration include: assent and consent of patients, ethical suitability of patients, medical suitability of patients, posthumous management of gonadal tissue and gametes and follow up of patients.

Collaboration of multidisciplinary healthcare professionals – in order for oncofertility care to be developed it requires the collaboration of both cancer and fertility health care professionals from a number of different multidisciplinary groups (doctors, nurses, social workers, psychologists and counsellors). Within a cancer centre oncologist, hematologists, radiation oncologist and paediatric oncologist may individually or separately have their own referral pathways which can be very confusing for staff and these referral pathways may change depending on who on the team making the referral. Oncofertility Services need referral pathways that define multidisciplinary teams working together, how to refer patients especially if patients come in over the weekend and what tests are required prior to referral. Pathways need to be consistent across cancer centres so there is no confusion for staff. Consideration has to be taken as to how patients are transferred between public and private health providers and the suitability of transferring inpatients.

Additionally, the suitability of fertility services for paediatric patients having fertility preservation, due to the need for paediatric anesthetic and surgical techniques, needs to be taken into account. New models of care need to be developed to ensure that patients can be seen expediently and in a timely fashion and that those patients who are having a procedure can have these procedures at the same time as other theatre procedures; for example bone marrow aspirates, lumbar puncture and central line insertions. To ensure that fertility specialist have all the information they need to make decisions about the risks of cancer treatment, the referral needs to have information about treatment and dose intensity. To make this as easy as possible referral templates can be developed which makes this process very easy.

Staff Expertise - oncofertility services require a multidisciplinary group of health care professionals with oncofertility expertise. The difficulty is that the staff required to deliver these services work across a number of different services (cancer services, fertility and andrology services) and may often not attend the same meetings. Thus, it would be difficult to persuade fertility clinicians to attend a cancer meeting and vice versa if the meeting has a limited number of interested participants from either vocation.

Communication Skills - Oncofertility consultations need time, expertise and in many situations need the health care professionals to quickly ascertain the health literacy and knowledge of patients/parents about reproductive health. The consultations have to be able to provide confidential consultations that often have ethical considerations that need to be considered by patients and therefore these consultations giving patients suitable time are needed. Communication skills training is also required to ensure that staff working in these services have the appropriate expertise.

Data collection and Evaluation of service – continual development of these new services will not be possible without data to show that they are providing the care patients require in a safe and efficient manner.

Empowering patients and families – enhancing the ways that health care professional's work with patients, parents, partners to deliver oncofertility care requires consumer inclusion in the development of all these services as well as having regular consumer evaluation and review.

Recommendations

- Oncofertility Models of care need to be established to ensure that all cancer centres can implement the Australasian Oncofertility Charter Recommendations:
- Oncofertility care models need to be developed at a local and state level to ensure that all cancer patients have access to fertility preservation options and provide fertility related support during and after fertility preservation treatments.
- The models of care need to ensure that paediatric and AYA patients have an opportunity to receive experimental fertility preservation procedures in a framework that provides ethical and psychological support under a clinical trials protocol.
- Clear oncofertility referral pathways should be developed between each cancer centre and fertility/andrology centre to ensure that all patients have timely access to oncofertility services.
- Patients in rural and regional locations need to be able to access fertility preservation consultation using telemedicine.
- Fertility related psychological distress needs to be identified in cancer patients and supported by adequate referral to allied health professionals during fertility preservation, during cancer

treatment and in the survivorship period.

- An assessment of reproductive needs following successful cancer treatment needs to be included in the survivorship assessment.

Education for Health Care Professionals (HCP's)

My fellowship has given me an opportunity to meet a large number of doctors, nursing and allied health staff supporting models of oncofertility care. Cancer staff have sought a number of different methods and skills for delivering new oncofertility services. Oncofertility education needs to address four main areas including: medical oncofertility care, fertility related psychosocial care, ethical management of oncofertility care and communication skills training. The challenge is that education has to provide support for cancer and fertility health care providers who traditionally do not attend the same meetings and whose staff have different levels of understanding regarding cancer patient's needs and the gonadotoxic risks that patients face. It is also a challenge as the level of evidence is not always available to support changes in practice or oncofertility care in paediatric patients.

Fertile Action has developed education modules for training staff. These resources are easy to access online and free, they also allow individual healthcare professionals to complete the modules in their own free time. The feedback from staff has been positive and it seems that this would be an effective way for cancer and fertility departments and oncofertility services to ensure staff receive adequate training.

Colleagues in the USA also agree that the challenge is to ensure that oncofertility care is embedded into core syllabus for all new health care professional trainees and that current staff have access to career development.

Recommendations

Cancer and fertility centres in Australia need to ensure that oncofertility services have staff who have the expertise to deliver holistic and comprehensive oncofertility services.

- To address the current gap in knowledge and education programs should be developed to include core curriculum for training oncology medical, nursing and allied health staff. The aim would be to ensure that all staff in a cancer centre have basic knowledge regarding the gonadotoxic risks of cancer treatment including new novel immunotherapy in addition to having information on current fertility preservation options and the advantages and disadvantages of oncofertility options in cancer patients of different ages.

- To address the current gap in communication skills and communication skills programs that need to be developed. The aim would be to ensure that all staff in a cancer centre have the communication skills to deal confidently with the practical, psychological and ethical elements of oncofertility consultations.

- The Future Fertility research group will be reviewing the modules with healthcare professional staff to see if the modules would be suitable for the Australian context without modification. If they do require modifications, we will have to look at the extent of these modification from a practical and financial point of view. The future Fertility Research Group are committed to either proceeding with rolling out of these modules or developing new ones.

- It is also important for our Research team to advocate for oncofertility care to be included into healthcare professional curriculums and I intend to discuss this with colleagues who are part of our multidisciplinary team of medical, nursing and allied health professional post- graduates when training for oncology services.

International Medicare Advocacy Campaign

Although Australia and America have different health care provisions in both countries the cost of oncofertility care is not universally covered by public health or insurance companies. Like Australia differences in health policy in each state also contribute to the inequity patient's face when it comes to fertility preservation. This also poses challenges for patients to find the correct information based on insurance company and state provisions. These factors contribute to significant barriers for patients and one that has an effect on how new oncofertility services are developed and therefore how clinicians can follow international guidelines on fertility preservation management. Without a formal way of reimbursement currently patients are accessing fertility preservation in three ways:

1. Patients are benefiting from free fertility preservation as a result of cancer clinicians or fertility practices covering the costs for fertility preservation. This highlights the importance of providing oncofertility care as part of an integrated care package. As the numbers of patient's seeking fertility preservation increases this method of providing care may not be supported by hospital executives.

2. If patients have an insurance plan, patients may be eligible to access to fertility preservation by getting urgent prior authorization for fertility preservation counselling and procedures. The cancer or fertility specialists will have to send a statement of immediate health threat. If prior authorization is denied, then they can seek a review from a Department of Managed Healthcare.

Discussions with patients and staff indicate that insurance companies are covering the cost for fertility preservation, however it has been a time consuming process and distressing to families who have complete the paperwork at a time when they have received an overwhelming cancer diagnosis.

3. In the USA philanthropic support from advocacy groups such as Livestrong and Fertile Action has allowed some patients to have access to fertility preservation though small grants. Care navigators spend time providing patients with advice about the services involved. Talking to patients and parents regarding these available grants provides patient with access to financial asistance but it requires patients having to complete needs assessment forms and for staff and patients to know about methods for accessing grant funding As the number of patients seeking fertility preservation increases the philanthropic models may not be able to support the growing number of patients requiring oncofertility care.

Recommendations

In both countries different strategies are in place to increase public and insurance cover of fertility preservation. In Australia, I have lead the Medicare Oncofertility applications for 7 new item numbers covering AMH assessment for female cancer patients, processing and handling of gonadal tissue and gametes, ovarian transposition and fertility related psychological support during and after cancer treatment.

Following discussions with colleagues during my fellowship I will work with America the Coalition to Protect Parenthood After Cancer (CPPAC) colleagues to explore the similarities and differences between our health models to successfully support change.

Data

Predicting the risk of infertility for an individual prior to the commencement of cancer treatment is difficult, particularly in paediatric or adolescent patients, and depends on multiple factors such as their age, pubertal status, gynaecological and reproductive health history, underlying medical conditions, (including genetic or endocrine conditions), cancer type, and importantly, the nature of treatment required.[79, 80] Unfortunately there is a lack of data on uptake and utilization of fertility preservation, safety of fertility preservation, gonadotoxic risk of infertility and family planning after cancer treatment.

The Future Fertility Research team, have developed the Australasian Oncofertility Registry (AOFR)[81] which captures a patient's cancer and fertility journey from cancer diagnosis through to survivorship. Throughout my fellowship I was able to learn a lot from colleagues across the USA but I was also able to showcase some of the groundbreaking work currently conducted in Australia. I am pleased that following a number of presentations that I have given across the USA, I have seen real interest in opening the Australasian Oncofertility Registry study as an international study collaboration across the United States.

Recommendations

The Australasian Oncofertility Registry study will be rebranded as the International Oncofertility Registry Study to ensure that ongoing collaboration is possible. The Children's Hospital of Orange Country has ethics approval and we are finalizing the contracts between the University of New South Wales and The Children's Hospital of Orange Country.

Over the next year my aim will be to continue the collaboration with colleagues ensuring we have future data that will help us to direct further research and change in models of care.

Competency Frameworks

Despite international evidence about fertility preservation and current international guidelines there are several barriers that have prevented the implementation of equitable fertility preservation practice around the world. These barriers include: a lack of clear referral pathways and models of care for oncofertility services, a lack of collaboration between cancer and fertility doctors to deliver services, inequitable access based on cost, health literacy and a lack of training of staff who can deliver these services as well as no consensus about the best way to deliver information to patients.

Competencies are used by health care services and health care providers to ensure that they develop the knowledge, skills and processes to deliver services of a high standard. Competency frameworks are based on the hypothesis that health care professionals need to have the skills to turn the available knowledge into service development and reliable outcomes. The competency framework clearly defines and describes the individual competencies required by a member of staff to be successful and fully effective. Competencies should be both observable and measurable so that they can be evaluated.

The availability of oncofertility competencies would allow health care staff to define how oncofertility should be developed and outline clearly the specific competency for each deliverable component of care. Training and service development would be instrumental in developing and maintaining the skills and knowledge needed for oncofertility care of a high standard.

It is important that continuous improvement becomes a part of oncofertility care so patient reported outcomes will be developed to allow for the evaluation of the competency framework.

Recommendations

Across Australia, America, Canada and Europe clinicians have the same issues in implementing oncofertility guidelines. As a result of the fellowship and collaborations that have been formed our objectives is to develop an international study that would help to develop an international multidisciplinary oncofertility competency framework. This will enable the development and implementation of oncofertility services as well as the ability to monitor and evaluate oncofertility care.

Aims

1. **To develop an international multidisciplinary comprehensive framework to assist clinicians with the implementation of local and international fertility preservation guidelines.**
2. **To develop an international multidisciplinary comprehensive framework to assist clinicians with the implementation of oncofertility services internationally guidelines.**
3. To define the scope of practice for health care professionals providing oncofertility services and assist in continual professional development of health care professionals.
4. To create patient reported outcome measures for oncofertility care evaluation.

Methods

The International oncofertility competency framework will be developed by multidisciplinary health care professional researchers across Australia, New Zealand, United States of America, Canada and the United Kingdom. We have chosen countries with similar health care clinical practices that have evidence for oncofertility practice that is largely consistent.

The study will be carried out in different phases: selection of international collaborators, literature review, competency questionnaire development, Delphi technique review and framework development and then publication and dissemination of the framework. We will also develop patient reported outcome measures to evaluate the outcome measures of the services.

The aim of the Delphi method is to construct consensus forecasts from a panel of experts in a structured iterative manner. The method relies on the key assumption that forecasts from a group are generally more accurate than those from individuals. In its traditional form, extensive questionnaires are distributed to the panel of experts. A facilitator is appointed in order to implement and consolidates the opinions and this information is sent back to the experts for further analysis and opinion refinement.

One of the advantages of the Delphi technique is that the health care professionals are totally independent and are not influenced by the opinion of other health care professionals. The final forecasts are usually constructed by giving equal weight to all experts' forecasts.

The Delphi study should report explicitly on the criteria and process used to select experts. These criteria should be made explicit prior to the Delphi study and the selection process should apply them systematically. There is very little empirical evidence on the effect of the number of participants on the reliability or validity of consensus processes. Studies in which the Delphi panel is to be homogeneous can be smaller than when the group is intended to represent diversity, as in a study where representation of different nationalities is needed.[82]Following a series of

questionnaires there can be a consensus conference to attain general agreement on a finite outcome of the Delphi procedure. A Delphi process may be stopped when results have stabilized without reaching consensus or after a pre-set number of rounds, even if no consensus has been achieved. The health care professionals do not have to be present at one location, so that an international expert group with diverse skills and expertise form varying locations can work together.

Furthermore, it makes the process cost-effective by eliminating the expense and inconvenience of travel, and it makes it flexible as the experts only have to meet a common deadline for submitting forecasts rather than having to set a common meeting time.

A preliminary round of information gathering from the 'Oncofertility Think Tank' in March 2016 has allowed us to set the initial domains for forecasting. These domains represent the core roles for health care professionals and services providing oncofertility care that require competencies to be developed. The domains are communication skills, use of decision aids, risk assessment, provisions of age appropriate care , documentation of medical care, training of cancer and fertility health care professionals, referral processes, supportive care during fertility preservation, reproductive needs (sexual health, fertility follow up and sexual dysfunction care) in survivorship care, fertility related psychosocial support, quality outcomes for oncofertility care, using big data to change patient outcomes

Implementation

1. Project team have been developed
    i. Australia – Dr. Antoinette Anazodo Paediatric and Oncologist, Prof Elizabeth Sullivan Epidemiologist, Dr. Shanna Logan Psychologist
    ii. America – Prof Leonard Sender Paediatric and Adolescent Oncologist, Miss Kirsten Smith Care Navigator, Dr. Irene Su Fertility Specialist, Dr. Leslie Appiah Fertility Specialist
    iii. United Kingdom- Prof Alan Pacey Andrology Consultant, Dr. Sheila Lane Paediatric Oncologist
    iv. New Zealand- Dr. Mary Birdsall Fertility Specialist, Dr. Simon McDowell Fertility Specialist
    v. Canada – Prof Ronnie Barr Paediatric and Adolescent Oncologist

2. Research proposal developed July 2016
3. Research funding has been sought to support the Delphi process.
4. First meeting with international team set for September

How will your project benefit the Australian community?

Although many survivors maintain their reproductive potential after cancer treatment, others experience infertility as a result of their disease or cancer treatment. Research and clinical experience has shown that the loss of reproductive potential is one of the most distressing adverse consequences of successful cancer treatment, which can affect the quality of life of a cancer survivor, their ability to have a family and may lead to psychological distress.

There is inequitable access to fertility preservation in Australia mainly due to lack of oncofertility programs, inadequate referral pathways, lack of access to fertility specialists and absence of oncofertility programs.

This fellowship has allowed me to review the delivery of successful models of oncofertility care and identify ways in which similar programs can be developed and integrated into Australian cancer centres and I have made some recommendations for developing these services and I will review this manuscript into a paper for publication covering this topic.

Successful oncofertility programs will benefit all patients of reproductive age and oncofertility staff in providing the opportunity to have a biological child following successful curative cancer treatment and will provide the necessary psychological support required.

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