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Fertility Preservation in Adolescent Males

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Abstract

Aim
Survival rates of childhood cancer are now above 80%, so there is increasing emphasis on survivorship. A major late effect of cancer treatment is fertility loss. International best practice indicates that post-pubertal boys with cancer should be offered sperm cryopreservation prior to treatment. The aim of this study was to demonstrate the feasibility of a national sperm cryopreservation program for adolescent males and to examine outcomes for a pilot.

Methods
Patient demographics and semen parameters of adolescent male oncology patients referred to our service were analysed. Sperm analyses were performed in accordance with WHO guidelines.

Results
Fifteen patients were referred, 12 of whom (80%) attempted sperm production. Of these 12 samples, 25% (3/12) were unsuitable for freezing. One patient was too unwell to produce a sample. Eight patients (age range 12–17 years) had sperm successfully cryopreserved. Of these 8 samples, 25% were within WHO 'normal' limits, 50% had reduced sperm concentration. The number of cryopreserved samples (straws) ranged from 4-8 per patient.

Conclusion
We have established a successful, structured fertility preservation service for adolescent males in Ireland. Sperm cryopreservation is an accessible method of safeguarding fertility in male patients facing cancer treatment and should be offered to all.

Introduction

The incidence of both childhood and adolescent cancer is increasing throughout Europe [1]. Around 200 children and young adolescents (0-16 years) are diagnosed with cancer in the Republic of Ireland every year. Thanks to advances in medicine and surgery, survival rates in this group are now greater than 80%.[2]

As a result, there is increased emphasis on the long-term effects of cancer treatment. Large cohort studies have shown that approximately 70% of childhood survivors of cancer will experience at least one late effect of their treatment, one of these being impaired reproductive health.[3] Future fertility is a primary concern of survivors of childhood, adolescent and young adult (CAYA) cancer.[4] After cancer diagnosis, patients and parents will often, understandably, be primarily focused on treatment and prognosis. However, international guidelines recommend that the risk of infertility from disease and/or treatment modality and fertility preservation options should be discussed as early as possible following diagnosis.[5] The term 'oncofertility' encompasses a new interdisciplinary approach dedicated to preserving future fertility in light of gonadotoxic cancer treatment.[5]

Fertility of male cancer survivors may be compromised by chemotherapy and radiotherapy that impair the production of both spermatozoa and of male sex steroid hormones, which are vital for normal male sexual development and fertility. Thirty percent of male survivors of childhood cancer suffer from azoospermia and 18% suffer from oligospermia.[6] Treatments known to pose the most significant risk to fertility in both male and female patients include total body irradiation, chemotherapy conditioning prior to bone marrow transplantation, radiotherapy to a field that includes the sex organs, and specific chemotherapy drugs, including alkylating agents.

For post-pubertal males who are able to ejaculate, conventional sperm cryopreservation provides an excellent opportunity for future fertility and usually does not delay oncology treatment to a significant degree. Even if collected semen quality is poor, in-vitro fertilization (IVF) and, particularly intracytoplasmic sperm injection (ICSI), can be considered in the future with excellent pregnancy success outcomes.

Conversely, for pre-pubertal boys and post-pubertal boys who are unable to provide a sperm sample by ejaculation, fertility preservation remains a challenge as techniques involving gonadal (testicular) tissue cryopreservation are still experimental, with no embryo development or pregnancy to date.

A fertility risk assessment is central to the process of fertility preservation. This assessment must consider factors including the age and pubertal developmental stage of the patient, the oncology treatment required and the prognosis for long-term survival after treatment. The aim of a dedicated clinical oncofertility program is to assist medical staff, patients and their families to discuss and pursue fertility preservation options. Clear and simple referral and treatment pathways are essential. [7]

In Ireland, the majority of patients with childhood and adolescent cancers are treated in Children's Health Ireland (CHI) at Crumlin. Historically, some male adolescent boys were referred for sperm cryopreservation at private fertility clinics, but the system tended to be ad hoc. In August 2018, in conjunction with CHI at Crumlin, Merrion Fertility Clinic (MFC) at the National Maternity Hospital set up a structured sperm cryopreservation service for adolescent males. Post-pubertal adolescent males due to undergo gonadotoxic treatment or surgery can be referred to our service if they wish to cryopreserve sperm. This is a pilot service, funded on a pro bono basis by Merrion Fertility Clinic.

The aims of this study were to review the establishment of this national sperm cryopreservation service in this population, to evaluate patient outcomes in terms of ability to store sperm and to analyse the sperm parameters of samples deemed suitable for cryopreservation.

Methods

Multidisciplinary approach: To facilitate this service, we initially developed a National CAYA Fertility Preservation Consortium with fertility specialists at our clinic and paediatric oncology specialists at CHI. This combined expertise allowed us to develop a streamlined sperm cryopreservation service for adolescent boys. Patients are identified through the National Paediatric Haematology/Oncology Programme and they and their parents are seen and counselled by their primary physician in CHI, Crumlin.

Patient selection criteria: Patients are deemed suitable for sperm cryopreservation if they are Tanner staged II or above. Tanner staging is a sexual maturity scale used to assess sexual development in males by assessing pubic hair and genitalia, including scrotal development, testicular volume, and penile length. This examination is performed by the patient's paediatrician prior to referral for cryopreservation. All young males deemed Tanner stage II or above should be considered for sperm cryopreservation before embarking on treatment likely to affect the spermatogenesis process.

Patient referral for oncofertility preservation: The referring oncology consultant has a discussion with a boy and his parents and counsels them regarding the options. If the boy wishes to proceed, oncology nurse specialists at CHI Crumlin (the primary treatment site) liaise with the fertility nurse specialist in MFC. Patients have the option of attending either MFC or CHI to produce a semen sample. As this is a national service, patients and their parents travel from all over Ireland.

Patient information: Patients and their families are provided with age-appropriate written information designed specifically in response to this initiative. This leaflet outlines the reasons why it is important to consider sperm freezing, what the process involves, how long the sperm can be stored, who to contact in MFC and how it may be used in the future. Copies of the Patient information leaflets are available in Crumlin and may be given to the family during their early discussions.

Viral screening: Documentation of a negative viral screen is a pre-requisite to any cryopreservation in our centre. Assessment of infection risk is important to identify any current infection which may predispose any patient to potential complications and lead to cross-contamination in the clinic / lab or in the storage of frozen gametes. Blood is taken at CHI and sent urgently to the National Viral Reference Laboratory for screening for Hepatitis B, Hepatitis C, HIV1 and HIV11 as per the European Commission Tissue and Cells Directives guidelines.

The clinical encounter: At the clinic, our priority is to provide a patient and adolescent friendly fertility service. As part of this we schedule appointments for quiet times at the clinic, and also facilitate parents and patients travelling from far distances. A designated nurse specialist meets with the patient and their parent(s) to sign tissue cryopreservation consent forms. This nurse also fulfills the role of the patient's keyworker, and acts as a point of contact for any questions the patient or parent(s) may have during their journey with us in Merrion Fertility Clinic. The designated nurse will have completed the appropriate Garda vetting process for both MFC and Crumlin and will also have completed the HSE "Children First" course. Unlike our adult patients, the adolescents who undergo sperm cryopreservation often require more than one appointment or visit.

Patient demographics: Clinical and demographic patient data is recorded, according to the information supplied by their primary physician in CHI Crumlin. Disease diagnosis is provided by the referring doctor.

Semen and sperm parameter evaluation: Semen samples are collected by masturbation and semen analysis is performed in accordance with World Health Organisation (WHO) recommendations.[8] Sperm parameters analyzed are volume, sperm concentration and sperm motility. If of suitable quality, sperm is prepared and stored in labelled straws. A test straw is thawed to check for viability. In the event that a young boy is unable to produce a sample or there is no sperm present in the sample or if they wish to produce a second sample, another appointment is facilitated. This is made in conjunction with CHI treatment timelines.

Results

This study represents a retrospective review of all adolescent male patients referred to our service for consideration of sperm cryopreservation in a 16-month period.

Patient characteristics

Fifteen patients, aged between 12 and 17 years old, were referred between August 2018 and December 2019. Because all patients were under the age of 18, informed consent for cryopreservation was signed by both the patient and their parents/legal guardians. Of this cohort, 93% (14/15) presented with malignant disease: diagnoses included Hodgkin's lymphoma, non-Hodgkin's lymphoma, rhabdomyosarcoma, testicular germ cell tumour, acute lymphoblastic leukaemia, acute myeloid leukaemia, Ewing's sarcoma, medulloblastoma and osteosarcoma. One patient was referred for sperm cryopreservation prior to starting gonadotoxic treatment for Sickle Cell Disease (Table 1).

Table 1: Characteristics of patients who produced a sample (n=11).

	Sperm to freeze n=8	**No sperm to freeze n=3**	**WHO threshold Normal (2010)**
Age, years (median, range)	15.5 (12-17)	15 (15-16)	
Sperm concentration (x10^6/ml)	28 (1-59)	0 (0-0.01)	15 x 10^6/ml
Motility (%)	34 (16-48)	0 (0-0)	32%
Volume (ml)	0.9 (0.25-1.5)	0.8 (0.15-1.4)	1.5ml
Number of straws frozen	6 (4-8)	0	
Diagnosis (n)			
Hodgkin's lymphoma	3	1	
Rhabdomyosarcoma	1	0	
Testicular GCT	1	0	
AML	0	1	
Non-Hodgkin's lymphoma	0	1	
Sickle cell disease	1	0	
Ewing's Sarcoma	1	0	
Osteosarcoma	1	0	

All values are given as median and range (minimum to maximum), unless otherwise indicated.

Sperm analyses and cryopreservation outcomes

Of the 15 patients referred, 12 attempted sperm production. All elected to attend MFC rather than to produce the sample at CHI. Eight of these patients (67%) had sperm successfully cryopreserved. The youngest patient in our study was 12 years old and successfully obtained semen samples. The oldest patient was 17 years old. Four patients (36%) did not achieve sperm cryopreservation: 1 patient failed to collect any sample, 2 had no sperm in the sample produced, and 1 had very poor semen quality that was not sufficient for freezing. Five patients attended the clinic twice to attempt specimen production. Samples were further categorized into 'normal' and 'subnormal' (Table 2); only one patient had sample parameters entirely within the WHO normal range. Three patients did not attend for sperm cryopreservation - one patient declined, as cryopreservation was deemed not to be indicated based on his diagnosis, one did not wish to pursue cryopreservation and one patient tragically died secondary to his disease, prior to his appointment at MFC.

Table 2: Semen and sperm parameter ranges (normal, subnormal) in adolescent patients who produced a sample (n=11)**.**

	Sperm concentration ($x10^6$/ml)		**Motility (%)**		**Volume (ml)**	
	Normal (≥15)	Subnormal (<15)	Normal (≥32)	Subnormal (<32)	Normal (≥1.5)	Subnormal (>1.5)
n (%)	5 (45)	6 (55)	5 (45)	6 (55)	10 (91)	1 (9)
Age (yrs)	14 (12-17)	16 (15-17)	15 (14-17)	15.5 (12-17)	15.5 (12-17)	14

Ages are given as median and range (minimum to maximum).

Discussion

This work demonstrates the feasibility of sperm cryopreservation for post-pubertal adolescent males in Ireland, regardless of age or disease diagnosis. A streamlined service with a clear referral process has been established.

Adolescent males have a higher prevalence of azoospermia and lower semen and sperm parameters compared to adults.[9] However, over 65% of our cohort managed to successfully produce a sperm sample that was suitable for cryopreservation with the potential for future use in clinical assisted reproduction.

This data can help to inform patients and their families about the potential for fertility preservation, even in very young adolescent patients. Importantly, in our cohort, age was not a predictor of successful sperm production and subsequent freezing. Age alone should therefore not preclude patients for referral to our service.

Sperm cryopreservation is the safest and most accessible method of safeguarding fertility in male patients facing cancer treatment and should be recommended for post pubertal adolescent male patients with a new diagnosis of cancer. Patients should be referred for semen cryopreservation soon after they receive their diagnosis, and ideally prior to commencing cytotoxic treatment.

We currently have no long-term data on the rate of sperm utilization, given that this is a very new service in our clinic and the age range of our patients. Larger studies have demonstrated that only small numbers of patients return to use their cryopreserved samples for treatment in the future. In one epidemiological French study <5% of patients went on to utilize their specimens. [10] Despite this, international guidelines recommend that sperm cryopreservation should be routinely offered to adolescent males undergoing gonadotoxic treatment to give the best chance of preserving fertility for the future. Studies in this area, including the aforementioned French study, are from prior to 2009 and there has since been a huge increase in public knowledge and interest in this area. In recent years the numbers availing of this service have increased, and the numbers using their sperm in the future will likely also grow. Daudin et al demonstrated a yearly increase in referred adolescents of 9.5% per year across their study period. [11]

Prior to this study, the number of adolescent males availing of cryopreservation in Ireland was unknown. This service will enable collection of data and the establishment of a national database for patients availing of sperm cryopreservation. An important aspect of further research will be a comprehensive cost analysis of the service. The programme is the first structured fertility preservation service for adolescent males in Ireland, with a clear referral pathway and defined service user interface. Our clinic's partnership with the National Paediatric Oncology hospital has helped streamline the process for fertility preservation. This is a critical development for adolescent and young adult cancer patients and should be available and recommended to all adolescent males, prior to initiation of gonadotoxic therapy.

Declaration of Conflicts of Interest:
The authors declare no financial interests in any of the work submitted here.

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