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A 2-year follow-up study of ovarian reserve in female survivors of childhood cancer

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Abstract

Aim

The overall likelihood of a woman achieving a pregnancy following childhood cancer treatment is reduced by nearly 40%. There is limited prospective data examining changes to ovarian reserve in young survivors over time. We sought to provide fertility assessment for a cohort of young adult female survivors of childhood cancer with the aim of developing a comprehensive national follow up program.

Methods

Female survivors of childhood and adolescent cancer were invited to attend for fertility assessment and consultation. As measures of ovarian reserve, antral follicle count (AFC) and serum Anti-Mullerian Hormone (AMH) levels were measured.

Results

AMH levels at first consultation ranged from critically low 0.3pmol/L up to 64.3pmol/L. A similarly broad range was noted in the AFC (3-33 follicles). Of 23 patients who attended for initial assessment, 3 (13%) presented with critically low AMH levels (<5pmol/l). Follow up fertility assessment data was obtained for 13 of the 23 women.

Discussion

This study of childhood cancer survivors demonstrates a genuine need for specialized follow up of these young patients to ensure their future reproductive potential is optimized. We hope that by highlighting this service, care providers will be encouraged to refer such survivors for assessment.

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Introduction

Around 300 children, adolescents and young adults (CAYA) are diagnosed with cancer in the Republic of Ireland every year. [1] For Irish patients diagnosed between 2004 and 2013, the five-year survival rate was 81%, with an associated steady decline in mortality in the past 50 years.[2] There is now increasing emphasis on survivorship, with approximately 70% of childhood survivors of cancer experiencing at least one late effect of their treatment. One of these is impaired reproductive health. [3]

Future fertility is a primary concern of survivors of CAYA cancer. [4] Cancer survivors are less likely to become pregnant compared to their siblings and have an increased risk of premature menopause. [5,6] Long-term risks of impaired fertility depend on the chemotherapeutic agents used, site and dose of the radiotherapy, and whether surgery involves the reproductive organs. International guidelines recommend that risk of infertility from disease and/or treatment modality should be discussed as early as possible following diagnosis, ideally before starting treatment, and that options for fertility preservation should be explained and offered. [7] Recently published Clinical Practice Guidelines from the European Society for Medical Oncology (ESMO) and a large international guideline harmonisation group recommend that close links with reproductive medicine centres be established to facilitate timely referral for counselling and access to fertility preservation techniques. [8,9] Recommended techniques include sperm and oocyte cryopreservation for post-pubertal males and females, respectively, and ovarian tissue cryopreservation for pre-pubertal females.

In 2018, the Childhood Cancer Fertility project was launched at Merrion Fertility Clinic (MFC), in collaboration with Children's Health Ireland (CHI) at Crumlin and the Irish Cancer Society (ICS), which has funded the service. Sperm and oocyte freezing have been provided prior to oncology treatment in suitable post-pubertal males and females. For young women who received gonadotoxic oncology treatment prior to 2018 and who were unable to avail of pre-treatment fertility preservation, fertility concerns are a major source of stress. To aid fertility counselling of these women, a post-treatment assessment of their current fertility status (i.e. ovarian reserve) was set up as part of the MFC/CHI/ICS collaboration.

Circulating levels of anti-Mullerian hormone (AMH) may be valuable in predicting the long-term return of ovarian function post cancer treatment. While the negative impact of gonadotoxic treatment on ovarian reserve is well documented and retrospective studies have shown lower antral follicle counts and AMH levels in cancer survivors compared to their peers, [10] there is limited prospective data examining changes to ovarian reserve in young survivors over time. In this study, we therefore sought to assess fertility potential, as evidenced by ovarian reserve, in a cohort of young adult female survivors of childhood cancer who had not been offered cryopreservation prior to oncology treatment.

Methods

Female survivors of childhood cancer who had their primary oncology treatment at CHI, Crumlin, and who were deemed to have had gonadotoxic therapy, were invited to attend for fertility assessment and consultation as part of the Childhood Cancer Fertility Project. [11] An at-risk cohort of young women was identified by oncologists with a special interest in survivorship and GPs providing care to survivors. All patients were deemed suitable for referral if they were postmenarchal, had undergone cancer treatment with curative intent and were considered to be in full remission. At the time of assessment, participants were required to be aged between 17-25 years old and to have been treated for cancer at ≤17 years.

Demographic details, including age at menarche, cancer diagnosis and treatment type, menstrual, sexual and fertility history were recorded. As measures of ovarian reserve, antral follicle count was determined by transvaginal ultrasound scanning and serum AMH levels were analyzed by electrochemiluminescence immunoassay (Roche Diagnostics; NMH Clinical Biochemistry). An AMH value ≥10pmol/l was deemed normal/adequate and ≥20pmol/l was excellent. AMH levels <10 pmol/l and < 5 pmol/l were deemed low and critically low, respectively. Similar values were used in a study of gonadal function 20 years post-cancer treatment. [16] In that study, AMH ≤1.0 ng/ml (7.14 pmol/l) was indicative of reduced fertility, while AMH ≤0.3 ng/ml (2.1 pmol/l) indicated critically low ovarian reserve, predictive of menopause onset within 7 years. Our study protocol recommended careful annual monitoring for young women with AMH level circa 10 pmol/L or less and consideration of oocyte vitrification for those with a level <10 pmol/L.[12,13] We also aimed to collect prospective longitudinal data and to re-examine the ovarian function of this cohort over an 18-24 month period. All women who participated in the initial fertility assessment were offered further follow up one year later.

Results

Patient referrals to service

In total, 23 survivors attended for fertility assessment. All twenty-three individuals identified as females aged 17 to 25 years (Table 1). Other demographic parameters are shown in Table 1.

Table 1: Demographics of young female survivors of CAYA cancer

CHARACTERISTIC	VALUE
Median Age at initial consult	23 (17-25)
Median Age at cancer diagnosis	13.3 (6-17)
Median Age at menarche	12.9 (10-16)
Mean Anti-Mullerian hormone (AMH), pmol/L	20.8 ± 16.9

Mean Antral follicle count (AFC)	18 ± 8.6
Clinical diagnosis	**n (%)**
Hodgkins Lymphoma	11 (48)
Sarcoma	7 (30)
Leukemia / Burkitts Lymphoma	2 (9)
Other (Medulloblastoma, Langerhans cell histiocytosis)	3 (13)

Values given as median (range), mean ± S.D. or n (%), as indicated

Cancer Diagnosis and treatment

The age range at cancer diagnosis and commencement of treatment was between 6-17 years. All of the study participants had received potentially gonadotoxic chemotherapy, while eight (36%) had also received radiotherapy, though not exclusively pelvic radiotherapy. Seven patients (30.4%) who had been treated for sarcomas had also undergone surgery. Patients referred to us for review were an average of 9 ± 0.2 years from their initial date of diagnosis.

Menstrual and Fertility History

Seven participants were taking the combined oral contraceptive pill at the time of ovarian reserve testing, while one was taking the progesterone only pill Cerazette®, one had a long-acting progesterone implant (Implanon®) and one had a progesterone-releasing intrauterine device (Mirena). Menstrual cycles were recorded as regular in 17/23 (74%) of the women, including women having withdrawal bleeds on hormonal contraception. In our cohort there was one spontaneous conception and successful live birth at the age of 27 years during the study period. No other pregnancies have been recorded thus far.

Initial ovarian reserve in female survivors of childhood cancer

There was a wide range of ovarian reserve test results in the cohort. Serum AMH levels at first consultation ranged from a critically low 0.3pmol/L up to 64.3pmol/L. A similarly broad range was noted in the antral follicle count (AFC), which ranged from 3-33 (Table 1 and Figure 2). Of the 23 patients we reviewed, 3 had critically low AMH levels (<5pmol/l) at the time of their first interaction with us (Table 2).

Table 2: AMH level of female cancer survivors (n=23) at first consultation

AMH (pmol.L)	WOMEN (n)	%	Diagnoses
Normal'			
≥ 20	9	39.1	
≥ 10	8	34.8	
'Low'			
5-9	3	13	
'Critically low'			
< 5	3	13	HL, HL, Medulloblastoma

Neither AMH level nor antral follicle count showed correlation with patient age at first fertility consultation (Pearson r = -0.047 and -0.031, respectively). In contrast, a strong correlation was noted between AMH levels and AFC (Figure 1; p<0.0001).

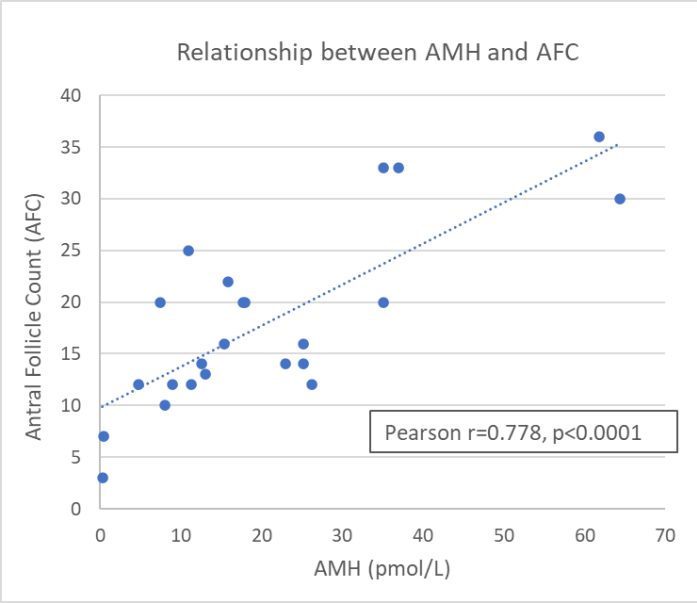

Figure 1: Ovarian reserve tests post cancer treatment in childhood cancer survivors.
AMH levels and antral follicle counts were investigated in young women presenting for fertility assessment 9 ± 0.2 years after their cancer diagnosis and treatment. Each data point corresponds to a single patient.

Of those patients deemed to have low or critically low AMH levels, two declined any further follow up: one patient declined the opportunity to pursue fertility preservation; one patient underwent fertility preservation and successfully cryopreserved 9 mature oocytes; one patient is awaiting oocyte vitrification, and one patient had reassuring ovarian reserve tests on repeat analysis and is having ongoing surveillance.

Trend in AMH over 12-24 months

Of 23 patients who attended for initial assessment, we obtained follow up data for 13 women (Figure 2). AMH levels at 12-24 months post initial assessment ranged from again critically low at 0.6pmol/L up to 103.1pmol/L, a value consistent with a polycystic ovarian syndrome (PCOS) range. AFC ranged from 1 to 59 antral follicles on follow up assessment. Overall, there was a reassuring trend in AMH levels, with 12 patients demonstrating either an increase or stability of AMH and AFC, and only one patient demonstrating a fall in AMH level from 35.1 to 15.6 in a one-year timeframe. Repeat testing was discussed and will be provided in 12 months.

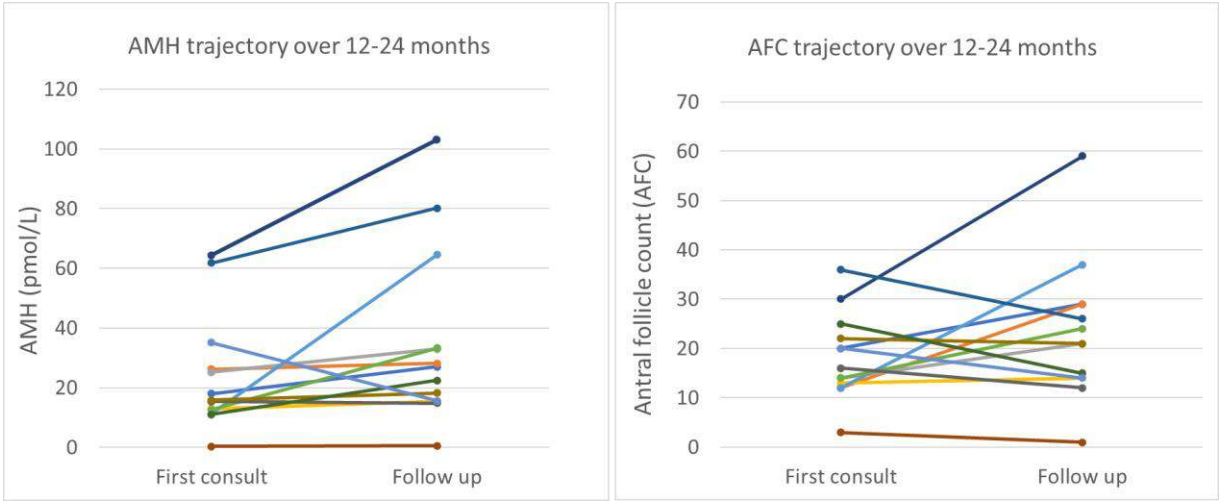

Figure 2: Quantification of ovarian reserve over time.

AMH levels (pmol/L) and antral follicle counts (AFC) in young female survivors of childhood cancer at first assessment and at follow up after 1-2 years.

Discussion

Cancer treatments can be damaging to the ovary, with negative implications for a woman's reproductive lifespan.[14] Measuring ovarian reserve in survivors of cancer treatment can help both clinicians and patients understand their current and projected future ovarian and reproductive function. [15]

Ours is the first study to assess the ovarian reserve of young women in Ireland who received gonadotoxic therapies in childhood or adolescence. Our findings demonstrate that, while the majority (77%) had reassuring results, a sizeable proportion (23%) had evidence of clinically significant fertility compromise and impairment. Those survivors with reassuring ovarian reserve test results at initial assessment did not appear to have an exaggerated decline in AMH level on follow up testing. This finding is similar to a 2013 Danish study, which demonstrated that the

majority of cancer survivors who regained ovarian function in their mid-twenties had almost unchanged ovarian reserves during a 10-year follow up period, with a yearly decline similar to age-matched controls. [16] More recent studies similarly show that, for those who receive low or moderately gonadotoxic treatments, AMH values return to pre-treatment levels within 2-3 years and remain stable for a period of 10 to 15 years or so.[15] Regular follow up is essential to ensure fertility awareness and the risks of postponing parenthood.

Unfortunately, recent data confirms that in those receiving high toxicity therapies, ovarian function deteriorates rapidly and irreversibly. [15,17] Patients with low AMH levels at the time of preliminary assessment are at higher risk of premature ovarian insufficiency (POI) and should be counseled regarding fertility preservation and/or prioritizing pregnancy if desired. [14] If patients in this group follow the current female trend of delaying childbearing, they will be at high risk of developing POI first. Data from The Childhood Cancer Study (CCSS) reported an 8% incidence of premature ovarian insufficiency (POI) in survivors of cancer treatment. [5] It is critical that these patients are recognized quickly once they complete their treatment as they may have a narrow window in which to consider oocyte vitrification. A preferable alternative is to offer fertility preservation to this group, prior to treatment. This is another aim of the Childhood Cancer Fertility Project. Unfortunately, a large percentage of patients do not pursue fertility preservation prior to treatment due to the burden of both their new diagnosis, their impending treatments and, in some cases, a lack of awareness of practitioners to refer.

A primary aim of this study was to evaluate and identify ways to improve our survivor program. A significant challenge that arose as part of establishing our service was accessing this patient cohort. The nature of the care pathway followed by these patients, who had their cancer treatment as children or adolescents, means they have likely been discharged from their primary oncologist or moved on to adult services at the time of requiring a fertility assessment and consultation. In contrast to the highly centralized treatment of paediatric cancer patients aged < 16 years, AYA patients are treated at a wider range of locations. [18] For most survivors attending for assessment post cancer treatment, their primary healthcare provider is their general practitioner. This observation underscores the need for robust, nationwide dissemination of information surrounding this service. Unfortunately, there is a paucity of oncology survivorship clinics in Ireland at present. The HSE National Cancer Survivorship Health Needs Assessment 2018, outlined the minimal research on survivorship after childhood cancer in Ireland to date. [2] In April 2018, the National Cancer Control Programme identified the need for a “more standardised approach to provision of fertility-related information” and confirmed that the “transition from paediatric services was regarded as a particularly challenging time for survivors”.

It is disappointing that, of those deemed to have a low or critical ovarian reserve, several did not attend for follow up and some declined the offer of funded oocyte vitrification. As the service

expands, there will be a need for education and professional counselling services for this group. Diminished fertility is a difficult concept at any age, and particularly so in this young population.

In summary, this pilot study of childhood cancer survivors demonstrates a genuine need for specialized follow up of these young patients to ensure their later reproductive ability is optimized. For those with a normal ovarian reserve post treatment, this reassurance is vital for wellbeing. For those with diminished reserve, fertility preservation can offer those women at highest risk of impaired fertility a valuable opportunity to potentially prolong their reproductive lifespan. It is vital, however, that public funding is provided, as it currently is in virtually all European countries.

Declarations of Conflicts of Interest:
None declared.

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