FERTILITY PRESERVATION FOR CHILDREN AND ADOLESCENTS
A REPORT OF CURRENT PRACTICE

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INTRODUCTION

Advances in cancer treatment have led to improved long term survival of children with childhood cancer. Long term and late effects of past cancer treatment regimes include impaired fertility. Chemotherapeutic regimes are also utilized for young people undergoing bone marrow transplant or non cancer conditions such as severe immunologic disorders and chronic diseases with transfusion requirements such as Thalassaemia major

Fertility Preservation (FP) in children and adolescents poses unique challenges as efficacy is unproven.

Aims: We sought to describe the characteristics of ovarian and testicular tissue collected from paediatric and adolescent patients for the purpose of FP, stratified according to previous chemotherapy and pubertal status at the time of FP intervention. We also looked at evidence for potential fertility in ovarian and testicular tissue cryopreservation specimens (OTCP and TTCP respectively) in these patients.

METHODS

This was a retrospective review of gonadal biopsies and clinical records of patients consented into the Royal Children's Hospital FP program between 1987-2015. Tissue was sectioned, with one section sent for histopathology prior to cryopreservation.

In boys ≥ 12 years where spermatogenesis could be expected, a portion of tissue was dissected to look for mature sperm . If sperm were seen, additional tissue was dissected and the suspension frozen.

In girls, follicle density was assessed on histology. Cumulus oocyte complexes if recovered were cultured for 48 hours and mature oocytes frozen.

RESULTS – MALE FP

TTCP specimens were obtained from 44 males (0.3-16.8 years). An average of 7.8 slices were taken per sample. Each slice was approximately 2-5 mm.

Figure 1 shows the distribution by primary diagnosis. The majority of testicular biopsies were done in the setting of an underlying malignancy. 12 of the patients were pubertal and 32 were pre-pubertal. All the testicular biopsies were timed to be done with another existing procedure under general anaesthesia. There was no delay in the treatment of underlying malignancy.

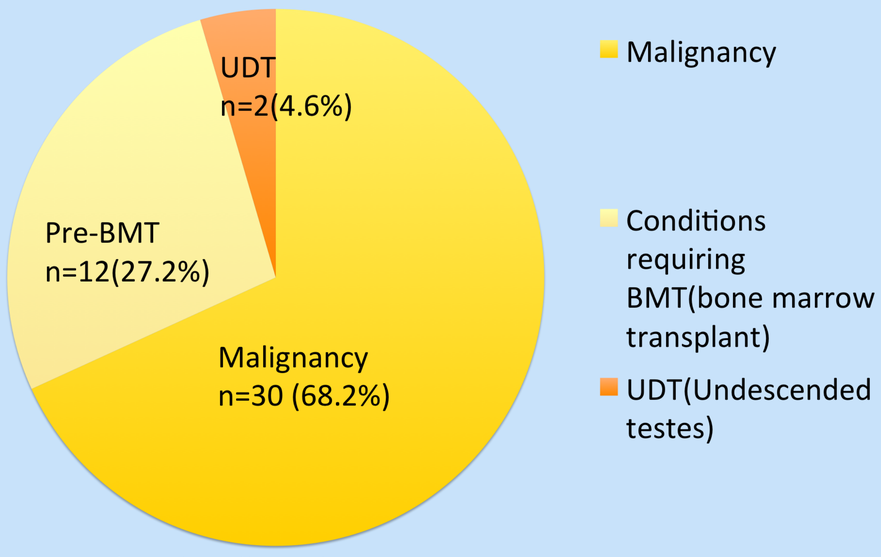

Figure 1. Male patient diagnosis

Table 1 summarises the characteristics of collected testicular tissue. Most patients had tissue size of at least 10x5mm collected. 11 patients had tissue dissected, mature sperm were found in 8 of these patients. Of these 8 patients, all were pubertal and had testicular size of 10-12ml. The youngest patient with sperm found was 12.7 years old. In patients where histology was available and tissue was dissected but no sperm found, histological evidence of spermatogenesis was also absent. There was no evidence of malignancy in any tissue. One patient with sperm found had prior low-risk gonadotoxic therapy.

Patients with tissue collected	44	Age range: 0.3 – 16.8 years 12 pubertal, 32 pre-pubertal
Patients with tissue stored	40	Ave slices / patient: 7.8 4 patient had only sperm stored
Patients with tissue dissected for attempted sperm recovery	11	Age range: 12.7 – 16.8 yrs
• with sperm recovered & stored	8	Testicular size 10-12ml
• without sperm recovered	3	Testicular size <10ml

Table 1. Summary of testicular tissues collected

RESULTS – FEMALE FP

OTCP specimens were obtained from 50 females (1.0 -19.6 years) providing 12-222 slices (1x1x3 mm). Figure 2 shows the distribution by primary diagnosis. The vast majority were done in the setting of an underlying malignancy. 3 patients categorised as "others" included Turner syndrome, galactosaemia and systemic lupus erythematosus before use of cyclophosphamide.

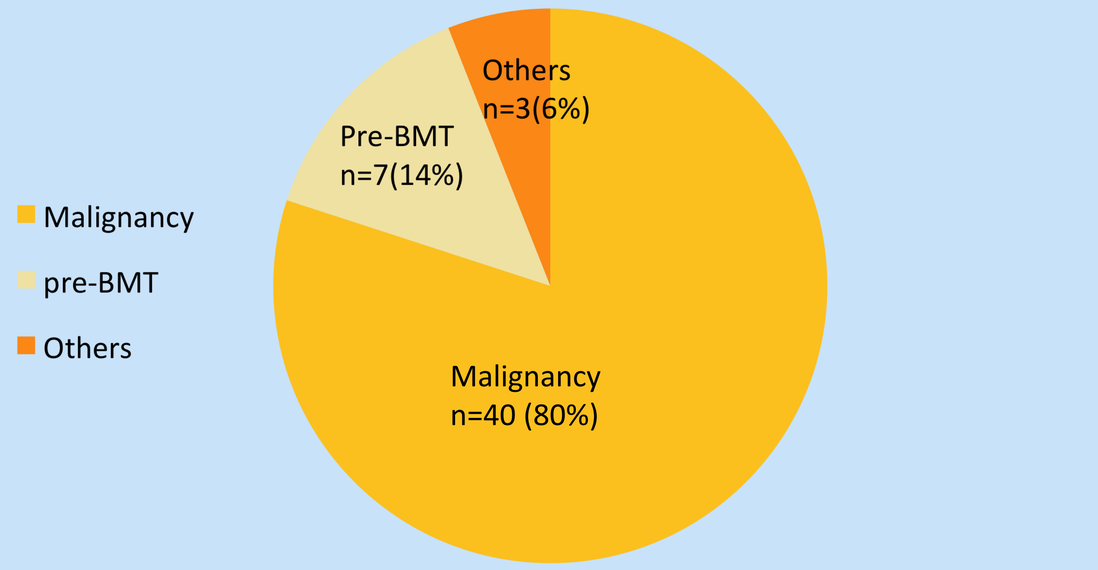

Figure 2. Female patient diagnosis

31 patients were pubertal and 19 were pre-pubertal. Most of the procedures were timed with another existing procedure. Tissue collected had no evidence of malignancy on histology. Follicle density was 0.3-134/mm^2. 4 patients had mature oocytes obtained from OTCP and their details are shown in Table 2 below. The youngest patient with mature oocytes collected was 13.3years old.

Age	Diagnosis	Infertility Risk (>80%)	Menar-chal age	Ovarian volume (mm^3)	Primordial follicles	Slices	Follicular density (mm^2)	NR	Mature oocytes	AMH (pmol/L)
13.3	Ewing sarcoma	High	11	20x16x5	>20	122	4.9	10.04	9	11.4
13.9	B cell lymphoma	High	12	10x7x3	95	104	19		12	10.8
17.7	Aplastic anemia	High	12	4x2x3	Nil	73	-	2.53	1	-
14.7	Ewing sarcoma	High	11	8x6x2	50	70	6.1	-	9	87.1

Table 2. Characteristics of 4 patients with mature oocytes obtained

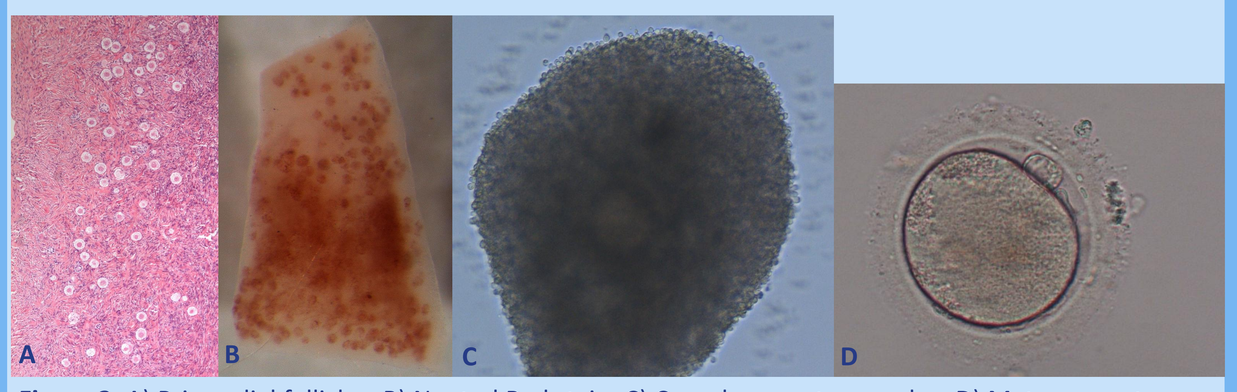

Figure 3. A) Primordial follicles; B) Neutral Red stain; C) Cumulus oocyte complex; D) Mature oocyte with polar body

CONCLUSIONS

Both TTCP and OTCP can be offered to young patients without delay in cancer treatment or conditioning regimes prior to bone marrow transplant for any disorder.

Retrieval of spermatogonial cell lines and / or mature sperm and oocytes from some pubertal patients may offer realistic hope for future fertility.

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