FERTILITY PRESERVATION FOR CHILDREN AND ADOLESCENTS
A REPORT OF CURRENT PRACTICE

Cindy Ho1,3, Harold Bourne2, Debra Gook2, Matthew Kemertzis1, Kate Stern3,4, Franca Agresta2, Hves Heloury5, Hannah Clarke6, Lisa Orme7, Shlomi Barak8, Gary Clarke4, Margaret Zacharin1, Yasmin Jayasingh1,8 for the PAEDIATRIC & ADOLESCENT FERTILITY PRESERVATION TASKFORCE, MELBOURNE

1) Department of Endocrinology Royal Children’s Hospital, 2) Melbourne IVF, 3) Department of Obstetrics & Gynaecology, Royal Women’s Hospital, University of Melbourne, 4) Reproductive Services Royal Women’s Hospital, 5) Department of Surgery, Royal Children’s Hospital, Monash University, Melbourne, 6) Children’s Cancer Centre Royal Children’s Hospital, 7) Department of Paediatric & Adolescent Gynaecology Royal Children’s Hospital, 8) Department of Paediatrics, Khoo Teck Puat-National University Children’s Medical Institute

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 limited. 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 spermatogonias 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 or non cancer conditions such as severe immunologic disorders and chronic diseases with transfusion requirements such as Thalassaemia major.

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 spermatogonias was also absent. There was no evidence of malignancy in any tissue. One patient with sperm found had prior low-risk gonadotoxic therapy.

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.

Table 2. Characteristics of females with mature oocytes obtained

<table>
<thead>
<tr>
<th>Age</th>
<th>Diagnosis</th>
<th>Infertility Risk (&gt;80%)</th>
<th>Menarcheal age</th>
<th>Ovarian volume (mm³)</th>
<th>Primordial follicles</th>
<th>Slices</th>
<th>Follicle density (mm²)</th>
<th>NR</th>
<th>Mature oocytes</th>
<th>AMH (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.3</td>
<td>Ewing sarcoma</td>
<td>High</td>
<td>11</td>
<td>20±16±3</td>
<td>&gt;20</td>
<td>12</td>
<td>4.9</td>
<td>10.04</td>
<td>9</td>
<td>13.4</td>
</tr>
<tr>
<td>13.9</td>
<td>B cell lymphoma</td>
<td>High</td>
<td>12</td>
<td>16±7±3</td>
<td>95</td>
<td>104</td>
<td>19</td>
<td>12</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>17.7</td>
<td>Aplastic anemia</td>
<td>High</td>
<td>12</td>
<td>4±2±3</td>
<td>0±0</td>
<td>73</td>
<td>2.3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.7</td>
<td>Ewing sarcoma</td>
<td>High</td>
<td>11</td>
<td>8±6±2</td>
<td>50</td>
<td>70</td>
<td>6.1</td>
<td>9</td>
<td>87.1</td>
<td></td>
</tr>
</tbody>
</table>

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.

ACKNOWLEDGMENTS

Funding for this research was in part provided by the Victorian Cancer Agency.

CONTACT

Dr Cindy Ho at cindy_ho@nuhs.edu.sg