Spermatogonial stem cell autotransplantation: towards clinical application

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Parents’ attitudes towards fertility preservation in young boys with cancer

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Submitted
PURPOSE
Survival rates among children with cancer have increased tremendously. Gonadal failure and subsequent poor long-term reproductive outcomes after treatment are important issues in cancer survivors. The attitudes of parents of boys with cancer towards fertility preservation in the context of different risk levels of infertility and success rates of fertility restoration have not previously been evaluated.

METHODS
A questionnaire was mailed to 465 families whose son was treated for cancer between December 1990 and December 2009 at Mahak-Institute in Iran. The questionnaire was designed for two age groups, i.e. children <12 or ≥ 12 years old. Univariate and multivariate logistic regression were used to analyze associations of various parameters.

RESULTS
The response rate was 78%. At the time of cancer treatment only 15% of parents were aware of the effect of cancer treatment on fertility. Sixty-four percent of parents of boys ≥12 years would agree to store sperm obtained by masturbation and/or electro-ejaculation, while 54% of parents of boys <12 years would agree to store a testicular biopsy. If the risk of infertility or the success rate of fertility restoration would be 20% at most, more than one-fourth of parents would still opt for fertility preservation.

CONCLUSION
Parents of boys with cancer have limited knowledge about the risks of infertility due to cancer treatment. All parents should be counseled about this issue, as many parents want to preserve their son’s fertility even if the risk of becoming infertile or the chances on fertility restoration are low.
INTRODUCTION

In the last three decades survival rates in children with cancer have improved tremendously and the current 5-year relative survival rate for all cancers combined is around 80%\(^1\). Gonadal failure and subsequent poor long-term reproductive outcomes are important sequelae of childhood cancer treatment\(^2,3\). Fertility preservation is thus an important aspect of childhood cancer treatment and should be considered as early as possible during treatment planning\(^4\). The preferred option in adolescent patients is cryopreservation of ejaculated semen after masturbation, if feasible\(^5\). If not, mature sperm may be collected by electro-ejaculation or by a testicular biopsy\(^6,7,8\). In prepubertal boys the only option is to store testicular tissue containing spermatogonial stem cells (SSCs) for future SSCs autotransplantation or tissue engraftment\(^9,15\) (figure 1).

Previous studies showed that parents eagerly await new options for fertility preservation for their prepubertal sons, but these studies were performed in small cohorts and did not address the attitudes of parents towards fertility preservation in the context of different risk levels of infertility and success rates of fertility restoration\(^9,16\).

Therefore, we explored parents’ attitudes towards fertility preservation in the context of different risk levels of infertility and success rates of fertility restoration.
METHODS

Recruitment procedure and evaluated variables
Parents of all boys who were diagnosed with cancer between December 1990 and December 2009 at the Mahak institute in Tehran, Iran – a tertiary center for the treatment of childhood cancer – and who were still alive in 2010 were included in this study. The study was approved by the institutional review board of Mahak Institute and Avicenna Research Institute, Tehran, Iran. We designed two questionnaires (<12 and ≥12 years of age), which were both validated in a pilot study of 61 families. The pilot study did not reveal any difficulties with the questionnaires and therefore those questionnaires were also included in the main study. The difference between the two questionnaires was that questions about masturbation and electroejaculation were omitted for parents of boys younger than 12 years of age. The relevant questionnaire was sent by mail to the parents. By default, each mother and father were asked to fill out the questionnaire together. When this was not possible, the relationship between the person(s) who filled the questionnaire and the boy was noted.

The questionnaires first provided basic information for parents to understand the effects of cancer treatment on fertility and the issue of fertility preservation. Next, the questionnaires contained data on their sons, extracted from their medical file at Mahak Institute; like date of birth, place of birth, type of cancer, treatment start and stop date (if completed) and relapse information (if present).

After having read this information, parents were asked to fill in their age, educational level, employment status, history of infertility in relatives and the current health condition of their son, and to answer questions on their knowledge of cancer treatment induced infertility and when and how they received information on this topic. Parents were then asked about their opinion on current and future fertility preservation options. Finally, quantitative questions were asked about chances of infertility and success rates of fertility restoration and how this related to their willingness to have their son undergo fertility preservation.

Statistical Analysis
Data are presented by age group of the boys, i.e. <12 and ≥12 years of age. Main outcome was a positive or negative attitude of parents towards fertility preservation options. To assess whether baseline characteristic of parents and boys were associated with the attitudes towards fertility preservation, univariate and multivariate logistic regression analysis were performed to control the age group.
RESULTS

Response Rate and parents/boys characteristics
A total of 465 parents were sent a questionnaire of which 365 (78%) responded and 100 declined to participate in this study. Based on current residency, the families were from all 31 provinces of Iran. In 76% of cases, the mother and father had filled out the questionnaire together. The most common malignancies were Acute Lymphoblastic Leukemia (ALL, 43%), Hodgkin lymphoma (13%) and Acute Myelocytic Leukemia (AML, 6%). The distribution of malignancies is summarized in Table 1.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>&lt;12 (n=299)</th>
<th>&gt;12 (n=66)</th>
<th>Overall (n=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Lymphoblastic Leukemia (ALL)</td>
<td>136</td>
<td>22</td>
<td>158</td>
</tr>
<tr>
<td>Acute Myelocytic Leukemia (AML)</td>
<td>9</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Brain tumor</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Burkitt's lymphoma</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Chronic Myelogenous Leukemia (CML)</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ependymal tumor</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ewing's sarcoma</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ganglioneuroblastoma</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hepatoma</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Histioctyosis</td>
<td>6</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>30</td>
<td>16</td>
<td>46</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Mixed leukaemia</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>12</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Non Hodgkin Lymphoma (NHL)</td>
<td>10</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Primitive Neuroectodermal Tumor (PNET)</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Renal sarcoma</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>16</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Rhabdomyosarcoma (RMS)</td>
<td>13</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Small round cell</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Spindle cell</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Wilms Tumor</td>
<td>17</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Yolk sac tumor</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
The boys' age at cancer diagnosis ranged from 10 months to 15.5 years. Survival duration from cancer ranged between 1 month to 19 years. Seventy-seven percent of boys were in a good or very good health condition and only 2% were in a poor or very poor health condition according to their parents. Baseline characteristic of parents and boys are shown in Table 2.

<table>
<thead>
<tr>
<th>Group (Age at diagnosis-Year)</th>
<th>&lt;12 (n=299)</th>
<th>&gt;12 (n=66)</th>
<th>Overall (n=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boy's age (year) at diagnosis, mean (95% CI)</td>
<td>5.0 (4.6-5.4)</td>
<td>13 (11.0-13.7)</td>
<td>6.5 (6.0-7.0)</td>
</tr>
<tr>
<td>Boy's survival duration (Months), median (min-max)</td>
<td>39 (2-230)</td>
<td>34 (1-116)</td>
<td>37 (1-230)</td>
</tr>
<tr>
<td>Relapse of cancer, n (%)</td>
<td>33 (11)</td>
<td>6 (9)</td>
<td>39 (11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Boy’s health condition in parents’ point of view at the time of study, n (%)</th>
<th>Overall (n=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>130 (36)</td>
</tr>
<tr>
<td>Good</td>
<td>155 (41)</td>
</tr>
<tr>
<td>So so</td>
<td>67 (19)</td>
</tr>
<tr>
<td>Poor</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Very poor</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (2)</td>
</tr>
</tbody>
</table>

| Mother’s age (year), mean (95% CI) | 35 (34.6-36.3) | 40 (38.8-41.3) | 36.2 (35.5-37.0) |
| Father’s age (year), mean (95% CI) | 40 (39.3-41.1) | 46 (44.3-48.7) | 41.4 (40.5-42.2) |

<table>
<thead>
<tr>
<th>Highest education level in family (Father or Mother), n (%)</th>
<th>Overall (n=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic</td>
<td>68 (19)</td>
</tr>
<tr>
<td>High school</td>
<td>101 (28)</td>
</tr>
<tr>
<td>Middle school</td>
<td>77 (21)</td>
</tr>
<tr>
<td>Primary school</td>
<td>99 (27)</td>
</tr>
<tr>
<td>Illiterate</td>
<td>20 (5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of children, median (min-max)</th>
<th>Overall (n=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (1-11)</td>
<td>5 (1-11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Who filled-in questionnaire, n (%)</th>
<th>Overall (n=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother and father together</td>
<td>276 (76)</td>
</tr>
<tr>
<td>Only mother</td>
<td>31 (8)</td>
</tr>
<tr>
<td>Only father</td>
<td>32 (8)</td>
</tr>
<tr>
<td>Third person as guardian</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fertility problems in relatives, n (%)</th>
<th>Overall (n=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42 (14)</td>
<td>52 (14)</td>
</tr>
</tbody>
</table>

### Parent’s knowledge

Only 22% of all parents reported that they knew about the effect of cancer treatment on fertility before they received this questionnaire. Only 15% said they were already aware of the effect of cancer treatment on fertility before the start of cancer treatment. Of those parents that were aware of the effects of cancer treatment on fertility before they received this questionnaire, only one third had been informed about this by the treating physician (table 3).
The educational level of all parents was linearly associated with their knowledge on the effect of cancer treatment on fertility (chi² of 10.7 p<0.01), i.e. parents with higher levels of education have a greater understanding of the treatment effect on fertility.

### Table 3. Parents’ knowledge

<table>
<thead>
<tr>
<th>Group (Age at diagnosis-Year)</th>
<th>&lt;12 (n=299)</th>
<th>&gt;12 (n=66)</th>
<th>Overall (n=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aware of the risk of adverse effects of treatment on fertility, before receiving this questionnaire, n (%)</td>
<td>63 (21)</td>
<td>16 (24)</td>
<td>79 (22)</td>
</tr>
<tr>
<td>How did you know it? n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treating physician</td>
<td>22 (35)</td>
<td>9 (56)</td>
<td>31 (39)</td>
</tr>
<tr>
<td>Own general knowledge</td>
<td>40 (63)</td>
<td>7 (44)</td>
<td>47 (60)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Aware of the risk of adverse effects of cancer treatment, before initiation of cancer treatment, n (%)</td>
<td>42 (14)</td>
<td>11 (17)</td>
<td>53 (15)</td>
</tr>
<tr>
<td>How were you aware of the risks? n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treating physician</td>
<td>12 (28)</td>
<td>5 (46)</td>
<td>17 (32)</td>
</tr>
<tr>
<td>Own general knowledge</td>
<td>25 (60)</td>
<td>5 (46)</td>
<td>30 (57)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>5 (12)</td>
<td>1 (8)</td>
<td>6 (11)</td>
</tr>
</tbody>
</table>

### Parents’ attitudes towards fertility preservation options

Sixty-four percent of parents of boys ≥12 years of age would agree with masturbation, electro-ejaculation or both to collect semen. If semen collection failed, testicular biopsy would be an acceptable option for 41% of these parents.

Fifty-four percent of parents of boys <12 would agree with a testicular biopsy to store SSCs. In both age groups, the primary reason to decline testicular biopsy was the concern that the procedure would negatively affect the health of their son (Table 4).

In the group ≥12 years of age there was a significant association between the boys’ age and his parents’ acceptance of masturbation and/or electro-ejaculation (OR 2.3, 95% CI 1.35-3.8, p=0.002), i.e. the older the boy the higher the acceptance of his parents. Acceptance of masturbation and/or electro-ejaculation in the group ≥12 years of age was not associated with the number of children within the family, survival duration, current health condition, occurrence of a relapse, completion of treatment or family education level. In both age groups there was no association between acceptance of a testicular biopsy and any baseline characteristic.
<table>
<thead>
<tr>
<th>Table 4. Parents, attitudes to fertility preservation options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group (Age at diagnosis-Year)</strong></td>
</tr>
<tr>
<td>Agree with sperm collection by means of masturbation or electro-ejaculation? n (%)</td>
</tr>
<tr>
<td>Agree</td>
</tr>
<tr>
<td>With both</td>
</tr>
<tr>
<td>Only masturbation</td>
</tr>
<tr>
<td>Only electroejaculation</td>
</tr>
<tr>
<td>Disagree</td>
</tr>
<tr>
<td>No idea/no answer</td>
</tr>
<tr>
<td>Agree with testicular biopsy to preserve SSCs if sperm collection failed? n (%)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>No idea</td>
</tr>
<tr>
<td>Agree with testicular biopsy to preserve SSCs? n (%)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>No idea</td>
</tr>
<tr>
<td>If disagree with testicular biopsy, what is the main reason? n(%)</td>
</tr>
<tr>
<td>Personal opinion</td>
</tr>
<tr>
<td>Worry to hurt my son</td>
</tr>
<tr>
<td>My son should decide by himself and it's not possible</td>
</tr>
<tr>
<td>Combination of the above</td>
</tr>
<tr>
<td>Other reasons</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5. Parents’ attitudes towards different chances of infertility and different success rates of fertility preservation*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group (Age at diagnosis-Year)</strong></td>
</tr>
<tr>
<td>Agree with fertility preservation if chance of infertility is at most 20%? n (%)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>No idea</td>
</tr>
<tr>
<td>Agree with fertility preservation if chance of infertility is at least 80%? n (%)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>No idea</td>
</tr>
<tr>
<td>Agree with fertility preservation, if success rate of using stored material will be at most 20%? n (%)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>No idea</td>
</tr>
<tr>
<td>Agree with fertility preservation, if success rate of using stored material will be at least 80%? n (%)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>No idea</td>
</tr>
</tbody>
</table>

These questions were not included in the questionnaires sent in the pilot study (n=61).
Parents’ attitudes toward different chances of infertility and success rates of fertility restoration

Parents were informed that the chances of infertility depend on the type of treatment given and that no fertility preservation method can guarantee with certainty that fertility will be restored in the future. Parents’ attitudes towards different chances of infertility and different success rates of fertility restoration are shown in Table 5. More than one third of all parents (36%) wanted some sort of fertility preservation even if the chances of infertility were 20% at most. Similarly, 27% of parents wanted some sort of fertility preservation even if the success rates in terms of restoring fertility in the future were at most 20%.

**DISCUSSION**

The results highlight that a limited number of parents (14% in the group <12 years and 17% in the ≥12 years) had knowledge about the risk of infertility when the cancer treatment of their son was initiated. Once parents became aware of the risks, more than half of them wanted some sort of fertility preservation for their son. Our results also show that the acceptance rate of fertility preservation is not affected by differences in family demographic parameters or patients’ characteristics, illustrating that fertility preservation is of universal importance in most families.

We found that even with low risks of infertility (20%) and/or low success rates of restoring fertility in the future (20%), at least one-fourth of parents would want to preserve fertility of their son. These findings underscore the importance parents give to the fertility of their son and are in line with previous data on the importance of fertility on long-term quality of life for cancer survivors.17,19.

The number of participating families in our study (365 families) was more than the two previous studies (117 and 21 families). The acceptance rate for different fertility preservation options in our study was in the same range as previous studies, which shows that parents’ attitudes towards fertility preservation in different geographical and cultural areas (Iran, Netherlands and USA) are similar highlighting the global importance of reproduction among parents of boys with cancer. A lower acceptance rate was expected for testicular biopsy in prepuberal boys in our study in Iran (54%) and a previous study in the Netherlands (62%) compared to the study conducted in the USA (76%), because of different methods of approaching parents, i.e. face to face consultation in the USA study versus sending questionnaires by post in the studies in Iran and the Netherlands.
and the different timing of the questionnaire, i.e. at the time of cancer diagnosis and after treatment. Moreover, the studies in Iran and the Netherlands were retrospective scenario ones while the study in the USA was a prospective study in which the testicular biopsy procedure was a real option for these patients.

We explained to the parents that although cryopreservation of testicular tissue including SSCs is now feasible, more research is required for SSC transplantation or tissue engraftment to become clinically available. For this future research, access to human prepubertal testis tissue is imperative. In this respect it is important to mention that more than half of the parents (56%) in the current study said they would agree with donating a maximum of one-third of the obtained testicular material for research if asked to do so (data not shown).

It has been reported that half of the families who were given information about the risks of infertility due to cancer treatment at the time of cancer diagnosis, were not able to recall it later. It is in our view essential to have an active program in place with a multidisciplinary team – including pediatric oncologists and fertility specialists – to counsel parents of boys with cancer adequately about infertility risks and preservation options before starting cancer treatment.

Although assessment of the risks of infertility induced by cancer treatments may be difficult, it is important to decide who should be counseled and offered fertility preservation. The results of our study show that at least one fourth of parents of boys with cancer would opt for fertility preservation, even if the chance of infertility and/or the chance of successful restoring fertility using stored material would be 20% at most. This data thus demonstrate that all parents should receive consultation on fertility issues so that each family can make its own individual informed decision.

In conclusion, this study demonstrated that parents of boys with cancer have limited knowledge on the risks of infertility due to cancer treatment, but the majority would want some sort of fertility preservation once informed about these risks. Moreover, many parents still want some sort of fertility preservation even if the risks of infertility or the success rates in restoring fertility are as low as 20%. Assembling a multidisciplinary team is necessary to support boys with cancer and their parents to make fully informed decisions about fertility preservation.

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REFERENCES


