

Parental attitudes toward fertility preservation in boys with cancer: context of different risk levels of infertility and success rates of fertility restoration

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Objective: To measure the parental attitudes toward fertility preservation in boys with cancer.

Design: Retrospective cohort study.

Setting: Questionnaire survey via regular mail.

Patient(s): A total of 465 families whose sons were already treated for cancer.

Intervention(s): The questionnaire was designed for two groups based on child's age at the time of cancer diagnosis: <12 and ≥12 years old.

Main Outcome Measure(s): Descriptive statistics regarding a positive or negative attitude of parents toward fertility preservation options in the context of different risk levels of infertility and success rates of fertility restoration.

Result(s): The response rate was 78%. Sixty-four percent of parents of boys ≥12 years old would agree to store sperm obtained by masturbation and/or electroejaculation, and 54% of parents of boys <12 years old would agree to store a testicular biopsy. If the risk of infertility or the success rate of fertility restoration were ≤20%, more than one-fourth of parents would still opt for fertility preservation.

Conclusion(s): All parents should be counseled about the risks of infertility due to cancer treatment, because many parents want to preserve their son's fertility even if the risk of becoming infertile or the chances on fertility restoration are low. (Fertil Steril® 2013;99:796–802. ©2013 by American Society for Reproductive Medicine.)

Key Words: Childhood cancer, infertility, fertility preservation, spermatogonial stem cell, testicular biopsy

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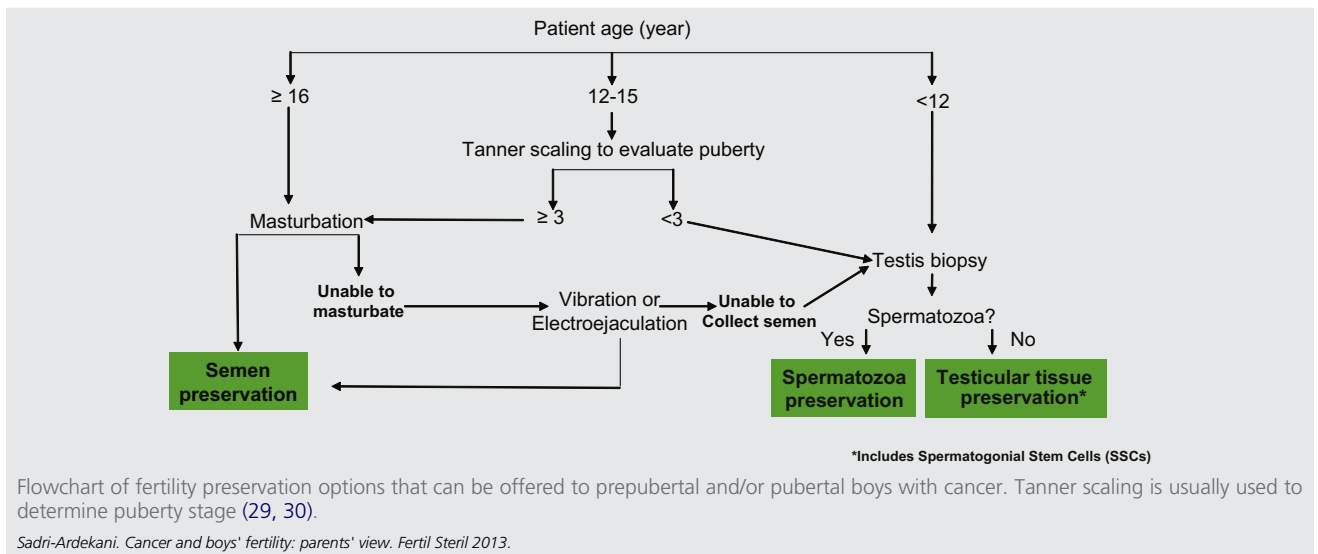
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In the past three decades, survival rates in children with cancer have improved tremendously, and the current 5-year relative survival rate for all cancers combined is ~80% (1, 2). Gonadal failure and subsequent poor long-term reproductive outcomes are important sequelae of childhood cancer treatment (3–5). Fertility preservation is therefore an important aspect of childhood cancer treatment and should be considered as early as

FIGURE 1



possible during treatment planning (6, 7). The preferred option in adolescent patients is cryopreservation of ejaculated semen after masturbation, if feasible (8). If not, mature sperm may be collected by electroejaculation or testicular biopsy (7, 9–11). In prepubertal boys the only option is to store testicular tissue containing spermatogonial stem cells (SSCs) for future autotransplantation or tissue engraftment (Fig. 1) (12–18).

Earlier studies show that parents of pediatric cancer patients have concerns about fertility-related side effects of cancer treatments (19) and they eagerly await new options for fertility preservation for their prepubertal sons, but none of those studies addressed the attitudes of parents toward fertility preservation in the context of different risk levels of infertility and success rates of fertility restoration (12, 20), which is important in clinical practice.

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

MATERIALS AND METHODS

Recruitment Procedure and Evaluated Variables

Parents of all boys who were diagnosed with cancer from December 1990 to December 2009 at the Mahak institute in Tehran, Iran, a tertiary center for the treatment of childhood cancer, and their children 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 old at the time of cancer diagnosis), 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 <12 years old. The relevant questionnaire was sent by mail to the parents. By default, each mother and

father pair 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, such as 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 out 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 (21) and success rates of fertility restoration and how this related to their willingness to have their son undergo fertility preservation.

Statistical Analyses

This was a retrospective cohort study. Data are presented by age group of the boys, i.e., <12 and ≥ 12 years of age at the time of cancer diagnosis. The main outcome was a positive or negative attitude of parents toward fertility preservation options. To assess whether baseline characteristics of parents and boys were associated with the attitudes toward fertility preservation, univariate and multivariate logistic regression analyses 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.

TABLE 1

Demographic characteristics of boys and parents.^a

	Age at diagnosis, y		Overall (n = 365)
	< 12 (n = 299)	≥ 12 (n = 66)	
Boy's age (y) at diagnosis, mean (95% CI)	5.0 (4.6–5.4)	13 (13.0–13.7)	6.5 (6.0–7.0)
Types of boys' cancer			
Acute lymphoblastic leukemia	136	22	158
Acute myelocytic leukemia	9	11	20
Astrocytoma	2		2
Brain tumor	5	1	6
Burkitts lymphoma	3		3
Chronic myelogenous leukemia	2		2
Craniopharyngioma	2		2
Ependymal tumor	2		2
Ewing sarcoma	5	2	7
Fibrosarcoma	1		1
Ganglioneuroblastoma	3	1	4
Germ cell tumor	1		1
Hepatoma	2		2
Histocytosis	6		6
Hodgkin lymphoma	30	16	46
Medulloblastoma	6		6
Mixed leukemia	1		1
Nasopharyngeal carcinoma	2		2
Neuroblastoma	12		12
Non-Hodgkin lymphoma	10	3	13
Osteosarcoma	2	3	5
Primitive neuroectodermal tumor	1	2	3
Renal sarcoma	1		1
Retinoblastoma	16		16
Rhabdomyosarcoma	13		13
Sarcoma	1	1	2
Small round cell	3	2	5
Spindle cell	2	1	3
Synovial sarcoma	1		1
Wilms tumor	17	1	18
Yolk sac tumor	2		2
Boy's survival duration (mo), median (range)	39 (2–230)	34 (1–116)	37 (1–230)
Relapse of cancer, n (%)	33 (11)	6 (9)	39 (11)
Boy's health condition in parents' point of view at the time of completing the questionnaire, n (%)			
Very good	106 (36)	24 (37)	130 (36)
Good	128 (43)	27 (41)	155 (41)
So so	52 (17)	15 (22)	67 (19)
Poor	4 (1)	–	4 (1)
Mother's age (y), mean (95% CI)	35 (34.6–36.3)	40 (38.8–41.3)	36.2 (35.5–37.0)
Father's age (y), mean (95% CI)	40 (39.3–41.1)	46 (44.3–48.7)	41.4 (40.5–42.2)
Highest education level in family (father or mother), n (%)			
Academic	57 (19)	11 (17)	68 (19)
High school	89 (30)	12 (18)	101 (28)
Middle school	63 (21)	14 (21)	77 (21)
Primary school	76 (25)	23 (35)	99 (27)
Illiterate	14 (5)	6 (9)	20 (5)
No. of children in family, median (range)	2 (1–11)	3 (1–11)	5 (1–11)
Who completed questionnaire, n (%)			
Mother and father together	221 (74)	55 (84)	276 (76)
Only mother	29 (10)	2 (3)	31 (8)
Only father	28 (9)	4 (6)	32 (8)
Third person as guardian	10 (3)	3 (4)	13 (4)
Unknown	11 (4)	2 (3)	13 (4)
Fertility problems in relatives, n (%)	42 (14)	10 (15)	52 (14)

^a Parents' characteristics refer to their status at the time of completing the questionnaire.

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Based on current residency, the families were from all 31 provinces of Iran. In 76% of cases, the mother and father filled out the questionnaire together. The most common malignancies were acute lymphoblastic leukemia (43%), Hodgkin

lymphoma (13%), and acute myelocytic leukemia (6%). The distribution of malignancies is summarized in Table 1.

The boys' ages at cancer diagnosis ranged from 10 months to 15.5 years. Survival duration from cancer ranged from 1 month

TABLE 2

Parents' knowledge and attitudes to fertility preservation options.

	Age at diagnosis, y		Overall (n = 365)
	< 12 (n = 299)	≥ 12 (n = 66)	
Aware of the risk of adverse effects of treatment on fertility before receiving this questionnaire, n (%)	63 (21)	16 (24)	79 (22)
Source of awareness of these effects, n (%)			
Treating physician	22 (35)	9 (56)	31 (39)
Own general knowledge	40 (63)	7 (44)	47 (60)
Other or unknown	1 (2)	0 (0)	1 (1)
Aware of the risk of adverse effects of cancer treatment before initiation of cancer treatment, n (%)	42 (14)	11 (17)	53 (15)
Source of awareness of these effects, n (%)			
Treating physician	12 (28)	5 (46)	17 (32)
Own general knowledge	25 (60)	5 (46)	30 (57)
Other or unknown	5 (12)	1 (8)	6 (11)
Reason not to apply for fertility preservation? n (%)			
It was not necessary	21 (50)	0 (0)	21 (40)
No access to a center to preserve semen or testis biopsy	4 (9.5)	4 (36)	8 (15)
Time was limited	13 (31)	7 (64)	20 (38)
Other or unknown	4 (9.5)	0	4 (7)
Agreement with sperm collection by means of masturbation or electroejaculation, n (%)			
Yes	–	42 (64)	
With both		29 (44)	
Only masturbation		3 (5)	
Only electroejaculation		10 (15)	
No	–	16 (24)	
No idea/no answer		8 (12)	
Agreement with testicular biopsy to preserve testicular tissue if sperm collection failed, n (%)			
Yes	–	27 (41)	
No	–	34 (51)	
No idea	–	5 (8)	
Agreement with testicular biopsy to preserve testicular tissue (as the only option in boys <12 years old), n (%)			
Yes	161 (54)	–	
No	121 (40)	–	
No idea	17 (6)	–	
Main reason of disagreement with testicular biopsy, n (%)	(n = 121)	(n = 34)	(n = 155)
It may hurt the boy	86 (71)	22 (64)	108 (69)
Boy should decide by himself and it's not possible at his age	17 (14)	6 (18)	23 (15)
It may hurt the boy, and he should decide by himself and it's not possible at his age	9 (7)	1 (3)	10 (7)
Other reasons	9 (8)	–	14 (9)
Agreement with donating a maximum of one-third of the obtained testicular material for research, n (%)			
Yes	173 (58)	31 (47)	204 (56)
No	104 (35)	26 (39)	130 (36)
No answer	22 (7)	9 (14)	31 (8)

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to 19 years. Seventy-seven percent of the boys were in a good or very good health condition, and only 20% were in a poor or very poor health condition, according to their parents. Baseline characteristics of parents and boys are presented in Table 1.

Parents' 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 that 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 2).

The educational level of all parents was linearly associated with their knowledge of the effect of cancer treatment on fertility ($\chi^2 = 10.7$; $P < .01$), i.e., parents with higher levels of education had a greater understanding of the treatment effect on fertility.

Parents' Attitudes toward Fertility Preservation Options

Sixty-four percent of parents of boys ≥ 12 years of age would agree with masturbation, electroejaculation, or both to collect

TABLE 3

Parents' attitudes toward different chances of infertility and different success rates of fertility preservation.

	Age at diagnosis, y		Overall (n = 304)
	< 12 (n = 259)	≥ 12 (n = 45)	
Agreement with fertility preservation if chance of infertility is ≤20%, n (%)			
Yes	94 (37)	14 (31)	108 (36)
No	77 (30)	12 (27)	89 (29)
No idea	88 (33)	19 (42)	107 (35)
Agreement with fertility preservation if chance of infertility is ≥80%, n (%)			
Yes	168 (65)	25 (55)	193 (64)
No	37 (14)	7 (16)	44 (14)
No idea	54 (21)	13 (29)	67 (22)
Agreement with fertility preservation, if success rate of using stored material is ≤20%, n (%)			
Yes	68 (26)	12 (27)	80 (27)
No	114 (44)	24 (53)	138 (45)
No idea	77 (30)	9 (20)	86 (28)
Agreement with fertility preservation, if success rate of using stored material is ≥80%, n (%)			
Yes	169 (65)	30 (67)	199 (66)
No	36 (14)	5 (11)	41 (14)
No idea	54 (21)	10 (22)	64 (20)

Note: These questions were not included in the questionnaires sent in the pilot study.

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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 2).

In the group ≥ 12 years of age, there was a significant association between the boy's age and his parents' acceptance of masturbation and/or electroejaculation (odds ratio [OR] 2.3, 95% confidence interval [CI] 1.35–3.8; $P = .002$), i.e., the older the boy, the higher the acceptance by his parents. Acceptance of masturbation and/or electroejaculation 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.

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 toward different chances of infertility and different success rates of fertility restoration are presented in Table 3. More than one-third of all parents (36%) wanted some sort of fertility preservation even if the chances of infertility were ≤20%. Similarly, 27% of parents wanted some sort of fertility preservation even if the success rates of restoring fertility in the future were ≤20%.

DISCUSSION

The results highlight that a limited number of parents (14% in the <12 years group and 17% in the ≥ 12 years group) 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 one-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 the fertility of their son. These findings underscore the importance that parents give to the fertility of their sons and are in line with earlier data on the importance of fertility on long-term quality of life for cancer survivors (22–25).

The number of participating families in our study (365 families) was more than the two previous studies (117 [20] and 21 [12] families). The acceptance rate for different fertility preservation options in our study was in the same range as earlier studies (12, 20), which shows that parents' attitudes toward fertility preservation in different geographic and cultural areas (Iran, The Netherlands, and USA) (12, 20) are similar, highlighting the global importance of reproduction among parents of boys with cancer. Our study and the one in USA (12) showed that other factors than parental sense and responsibility, such as educational level, religious, financial situation, and having other children, did not appear to be major factors in the decision-making process. A lower acceptance rate was expected for testicular biopsy in prepubertal boys in our study in Iran (54%) and an earlier study in The Netherlands (62%) compared with the study conducted in the USA (76%), because of different methods of approaching parents, i.e., face-to-face consultation in the USA study (12) versus sending questionnaires by post in the studies in Iran and The Netherlands (20) and the different timing of the questionnaire, i.e., at the time of cancer diagnosis (12)

and after treatment. Moreover, the studies in Iran and the Netherlands were retrospective scenario ones, whereas the study in the USA (12) was a prospective study in which the testicular biopsy procedure was a real option for these patients. These data together promise a high acceptance of parents for testicular biopsies before anticancer treatments in real clinical services everywhere.

We explained to the parents that although cryopreservation of testicular tissue including SSCs is now feasible (13–15), 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 one-half of the parents (56%) in the present study said they would agree with donating a maximum of one-third of the obtained testicular material for research if asked to do so.

It has been reported that one-half of the families who were given information at the time of cancer diagnosis about the risks of infertility due to cancer treatment were not able to recall them later (26). 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 precise prediction of the risks of infertility induced by cancer treatments may be difficult (21), it is important to decide who should be counseled and offered fertility preservation (27, 28). 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 chances of infertility and/or the chance of successful restoration fertility using stored material were $\leq 20\%$. These 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 $\leq 20\%$. 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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