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Poor semen quality from patients with malignancies does not rule out sperm banking

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Abstract Cancer therapy can further impair the already poor semen quality in cancer patients. This study evaluated the prefreeze and postthaw semen quality before treatment of patients with malignancies to examine the rationale for sperm banking for these men. Records of nine patients with different malignant tumors, who had been referred for sperm cryopreservation between 1982 and 1997, were reviewed and the results were compared with those of 50 normal healthy donors. Patients did not differ from donors in age, ejaculate volume, or duration of sexual abstinence. The total motile sperm count (median and interquartile range) was significantly different between patients and donors for prefreeze specimens ($P = 0.026$) and postthaw specimens ($P = 0.008$). Also, the percent motility was significantly lower in the patients as compared with the donors in prefreeze ($P = 0.035$) and postthaw specimens ($P = 0.005$). The percentage change in motility after thawing was also larger for patient samples (-54% versus -47% , $P = 0.39$). Other sperm motion characteristics did not significantly differ between the two groups except for postthaw curvilinear velocity ($P = 0.01$). This study concludes that fresh and frozen-thawed semen from patients with malignant tumors is poor in quality but is still adequate for assisted reproductive techniques. As cancer therapy may further impair semen quality, patients should be offered the chance to bank sperm before undergoing cancer therapy.

Key words Sperm cryopreservation · cancer · male infertility · neoplasm

Introduction

Improved survival after the treatment of cancer in general, and adolescent or childhood cancer in particular, is the trend of modern cancer medicine. The number of survivors can be expected to increase with further advances in therapy [6]. However, the treatment regimens frequently result in permanent infertility [13]. Infertility can be caused by chemotherapy, radiotherapy, surgery, or a combination of these treatments [6]. However, men with newly diagnosed cancer frequently have poor semen quality, which may limit success in cryobanking and conventional methods of assisted reproduction [12, 15]. Furthermore, cryopreservation itself decreases sperm quality by 30–70% [1, 5]. Because of this, the medical community, in general, has been pessimistic and hesitant about recommending semen cryobanking for these men [13]. However, recent advances in assisted reproductive techniques, namely intracytoplasmic sperm injection (ICSI), which allows the use of a single sperm for fertilization, have made sperm cryopreservation an important option [10, 17].

To establish the value of sperm cryopreservation for cancer patients, we (1) examined semen quality in a group of patients with malignant tumors who were referred for sperm banking before beginning cancer therapy over a 15-year period, and (2) compared prefreeze and postthaw semen characteristics in patients and donors.

Materials and methods

Subjects

This study was approved by the Institutional Review Board of the Cleveland Clinic Foundation and the written informed consent was obtained from all subjects.

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Records of nine patients with different malignant tumors, aged 14–47 years and who had been referred to the Male Infertility Clinic and Andrology Laboratory of the Department of Urology at The Cleveland Clinic Foundation for sperm banking between 1982 and 1997 were reviewed. The results were compared with those of 50 normal healthy donors, aged 19–45 years. The criterion for inclusion of the patients in this study was that all of them had their specimens banked before starting treatment. Those patients who had the following diagnoses: pituitary tumor ($n = 4$), brain tumor ($n = 2$), neuroendocrine tumor ($n = 1$), medulloblastoma ($n = 1$), and multiple myeloma ($n = 1$), were included in this study.

Patient information (age, type of disease) was obtained from medical records and, when necessary, by phone calls to the patients or to the referring physician. For the donor population, inclusion criteria were an ejaculate volume of at least 2.0 ml and a sperm concentration of at least 20×10^6 per ml, of which at least 50% were motile and 30% had normal sperm morphology according to the World Health Organization (WHO 1999) classification [18].

Assessment of semen variables

Semen specimens were collected by masturbation after 2 days of sexual abstinence and liquefied at 37 °C for 30 min. Five microliters of the specimen were loaded into a 20- μ l MicroCell chamber (Conception Technologies, San Diego, Calif.) and analyzed on a semen analyzer (Cell-Trak Semen Analyzer, CTS Version 4.0, Motion Analysis Corporation, Palo Alto, Calif.) before freezing and after thawing. Manual verification of the semen analyzer results was performed by microscopic examination. The motile sperm count (MSC), percent motility, curvilinear velocity (VCL), linearity (LIN), and amplitude of lateral head displacement (ALH) were measured. According to the WHO criteria, sperm characteristics of normal healthy donors were as follows: MSC $> 10 \times 10^6$ per ml, motility $> 50\%$, VCL $> 30 \mu\text{m/s}$, LIN $> 19\%$, and ALH $> 1.4 \mu\text{m}$ [18].

Semen cryopreservation

Sperm were cryopreserved with a glycerol-based cryoprotectant. An aliquot of freezing medium, equal to 25% of the original specimen volume, was added to the specimen and gently mixed for 5 min using an aliquot mixer (Hema-tek; Miles Scientific, Elkhart, Ind.). This procedure was repeated until the volume of cryoprotectant added equaled the volume of the ejaculate. Cryovials were frozen at -20°C for 8 min and then under nitrogen vapor at -100°C for 2 h. The vials were then transferred to liquid nitrogen at -196°C for long-term storage. On the day after the semen was

frozen, a vial was removed and thawed by incubation at 37 °C for 20 min. A 5- μ l aliquot was analyzed as described above.

Statistical analysis

All statistical analyses were performed with the SAS statistical software package (SAS Institute, Cary, N.C.). A Wilcoxon rank-sum test was performed to compare the semen analysis results of the healthy donors and the patients and to determine the effect of cryopreservation (the percentage change) in both groups. In addition, age and ejaculate volumes were also compared using a Wilcoxon rank-sum test. A P value of < 0.05 was considered significant, and all summary statistics are presented in median and interquartile range form.

The sample size of the study was sufficient to detect differences in percentage changes from prefreeze to postthaw with 90% power: 19% motility change, 70% VCL change, 19% LIN change, and 27% ALH change.

Results

The patients did not differ with respect to age [30 (27–41) versus 29 (23–35) years, $P = 0.44$] or ejaculate volume [2.1 (1.2–3.3) versus 2.5 (1.8–3.5) ml, $P = 0.49$].

Semen quality before cryopreservation

All semen characteristics before and after cryopreservation are summarized in Table 1. The median MSC was significantly lower in the patients than in the healthy donors (51.1×10^6 versus 129.6×10^6 per ml, $P = 0.026$). Median percent motility was significantly lower in the patients than in the healthy donors (48% versus 63.5%, $P = 0.035$). Other sperm motion characteristics did not significantly differ between patients and donors.

Semen quality after cryopreservation

Postthaw MSC was significantly lower in the patients than in the normal donors (14.4×10^6 versus 59.1×10^6

Table 1 Sperm characteristics before and after cryopreservation in normal donors and men with malignant tumors (VCL, curvilinear velocity; LIN, linearity; ALH, amplitude of lateral head displacement)

Sperm characteristics	Patients			Donors			P value*
	25%	Median	75%	25%	Median	75%	
Motile sperm count ($\times 10^6$ per ml)							
Prefreeze	21.0	51.1	107.6	61.5	129.6	240.0	0.026
Postthaw	7.8	14.4	43.0	23.0	59.1	90.8	0.008
Motility (%)							
Prefreeze	34	48	63	50	64	74	0.035
Postthaw	10	21	27	33	26	40	0.005
VCL (mm/s)							
Prefreeze	33.6	46.9	50.5	37.1	49.9	56.4	0.33
Postthaw	3.8	31.2	37.0	32.0	40.6	46.0	0.01
LIN (%)							
Prefreeze	4.5	5.6	6.2	4.4	6.2	39.0	0.63
Postthaw	4.7	5.3	6.1	5.0	6.2	37.0	0.44
ALH (mm)							
Prefreeze	2.5	2.9	3.6	2.4	2.7	3.2	0.56
Postthaw	1.8	2.1	2.7	1.8	2.2	2.5	0.98

* Comparison between patients and donors, $P < 0.05$ considered significant

Table 2 Percentage change in sperm characteristics after cryopreservation and thaw (VCL, curvilinear velocity; LIN, linearity; ALH, amplitude of lateral head displacement)

Sperm characteristics	Patients			Donors			<i>P</i> value*
	25%	Median	75%	25%	Median	75%	
Motile sperm count (10^6 per ml)							
% change	-80.5	-57.1	-49.3	-64.4	-53.8	-42.5	0.31
Motility (%)							
% change	-79.2	-54.3	-49.3	-57.6	-47.2	-30.6	0.039
VCL (mm/s)							
% change	-65.1	-29.7	-16.6	-34.1	-22.2	-6.7	0.27
LIN (%)							
% change	-10.5	-2.68	6.0	-12.7	2.03	12.5	0.65
ALH (mm)							
% change	-23.0	-17.8	-14.4	-34.4	-23.5	-11.6	0.51

* Comparison between patients and donors, $P < 0.05$ considered significant

per ml, $P = 0.008$) (Table 1). Percentage motility was significantly lower in the patients (21% versus 26%, $P = 0.005$). Also, VCL was significantly lower in the patients (31.2 versus 40.6 μ m, $P = 0.01$). However, the percentage change from prefreeze to postthaw was not different between the two groups for any sperm characteristic except motility, as shown in Table 2.

Discussion

The subject of male cancer has frequently been encountered in the field of male infertility. Several forms of cancer may influence fertility owing to the adverse effects of these malignancies, even before treatment on the testis or other endocrine glands [7]. For example, in this study we had one case of craniopharyngioma, the most common childhood tumor to involve the hypothalamus and the pituitary gland. Endocrine disturbances can be found in 80–90% of these patients, growth hormone deficiency in 75%, LH/FSH deficiency in 40%, ACTH deficiency in 25%, and TSH deficiency in 25%. These disturbances provide an ample explanation for the poor semen quality in these patients [16]. Also, several brain tumors can cause hyperprolactinemia, which in turn causes gonadal dysfunction, diminished libido, and impotence [7]. However, the explanation of the poor semen quality in many patients with other types of malignant disease is not immediately apparent [12]. Previous researchers [2] have suggested that stressful situations adversely affect sperm production in humans, and that the stress of discovering that one has a potentially fatal disease requiring unpleasant treatment might be sufficient to lower semen quality. Impaired semen quality may also result from nutritional deficiency or simply from the systemic consequences of the serious illness [7].

The present data show that patients with malignancies have poorer prefreeze semen quality than healthy donors have. In particular, the MSC and motility (the most important measures of semen quality) were significantly lower. After thawing, the MSC, motility, and VCL were significantly lower in the patients. The percentage drop in percent motility after thawing was larger in the patients, although the percentage change in the other semen characteristics was similar.

These findings may once have been grounds for pessimism about the value of sperm cryopreservation for cancer patients; however, not any more. Intracytoplasmic sperm injection (ICSI) now allows men with even the most severe forms of infertility to establish pregnancies, because an oocyte can be fertilized with a single motile sperm [9, 14]. Therefore, ICSI can be used even for cancer patients with extremely poor semen quality [3].

Twenty-one patients with cancer, who cryopreserved their sperm at our facility and used assisted reproduction, were followed to assess the fertilization and pregnancy outcome. The patients in this study included those with testicular cancer, Hodgkin's disease, prostate cancer, leukemia, metastatic neuroendocrine cancer, and thyroid cancer. These patients used intrauterine insemination, in vitro fertilization, and ICSI procedures. The overall fertilization, pregnancy, and live birth rates were 63.1%, 31.6%, and 21.05%, respectively. There were no differences among the three assisted reproductive procedures in terms of fertilization, pregnancy, and live birth rates. Our results indicate that cryopreserved spermatozoa from cancer patients, irrespective of the type of tumor, are able to fertilize and initiate pregnancy with assisted reproductive techniques (unpublished report).

For the best chances of success, sperm should be cryopreserved before cancer therapy as the therapy itself is likely to further impair sperm quality or induce infertility [8]. For example, cyclophosphamide (the most common agent given to patients in our study after they provided their semen samples) has been linked with azoospermia [9].

This study has limitations. First, the donors used for comparison were selected for normal sperm quality, and therefore may not be representative of the actual population [11]. Second, the semen analyses were conducted on a single specimen, which can be abnormal even in normal men. Therefore, the pretreatment semen quality among patients might be comparable with donors if the results from patients were analyzed against a randomly selected group of normal men with an unknown fertility status.

We recommend that sperm cryopreservation be offered to all men of reproductive age who have malignancies.

nancies. This procedure will give them the option of establishing pregnancy in the future with an assisted reproductive technique. Cryopreservation is safe and inexpensive. If cancer survivors spontaneously regain their fertility and choose not to have children, or die, they can instruct the sperm bank to destroy their samples [4]. Thus, there appears to be nothing to lose and much to gain by offering sperm banking to these patients.

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ANNOUNCEMENTS

2000

28th Munich Endourological Symposium with Nursing Staff Seminar 5–6 October 2000, Munich, Germany

Chairman: Prof. Dr. R. Hartung,

Information: Dr. R. Paul, Department of Urology, Technische Universität München, Klinikum rechts der Isar, Ismaninger Str. 22, 81675 München; Tel.: 089/41402507, Fax: 089/41402585, e-mail: mriu@lrz.tu-muenchen.de, Internet: <http://www.med.tu-muenchen.de/uro/endo.html>

4th International Symposium on Uro-Onkology: Advances in Diagnosis and Treatment of Prostate Cancer 19–21 October 2000, Marburg, Germany

Topics: Live Surgery (ascending, descending, nerve-sparing retropubic prostatectomy, perineal prostatectomy, laparoscopic prostatectomy, art. Sphincter implantation, penile prosthesis implantation), pathology and molecular biology of PCA, therapeutic options in organ confined PCA, treatment of locally advanced and metastatic PCA.

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