Rationale for sperm banking in men with cancer[1]

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As treatment for malignant and nonmalignant diseases increases survival, the ability to preserve spermatozoa for long periods of time by low-temperature freezing has opened the possibility of preserving fertility in men who would otherwise be made subfertile or sterile by various treatments and disease processes. Mechanisms of reduction in sperm number or function may include surgery, irradiation, chemotherapy, or the disease process itself. Sperm banking technique is discussed, and recent data are presented on sperm cryopreservation from men with various diseases who were seen at the Cleveland Clinic. Sperm banking remains a promising technique for restoring fertility in some men with cancer.

Index terms: Spermatozoa • Tissue banks

Cleve Clin Q 53:89–94, Spring 1986

The ability to preserve spermatozoa for long periods of time by low-temperature freezing has opened the possibility of preserving fertility in men who would otherwise be made subfertile or sterile by various treatments and disease processes. Survival rates for patients with some malignancies, especially testicular cancer, acute leukemia, sarcomas, and Hodgkin's disease, have improved with new techniques in surgery, chemotherapy, and radiation. As a consequence, men with these disorders are unable to father children due to iatrogenic infertility or permanent sterility. This review will discuss mechanisms of therapeutically induced decreases in sperm number and function, our technique for semen cryopreservation, and recent data on sperm cryopreservation obtained from men with various diseases who were seen at the Cleveland Clinic.

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0009-8787/86/01/0089/06/$2.50/0

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Table 1. Semen analyses before and after freezing*

	Normal	Testicular cancer	Hodgkin's disease	Lymphoma	Sarcoma
Number of patients	15	16	14	4	3
Age (yr)	24 (20–30)	26 (19–31)	27 (19–38)	25.5 (21–29)	22 (19–26)
Number of specimens	1.5 (1–3)	4 (2–5)	4 (3–6)	3.8 (3–5)	4 (3–5)
Volume (ml)	3.0 (1–6.8)	3.1 (0.7–8)	2.7 (0.9–7.2)	3.8 (2–5)	4 (2.9–4.6)
Pre-freeze					
Motility grade	2.4 (2–3)	2.3 (1.5–3)	2 (1.5–3)	2.1 (1.5–2.5)	2.5 (2–3.5)
Motility (%)	63 (20–85)	57 (15–90)	50 (10–80)	56 (30–80)	69 (40–90)
Count/ml ($\times 10^6$)	111 (13.6–343)	29 (1–100)	50 (1–231)	41 (2–133)	54 (10–130)
Post-thaw					
Motility (%)	36 (15–65)	30 (1–70)	22 (1–80)	23 (5–45)	23 (8–55)
Total motile ($\times 10^6$)	132 (8–824)	80 (0.8–250)	96 (0.3–358)	87 (49–196)	216 (18–357)

* Mean values were determined from the mean of each patient's specimens. Values in parentheses indicate the lower and upper range of values for all specimens obtained.

Iatrogenic causes of reproductive system damage

Surgical

Any extensive abdominal dissection carries a risk of ejaculatory disturbance[1,2] or impotence.[3] (It is important during counseling to distinguish between the two, as patients often are confused about the different consequences.) The ejaculatory mechanism consists of a series of neuromuscular events requiring an intact autonomic nervous system in order to transport semen into the urethra and propel semen from the urethra during orgasm while concomitant closure of the bladder neck occurs.[4]

The best-documented occurrence of ejaculatory dysfunction following surgery is that associated with radical bilateral retroperitoneal lymphadenectomy used for treatment of nonseminomatous testicular tumors. Kedia et al[5] reported that 49 of 52 men had loss of emission after retroperitoneal node dissection, with preservation of orgasmic and erectile function. Although it has been assumed previously that this surgical procedure resulted in retrograde ejaculation, the defect appears to be failure of emission, as neither sperm nor fructose have been detected in alkalinized urine specimens after ejaculation was attempted.[5]

Ejaculatory failure is probably due to removal or injury of lumbar sympathetic ganglia or damage at the presacral hypogastric plexus.[6] This may cause continuous slow transport of seminal fluid through the vas deferens as a consequence of persisting segmental contraction and continuous secretion from the accessory genital glands, or may lead to paralysis of the motor innervation to the vas deferens, both resulting in failure of emission and subsequent infertility.[5,7] When a modified resection was used, ejaculation resumed spontaneously within a 3-year period in 25 of 55 cases of Stage I or II nonseminomatous germ-cell tumors and was induced with sympathomimetic agents in five others.[8] In a follow-up study, 51% of 63 patients had return of ejaculatory function and 12 (of an unknown number who had tried) had fathered children.[9]

Unilateral orchiectomy does not appear to be associated with a significantly decreased sperm count or motility if the remaining testis is normal.[10,11]

Testicular irradiation

Direct irradiation of the testes causes a dose-dependent decline in sperm count at doses as low as 50 rad (0.5 Gy).[12] At low doses under 100 rad (1 Gy), oligospermia or azoospermia may last for nine to eighteen months, and at higher doses, for periods of up to two to three years.[12] Total body irradiation used for bone marrow transplant preparation (1000 rad [10 Gy] or greater) usually is associated with permanent sterility.[13] Oligospermia or azoospermia may occur in patients who received only scattered irradiation to the testicles, for example, from total abdominal irradiation given for Wilms' tumor,[14] seminoma,[15] and "inverted Y" irradiation for Hodgkin's disease[16] in spite of testicular shielding. In many cases, the sperm count will return to the pre-irradiation level within 3–4 years.[15]

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Chemotherapy

The primary testicular lesion in adult men caused by most antitumor agents is depletion of the germinal epithelium that lines the seminiferous tubules, resulting in complete aplasia of germinal cells with only Sertoli cells remaining in the tubular lumen. Only occasional immature sperm are observed.[17] Consequently, serum follicle stimulating hormone (FSH) levels are elevated and androgen binding protein levels are decreased.[18] The interstitial cells of Leydig are usually normal in appearance and continue to produce testosterone in response to luteinizing hormone (LH), although subclinical functional defects may be present. However, in adolescent males, overt Leydig cell damage may occur as well, with subsequently decreased serum testosterone and elevated LH levels.[17,19]

Individual antineoplastic drugs that are best characterized as causing testicular damage are alkylating agents,[17,20] such as cyclophosphamide[21] and chlorambucil,[22] and DNA-synthesis inhibitors such as procarbazine.[21,23] Few data are available on short or long-term effects of newer antitumor agents on gonadal function and fertility, which probably reflects the relatively recent successes of such therapy in producing long-term remissions.[24] It is likely that many of these cytotoxic drugs will be associated with at least temporary decreases in sperm production.

With single-agent therapy, the damage is clearly dose-related,[21] but combinations of cytotoxic agents may act synergistically to cause testicular impairment. Treatment of Hodgkin's disease with MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) or related regimens has produced azoospermia in 100% of men within one to two cycles.[25,26]

The recovery of spermatogenesis after cessation of drug treatment is variable and probably is related to type of drug, dose, and duration of administration, as well as to interval of therapy. Few prospective studies of gonadal function have been reported, but retrospective studies suggest that oligospermia persists for several years following completion of treatment with most single alkylating agents, and longer after combination chemotherapy, especially when procarbazine is used.[17,20] In a study of 64 men with Hodgkin's disease treated with MOPP, less than 10% (4/64) had evidence of spermatogenesis for 15–51 months after treatment[25] and less than 5% were fertile 6 years after therapy. Lange et al[9] reported that 10 patients with nonseminomatous testicular tumors treated with vinblastine sulfate and bleomycin ± platinum (VB±P) had no evidence of sperm production within 18 months of chemotherapy; however, 10 of 24 men evaluated 18 months after completing chemotherapy had live sperm present in ejaculates (average 40.3 ± 68.4 × 10^6), eight had normal serum FSH, and two had fathered children. A retrospective study of 16 patients treated with VB±P showed that half had sperm counts greater than 20 million per ml and five had fathered children.[27]

Table 2. Pretreatment sperm analysis in men with cancer

Reference	Disease*	Sperm density >20 × 10^6/ml†	Motility >40%†
Sanger et al[29]	HD	8/11	5/8
Whitehead et al[30]	HD	15/19	15/15
Rothmann (present study)	HD	8/14	11/14
		34/56†	42/56†
Sanger et al[29]	TC	8/10	7/8
Fritz and Weissbach[11]	TC	29/36‡	ND
Thachil et al[10]	TC	20/42	ND
Bracken and Smith[31]	TC	9/25	12/25
Rothmann (present study)	TC	8/16	15/16
		28/64†	56/64†

* *HD* = Hodgkin's disease; *TC* = testicular cancer.
† All denominators are number of patients, except those with †, which have number of specimens as the denominator.
‡ Lower limit given as 10 × 10^6 ml.

Clearly, spermatogenesis will resume in some men after years have elapsed and conception has been reported increasingly as more men survive 5–10 years. Unfortunately, this long time interval often coincides with the time when many couples will want to have children. Furthermore, it is not possible to predict accurately which men will have resumption of sperm production. The long-term effects may be more severe in patients receiving therapy during puberty, in contrast to effects on the prepubertal testis, which appears to be the most resistant to deleterious effects of cytostatic agents.[19,28]

Disease-related subfertility

Few well-controlled prospective studies of pretreatment sperm quality in cancer patients have been published; nevertheless, several reports have reinforced a general presumption by practitioners that men with cancer are subfertile.

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Oligospermia and azoospermia have been demonstrated before treatment in some men with different tumors,[10,29–31] but the precise frequency is unknown. In most reports the pathologic type and clinical stage of disease have not been described or related to sperm quality, and often spermograms are reported from a single specimen, which can be misleading even in normal individuals. Furthermore, control subjects used for comparison are often artificial insemination donors, who may not be representative of the actual normal population, as they usually are chosen for their high sperm counts and exceptional motility.

Our own experience suggests that counts can vary markedly in a population of men with a particular disease (or no disease), but often will be sufficient for banking. *Table 1* shows a summary of our results obtained from men with different tumors. Although the series is too small for meaningful analysis by factors such as presence and location of metastases, stage of disease, complicating clinical symptoms, or history, the results suggest that many men with cancer have normal counts and motility and should be considered candidates for sperm banking until proved otherwise. This observation has been substantiated by other investigators, as summarized in *Table 2.*

When present, the causes of oligospermia in untreated cancer patients are not well understood, but may be an effect of a particular disease or may be related to fever, inflammatory or infectious processes, nutritional state, metabolic or hormonal disturbances, and emotional stress. The presence of metastatic disease has been associated with lower sperm counts in patients with testicular cancer,[10] which we also have observed. In addition, previously undiagnosed infertility may be present in some patients.

Sperm banking

Technique

The technique of sperm banking has been available for many years.[32] The currently best accepted method is nitrogen-vapor freezing followed by liquid nitrogen storage.[33] The patient's semen is collected by masturbation into a clean nonspermicidal container or emission into a silicone container and should be delivered to the laboratory within one-half hour. After analysis, the semen may be extended with a buffer solution or hen egg yolk and then is mixed slowly with a glycerol cryoprotectant.[34] The semen is cooled gradually to −100°C and finally stored in liquid nitrogen at −196°C. About 25–50% of the motile sperm become nonmotile during the freezing process (*Table 1*); however, once stored in liquid nitrogen, sperm viability appears to be stable for long periods.[35,36] Although the precise duration of preservation of sperm function is unknown, properly stored sperm remain functional for at least 3 years[37] and may be functional upward of 10 years, as shown by the studies of Sherman.[32] The technique is not associated with increased pregnancy complications or birth defects in offspring[32,33,38] and one group has reported a 45% pregnancy rate using cryopreserved sperm from oligospermic men.[38]

Collection considerations

Potential candidates for sperm banking need to be identified and referred to the sperm bank as soon as possible to establish the baseline sperm count and schedule collection times. In order to optimize chances of later fertilization, 3–6 ejaculates should be frozen, each collected 2–4 days apart. Sexual activity with ejaculation within 24–48 hours of semen collection must be avoided during the collection period, in order to allow maximum numbers of sperm to be collected. The urgency for disease treatment will determine the number of specimens that can be collected. Patients with testicular cancer or other malignancies requiring abdominal debulking surgery should bank their sperm after unilateral orchiectomy or biopsy and before lymphadenectomy or resection.

Problems encountered in therapeutic sperm banking

A principle problem in therapeutic sperm banking is communication to the patient that reproductive options are available and that fertility may be salvaged by sperm banking. Some physicians are reluctant to recommend sperm banking under the assumption that the procedure will delay the initiation of treatment, or that sperm counts will be inadequate. Many of the patients who have the best chance for survival and good sperm quality are those presenting with few symptoms and little likelihood of metastatic disease, thus the optimum 10–14 day collection period should present an insignificant delay. In the few patients in whom the likelihood of rapidly

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growing tumor makes this delay unacceptable, one or two specimens may be collected in 48 hours, with the possiblity of using in vitro fertilization to conserve the number of sperm during subsequent conception attempts. Direct communication with the oncologic physician is of great importance in determining a realistic collection schedule.

When oligospermia is observed in the initial specimen, possible causes should be sought, and a second specimen obtained in 2–3 days. Often patients are extremely anxious before and during the first collection attempt, and need to be given ample opportunity to relax and discuss their concerns. After counseling, the second specimen may be improved considerably. Where possible, patients are encouraged to involve their sexual partner in the collection procedure. When travel distance requires collection at the banking facility, absolute privacy must be guaranteed.

In some patients sperm banking is not possible due to extent of disease, azoospermia, or collection difficulties. *Table 3* lists the problems encountered in 14 patients that prevented sperm storage. Two patients were too ill to delay treatment and four were azoospermic after induction or consolidation chemotherapy was completed. The time after therapy ranged from one month to 6 years (in a patient with prior Hodgkin's disease in whom leukemia subsequently developed). Three men had idiopathic azoospermia and one had no motile sperm. Two patients were unable to obtain a specimen on several occasions, and two elected not to attempt sperm banking.

Several authors have attempted to set sperm quality criteria for cryopreservation, however, the advent of successful in vitro fertilization techniques has made such standards obsolete. Frozen sperm can be used for in vitro fertilization[39–41] and in a recent study, eight pregnancies (seven successful) were achieved with sperm from men with motile sperm counts less than 0.5 million/ml, including two from sperm cryopreserved from a man with testicular teratoma. In all eight specimens sperm progression was poor to moderate, demonstrating that conception can be achieved with low-quality sperm when this technique is used instead of conventional artificial insemination.

As treatment for malignant and nonmalignant diseases increases survival, the impact of therapies on fertility will become more apparent. Until disturbance of reproductive function can be minimized or eliminated, sperm banking remains a promising technique for restoring fertility in some men. Research on new freezing media and techniques, and the use of in vitro fertilization as well as better-timed artificial insemination, should lead to greater success, especially for oligospermic men.

Table 3. Reasons for not banking sperm

Reason	No.
Previous chemotherapy, azoospermic	4
Idiopathic azoospermia	3
Too ill	2
Unable to obtain specimen	2
Not interested	2
No motility post-thaw	1

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