

# Fertility after cancer: a prospective review of assisted reproductive outcome with banked semen specimens

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**Objective:** To examine the outcome of assisted reproduction techniques (ART) using cryopreserved semen from patients with cancer.

**Design:** Prospective.

**Setting:** Therapeutic semen banking program at a tertiary healthcare center.

**Patient(s):** Twenty-nine men with cancer who cryopreserved their sperm before treatment at our facility from 1982 to 2001 and withdrew their samples for assisted reproduction (IUI, IVF, or intracytoplasmic sperm injection [ICSI]).

**Intervention(s):** Sperm bank records were used to identify the patients. Information on fertility potential indices was obtained from medical records and through interviews. Of the 29 patients, 9 had testicular cancer, 12 had Hodgkin's disease, and 8 had other types of cancer.

**Main Outcome Measure(s):** Pregnancy and live births.

**Result(s):** A total of 87 ART cycles (42 IUI, 26 IVF, and 19 ICSI) was performed. Of those cycles, 18.3% resulted in pregnancy (7% IUI, 23% IVF, and 37% ICSI), and 75% of the pregnancies resulted in a live birth (100% IUI, 83% IVF, and 57% ICSI). There was no significant difference in the outcomes when the results were stratified by type of ART and malignancy. None of the 11 infants who were born had congenital anomalies.

**Conclusion(s):** Our findings emphasize the need for physicians to discuss the issue of semen cryopreservation with all men of reproductive age who have cancer before antineoplastic therapy is started. (Fertil Steril® 2004; 81:342–8. ©2004 by American Society for Reproductive Medicine.)

**Key Words:** Cancer, cryopreservation, assisted reproduction technique, infertility, semen

Therapeutic advances in the last 10 years have improved the long-term survival of patients with cancer. More than 60% of patients treated for their malignancies can now expect to live at least 5 years (1). With increasing numbers of cancer survivors, quality of life issues are receiving increased attention.

Cancer therapy can extend life or cure the disease, yet it may deprive patients of the human joy of genetically contributing to a family. Cancer treatment, whether surgical, radiological, or pharmacologic, can have severe and adverse long-term iatrogenic effects on male fertility (2–6). Irradiation and chemotherapy each compromise fertility by exerting cytotoxic effects on gametogenesis. The degree of gona-

dotoxic effect is governed by the regimen used (that is, type, dose, regimen) and duration of the treatment.

Numerous clinical studies have clearly shown the adverse effect that cancer therapy has on a man's fertility (7–9). The fertility may return in some but not in all, and who will be affected cannot be predicted. Therefore, all men deserve a chance to consider fertility-sparing opportunities before the onset of the sterilizing cancer regimens (9).

The present clinical means for preserving the potential reproductive capacity of men at risk is cryopreservation of sperm before the treatment begins, followed by assisted reproductive techniques (ART) when pregnancy is

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desired (10, 11). Although many men diagnosed with cancer have low sperm counts and motility at the time when banking sperm would be possible (7, 8, 12), these samples do not suffer any incremental damage from the freezing and thawing process, so that some spermatozoa are likely to survive in most cases (4, 11). With the advent of the intracytoplasmic sperm injection (ICSI) technique in 1992, a single sperm can now be used to create an embryo (13).

Because only a few reports have been published regarding fertility outcome with ART, namely IVF and ICSI, using cancer patients' cryopreserved sperm (14–17), there is inadequate evidence to support routine sperm cryopreservation. Furthermore, only scarce data exist on the possible risks of birth defects and genetic risks for the offspring of these patients (18, 19).

This study presents a comprehensive follow-up of all the cancer patients who had cryopreserved their sperm since the founding of the Cleveland Clinic's sperm bank in 1982 up until January 2002. Our objectives were the following: [1] examine the prefreeze and postthaw semen quality in patients with cancer before their treatment for cancer; [2] report the utilization rates and outcome of ART cycles, including data on the type of procedure, oocytes retrieved (in case of ICSI/IVF), oocytes fertilized, number of embryos formed, and the implantation rates using pretreatment cryopreserved semen samples; and finally [3] correlate ART outcomes with the duration and nature of cancer treatment as well as the current status of the patients.

## MATERIALS AND METHODS

### Data Collection

After approval from our institutional review board, we reviewed the Cleveland Clinic Foundation's Sperm Bank records of the individuals with cancer ( $n = 318$ ) who had cryopreserved their sperm before treatment, from 1982–2001. Semen specimens from these patients had been obtained at the Andrology Laboratory before initiation of any treatment and were obtained by masturbation after 48 to 72 hours of abstinence. Samples were cryopreserved by using a liquid nitrogen vapor freezing method (20) using TES and Tris/yolk buffer with 20% egg yolk and 12% glycerol (Irvine Scientific, Santa Ana, CA) as the medium for cryopreservation.

Data collection entailed the following three-part procedure. To maintain continuity, the same person performed all three parts. A comprehensive questionnaire was prepared to aid in a telephone survey and to document all parts of the study.

- Part 1: Patients who withdrew their samples for ART were contacted by telephone. The patients granted their informed consent either in written form or orally (patients called their respective doctors and ART laboratories to allow them to

release this information to study authors). Information on their ART outcomes and the status of their offspring was collected.

- Part 2: The reproductive centers to which the semen specimens from each cancer patient were transferred were contacted. Information was requested on the method used (IUI, IVF, ICSI), number of ART cycles performed (with dates), ovulation protocols used, number of oocytes retrieved, oocytes fertilized, embryos obtained, embryos transferred, and the quality and stage of the embryos.
- Part 3: Oncologists who treated these patients for the malignancies were contacted. Information was obtained on cancer diagnosis, modalities of intervention, treatment regimens, duration of treatment, and the status of patients after therapy (whether in remission or with recurrence).

### Statistical Analysis

Diagnostic groups were compared on categorical variables using Fisher's exact test and on continuous variables using the Kruskal-Wallis test (overall) and Dunn's multiple-comparison procedure (pairwise). The significance level for Fisher's exact test and the Kruskal-Wallis test was .05; a Bonferroni correction to the significance criteria was made for multiple comparisons, so  $P < .0167$  was considered significant (3 comparisons:  $.05/3 = .0167$ ).

The Cox proportional hazards model, with length of ART trial as the time variable, was fit to assess the relationship of ART variables with the outcomes of pregnancy and live birth. We adjusted for the number of cycles in all models. Variables were transformed logarithmically where necessary. A significance level of .05 was used for each hypothesis. We illustrated the percentage of pregnancies and live births in relation to the length of the ART trial (assuming the median of 2 ART cycles) for the first and third quartiles (Q1 and Q3, respectively) of postwash motility. All tests were two tailed. Analyses were performed with SAS 8.2 (SAS Institute Inc., Cary, NC).

## RESULTS

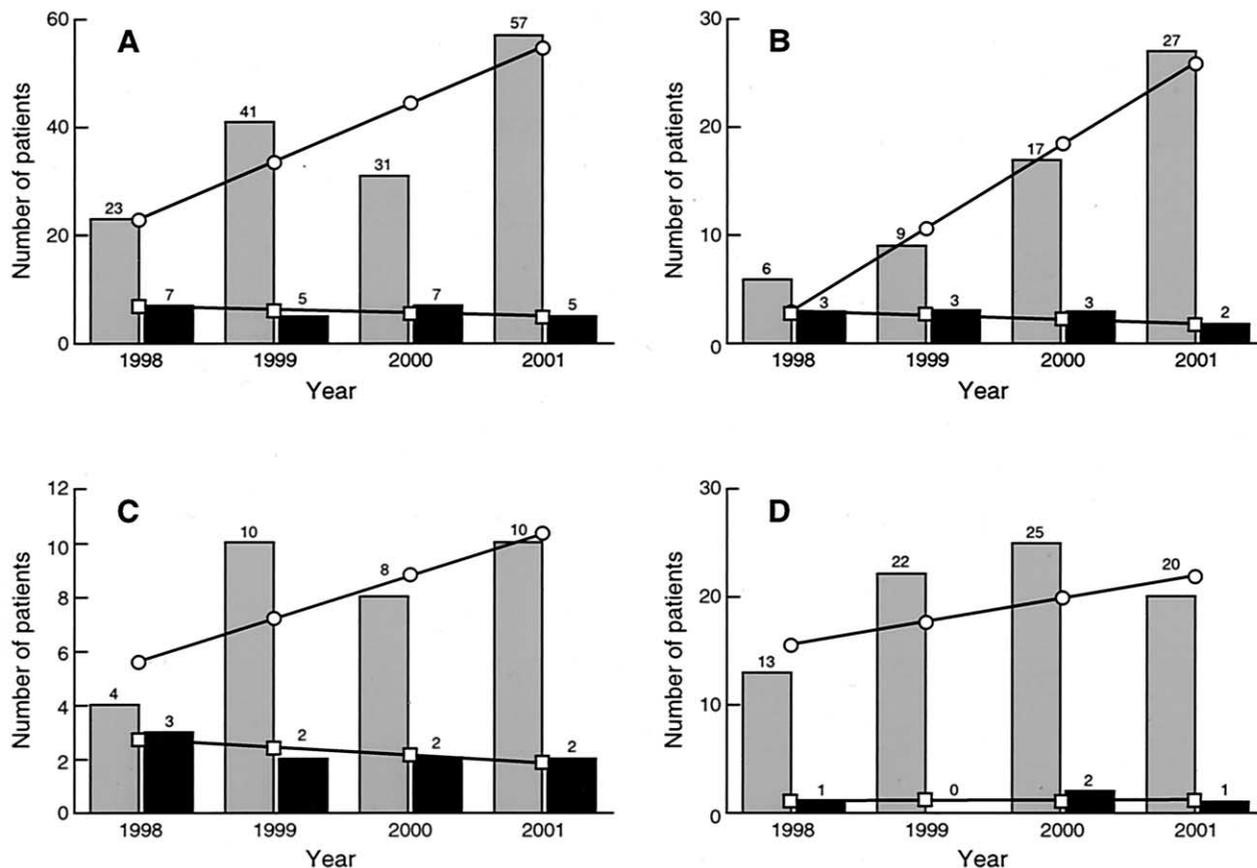
### Patient Population

Over the last 20 years, 31 patients had withdrawn their sperm specimens for assisted reproductive procedures; 26/31 withdrawals (84%) occurred from 1998–2001. A steady increase in the number of cancer patients banking sperm before treatment was also notable (Fig. 1). Of the 31 patients, 11 (35%) had testicular cancer, 12 (39%) had Hodgkin's disease, and 8 (26%) had other types of cancer. The distribution of other cancer cases by diagnosis was as follows: carcinoma prostate ( $n = 3$ ), lymphomas ( $n = 2$ ), neuroendocrine cancer ( $n = 1$ ), thyroid cancer ( $n = 1$ ), and leukemia ( $n = 1$ ). The median (interquartile range) age of patients was 30 (25, 32) years.

Overall, 18 of the 31 couples achieved a pregnancy (58.1%), and 14 had live births (45.2%). There were two triplet pregnancies and three twin pregnancies. One couple was able to achieve pregnancy twice. There were no mal-

**FIGURE 1**

Semen banking and ART utilization in patients with cancer from 1998–2001. (A) Overall cancers. (B) Testicular cancers. (C) Hodgkin's disease. (D) Other cancers. Banking rates are indicated in *gray columns*; utilization rates are indicated in *black columns*.



Agarwal. ART outcome in cancer patients. *Fertil Steril* 2004.

formations or obvious abnormalities in any of the children born. Within the 31 couples, five patients had confounding female factor infertility (fibroid uterus [n = 2], tubal block with stricture [n = 2], and ovarian torsion [n = 1]). Two patients with testicular cancer achieved natural pregnancy and were excluded from analyses dealing with ART pregnancy and live birth. Of the 29 remaining patients, 15 (52%) achieved pregnancy, and 11 (38%) had a live birth via an ART.

Depending on where individual patients lived and based on their choice, ART procedures were carried out at 20 different reproductive centers around the country. Follistin sulfate and clomiphene citrate were the most common drugs used for induction of ovulation in all three modalities of ART (IUI, IVF, and ICSI).

All 11 patients with testicular cancer underwent orchidectomy. Eight of these 11 patients also underwent chemotherapy. Adriamycin, bleomycin, cisplatin, and vinblastin were

the most common chemotherapeutic agents used in various regimens used for treatment of testicular cancer. One patient received all three modalities (surgical, radiological, and pharmacological) of treatment. All patients with Hodgkin's disease received mustangen, vincristine, procarbazine, prednisone-adriamycin, bleomycin, vinblastine, dacarbazine (MOPP-ABVD) regimens. Three of the 12 patients also underwent surgery, and another 3 had all three modalities of treatment.

### Comparison Among the Diagnostic Cancer Groups

There was an overall difference among diagnostic cancer groups for total count, age at diagnosis, duration of storage, and number of embryos transferred (Table 1). Specifically, the patients in the "other cancer" group were older than the patients with Hodgkin's disease at the time of diagnosis. On the other hand, the "other cancer" group patients had lower duration of storage than patients with Hodgkin's disease.

TABLE 1

Comparisons among diagnostic cancer groups.<sup>a</sup>

Factors	Group 1: Testicular cancer (N = 11)				Group 2: Hodgkin's disease (N = 12)				Group 3: Other cancer (N = 8)				P values in group compositions <sup>b</sup>			
	n	Median	Q1	Q3	n	Median	Q1	Q3	n	Median	Q1	Q3	Overall	1 vs. 2	1 vs. 3	2 vs. 3
Last ART procedure													.81 <sup>c</sup>			
ICSI	5				5				3							
IUI	2				3				2							
IVF	2				4				3							
Natural	2				0				0							
Prefreeze TMSC ( $\times 10^6$ )	10	44.6	23.1	55.5	12	84.5	43.0	148.9	8	52.8	3.6	89.2	.06			
Motility (%)	10	48.8	33.5	59.2	12	47.0	35.8	66.0	8	42.6	35.8	65.2	.95			
Total count ( $\times 10^6$ )	10	96.6	47.2	113.5	12	179.4	94.8	275.7	8	96.0	11.4	144.8	<b>.04</b>	.017	.72	.06
Postthaw TMSC ( $\times 10^6$ )	9	19.9	13.1	20.2	12	26.2	11.6	69.6	8	8.7	0.9	43.0	.29			
Postwash motility (%)	10	20.2	13.0	22.7	12	15.1	11.5	29.8	8	13.6	6.2	35.0	.87			
Age at diagnosis (y)	11	28.0	25.0	32.0	12	25.5	23.0	31.0	8	32.0	29.5	59.5	<b>.03</b>	.29	.09	<b>.007</b>
Duration of storage (y)	9	6.0	3.0	8.0	12	7.5	5.0	11.5	8	2.0	1.5	3.0	<b>.003</b>	.23	.03	<b>&lt;.001</b>
Length of ART trial (mo)	9	12.0	2.0	12.0	12	12.0	7.5	20.0	8	6.5	1.0	18.0	.49			
No. cycles	9	2.0	2.0	5.0	12	2.5	1.5	3.5	8	2.0	1.0	3.5	.67			
Average eggs retrieved (n)	7	10.0	10.0	13.0	10	9.5	4.0	12.0	6	12.5	3.0	17.0	.51			
No. fertilized	6	5.0	2.0	10.0	10	7.0	3.0	8.0	6	7.5	3.0	8.0	.95			
No. embryos	6	2.0	2.0	4.0	9	4.0	3.7	5.0	6	3.0	3.0	7.0	.16			
Embryos transferred	6	2.0	2.0	2.0	9	3.0	3.0	3.0	6	3.0	3.0	3.0	<b>.03</b>	.019	.08	.69
No. offspring	5	1.0	1.0	1.0	2	2.0	1.0	3.0	4	1.0	1.0	2.0	.63			

ICSI = intracytoplasmic sperm injection; Q1, Q3 = first and third quartiles; TMSC = total motile sperm count.

<sup>a</sup> Two patients with natural pregnancies included.<sup>b</sup> Overall: Kruskal-Wallis test, unless noted otherwise. P values <.05 are significant and in bold. Right most three subcolumns (pairwise): Dunn's multiple comparison procedure. P values <.0167 (.05/3 comparisons) are significant and in bold.<sup>c</sup> Fisher's exact test.

Agarwal. ART outcome in cancer patients. Fertil Steril 2004.

Hodgkin's disease patients had a higher but nonsignificant total count and number of embryos transferred than did testicular cancer patients.

### ART Outcomes by Malignancy

In the testicular cancer group (n = 9), six couples achieved a pregnancy (67%) in 32 ART cycles, and four had live births (44%). Five of 12 couples (42%) in the Hodgkin's disease category achieved a pregnancy in 37 ART cycles, and 3 had live births (25%). Four of the eight couples in the "other cancers" category achieved pregnancy (50%), and four had live births (50%) in 19 ART cycles. Overall, there was no statistically significant difference in the ART outcomes between different cancer groups (P=.63).

### Fertility Outcomes by ART Type

A total of 42 IUI cycles, 26 IVF cycles, and 19 ICSI cycles were performed on 29 cancer patients. The overall average number of attempts for all cycles was  $2.7 \pm 1.8$ . The greatest number of fertilizations (n = 13, 68%) and pregnancies (n = 7, 37%) occurred with ICSI as compared with IVF (n = 10, 38% and n = 6, 23%, respectively). Three of the 42 IUI cycles (7.1%), 5 of the 26 IVF cycles (19%), and 4 of the 19 ICSI cycles (21%) resulted in live births.

### Comparison of Successful and Unsuccessful Cases

Eighteen of 29 couples had not yet achieved a pregnancy after 54 trials with ART. The distribution of unsuccessful cancer patients by diagnosis was testicular cancer (n = 5), Hodgkin's disease (n = 9), and other malignancies (n = 4). Of the 18 couples who did not achieve pregnancy, 1 had confounding female factor infertility, in 1 the patient died, and 2 couples chose to adopt. Four of the 18 couples did achieve pregnancy but were unsuccessful in carrying it to term.

The mean number of ART trials for the unsuccessful couples was  $3 \pm 2$  vs.  $2.75 \pm 1.54$  for successful cases. The number of patients who tried IUI, IVF, and ICSI was comparable among successful cases: IUI: n = 14, IVF: n = 14, and ICSI: n = 13. The most common ART employed by patients who failed was IUI, especially among Hodgkin's disease (23 cycles). This was 64.2% more than IVF and ICSI cycles together for Hodgkin's disease.

Looking at the association between baseline factors and ART length resulting in pregnancy or live birth, postwash motility (adjusting for number of cycles) and number of

TABLE 2

Association between ART time resulting in live birth and baseline factors.

Factor	No live birth (N = 18)		Live birth (N = 11)		Hazard ratio (95% CI)	P value <sup>c</sup>
	n	Statistic <sup>b</sup>	n	Statistic <sup>b</sup>		
Cancer type (%)						.29
Hodgkin's disease	9	50.0	3	27.3	1.0 (N/A)	N/A
Testicular	5	27.8	4	36.4	1.5 (0.31, 6.8) <sup>d</sup>	.63 <sup>d</sup>
Other	4	22.2	4	36.4	3.5 (0.73, 17.1) <sup>d</sup>	.12 <sup>d</sup>
Prefreeze TMSC <sup>a</sup> ( $\times 10^6$ )	17	61.4 (5.1–86.8)	11	55.5 (24.6–113.4)	2.6 (0.67, 10.0)	.17
Motility (%)	17	46.7 (34.0–58.4)	11	40.9 (36.0–77.0)	1.03 (0.99, 1.07)	.10
Total count <sup>a</sup> ( $\times 10^6$ )	17	99.5 (28.3–188.1)	11	127.8 (60.2–155.6)	2.2 (0.46, 10.7)	.32
Postthaw TMSC <sup>a</sup> ( $\times 10^6$ )	16	20.1 (3.9–33.6)	11	22.7 (9.7–49.7)	3.8 (0.88, 16.2)	.07
Postwash motility (%)	17	15.5 (10.7)	11	27.0 (14.2)	1.08 (1.02, 1.1)	<b>.01</b>
Age at diagnosis (yr)	18	30.0 (26.0–32.0)	11	29.0 (25.0–32.0)	1.03 (0.98, 1.08)	.21
Duration of storage (yr)	18	4.5 (2.0–8.0)	11	6.0 (2.0–10.0)	1.02 (0.88, 1.2)	.79
No. cycles <sup>a</sup>	18	2.0 (2.0–4.0)	11	2.0 (1.0–3.0)	0.02 (0.001, 0.42)	<b>.01</b>
Average eggs retrieved (n)	14	8.8 (4.4)	9	12.2 (6.9)	1.1 (0.99, 1.3)	.07
No. fertilized	14	8.0 (4.0–8.0)	8	3.0 (2.0–7.5)	0.91 (0.71, 1.2)	.42
No. embryos	13	4.0 (3.0–5.0)	8	3.0 (2.0–5.0)	0.92 (0.61, 1.4)	.68
Embryos transferred	13	3.0 (2.0–3.0)	8	3.0 (2.0–3.0)	0.97 (0.31, 3.0)	.96

TMSC = total motile sperm count.

<sup>a</sup> Logarithmically transformed for Cox regression analysis.<sup>b</sup> Unless otherwise noted, data are median (Q1–Q3 interquartile range) or mean (SD).<sup>c</sup> Cox regression of ART time resulting in live birth, adjusting for log-transform of number of cycles. Bold indicate statistical significance.<sup>d</sup> Compared with Hodgkin's disease group (largest group).Agarwal. ART outcome in cancer patients. *Fertil Steril* 2004.

cycles seemed to play a role (Tables 2 and 3). The chances of a pregnancy or live birth increased with postwash motility, whereas they decreased with the number of cycles. Figure 2 shows that the third quartile of postwash motility (assuming the median of 2 ART cycles) resulted in higher percentages of live births and pregnancies than did the first quartile as the length of the ART trials increased (using Cox proportional hazards model).

## DISCUSSION

According to the National Cancer Institute, approximately 8.9 million Americans were living with a history of cancer in 1997. The 5-year relative survival rate for all cancers combined is 60% (1). Hodgkin's disease, testicular cancer, leukemia, non-Hodgkin's lymphoma, and thyroid cancers are the most common malignancies seen among men of reproductive age, and they account for 497,000 of the total prevalence. Infertility is a major concern for men with malignant diseases who undergo sterilizing treatments because therapeutic advances in modern medicine have made cure a realistic goal. Our study is by far the largest and longest follow-up, known to us, of ART outcomes in cancer patients who had cryopreserved their sperm before therapy.

Indeed, we and others found that only a small minority of patients (<10%) who bank their spermatozoa before initiation of chemotherapy or radiotherapy return for assisted reproduction (21–23). These findings are explicable for sev-

eral reasons: recovery or waiting for possible resumption of spermatogenesis, short period from original illness, anxiety regarding potential risks for the children, and uncertainty about their long-term health and therefore suitability to be parents. However, trends have begun to change, and there appears to be an increased awareness of sperm banking over the last 4 to 5 years, coinciding with the advent of ICSI. Our sperm bank records show a steady increase in the number of patients who bank their spermatozoa and also use it for assisted reproduction after their treatments.

Many men diagnosed with cancer already have poor semen quality, and after freezing and thawing, it is estimated that the sperm motility further decreases by 25% to 75%. The results from our clinic show that the postwash total motile sperm count is well above the World Health Organization standard, indicating adequacy of sperm for assisted reproduction. Despite inherent differences between institutions in equipment, expertise, and technique, a normal pregnancy rate of 52% was obtained in our study. Moreover, with the advent of newer assisted reproductive techniques like IVF-ICSI, it is now possible to achieve pregnancy with just a handful of sperm, making it worthwhile for men to cryopreserve their semen before initiation of cancer treatment.

Postwash motility is an important predictor of successful ART outcomes, not only in cases with IUI, but also in IVF or ICSI (24). We observed that the chance of a pregnancy or live birth increases with a better postwash motility. This may

TABLE 3

Association between ART time resulting in pregnancy and baseline factors.

Factor	No pregnancy (N = 14)		Pregnancy (N = 15)		Hazard ratio (95% CI)	P value <sup>c</sup>
	n	Statistic <sup>b</sup>	n	Statistic <sup>b</sup>		
Cancer type (%)						.63
Hodgkin's disease	7	50.0	5	33.3	1.0 (N/A)	N/A
Testicular	3	21.4	6	40.0	1.5 (0.45, 5.0) <sup>d</sup>	.51 <sup>d</sup>
Other	4	28.6	4	26.7	1.9 (0.49, 7.2) <sup>d</sup>	.36 <sup>d</sup>
Prefreeze TMSC <sup>a</sup> ( $\times 10^6$ )	14	54.5 (4.8–118.9)	14	56.7 (37.0–86.8)	2.5 (0.77, 8.4)	.12
Motility (%)	14	45.3 (21.5–55.0)	14	46.0 (37.3–70.0)	1.03 (1.00, 1.06)	.08
Total Count <sup>a</sup> ( $\times 10^6$ )	14	99.4 (12.4–237.8)	14	130.9 (92.7–155.6)	2.2 (0.56, 8.6)	.26
Postthaw TMSC <sup>a</sup> ( $\times 10^6$ )	13	15.9 (2.3–28.2)	14	23.4 (13.1–41.1)	3.4 (0.96, 11.9)	.06
Postwash Motility (%)	14	14.3 (11.4)	14	25.7 (12.8)	1.06 (1.01, 1.1)	<b>.01</b>
Age at diagnosis (y)	14	29.5 (23.0–32.0)	15	30.0 (25.0–32.0)	1.02 (0.98, 1.07)	.27
Duration of Storage (y)	14	4.5 (2.0–8.0)	15	5.0 (2.0–10.0)	1.02 (0.90, 1.2)	.74
No. cycles <sup>a</sup>	14	2.5 (2.0–4.0)	15	2.0 (1.0–3.0)	0.03 (0.002, 0.39)	<b>.007</b>
Average eggs retrieved (n)	11	8.2 (4.7)	12	11.9 (5.9)	1.1 (0.99, 1.2)	.07
No. fertilized	11	8.0 (3.0–10.0)	11	7.0 (2.0–8.0)	0.97 (0.82, 1.2)	.76
No. embryos	10	3.9 (3.0–5.0)	11	3.0 (2.0–7.0)	1.05 (0.77, 1.4)	.77
Embryos transferred (n)	10	3.0 (2.0–3.0)	11	3.0 (2.0–3.0)	1.2 (0.45, 3.0)	.76

TMSC = total motile sperm count.

<sup>a</sup> Logarithmically transformed for Cox regression analysis.<sup>b</sup> Unless otherwise notes, data are median (Q1–Q3 interquartile range) or mean (SD).<sup>c</sup> Cox regression of ART time resulting in live birth, adjusting for log-transform of number of cycles. Bold indicates statistical significance.<sup>d</sup> Compared with Hodgkin's disease group (largest group).Agarwal. ART outcome in cancer patients. *Fertil Steril* 2004.

be because the motility of the spermatozoa is an independent predictor of its functional, metabolic, and DNA integrity. Sperm that are motile after thaw are the ones that have survived the stress of freezing and thawing and have proven themselves to be functionally intact to fertilize the oocytes and give rise to a viable embryo.

It is crucial for clinicians to address fertility issues with patients at diagnosis. It is important to gather information about the patient's level of concern, to consider his wishes while developing a treatment regimen, and to address future pregnancy options such as semen cryopreservation (8, 22, 25, 26). Sperm cryopreservation should be discussed as a routine part of therapeutic management to preserve fertility in young men with cancer who undergo surgery or receive chemotherapy or radiation therapy. Depending on post-thaw semen quality, patients may be advised to undergo IUI, IVF, or ICSI. Patients with a strong family history of various types of cancer should be counseled thoroughly.

Evidence of recovery of spermatogenic function after chemotherapy in patients with testicular cancer is convincing. Cryopreservation of semen after the start of cancer therapy may have adverse effects on chromosomal structure of spermatozoa, causing de novo mutations (27). For these reasons, it is crucial to cryopreserve sperm before initiation of chemotherapy or radiotherapy and also to advocate use of contraception during and for 6 months after completion of therapy. Awareness should be created among patients with

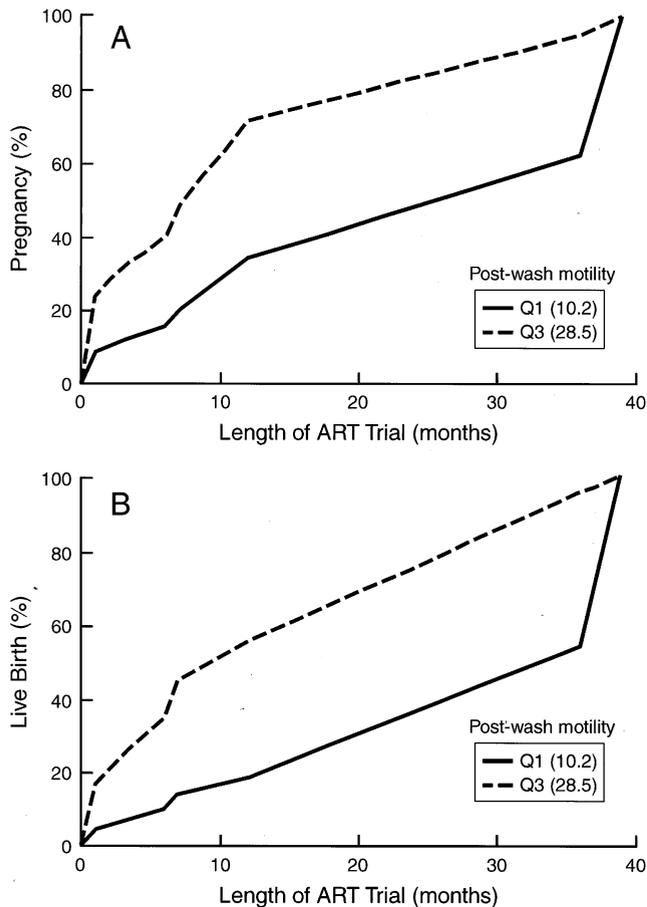
malignancies regarding the possibility of banking their semen before treatment. Oncologists, surgeons, and physicians involved in their treatment should discuss available options to bank spermatozoa before treatment. This offers a chance to have children and is also a psychological guarantee for preserving reproductive potential.

The limitations of our study include the following: [1] center-to-center variability in success rates of ARTs (20 different centers for 29 patients); [2] inability to obtain information on stage and grade of cancer at the time of diagnosis, which affects semen quality and has an impact on ART outcomes; [3] recall bias on the part of the patient; and [4] inability to obtain complete information from certain centers. We were unable to reach two patients, and we were only able to receive minimal information from the infertility clinics without consent from the patient. Some of these patients plan to continue to try ART in the future, and this may change the rates obtained in our study. Despite these differences, the fertilization, pregnancy, and birth rates are comparable to routine ART procedures done using sperm from male-factor infertility patients (28). Some patients have achieved pregnancies despite confounding factors like female infertility.

In conclusion, this is the first report that provides data on pregnancy and live birth rates for a large series of patients who used their cryopreserved sperm for ART. Almost 40% of the patients were able to achieve a healthy live birth, and

**FIGURE 2**

(A) Association between ART live birth and postwash motility (Cox proportional hazards model, assuming the median of 2 ART cycles). (B) Association between ART pregnancy and postwash motility (Cox proportional hazards model, assuming the median of 2 ART cycles). This figure shows that the third quartile of postwash motility results in higher percentages of live births and pregnancies than in the first quartile as the length of the ART trials increases.



Agarwal. ART outcome in cancer patients. *Fertil Steril* 2004.

their chances for success were not affected by the type of ART or malignancy. Prospective randomized studies are needed to determine the effectiveness of any particular assisted reproduction technique in cancer patients with specific malignancies. Our findings emphasize the need for physicians to offer all men of reproductive age who have cancer the opportunity to cryobank their semen before starting antineoplastic treatment.

## References

1. American Cancer Society. Cancer facts and figures, American Cancer Society statistics. ([www.cancer.org/docroot/STT/content/STT\\_1X\\_cancerFacts\\_Figures\\_2002.asp](http://www.cancer.org/docroot/STT/content/STT_1X_cancerFacts_Figures_2002.asp)) 2002:5–18.

2. Fossa SD, Aass N, Kaalhus O, Klepp O, Tvetter K. Long-term survival and morbidity in patients with metastatic malignant germ cell tumors treated with cisplatin-based combination chemotherapy. *Cancer* 1986; 58:2600–5.
3. Shekarriz M, Tolentino MV, Ayzman I, Lee J-C, Thomas AJ Jr, Agarwal A. Cryopreservation and semen quality in patients with Hodgkin's disease. *Cancer* 1995;75:2732–6.
4. Agarwal A, Tolentino MV, Sidhu RS, Ayzman I, Lee J-C, Thomas AJ Jr, et al. Effect of cryopreservation on semen quality in patients with testicular cancer. *Urology* 1995;46:382–9.
5. Turek PJ, Lowther DN, Carroll PR. Fertility issues and their management in men with testis cancer. *Urol Clin North Am* 1998;25:5217–31.
6. Meistrich ML. Restoration of spermatogenesis by hormone treatment after cytotoxic therapy. *Acta Paediatr* 1999;59:3557–60.
7. Naysmith TE, Blake DA, Harvey VJ, Johnson NP. Do men undergoing sterilizing cancer treatments have a fertile future? *Hum Reprod* 1998; 13:3250–5.
8. Lass A, Akagbosu F, Abusheikha N, Hassouneh M, Blayney M, Avery S, et al. A program of semen cryopreservation for patients with malignant disease in a tertiary infertility centre: lessons from 8 years' experience. *Hum Reprod* 1998;13:3256–61.
9. Pont J, Albrecht W. Fertility after chemotherapy for testicular germ cell cancer. *Fertil Steril* 1997;68:1–5.
10. Hallak J, Kolettis P, Sekhon V, Thomas AJ Jr, Agarwal A. Sperm cryopreservation in patients with testicular cancer. *Urology* 1999;54: 894–9.
11. Padron OF, Sharma RK, Thomas AJ Jr, Agarwal A. Effects of cancer on spermatozoa quality after cryopreservation—a 12-year experience. *Fertil Steril* 1997;67:326–31.
12. Agarwal A, Shekarriz M, Lee J-C, Sidhu RS, Thomas AJ Jr. Value of clinical diagnosis in predicting the quality of cryopreserved sperm from cancer patients. *J Urol* 1996;155:934–9.
13. Palermo GD, Cohen J, Alikani M, Adler A, Rosenwaks Z. Intracytoplasmic sperm injection: a novel treatment for all forms of male factor infertility. *Fertil Steril* 1995;63:1231–40.
14. Horne G, Atkinson A, Brison DR, Radford J, Yin JAL, Edi-Osagie EC, et al. Achieving pregnancy against the odds: successful implantation of frozen-thawed embryos generated by ICSI using spermatozoa banked prior to chemo/radiotherapy for Hodgkin's disease and acute leukemia: case report. *Hum Reprod* 2001;16:107–9.
15. Agarwal A. Semen banking in patients with cancer: 20 years experience. *Int J Androl* 2000;23:16–9.
16. Roselund B, Sjoblom P, Tornblom M, Hulting C, Hillensjo T. In vitro fertilization and intracytoplasmic sperm injection in the treatment of infertility after testicular cancer. *Hum Reprod* 1998;13:414–8.
17. Rangi G, Somigliana E, Restelli L, et al. Sperm banking and rate of assisted reproduction treatment—insights from a 15-year cryopreservation program for male cancer patients. *Cancer* 2003;97:1624–9.
18. Sankila R, Jorgen HO, Anderson A, et al. Risk of cancer among offspring of child hood- cancer survivors. *N Engl J Med* 1998;338: 1339–44.
19. Nicholson HS, Bryne J. Fertility and pregnancy after treatment for cancer during childhood or adolescence. *Cancer* 1993;71:3392–9.
20. Sharma RK, Agarwal A. Sperm quality improvement in cryopreserved human semen. *J Urol* 1996;156:1008–12.
21. Audrins P, Holden CA, MacLachlan RI, Kovas GT. Semen storage for special purposes at Monash IVF from 1977 to 1997. *Fertil Steril* 1999;72:179–81.
22. Schover LR, Rybicki LA, Martin BA, Bringeisen KA. Having children after cancer. A pilot survey of survivors' attitudes and experiences. *Cancer* 1999;86:697–709.
23. Lass A, Akagbosu F, Brinsden P. Sperm banking and assisted reproduction treatment for couples following cancer treatment of the male partner. *Hum Reprod Update* 2001;7:370–7.
24. Hendin B, Falcone T, Hallak J, Goldberg J, Thomas AJ Jr, Nelson D, et al. Effect of clinical and semen characteristics on efficacy of ovulatory stimulation in patients undergoing intrauterine insemination. *J Assist Reprod Genet* 2000;17:189–93.
25. Schover LR, Brey K, Lichtin A, Lipschultz LI, Jeha S, et al. Knowledge and experience regarding cancer, infertility, and sperm banking in younger male survivors. *J Clin Oncol* 2002;20:1880–9.
26. Schover LR, Brey K, Lichtin A, Lipschultz LI, Jeha S, et al. Oncologists' attitudes and practices regarding banking sperm before cancer treatment. *J Clin Oncol* 2002;20:1890–7.
27. Meistrich ML. Potential genetic risks of using semen collected during chemotherapy. *Hum Reprod* 1993;8:8–10.
28. Assisted reproductive technology in the United States: 1999 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. *Fertil Steril* 2002;78:918–31.