Intracytoplasmic sperm injection (ICSI) using cryopreserved sperm from men with malignant neoplasm yields high pregnancy rates

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Objective: To investigate the efficacy of IVF–intracytoplasmic sperm injection (ICSI) in patients who cryobanked semen before cancer treatment.
Design: Retrospective consecutive study.
Setting: University-based IVF unit.
Patient(s): One hundred eighteen couples undergoing IVF-ICSI using pretreatment frozen sperm.
Intervention(s): Treatment follow-up.
Main Outcome Measure(s): Semen parameters and clinical pregnancy rates.
Result(s): One hundred eighteen couples underwent 169 IVF cycles using pretreatment cryopreserved sperm; the average sperm count was 66.5×10^6/mL, and the average motility was 45.6%. Post-thaw sperm average density was 40.9×10^6/mL with 14.2% motility. The clinical pregnancy rate was 56.8% per retrieval; 96 pregnancies were achieved, resulting in 126 children born and 11 spontaneous abortions. Patients with prostate cancer had the worst semen parameters before sperm banking and the lowest clinical pregnancy rates.
Conclusion(s): IVF-ICSI is the recommended treatment for most couples with cryopreserved sperm for male cancer. High pregnancy and delivery rates after IVF-ICSI using cryopreserved sperm from patients with cancer should encourage all reproductive-age males to cryobank semen immediately after diagnosis; physicians should discuss this and advise freezing multiple samples before treatment. (Fertil Steril® 2008;90:557–63. ©2008 by American Society for Reproductive Medicine.)

Key Words: IVF, ICSI, male cancer, sperm, cryobanking

Survival after different types of cancer has improved dramatically in recent years because of advances in diagnostic techniques and current therapeutic modalities including chemotherapy, surgery, radiotherapy, and bone marrow transplantation (BMT). Cure rates for some malignancies exceed 95% (1). Consequently, many of the most common malignancies in men of reproductive age have high long-term survival rates, for example, testicular cancer and Hodgkin's disease. However, antineoplastic therapy is associated with significant morbidity, and testicular dysfunction is among the most common long-term side effects of cytotoxic chemotherapy in men. The degree to which testicular function is affected is dose and agent dependent (2). Alkylating agents (e.g., cyclophosphamide and busulfan) and ionizing radiation frequently induce azoospermia, rendering the patient infertile.

Meanwhile, cancer survivors often have a strong desire to foster biological children. This natural desire to have a family may even increase after the experience of cancer. At present, the best available way to enable these patients to realize their procreative abilities is by sperm cryostorage before cancer treatment. The developments in IVF and intracytoplasmic sperm injection (ICSI) (3) have revolutionized the treatment of male-factor infertility and have made sperm cryopreservation both cost-effective and the most successful treatment option for men who have viable sperm. Notably, no increased risk of birth defects has been observed in offspring of cancer survivors conceived after cancer treatment (4).

To date, there are only very limited data in the literature regarding the use of cryopreserved sperm from patients with malignant disease, most consisting of case reports (5–10) or limited case series (11–18). Moreover, it is yet unclear whether ICSI should be performed in all cases or in just those with poor sperm quality. The objective of the current study was to report on our experience with patients who cryobanked semen before treatment for a variety of malignant diseases and to compare our results in similar patients who underwent standard IVF insemination.

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MATERIAL AND METHODS

Subjects

All consecutive couples treated with IVF using frozen sperm obtained before cancer treatment between January 1994 and

April 2005 were included in this study. Charts were reviewed to obtain data regarding type of malignancy, duration of cryopreservation, pre- and post-thaw semen quality, the ovarian stimulation protocol used, number of mature oocytes retrieved, fertilization rate, the number of embryos transferred, and pregnancy outcome. The Institutional Review Board committee approved the study.

Sperm Cryopreservation

The samples were collected by masturbation before cancer treatment. The sperm was preserved in liquid nitrogen until needed. Because semen was processed in different laboratories throughout the world, specific freezing methodologies will not be herein described.

IVF Treatment Protocol

Two main stimulation protocols were used for the induction of follicular growth. In brief, approximately 85% of cycles used a long protocol of GnRH analog (GnRHa) injected in the midluteal phase of the previous menstrual cycle followed by ovarian stimulation with gonadotropins, hMG (Pergonal) and/or FSH (Metrodin or Gonal F [Serono, Waltham, MA] or Puregon [Organon, Roseland, NJ]), employing a step-down protocol. Approximately 15% began stimulation without down-regulation, using a GnRH antagonist in the late follicular phase to prevent premature LH surges. Human chorionic gonadotropin (3300–10,000 IU) was administered when at least two follicles with a 17-mm average diameter were observed by transvaginal ultrasound. Oocytes were harvested by transvaginal ultrasound–guided follicular puncture approximately 35–36 hours after hCG administration.

Thawed sperm samples were prepared by two different methods. Where adequate density was present, cryovials were warmed for 5 minutes at room temperature followed by 10 minutes in a 37°C water bath. An equal volume of culture medium was added slowly to the sample. After initial washing, tubes were centrifuged at 100 *g* for 10 minutes to pellet the spermatozoa and supernatants were removed. One milliliter of culture medium was layered over the pellets, the samples were mixed, and the tubes were centrifuged a second time in the same manner. After the second wash and removal of the supernatants, 0.1–0.3 mL of fresh medium was layered slowly over the pellets, the volume added being dependent on the pellet size. The tubes were placed inside a plastic beaker at a 45° angle to allow motile sperm to swim into the fresh medium layer. Tubes were then incubated, with loose caps, at 37°C under 5% CO_2 in air for 1 hour. After incubation, the medium layers were removed and analyzed for concentration, motility, and forward progression before being used for ICSI. Where significant oligospermia and/or asthenospermia were found, the sample was separated by centrifugation and Percoll gradient separation as described by Palermo et al. (19).

Microinjection of sperm (ICSI) was performed on all mature oocytes as previously described (19). Morphologically normal embryos were transferred into the uterine cavity approximately 72 hours after retrieval. As per our standard protocol, the number of embryos transferred was dependent on maternal age: 1–3 embryos were transferred in women under the age of 34 depending on developmental status and embryo morphology; 3–4 embryos were transferred to women 35–39 years of age; typically, 4 embryos (when available) were transferred in women 40 years or older. The remaining embryos of good quality were cryopreserved. Methylprednisolone (16 mg/day) and tetracycline (250 mg every 6 hours) were administered for 4 days to all patients, commencing on the day of oocyte retrieval. Progesterone supplementation was initiated on the third day after hCG administration (25–50 mg IM daily) and was continued until sonographic assessment of the pregnancy at 47–51 days of gestation, as determined by the day of oocyte insemination (day 14). A serum beta-hCG was performed 14 days after the ovum pickup (OPU). Pregnancy was defined as a serum hCG concentration of $\geq$10 IU/L on day 14 after transfer. A clinical pregnancy was defined as the presence of a fetal heartbeat at the 7-week sonogram. The implantation rate was defined as the average of the number of fetal hearts per number of embryos transferred for each patient.

Statistical Analysis

Data were collected using the Statistical Package for the Social Sciences for Windows program (SPSS, Chicago). Patient data were analyzed with respect to the male's cancer diagnosis. Fisher's exact test and nonparametric *t*-tests were performed for comparative analysis. $P<.05$ was considered statistically significant.

The effect of cancer type on semen parameters before and after sperm freezing was analyzed using analysis of variance and then analysis of covariance, where adjustment was made for the covariates length of freezing and age of the male at time of cancer diagnosis.

The effects of cancer type on pregnancy and delivery rates were analyzed using multiple logistic regressions, where covariates were length of freezing, age of the male at time of cancer diagnosis, and age of the female at time of IVF. The backward elimination method was used to fit the model. The results were presented as odds ratios (ORs) and the appropriate 95% confidence intervals (CIs). These analyses were performed using the SAS software (SAS V. 9.1; SAS Institute, Inc., Cary, NC).

For illustrative purposes, we compare fertilization and pregnancy outcomes in couples who underwent conventional IVF (before ICSI was performed routinely) with all ICSI cycles.

RESULTS

One hundred eighteen couples with pretreatment cryopreserved sperm underwent a total of 169 IVF cycles between January 1994 and April 2005. Parameters for male cancer patients are described in Table 1. The most frequent cancer types were testicular cancer (39.8%), lymphomas (31.4%), and prostate cancer (8.5%). The other diagnoses included

TABLE 1

Cancer data from 118 men.

Parameter	n (%)
Cancer type:	
Testicular	47 (39.8)
Lymphoma	37 (31.4)
Prostate	10 (8.5)
Other	24 (20.3)
Age at cancer diagnosis, mean ± SD (range)	31.4 ± 11.9 (11.9–68.8)
Cancer treatment:	
Surgery	72 (61.0)
Surgery only	20 (16.9)
Surgery + chemotherapy	28 (23.7)
Surgery + radiotherapy	17 (14.4)
Surgery + chemotherapy + radiotherapy	7 (5.9)
Chemotherapy only	26 (22.0)
Radiotherapy only	3 (2.5)
Chemotherapy + radiotherapy	17 (14.4)
BMT	11 (9.3)

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leukemia (n = 7), multiple myeloma (n = 4), brain cancer (n = 3), osteosarcoma (n =3), lung cancer (n = 3), bladder carcinoma (n = 2), pancreatic carcinoma (n = 1), and thyroid carcinoma (n = 1). Treatment protocols for these patients included surgery, chemotherapy, radiotherapy, and BMT as described in Table 1.

All patients cryopreserved sperm immediately after cancer diagnosis and before treatment. Before treatment, 43.4% had at least one abnormal parameter in their semen analysis and 20.5% had a total motile sperm count of less than 5 million. After treatment, 56 (77.8%) of 72 men with available data were azoospermic. Of the 16 men with sperm, four had less than 0.5 million total motile count, two had between 0.5 and 5 million, and 10 had more than 5 million. The sperm parameters at time of cryopreservation are shown in Table 2. As demonstrated, there was a significant deterioration in sperm parameters after thawing. The mean freezing interval was 7.1 ± 5.2 years, with a range of 3 months to 19 years.

The average age of the male partner at the time of IVF was 38.5 ± 9.5 years, and the average female age was 34.8 ± 3.9 years. In addition to the male factor, 13.6% of the women had another cause for infertility (Table 3). Moreover, 46 women (27.2%) were over the age of 35 years at the time of treatment, and 21 women (12.4%) were 40 years or older.

The mean number of oocytes retrieved was 12.1 per cycle, with a fertilization rate of 77.6%. Embryos were replaced in 162 cycles, with a mean number of 3.0 embryos per transfer. Embryo transfer did not take place in seven cycles for the following reasons: failure of fertilization (n = 1), failure of embryonic development (n = 5), and febrile illness (n = 1). A total of 96 pregnancies were achieved. There were 11 spontaneous abortions (11.5%) and 85 deliveries with 126 children born. The clinical pregnancy rate per OPU was 56.8%, and the delivery rate per OPU was 50.3% (Table 3). Freezing data were available for 104 cycles. In these 104 cycles, 112 embryos were frozen in 25 cycles, with an average of 4.5 embryos frozen per cycle. From these embryos, an additional seven pregnancies were achieved using thawed embryos.

Table 4 presents the semen parameters before cancer therapy and cryobanking by cancer diagnosis. Analysis of the semen profile revealed similarities between the lymphoma group and all other systemic cancers, and therefore these data were combined in one group (labeled "others"). These data were compared with the semen data of the reproductive tract cancers, namely, testicular and prostate carcinoma. Semen parameters in patients with lymphomas and all other systemic malignancies were associated with better semen profile than in patients with testicular or prostate carcinoma (Table 4).

Analysis of covariance, showed that cancer type was significantly associated with post-thaw semen concentration ($P<.0001$) and with total motile count ($P<.0005$), with significantly better semen parameters for the lymphomas and all other systemic malignancies. Furthermore, the effect of cancer type on post-thaw semen parameters was not influenced by the cryopreservation storage interval and the age at diagnosis.

Table 5 presents the clinical pregnancy rates, delivery rates, and age of couples according to the type of cancer. Logistic regression analysis revealed that only female age at IVF was correlated with pregnancy ($P<.013$; OR = 0.90; 95% CI, 0.83–0.98) and delivery rates ($P<.002$; OR = 0.875; 95% CI, 0.80–0.95). These data suggest that fecundity

TABLE 2

Semen parameters of 118 male patients before and after cryopreservation.

	Semen parameters before therapy	Semen parameters after thaw
Semen volume, mL	3.1 ± 1.7	0.6 ± 0.6
Mean, 10^6/mL (range)	66.5 (0.1–428)	40.9 (0.0–195)
Median, 10^6/mL	35.3	24.0
Motility, %	45.6	14.2
Mean total motile, 10^6 (range)	92.3 (0.03–569)	3.6 (0.0–28.6)
Median total motile, 10^6	52.8	0.8
Total motile <5.0 M, %	20.5	40.1
Total motile <0.5 M, %	2.6	72.0

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in this group of women was halved (0.51-fold) with aging every 5 years. Neither cancer type nor the other two covariates were associated with pregnancy or delivery rates.

Table 6 compares fertilization and pregnancies outcome between conventional IVF cycles (54 cycles) and ICSI cycles (169 cycles). The conventional IVF cycles were performed in 1992–94, before we changed our policy to perform ICSI for all patients with cryopreserved sperm.

DISCUSSION

The application of IVF and ICSI after pretreatment cryobanking of semen in men with malignant neoplasia offers renewed hope for the preservation of reproductive potential and the

TABLE 3

Characteristics of 169 IVF-ICSI cycles in a total of 118 couples.

Parameter	Value
Couples undergoing:	
One cycle	85
Two cycles	21
Three cycles	7
Four cycles	4
Five cycles	1
Wife's age at IVF, mean ± SD (range)	34.8 ± 3.9 (27.0–45.7)
Husband's age at IVF, mean ± SD (range)	38.5 ± 8.5 (27.2–71.7)
Infertility etiology:	
Male only, n (%)	102 (86.4)
Male and anovulatory/polycystic ovaries, n (%)	7 (5.9)
Male and mechanical, n (%)	5 (4.2)
Male and endometriosis, n (%)	4 (3.4)
No. of eggs retrieved, n ± SD	12.1 ± 6.3
No. of mature eggs, n ± SD	8.9 ± 4.8
Fertilization rate, % ± SD	77.6 ± 21.2
Embryo transferred, n ± SD[a]	3.0 ± 1.1
Implantation, %	31.1 (156/502)
Clinical pregnancy rate/OPU, %	56.8 (96/169)
Delivery rate/OPU, %	50.3 (85/169)
Deliveries:	
Singleton, n (%)	48 (56.5)
Twins, n (%)	33 (38.8)
Triplets, n (%)	4 (4.7)

Note: OPU = ovum pickup.

[a] One hundred sixty-two cycles of ET.

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TABLE 4

Semen parameters before freezing according to the type of cancer.

	Testicular cancer (n = 47)	Prostate cancer (n = 10)	Other[a] (n = 61)	Total (n = 118)	Unadjusted *P*	Adjusted *P*[b]
Semen volume, mL (range)	3.6 ± 1.9 (0.5–11.6)	1.5 ± 1.0 (0.1–3.4)	2.9 ± 1.3 (0.9–6.8)	3.1 ± 1.7 (0.1–11.6)	<.006	<.006
Count, 10^6/mL:					<.006	<.01
Mean	39.6	24.7	102.7	66.5		
Median	27.0	12.0	78.3	35.3		
Motility, %	49.5	35.6	44.1	45.6	NS	NS
Total motile, 10^6					<.05	<.05
Mean	64.1	28.1	134.1	92.3		
Median	51.3	5.1	68.0	52.8		

[a] The lymphoma group was combined and analyzed with the "other" because they had similar parameters of sperm analysis.

[b] Adjusted *P*-values were calculated by analysis of covariance where adjustment was made for the covariate age of the male at time of cancer diagnosis.

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chance of having biological children in men who are otherwise rendered sterile by cancer therapy. Each year, approximately 1.3 million patients are diagnosed with cancer in the United States, with an average 5-year survival rate of 60%, resulting in about 9.8 million cancer survivors (20). Hodgkin's disease, testicular cancer, leukemia, and non-Hodgkin's lymphoma are the most common malignancies seen in the male reproductive-age group. Infertility resulting from sterilizing cancer treatment is a major concern for the survivors. To date, there are limited data regarding the outcome of assisted reproductive technologies (ART) treatment using cryopreserved sperm from male cancer survivors (21).

The largest series to date (22) reports 29 pregnancies in 64 men who underwent 85 ART cycles (35 intrauterine insemination [IUI], 28 IVF cycles, and 22 IVF-ICSI cycles). Similarly, Agarwal et al. (11) recently reported their 20 years' experience with cryopreserved sperm in 29 patients and 87 ART cycles. In the present report, we describe the ART outcome in 118 male cancer survivors undergoing 169 IVF-ICSI cycles. To our knowledge, this is the largest series of couples treated with IVF-ICSI using cryopreserved sperm stored before cancer therapy.

The clinical pregnancy rate in our study was 56.8%, which is comparable to the average pregnancy rate achieved with other male-factor patients in our center. Previous reports have described comparably lower pregnancy rates. Lass et al. reported on 231 men referred for cryopreservation for malignant diseases. Only six couples returned for infertility treatment after chemotherapy. Two couples achieved a pregnancy after IUI, one couple after IVF, and two couples after ICSI (14). Another study described 258 patients who cryopreserved their semen before chemotherapy; only 18 of these returned for treatment, with six pregnancies achieved (12). Agarwal et al.'s (11) success rate with ICSI was 37% with cryopreserved sperm. A recent study from Copenhagen reported a total of 151 ART cycles (55 IUI cycles, 82 ICSI, and 14 ICSI-frozen embryo replacement) in which the clinical pregnancy rate per cycle was 14.8% after IUI and 38.6%

TABLE 5

Clinical pregnancy rate, delivery rate, and age of couples according to the type of cancer.

	Testicular cancer (n = 47)	Prostate cancer (n = 10)	Other (n = 61)	Total (n = 118)
Clinical pregnancy rate, %	58.0 (69 cycles)	18.2 (11 cycles)	60.7 (89 cycles)	56.8 (169 cycles)
Delivery rate, %	52.2 (69 cycles)	18.2 (11 cycles)	52.8 (89 cycles)	50.3 (169 cycles)
Husband's age at IVF	36.4 ± 3.7	55.4 ± 8.9	38.0 ± 8.9	38.5 ± 8.5
Wife's age at IVF	34.5 ± 3.2	40.0 ± 4.0	34.3 ± 4.0	34.8 ± 3.9

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TABLE 6

A comparison of ART results before and after ICSI.

	ICSI	IVF	*P*[a]
No. of cycles	169	54	
Mean age of wife, years	34.8	33.4	NS
Fertilization rate, %	77.6	31.5	<.001
Failed fertilization, n (%)	1 (0.6)	6 (11.1)	<.001
Delivery rate, %	50.3 (85/169)	24.1 (13/54)	<.001

[a] *P*-values calculated by Fisher's exact test and unpaired Student's *t*-test.

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after ICSI (18). Our high pregnancy rate may be attributable in part to the use of ICSI for all cases. The pregnancy outcome in such cases after conventional IVF, before the use of ICSI, was significantly lower, as can be seen in Table 6. Moreover, 11% of the patients experienced no fertilization, as compared with 0.6% after the introduction of ICSI. Based on these data, most IVF cycles using cryopreserved semen performed in our center now are undertaken with ICSI. These results are consistent with those of other investigators who report significantly higher pregnancy rates and better results using ICSI compared with IVF or IUI (11, 16, 18, 22). Our study was limited to IVF cycles and did not include patients treated by IUI. Certainly, patients with good post-thaw semen quality and sufficient samples can be treated initially by IUI before attempting ICSI-IVF cycles. However, the success rates may be low (11, 16, 18). Nevertheless, we believe that for all male cancer survivors who undergo IVF, ICSI should be performed to increase the fertilization rates, avoid the risk of failed fertilization, and avoid the exhaustion of a limited sperm supply.

It is of crucial importance that all newly diagnosed male cancer patients be advised to cryopreserve their sperm at the earliest stage and most importantly before starting treatment. Although many cancer patients have poor pretreatment semen quality, most have suitable sperm for freezing with good expectations for sperm survival (23). In the era of ICSI when only a few sperm are needed to achieve fertilization and pregnancy, even men with severely impaired sperm parameters will benefit from sperm cryopreservation and should be encouraged to do so. In this study, we were able to achieve a pregnancy with a sperm count as low as 100,000 sperm/mL. The average sperm count before treatment was 66.5×10^6/mL, with a motility rate of 45.6%. Although 43.4% of the patients had at least one abnormal semen parameter, and 20.5% of the men had less than 5 million total motile sperm, most had sufficient sperm for successful cryopreservation and subsequent ICSI. After treatment, 77.8% of patients were azoospermic, which emphasizes the importance of early cryopreservation.

Another major reason to freeze sperm before treatment is the concern for potential chromosomal aberrations in sperm exposed to chemotherapy. Although no increase in malformation rate has been reported in children born to patients who have had chemotherapy or radiotherapy (4), the available data and follow-up are still limited and these children should be closely monitored.

The effect of the type of cancer on sperm quality is controversial. Several studies have found impaired sperm quality associated with testicular cancer (14, 24, 25) and lymphoma (26, 27). However, Padron et al. have shown similar semen quality in men with Hodgkin's disease, leukemia, and testicular cancer (28). In our study, analysis of covariance of semen parameters clearly showed the greatest impairment in prostate cancer patients. Testicular cancer patients had relatively lower sperm counts but relatively good motility. Men with lymphomas and other systemic (nonreproductive) cancers had relatively normal semen parameters.

The cryopreservation storage interval does not seem to significantly affect the thawed semen quality. Indeed, we achieved a pregnancy after a freezing interval of 19 years. There was no correlation between the semen parameters after thawing and the duration of semen storage, nor was there a correlation between the male partner's age and post-thaw semen profile. It appears that the freezing and thawing process rather than the duration of storage is responsible for the deterioration in sperm quality.

The pregnancy rates were quite similar for all groups except for the prostate cancer group, in which the pregnancy rate was 18.2%. Logistic regression analysis revealed that the female partner age rather than sperm quality was responsible for the apparent differences. This is not surprising, since only a few functional sperm are required to achieve fertilization with ICSI.

Some investigators have raised a concern regarding the "underutilization" of cryobanked sperm, casting doubts about the justification of banking spermatozoa before chemotherapy (29). A minority of patients (usually less than 5%–10%) who bank their sperm before cancer treatment come back for infertility treatments (4, 11, 12, 30). There are certainly several reasons to explain this fact, including recovery of spermatogenesis after therapy, death, anxiety regarding ART treatment, financial considerations, and uncertainty about their long-term prognosis. Undoubtedly increased public awareness and the improving ART success rates will

encourage patients to use their cryopreserved sperm. We strongly believe that the medical community should continue to offer sperm freezing even if only relatively few individuals return for treatment.

Cryopreservation of sperm is a relatively inexpensive and simple method of preserving reproductive potential. The introduction of ICSI to the treatment armamentarium reduces the need for storage of many samples and increases the chance for future reproductive success. This is especially critical for those men who may only have the opportunity to preserve one or two specimens before initiating cancer treatment. Our 11 years' experience with ICSI in male cancer survivors shows great promise. The high success rate achieved with cryopreserved-thawed sperm should encourage all physicians involved in cancer care to offer cryopreservation to all men of reproductive age before initiating antineoplastic therapy. Semen cryopreservation is the standard of care for these individuals. Failure to offer this option ignores the patient's only reproductive option. Thus physicians and caregivers of male cancer patients should be aware of this important fertility preservation option and should therefore counsel patients regarding the high success rates that can be achieved with ICSI.

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