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An analysis of our experience in cryopreservation of semen from cancer patients

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Objective: To analyze the characteristics of patients with oncological problems who were users of the sperm bank, as well as use of cryopreserved semen.

Materials and methods: A retrospective analysis was made of all cryopreserved semen samples from males diagnosed with cancer from April 1992 to October 2007 at the province of Las Palmas.

Results: One hundred and one male patients with cancer were referred to the sperm bank before cancer therapy. Eighty percent of them were contacted by telephone. Mean freezing age was 25 years. Forty-one percent of patients had testicular tumors. Thirty-three percent had no prior biological children. Only one patient had known fertility problems before treatment. Sixty-seven percent of patients were warned by the healthcare team about the possibility of infertility at the time of cancer diagnosis. Only 1% of samples were not adequate for cryopreservation. The frozen sample was used by 4% of the patients. When patients were asked about future use of semen, 63% of them wanted to continue with semen cryopreservation, as compared to 17% who had no interest in having offspring in the future.

Conclusion: The number of fertile patients who cryopreserve semen is extremely low. It is very important that the healthcare team warns patients of potential infertility after treatment. A high proportion of patients have valid samples for cryopreservation, but semen is used by a low number of patients. A high proportion of patients want to maintain their semen frozen.

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Análisis de nuestra experiencia en la criopreservación del semen en pacientes oncológicos

RESUMEN

Palabras clave:
Criopreservación
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Objetivo: Analizar las características de los pacientes con problemas oncológicos, usuarios del banco de semen, así como el uso del semen criopreservado.

Material y métodos: De forma retrospectiva se han analizado todas las muestras de semen criopreservadas de varones con el diagnóstico de cáncer, entre abril de 1992 y octubre del 2007, en la provincia de Las Palmas.

Resultados: Fueron remitidos al banco de semen 101 varones con tumores, previo tratamiento oncológico. Se contactó por vía telefónica con el 80%. La edad media de congelación fue de 25 años. El 41% de los pacientes padecían de tumores testiculares; no tenían hijos biológicos previos el 33%. Sólo un paciente tenía problemas de infertilidad previo al tratamiento. En el momento del diagnóstico del cáncer el equipo sanitario advirtió al 67% de los pacientes de la posibilidad de infertilidad. Sólo el 1% de las muestras no fue apta para la criopreservación. Se usó la muestra congelada en el 4% de las muestras, y cuando se les preguntaba sobre el uso futuro del semen el 63% de los pacientes deseaba continuar con el criopreservado, frente al 17%, que no mostraba interés por tener descendencia en el futuro.

Conclusión: El número de enfermos en edad fértil que criopreservan el semen es extremadamente bajo. Advertir a los pacientes de la posibilidad de infertilidad tras el tratamiento, por parte del equipo sanitario, es de una vital importancia. Hay un alto porcentaje de pacientes con muestras válidas para criopreservación, un escaso número de pacientes hacen uso del semen, aunque existe un alto porcentaje de pacientes con deseo de continuar con su semen congelado.

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Introduction

The existing range of cancer therapies can produce undesirable effects such as irreversible sterility. It has been observed that 15-30%^{1,2} of all cancer patients remain sterile months or years after oncological treatment, and there is sufficient evidence of the alterations in spermatogenesis produced by chemotherapy and radiotherapy, with structural alterations in the sperm chromosomes. However, the degree of cytotoxicity is determined by the treatment regimen employed, and its duration. Fertility can be recovered in some cases, and it is not possible to predict who will not be affected. The existing alternatives to avoid alterations in spermatogenesis do not afford acceptable results.

Thus, the only option for preserving fertility in cancer patients remains sperm cryopreservation before starting oncological treatment. In this context, and in addition to efforts aimed at improving the quality of life of these patients, consideration is required of the possibility of maintaining their options to become parents.

The present study reviews our experience in semen preservation over the last 15 years.

Materials and methods

A retrospective analysis was made of all semen samples subjected to cryopreservation between April 1992 and October 2007, corresponding to 101 males diagnosed with cancer in the province of Las Palmas (Spain).

All the samples were evaluated by the same specialist in clinical analyses belonging to the Maternal-Children's University Hospital of Gran Canaria, after informing the patient and/or his relatives of the characteristics of the semen cryopreservation protocol in this laboratory, and after having signed the corresponding consent form.

A telephone-based data collection protocol was established, and a review was made of the interconsultations of the specialists who referred the patients to the semen bank. Patient data were collected, along with the center and service of origin, age at the time of cancer diagnosis, the characteristics of the tumor and the treatment provided, the characteristics of the cryopreserved semen, paternity antecedents, and fertility problems before and after oncological therapy. The medical personnel had duly informed the patient of the possibility of infertility after such therapy, together with the possibility of preserving the semen and the perspectives for its future use.

The statistical analysis was carried out with the Statistical Package for the Social Sciences version 13.0 (SPSS; Chicago, IL, USA), using means, standard deviations and ranges for continuous variables. All analyses were made using the Student t-test and analysis of variance (ANOVA) - statistical significance being accepted for $p < 0.05$.

Results

Between April 1992 and October 2007, a total of 101 male cancer patients were referred to the semen bank before oncological

therapy. All the patients of the sample had undergone surgical and/or chemotherapeutic and/or radiotherapeutic treatment at the time of this study, though no questions were asked about the specific treatments received. Eighty percent of the subjects were contacted by telephone, and 11 had died as a result of cancer.

Our semen bank is the reference center for four hospitals in the province, located on three islands within the archipelago. Of the total patients, 58% were from the Maternal-Children's University Hospital of Gran Canaria ($n = 101$).

The Services suggesting semen cryopreservation were mainly Clinical Oncology and Hematology (77%), and Urology (20%).

The mean patient age at the time of cryopreservation ($n = 92$) was 25.73 years (standard deviation (SD) 6.63; range 13-36 years) – no significant differences in mean age being observed between responders and non-responders ($p = 6.5$).

As expected, the most frequent malignancies in the sample were leukemias and Hodgkin and non-Hodgkin lymphomas (30.7% [$n = 31$]), followed by testicular tumors, which we have divided into non-seminomatous (26.7% [$n = 27$]) and seminomatous (14.9% [$n = 15$]). No significant differences were found between the different types of cancer and the response rate (fig. 1).

Regarding parental status prior to oncological treatment, 7% of the contacted patients had a single child, 2% had two children, and 33% had no children before treatment. Only one patient had prior testicular and infertility problems. The rest of the subjects either had no such problems or were unaware of any such problems. At the time of cancer diagnosis, the healthcare personnel warned of the possibility of infertility after oncological treatment and suggested semen cryopreservation in 67% of the cases. In only 11% of the cases was such preservation a patient personal or family initiative.

The semen sample was obtained by masturbation, followed by analysis and cryopreservation according to the guidelines of the World Health Organization (WHO). The protocol required three semen samples collected after three days of sexual abstinence. However, this was not possible in all cases – fundamentally due to the need to start oncological therapy.

All the samples were analyzed by the same specialist in clinical analyses. The mean sperm count ($n = 97$) was 46.48 million per ml (SD 35.68, range 0-160 million). Mean sperm motility ($n = 94$) was 38.74% (SD 26.35, range 0-95%). A mean number of 5.77 sample tubes were preserved (SD 6.96).

The final assessment ($n = 101$) showed 18% of the semen to be suitable for conventional *in vitro* fertilization (IVF), 47% for artificial conjugal insemination (CAI)/conventional IVF, and 25% for intracytoplasmic sperm injection (ICSI). In turn, 1% was found not to be apt (fig. 2).

Following the thawing test, 8% of the samples were found to be non-valid.

Based on the current semen quality criteria, it may be summarized that 33% of the patients presented oligospermia, while the rest were within normal limits – no statistically significant differences being observed between the different types of tumors and asthenospermia ($p = 0.97$). As regards sperm motility, asthenospermia was documented in

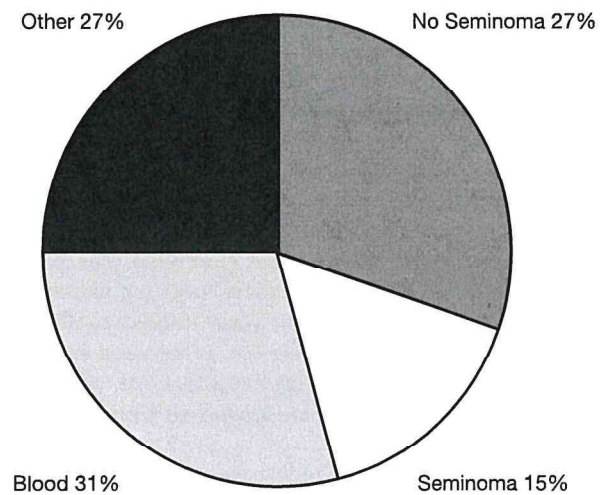


Figure 1 – Type of tumor.

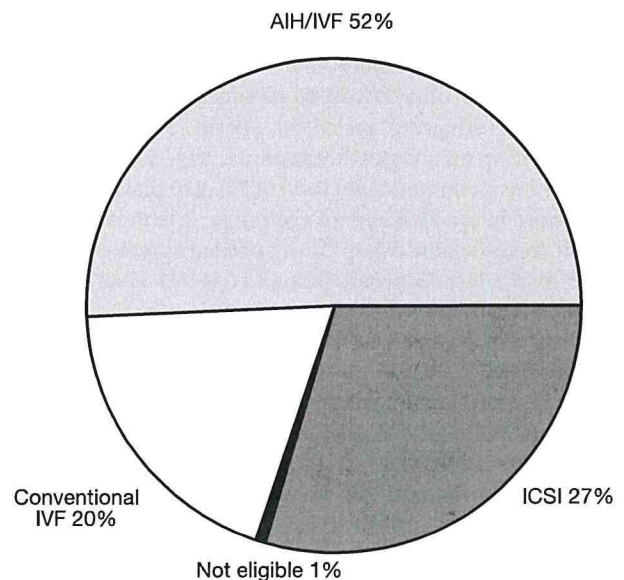


Figure 2 – Percentage semen apt for the different techniques.

63.4% of the normal samples – maximum asthenospermia corresponding to seminomatous testicular tumors (86.7%).

The number of spontaneous offspring in our series following oncological treatment, after a mean duration of follow-up of 87.8 months (SD 15.4, range 72.6-109 months) was one child in one patient and three children in two patients. In the patients in which semen was not used, the mean duration of follow-up was 64.5 months (SD 48.7).

Semen was used on 5 occasions, in 4 patients – this representing 4% of the sample ($n = 101$), with a time interval of between 20-32 months after the diagnosis of cancer, and with a mean patient age of 26.3 years.

When questioned about the future use of the semen, 63% of the patients expressed their wish to continue with

cryopreservation, while 17% declared no interest in having offspring in the future.

Discussion

It is not easy to find official data on oncological patients that have cryopreserved their semen in Spain, despite the fact that such activity is legal and controlled. The survival rates for the different types of cancer in young patients has improved substantially in recent years, thanks to advances in diagnosis and treatment. Over 60% of all patients treated for malignant diseases have a life expectancy of over 5 years. Approximately 100,000 males are diagnosed with cancer each year in Spain.

Of all the patients in our study, a total of 194 samples were stored, and although 80% of the subjects could be contacted by telephone, the classical problems of retrospective studies were found. The mean patient age at the time of preservation (around 30 years) coincides with other series found in the literature.

The number of patients of fertile age that cryopreserve their semen is extremely low. However, according to different studies, only 24% of all patients treated for cancer and without offspring resort to sperm cryopreservation before starting oncological treatment³. Based on data from 2005, our hospital attended a total of 235,530 males, of which 89,267 were in the 20-45 years age range. It is presently very difficult to know how many young patients were treated for cancer in the last 15 years, though it seems clear that the number of patients who have cryopreserved their semen must be quite different from that expected on the basis of other studies.

Sixty percent of all patients who are programmed for treatments potentially capable of affecting their fertility are adequately informed of the fact⁴. This coincides with our own observations, since 67% of the patients were informed by the healthcare personnel of the possibility of infertility after oncological treatment, and only 11% of the subjects decided cryopreservation as a personal or family initiative. While oncologists are the professionals most directly implicated in the management of these patients, a relevant finding was the disparity in patient referral to this Service from the different attending hospital centers – this suggesting important sensitization on the part of the evaluating professionals.

The use of cryopreserved semen for one assisted reproduction technique or other in principle depends on the number of samples, their quality after thawing, and the experience of the laboratory. Some studies have estimated that 13-30% of all patients show azoospermia at the time of sample collection, and logically these cases are not suitable for cryopreservation⁵. However, this was not seen in our series, where only 1% of the patients showed a non-suitable sample. Furthermore, after the thawing test, only 8% of the samples were found to be non-valid ($n = 194$).

In Spain, the existing legislation on assisted reproduction allows storage of the samples deposited in the semen bank for the full life of the patient. This allows such patients

to legally use these samples for assisted reproduction purposes when they consider it opportune. However, this situation implies a work burden for the semen banks, as well as an extra cost for society. In recent years there have been increasing doubts over the justification and need to cryopreserve semen in banks from young patients prior to chemotherapy and/or radiotherapy, since the number of infants born from the use of previously cryopreserved semen is relatively low. In the few available series, relatively few patients resort to frozen semen samples for fertility treatments. In effect, less than 10% of the males use their previously frozen semen⁶⁻⁹. This is fundamentally explained by uncertainty regarding a sufficiently prolonged period of adequate health, and the suitability of becoming parents. As has been seen in other studies, the utilization rate increases as the years of cryopreservation increase, and the mean patient age at the time of resorting to assisted reproduction techniques is 34 years according to some sources^{10,11}. In our experience, the utilization rate of cryopreserved semen was only 4%, with spontaneous biological offspring in only 3% of the patients, after a mean follow-up period of 5.5 years. Despite these results, when questioned about the future use of the semen, two-thirds of the patients expressed their desire to continue keeping their cryopreserved semen.

Lastly, in the short series of existing studies, the use of cryopreserved semen from cancer patients for assisted reproduction purposes has not been associated with an increased incidence of malformations or oncological problems in the resulting offspring, and although only three children were born in our series of subjects, none of them had problems of any kind.

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