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Procreation by Means of Cryopreserved Spermatozoa from Tumor Patients

W. Krause

Cryopreservation of spermatozoa is offered to patients undergoing cytotoxic treatment in order to improve fertility prognosis. The type of tumor does not influence sperm quality used for cryopreservation. Cryopreservation after the onset of chemotherapy is contraindicated since this increases the risk of DNA fractures in spermatozoa.

Spermatozoa are stored in liquid nitrogen at -196°C , a time limit for storage is not known. In Germany, cryopreservation of spermatozoa is not covered by the social health insurance system, thus leaving the cost to the responsibility of patients. Age and marital status do not influence the decision for cryopreservation.

The number of patients attempting to induce a pregnancy in the female partner by use of cryopreserved sperm is generally low. Due to the recovery of spermatogenesis, nearly half of the patients are able to father a child spontaneously after tumor therapy. In these patients, the risk of mutations in the children is low. Malformation rate was not enhanced in these children. Cryopreservation as a means to preserve male fertility prior to tumor therapy thus is not absolutely essential.

In Germany, postmortem use of cryopreserved spermatozoa is forbidden by law. Only anecdotal reports are available from other countries. J Reproduktionsmed Endokrinol 2007; 4 (2): 94–6.

Key words: spermatozoa, cryopreservation, fertility prognosis, cytotoxic treatment

Cryopreservation of spermatozoa is the most relevant technique to improve fertility prognosis if cytotoxic therapy threatens spermatogenesis and future fertility. Cytotoxic therapy is applied in childhood as well as fertile age, with patients suffering from tumors or severe autoimmune diseases. Cryopreservation of spermatozoa is also performed for patients undergoing assisted reproduction techniques (ART), if the synchronisation of oocyte maturation and the retrieval of spermatozoa proves to be difficult. A third group consists of patients requesting a vasectomy. For this group, cryopreservation serves as a “fertility back-up”.

In each of these cases, cryopreserved spermatozoa are stored in liquid nitrogen at -196°C . Obviously, there is no time limit for this storage of spermatozoa. There are reports on up to 30 years of storage [1], keeping in mind that the technique has been available only since 1940.

Prior to cryopreservation, the purpose and probability of success of the procedure should be thoroughly discussed with the patient. Cryopreservation is performed only after explicit patient consent. In Great Britain, a contract (HFEA [96] 6) is required [2].

For long-term storage (more than three months), the cryopreserved specimen usually are transferred to a commercial provider for safety reasons. In Germany, Cryo-Bank (Air liquide, Krefeld) offers this service.

For the cryopreservation procedure, patients are charged Euro 155,-, storage at the Cryo-Bank costs an additional Euro 332,- per year (in 2005). Only in rare cases, these expenses prevent patients from using cryopreservation of semen. In their study, Hallak et al [3] showed that in the US, none of the 342 patients claimed that the expenses were a reason for them to refrain from cryopreservation. The German health insurance system does not cover

expenses for the long-term storage while the treatment and prevention of infertility are partially carried by the system.

The transplantation of spermatogonial stem cells to animal or human testis is an experimental alternative method for cryopreservation [4].

Use of Cryopreserved Spermatozoa

The number of patients attempting to induce pregnancy in the female partner by the use of cryopreserved sperm is generally low [2]. A British survey reports on 2219 men who had cryopreserved sperm from 1977 until 1987 and of whom only 133 attempted to induce pregnancy with cryo sperm [5]. Sanger et al [6] report on 117 pregnancies and 115 births but they do not quote the number of total patients and cryopreserved specimen. In their own department, 16 of 73 patients attempted to induce pregnancy using cryo sperm, resulting in 7 pregnancies. In only 3 (3.6 %) of our patients, a fertilization of the partner using intrauterine insemination was attempted. No pregnancy occurred [7].

Kliesch et al [8] quote a rate of 8 % of their patients. Hallak et al [3] report in their study that 41 patients of the 55 % who had recovered from spermatogenesis fathered a child. From the 855 cryo sperm specimen quoted by Kelleher et al [9], only 68 were used in assisted reproduction. ART resulted in 29 pregnancies with 39 births. The median period of storage was 3 to 12 years but did not exceed 15 years. Ragni et al [10] quote a rate of 6.2 % of patients who used the cryopreserved spermatozoa. Agarwal et al [11] reported on 318 patients in the years 1982 to 2001, of whom only 31 patients used their cryo sperm in assisted reproduction, 18 pregnancies occurred, 14 children were born, 7.1 % of intrauterine inseminations, 19 % and 21 % of ICSI trials resulted in a pregnancy. Colpi et al [12] reported on a rate of semen samples used for assisted reproduction techniques of 5 %, similar to international data. Meseguer et al [13] report on a total of 320 sperm samples frozen, more than half (54.3 %) of the patients had no reproductive partner at the time of cryopreservation. Only 30 patients (16.3 %) attempted to induce a pregnancy by ART. In 30 cycles,

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ICSI and in 5 cycles, artificial insemination was applied. In general, no other technique than ICSI appears to be applied today.

The study providing most extensive data on the use of cryopreserved sperm in patients with testicular cancer is that of Magelssen et al [14] from the group of Fossa in Oslo/Norway. After a median time of 62 months (10–155) after tumor treatment, 29 patients (7 %) had used their frozen semen at least once for ART, inducing 16 pregnancies, and 14 patients became father. After a median observation time of 54 months (8–193) after treatment, 67 of 393 men (17 %), who had deposits of cryopreserved semen, fathered at least one child with fresh semen. On the other hand, 205 out of 966 patients (21 %), who had not deposited cryopreserved semen, fathered a child within 49 (8–202) months after treatment. Twenty years after tumor therapy, the cumulative incidence of naturally first post-treatment fatherhood was 35 % for 966 patients without, and 47 % for 393 patients with cryopreserved semen. These figures are strong arguments against the opinion that cryopreservation of semen is absolutely essential prior to tumor therapy in men interested in preserving fertility.

Factors Influencing the Use of Cryopreserved Spermatozoa

Several studies report on poorer semen quality in patients with testicular tumors and M. Hodgkin than in other cancers [15–17]. Meseguer et al [13], however, and our own study [7] contradict this assumption. Spermatozoa of tumor patients generally have a lower resistance to cryopreservation than those of healthy men.

On the basis of data from 36 patients with testicular tumors, Sibert et al [18] indicated that there is no difference in the outcome, regardless of whether cryopreservation is performed prior to the orchidectomy or after. However, cryopreservation after the onset of chemotherapy is contraindicated, since the risk of DNA fractures in spermatozoa is then increased.

Only a small number of patients died after the time of sampling. In our study, 2 of the patients were recorded deceased. This figure is low in comparison to other findings. Kelleher et al [9] published 141 cases of death among their 855 patients after spermatozoa cryopreservation (16,5 %). Chung et al [19] recorded death in only 5.5 % of the patients. It is likely that the decreasing number of deaths is due to the improvement of antitumor therapy over time.

One might assume that young men at the age of 25 and below would be less interested in long-term storage since they less often live in a stable partnership than older men.

Our data, however, do not support this assumption nor the assumption that patients living within a stable partnership are more often interested in long-term storage of spermatozoa than those without a female. Table 1 summarizes age and marital status in our patients [7].

Unfortunately, the results are not comparable to data in the literature, since only few references report on the correlation of long-term storage after cryopreservation, age, and marital status of the patients. Only Kelleher et al [9] quote that while the use of cryopreserved sperm is more likely in married men and when extremely toxic chemotherapy is applied, yet a prediction on the use of the cryo sperm cannot be concluded.

There is no age limit for cryopreservation of sperm. Whenever the patients are able to produce sperm, also adolescents at a in younger age, cryopreservation of sperm can be performed with overall success rates similar to those observed in adults and should be recommended [20].

Recovery of spermatogenesis and fertility after tumor therapy is frequent. In the study of Naysmith et al [16], 7/22 patients fathered a child by natural conception after tumor therapy, 11 pregnancies were induced by insemination with fresh spermatozoa. In some cases, more than 8 years following chemotherapy spermatozoa in azoospermic patients could be retrieved from the testis and used for successful ICSI.

Spermon et al [21] obtained data on the fertility of 305 patients with testicular tumors prior to and after treatment, 226 patients responded to the enquiries. Prior to the diagnosis of a tumor, 120/226 (53.1 %) had tried to father a child, 93 of them succeeded, resulting in the births of 194 children. In 84.9 % of conceptions, the time to pregnancy was less than a year. After tumor treatment, 88 patients attempted procreation, 54 of them fathered a total of 81 children. Of these, 7 were born after assisted reproduction, 43 % of the conceptions occurred within one year. 70 of the 93 patients, who had children born prior to the tumor disease, did not ask for a child after tumor treatment. In fact, none of the patients wanted to use cryopreserved sperm for fathering children even if their spermatogenesis was restored [22].

If fertility recovers after cytotoxic treatment, the risk of mutations in offspring is low. Studies demonstrate that children procreated after chemotherapy have no higher risk of chromosomal aberrations or malformations than those from healthy fathers. Sankila et al [23] report on 14,652 surviving cancer patients and their 5847 children in Scandinavia from 1940 to 1960. The rate of malformations was not increased in these children. There is also no evidence that children born after ART with cryo sperm have a higher rate of malformations [2, 21].

Table 1: Demographic parameters of patients asking for long-term storage of cryo sperm (percentages of the total number in the column). According to [7]

Group	20–24 years	25–29 years	30–34 years	35–39 years	No partnership	Stable partnership
No interest	2 (10 %)	2 (9.5 %)	4 (14.8 %)	0 (0 %)	4 (8.5 %)	4 (15.4 %)
No information	2 (10 %)	5 (26.3 %)	9 (33.3 %)	2 (66.6 %)	12 (25.5 %)	9 (34.6 %)
Ongoing storage	8 (40 %)	9 (42.8 %)	10 (37.0 %)	1 (33.3 %)	19 (40.4 %)	10 (38.5 %)
Recovery of spermatogenesis	8 (40 %)	5 (26.3 %)	4 (14.8 %)	0 (0 %)	12 (25.5 %)	3 (11.5 %)
Total number	20	21	27	3	47	26

Postmortem Use of Cryopreserved Spermatozoa

Postmortem retrieval of spermatozoa from the testis or the ductus as well as the procreation with cryospermatozoa after the donor's death constitute exceptional cases. In Germany, both procedures are prohibited by the "Embryonenschutzgesetz" (Embryo Protection Act). The situation in the US is described by Batzer et al [24]. *"Posthumous sperm procurement is fraught with ethical dilemmas, including informed consent, privacy, inheritance, and child welfare. To establish appropriate medical practice, it is important to consider all stakeholders in the decision-making process. We believe that an acceptable and ethical resolution can be obtained only through the collaborative input of all involved parties."* The paper thus discusses only parenthood with living spermatozoa retrieved from the genital tract postmortem. No remarks on the postmortem use of cryopreserved sperm are included. The dilemmas triggered by this procedure, however, appear to be similar.

Tash et al [25] demanded a 1-year waiting period of the female partner before the use of spermatozoa retrieved postmortem. They report on 22 families, who sought postmortem fertilization but after thorough consultation, only one wife used retrieved sperm for an attempt of IVF, from which no pregnancy occurred, however.

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