Male fertility preservation in cancer patients. Reasoned opinion

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ABSTRACT

Every day about thirty cancers are diagnosed in young Italian patients. Of these, 37.4% are cases of young men mainly affected by testicular, colon-rectal or thyroid cancer, melanoma or Hodgkin's lymphoma. The risk of infertility in some types of cancer is very high, but for others the risk is much lower. Due to numerous confounding factors, it is difficult to clarify a role of cancer itself in male fertility. Semen cryopreservation may represent the only chance of future genetic parenthood for many patients. Rapid freezing of semen in liquid nitrogen vapors, before cancer treatment is started, is considered the gold standard for male fertility preservation; nevertheless, no more than 10% of patients ask to use frozen sperm to obtain a pregnancy. Despite the efficacy of male fertility preservation methods, the rate of men achieving pregnancy with samples frozen prior to cancer treatment is about 3.9%. In this reasoned opinion, different reasons are given, which suggest the need for a personalized approach to male fertility preservation.

KEYWORDS

Male fertility, fertility preservation, cryopreservation, sperm freezing, male cancers, fertility preservation efficacy, cancer patients.

Introduction

Thirty cancers are diagnosed daily in Italian patients < 40 years of age. Of these, 37.4% are cases of young men mainly affected by testicular, colon-rectal or thyroid cancer, melanoma or Hodgkin's lymphoma [1-4]. Cancer itself and the related treatments can affect gonadal function leading to an irreversible impairment of spermatogenesis, although this scenario is observed only in some cases, being dependent on various factors: the patient's age, the disease localization, the treatment duration and regimen, the sperm quality before treatment, and individual susceptibility.

Since not all cancer patients are at risk of infertility, a customized approach considering the type of disease and therapy is required in order to optimize male fertility preservation efficacy and cost-effectiveness. Sperm cryopreservation is the only established option for male oncological patients wishing to preserve their fertility.

Cancer and infertility

Male infertility is associated with many cancer co-factors such as obesity, cigarette smoking, lack of physical exercise, poor nutrition, alcohol consumption, and stress [5]. Due to these confounding factors, it is difficult to clarify a role of cancer itself in male fertility. However, testicular cancer seems to be associated with a worsening of sperm concentration, as do lymphomas, whereas leukemia seems mainly to be responsible for a reduction in sperm motility and changes in sperm morphology [6,7]. Conversely, there is a paucity of data on the impact of gastrointestinal, prostate, and many other cancers on spermatogenesis.

Modern cancer treatments are not always associated with male infertility. The impact of the therapy on spermatogenesis depends on the length of treatment, drug/irradiation dosages, the patient's age, and the type of drug [1]. In fact, while, on the one hand, some data confirm an association of cisplatin, cyclophosphamide, procarbazine, and chlorambucil with azoospermia, on the other, cancer treatments with fluorouracil, vincristine, vinblastine, dacarbazine, interferon alpha, bleomycin, and others do not seem to induce irreversible infertility. Similarly, testicular irradiation seems to induce azoospermia only at dosages >6 Gy. The toxic effect of molecular targeted therapy on male gonads is still unclear [1].

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Sperm freezing

Semen cryopreservation may offer the only chance of future genetic parenthood for many patients. Time constraints,

treatment delays, and difficulty accessing resources are some of the factors that give most concern.

Following the achievement of the first human live birth, sperm cryopreservation quickly became widespread as a male fertility preservation method [8,9]. Nowadays, cryopreservation of ejaculated sperm is the only established technique strongly recommended for all post-pubertal patients of reproductive age before cancer treatments, as stated by the Scottish Intercollegiate Guidelines Network (SIGN) and American Society for Medical Oncology (ASCO). Sperm cryopreservation can be successfully performed in "high-risk" pubertal males before the initiation of customized therapy. Rapid freezing in liquid nitrogen vapors before starting cancer treatment is the gold standard for male fertility preservation [10].

Efficacy of male fertility preservation

"Efficacy" means the patient's chance of achieving one live and healthy baby from sperm frozen before cancer treatment.

Although less than 10% of cancer patients ask to use sperm frozen during fertility preservation, almost 50% of them obtain one live baby [11]. Moreover, the clinical pregnancy rate and live birth rate per cycle observed in IVF treatments with sperm frozen for oncological indications are similar to those observed in non-cancer patients submitted to IVF using fresh sperm, independently of the IVF technique used [12].

The high number of healthy babies born from sperm banked for fertility preservation today allows sperm freezing to be considered a highly recommended established technique.

Conclusions

The main conclusions are listed in Box 1.

Sperm freezing is an effective and efficient technique for fertility preservation in male oncological patients, does not involve the need to delay starting cancer treatment, and allows the achievement of pregnancy rates and live birth rates per IVF cycle similar to those observed in non-cancer patients using fresh semen. In our opinion, two main factors explain this: (i) the strong resistance of sperm to the cryopreservation and thawing processes; and (ii) the fact that partners of male cancer patients are usually young (< 37 years old) and fertile, submitted to ovarian stimulation and IVF due to the impairment of spermatogenesis subsequent to their male partner's cancer experience; this allows an optimal ovarian response to be obtained and gives these couples a good IVF prognosis [13,14].

Despite the efficacy of male fertility preservation, more than 60% of surviving patients do not use banked semen, which results in a pregnancy rate per patient submitted to sperm banking of 3.9% [11]. There are several possible reasons for this, such as recovery of spermatogenesis, the patient's personal choice to postpone fatherhood or not have children, and the patient's death. Moreover, in some cases sperm banking is performed in very young patients, and more than 10–15 years may elapse before the sperm is used. Of note, the proportion of patients asking to discard their banked samples is less than 20%, and modern cancer treatments allow an overall survival rate of 90% in patients undergoing fertility preservation techniques. So, sperm banks usually contain a high number of unused samples from surviving patients, which entails high costs for the public health system for many years. Moreover, the utilization rate recently reported by Ferrari *et al*. confirms data reported by van Casteren *et al*. in 2008, which seems to indicate that insufficient advances have been made in terms of policies designed to encourage the utilization or discarding of frozen sperm after cancer treatment.

In conclusion, a customized approach and follow up after cancer treatment should be suggested in order to: i) better select patients eligible for fertility preservation, ii) optimize the effectiveness of male fertility preservation, and iii) obtain better management of the cryopreserved material (use, destruction, transport, etc.). This is especially important in countries, like Italy, where the cost of fertility preservation in cancer patients is totally supported by the national health system.

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Box 1

MALE FERTILITY PRESERVATION – MAIN CONCLUSIONS
Sperm cryopreservation before antineoplastic treatments always needs to be suggested in patients of reproductive age.
Testicular cancer, seminoma, and hematological malignancies seem to be associated with a reduction in sperm concentration, and progressively worse motility and morphology.
Freezing of ejaculated sperm is an effective method in terms of live birth rate.
Customized counseling on the management of the cryopreserved material (use, destruction, transport, etc.) is highly recommended in order to optimize the cost-effectiveness of the procedure.

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