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Mini Review

Experimental Approaches for Fertility Preservation in Prepubertal Boys Undergoing Oncological Therapy

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HIGHLIGHTS

- An increasing number of prepubertal boys encountering infertility due to cancer treatment.
- Cryopreservation of immature testicular tissue (ITT) is being advised in infertility centres.
- This review describes studies done by researcher making effort on fertility restoration.

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ABSTRACT

An increasing number of prepubertal boys encountering infertility due to cancer treatment has prompted a range of studies to set up new methods for fertility restoration and male germ cell maturation. In this regard, cryopreservation of immature testicular tissue (ITT) from biopsy samples is being progressively advised in infertility centers. Different strategies to in vivo or in vitro male germ cell development using stored testicular tissues have been followed: autotransplantation or Xenotransplantation of testicular tissue pieces, spermatogonial stem cells (SSCs) isolation, and transplantation, in vitro spermatogenesis using three-dimensional (3D) culture and tissue culture. Combination of these strategies with assisted reproductive techniques (ART) like intracytoplasmic sperm injection (ICSI) and in vitro fertilization (IVF) has resulted from complete spermatogenesis resulting in offspring in several animal models but no achievement in producing mature spermatozoa from human prepubertal SSCs has yet been reported. This review describes studies done by researcher making effort on fertility restoration from ITT containing SSCs, Considering the limitations and specific concerns of each strategy.

Keywords: Fertility Preservation; Transplantation; Cancer; Germ Cell Maturation

Introduction

Although oncological therapy has resulted in significant improvements in life satisfaction of prepubertal boys with cancer, it has adverse effects on their gonads such as azoospermia and decreased fertility potential, when they become adults (1). Sperm banking is a reliable option for postpubertal adolescents and young men but cryopreservation of immature testicular tissue (ITT) is the only solution for prepubertal boys (2). Alternative methods for fertility protection for these younger patients are still at the research level and are not applicable

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to the clinic. At the present, to achieve these goals, two main experimental protocols have been addressed by the researcher: 1, testicular germ cell transplantation or testicular grafting into host animals (3-5) or 2, germ cell or testicular tissue culture (6, 7), as shown in Figure 1.

Xenotransplantation of ITTs or SSCs

Xenotransplantation provides a microenvironment by maintaining molecular interactions and a testicular compartment for spermatogonial stem cells (SSCs) similar to the situation in the donor. Although grafting efficiency is low, tissue maturation and complete spermatogenesis have been achieved in ITT grafted under the skin of immunodeficient mice in several animal species (3, 4, 8) and also the resumption of spermatogenesis in slow-frozen ITT xenografts from rabbits (9), pigs (10), lambs (11) and primates (12) has been reported with lower efficiency than fresh tissue. Despite the advances in animal studios, the study in which spermatogenesis became complete using xenotransplantation of human ITT has not yet been published (13). xenotransplantation is a useful option to study the potential of ITT grafts but its disadvantages such as animal contamination, hypoxia of grafted tissues, the endocrine difference between donor and recipient should be addressed and improved in future studies (1). Transplantation of testicular cell suspension to the testes of infertile mice was the first study for the SSC transplantation approach instead of xenotransplantation of human ITT, yielding offspring (5). This method was used to other species, such as non-human primates (14) and it has led to spermatozoa generation or offspring. Excluding cancer cells from testicular cell suspensions and using specific culture conditions for the suitable proliferation of SSCs are several concerns that still need to be considered before clinical use (1).

In vitro maturation of ITTs or SSCs

For elimination of concerns related to autologous SSC transplantation or ITT grafting, cited above, in vitro spermatogenesis using a 3D cell culture system or tissue culture can be an alternative method (6). Fertile sperm obtained in vitro organotypic culture of fresh mice ITTs led to offspring (7). This study has opened a new window for understanding developmental requirements of in vitro maturation of sperm such as cellular interaction, special arrangement, and paracrine communication (6). Concerning the importance of cell–cell contacts, conventional cultures were replaced with 3D culture

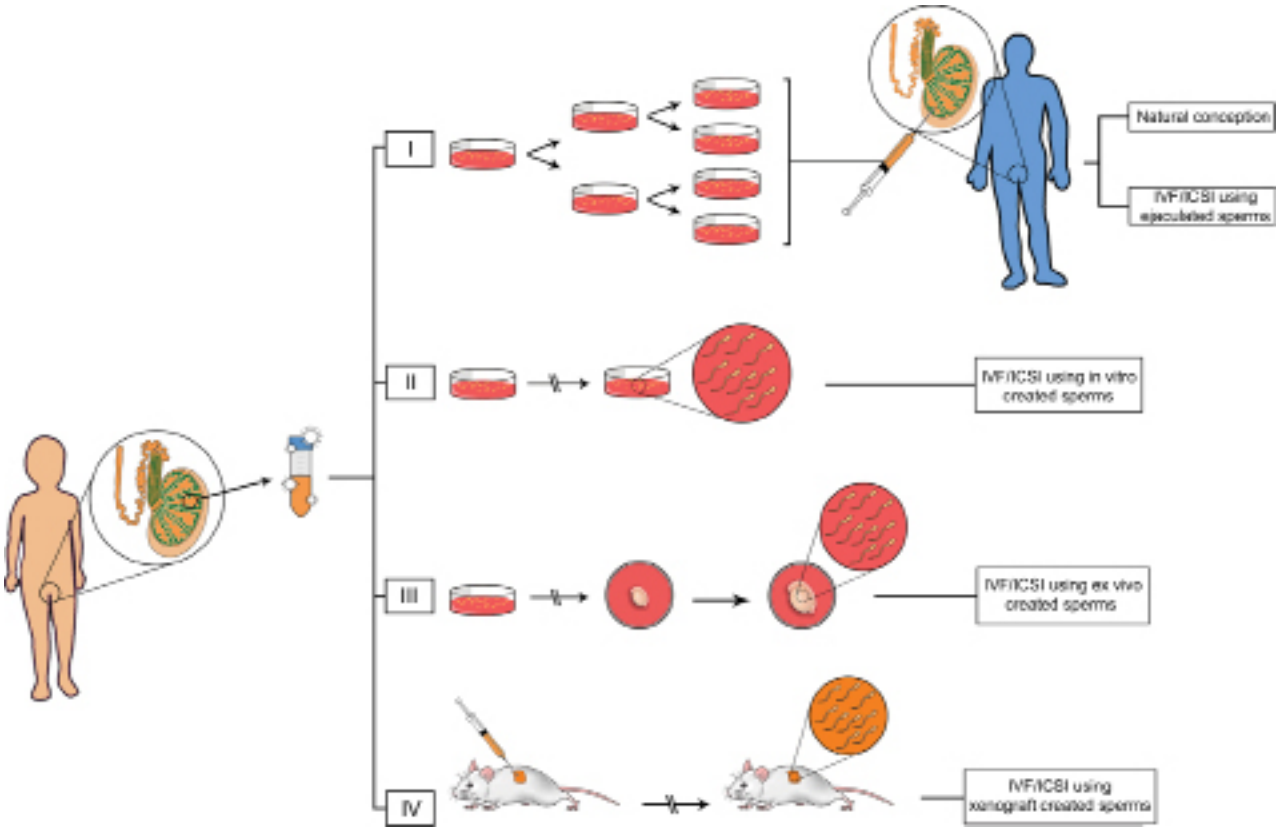

Figure 1. Experimental protocols for fertility protection in prepubertal boys with cancer and their possible clinical applications (17). Isolation and in-vitro proliferation and transplantation of SSCs. In vitro spermatogenesis using 3D or conventional culture systems. III. Ex vivo testicular tissue culture. IV. Xenografting of cryopreserved tissue under the skin of immunodeficient mice

systems providing a spatial arrangement in which the testicular cells can have interaction and communication (15). In 3D culture, testicular cell suspensions are embedded in a collagen (15), alginate, or agar matrix (6, 16) to provide the microenvironment which regulates germ cell maturation and cellular interactions. Stukenborg et al., reported a study in which the entire spermatogenic process occurred in vitro after embedding mouse testicular cells in a soft agar culture system (6).

Conclusions

Taking everything into account, cryopreservation of ITT before oncological therapy has now been accepted for more than a decade by infertility centers worldwide, and today, ITT banks have put much pressure on researcher and clinicians to respond to Patients' expectations hoping fertility restoration. All methods cited in this review for SSC maturation in vivo or in vitro led to complete spermatogenesis sperm or offspring in at least one animal model. With the knowledge of limitations like complex human spermatogenic process, the scarcity of human ITT, more efforts should be done for fertility protection in prepubertal boys with cancer.

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Conflict of interest

The author declares that there are no conflicts of interest.

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Ethical statements

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Abbreviations

ART	Assisted reproductive techniques
ICSI	Intra cytoplasmic sperminjection
ITT	Immature testicular tissue
IVF	In vitro fertilization
SSCs	Spermatogonial stem cells
3D	Three-dimensional,

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