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REVIEW ARTICLE

Established and Future Promising Fertility Preservation Options for Adolescent and Adult Cancer Patients: a Review of Current Advances

Hossein Yazdekhasti[1], Zahra Rajabi[2]

[1]*Cell biology department, University of Virginia, USA*

[2]*Department of Biomedical Engineering, University of Virginia, USA*

Corresponding Author: Hossein Yazdkhasti, E-mail: hosein.yazdekhasti@yahoo.com. Phone: hosein.yazdekhasti@yahoo.com.

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ABSTRACT

Background: Over the past decades, improved diagnostic and prognostic procedures have resulted in an increased number of cancer survivors; with this, the demand for fertility preservation options has risen dramatically. Cancer patients who are interested in fertility preservation have several options that can be pursued based on age, risk of gonadal involvement, time available, and type of cancer, each with different advantages and disadvantages. **Methods:** Relevant papers were identified using a computerized literature search on recent papers in PubMed and MEDLINE. **Results:** Of all possible options, embryo cryopreservation for women and semen freezing for men are the most common; however, gonadal tissue cryopreservation and oocyte cryopreservation are other promising options that can be considered if a partner is not available. Both women and men with cancer benefit from adequate consultation regarding possible fertility preservation options. **Conclusion:** Providing patients and their families with immediate and accurate information helps ensure that the best fertility preservation decisions are made.

INTRODUCTION

Based on World Health Organization (WHO) reports and those from other organizations, infertility is a common condition. Worldwide, 72.4 million women are estimated to be infertile; of these, an estimated 40.5 million are currently seeking medical treatment for infertility (1). In 2005, a national survey of family growth in the United States reported that, between 1995 and 2002, there was a 20% increase in American couples experiencing infertility (2). Another report found a rise in infertility from 42% to 48.5% from 1990 to 2010, which might be related to delayed parenthood and childbearing in the third decade of life, and which consequently resulted in a decrease in ovum and sperm quality in couples. Statistical reports predict an even lower future fertility rate and a higher infertility prevalence with the advent of some complex diseases, which decrease fertility potential in both women and men (3). Cancer is one of these complex diseases, and infertility is one of the most serious consequences of radio/cytotoxic treatment, which can affect the quality of life of cancer survivors. Some chemotherapeutic agents, particularly alkylating agents such as busulphan; ionizing radiotherapy to the abdomen or pelvic region; and surgical procedures can destroy the gonads and lead to infertility (4-7).

Thus, new treatments based on novel technologies need to be developed. One of the most promising is assisted reproductive technology (ART), which involves embryo production in vitro and then transfer of the embryos to the uterus. In addition, stem cell treatments can help couples have their own genetic babies and eliminate possible ethical considerations that might be raised from sperm, oocyte, or embryo donation (8-16).

Sterility after aggressive cancer treatment, especially in adolescence, is one of the most complicated and psychologically difficult issues that families face. Some studies have shown that cancer patients have a reduced fertility potential even before starting treatment (17-20). For this kind of infertility, some reasons have been proposed: primary or secondary hormonal imbalance; anatomic changes (retrograde ejaculation); damage to supporting cells or germinal stem cells; reduction of sperm DNA integrity, numbers, and mo-

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tility; and a decrease in pituitary gonadotropin levels, all of which can negatively affect fertility (11,12,21,22).

During certain cancer treatments, most germ cells in the gonads will be destroyed, resulting in the patient being permanently sterile. Therefore, the employment of fertility preservation methods is indispensable. These methods should also be affordable. Each year, many types of research are conducted to develop appropriate methods for fertility cryopreservation. Those who may also benefit from fertility preservation methods are patients who have non-oncologic diseases; patients with chromosomal abnormalities (e.g., Turner's syndrome); patients with autoimmune disorders; patients with severe or recurrent endometriosis; patients treated with gonadotoxic agents that can cause premature ovarian failure; and couples who postpone parenthood into their fourth or fifth decades of life (23).

It was reported that, by January 2012, approximately 13.7 million cancer survivors were living in the United States, with the number projected to approach 18 million by 2022. Because of this tremendous increase in the number of cancer survivors, developing new fertility preservation methods is a critical issue (24). In this article, we review the available and experimental fertility preservation methods for adolescent and adult cancer patients and discuss their advantages and disadvantages (Table 1). These options are a combination of recent developments in ART, cryotechnology, and innovative cell culture systems.

AVAILABLE AND EXPERIMENTAL FERTILITY PRESERVATION OPTIONS FOR MALES

I was estimated that one in every 640 young adults in the USA would be a survivor of childhood cancer (25), indicating that there is high demand for fertility preservation in adolescence. Unfortunately, prepubescent males have limited options and pose a particular challenge for fertility preservation due to their inability to produce semen for cryopreservation. There are some ways to produce semen samples from prepubescent males, but samples are frequently of poor quality (26,27). Although prepubescent testes have spermatogonial stem cells (SSCs), for fertility preservation purposes mature spermatozoa are indispensable. Research on the use of SSCs for the restoration of fertility in cancer survivors is ongoing. To date, these studies have led to the production of live offspring only in rodents. However, these significant achievements in rodents may possibly pave the way for the future use of SSCs for fertility preservation in routine ART procedures.

Another approach involves the cryopreservation of testicular tissue before the onset of aggressive cancer treatment. Then, years later, once the patient is ready to have a family, the testis tissue is thawed and used in either auto-transplantation of testicular tissue or in vitro maturation of SSCs until they can be used for intracytoplasmic sperm injection (ICSI) (10, 28, 29). Meanwhile, SSCs can be transplanted back into another host (xeno-transplantation) to encourage spermatogenesis; however, before such methods can be used in clinical settings, many legal, ethical, and clinical concerns must be adequately addressed (30). Most crucially, there is a risk of reintroducing cancer cells with testicular tissue transplantation, with potentially fatal consequences.

For adult patients, semen cryopreservation is a standard, established, and successful technique after cancer diagnosis, and treatments can be started as soon as possible. Studies indicated that cryopreservation led to the deterioration of semen quality by, on average, 31% in terms of motility, 37% in terms of morphology, and 36% in terms of mitochondrial activity (31). However, using ICSI and other ART procedures, these defects can be mitigated. For these reasons, it is highly recommended that 2-3 ejaculates per patient be obtained, because semen quality may be low.

Semen samples can be collected through masturbation. If there is a difficulty, alternative measures are penile vibratory stimulation, rectal electrostimulation under anesthetic, testicular sperm extraction from a biopsy, and collecting spermatozoa in urine samples (27,32). Cryopreservation of SSCs retrieved from mature testes is yet another option and is considered a promising future method. However, many additional studies are needed to investigate how SSCs can be used for fertility preservation purposes in routine ART clinical procedures.

Other methods exist, but these are still under investigation and in clinical trials. Gonadal shielding during radiation therapy is one of these methods with established clinical applicability. Shielding can be used to reduce the dose of radiation delivered to the testicles (33). Testicular suppression with gonadotropin-releasing hormone (GnRH) analogs or antagonists is another method. Using hormonal therapies, testicular tissue can be protected from the harmful effects of chemotherapy or radiation. There is, however, a body of evidence showing the ineffectiveness of this approach (34).

Although fertility preservation methods are highly recommended, they are not always offered to patients. Avoiding a delay in the onset of anti-cancer therapy is the primary reason. Others include the belief that sperm banking is less efficient in adolescents; high costs; poor prognostic procedures; lack of adequate facilities; and the belief that cancer treatment can have profound infertility consequences (35).

AVAILABLE AND EXPERIMENTAL FERTILITY PRESERVATION OPTIONS FOR FEMALES

For prepubescent girls, several fertility preservation strategies might be helpful, although most methods are experimental and require further investigation and clinical trials before they can be used prior to aggressive cancer treatment. Of these methods, ovarian tissue cryopreservation is the most promising. Recent reports showed that ovarian tissue transplantation resulted in more than 90 live births (36). Although live births have been achieved by this method, ovarian tissue cryopreservation and thawing after cancer treatment and puberty is not yet an available option for the public. This approach is still considered experimental. Additional studies and approval by institutional review boards are required before it can become a standard fertility preservation method in ART clinics (37).

Another experimental fertility preservation method that gives hope to female cancer patients is the isolation of follicles from cortical strips and ovarian biopsies (38). However, progress and achievements in this particular approach

Table 1. Advantages and disadvantages of fertility preservation options (* = options that are experimental and not clinically available)

Sex	Age	Options	Advantages and disadvantages
Males	Adolescents	Semen freezing, if applicable	Poor quality
		Cryopreservation of SSCs*	Expensive and requires further procedures; higher number of SSCs in adolescent boys than adults
		Cryopreservation of testis tissue*	Expensive and requires further procedures; risk of reintroduction of cancer cells; no available human success rates
		Radiation shielding of gonads	Not satisfying results; only possible with selected radiation fields and anatomy; expertise needed to ensure that shielding does not affect reproductive organs
	Adults	Semen freezing	The most applicable option; best results
		Testicular sperm extraction	Can be done after treatment; low rate of success required outpatient procedures
		Cryopreservation of SSCs*	Expensive and requires further procedures; lower number of SSCs in adolescent boys than adults
		Cryopreservation of testis tissue*	Expensive and requires further procedures; risk of reintroduction of cancer cells; no available human success rates; requires outpatient procedures
		Radiation shielding of gonads	Not satisfying results; only possible with selected radiation fieldss and anatomy; expertise needed to ensure shielding does not affect reproductive organs
		Testicular suppression with gonadotropin-releasing hormone (GnRH) analogs or astagonists	Controversial; not satisfying results in clinical trials; no surgery needed; not expensive and easy to perform; needs more evidence to be applicable
Females	Adolescents	Ovarian tissue cryopreservation*	Expertise required; expensive; risk of reintroduction of cancer cells; the only available approach for prepubescent girls; allows natural pregnancy after auto-transplantation; fewer ethical dilemmas; no ovarian stimulation required; low success rate; not available in every clinical setting
		Isolation and cryopreservation of immature follicles*	Requires outpatient procedures; expensive; no live birth evidence in humans
		Cryopreservation of ovarian stem cells*	Further evidence required; highly controversial; outpatient procedures needed
	Adults	Embryo cryopreservation	Well-established and most reliable option; high pregnancy rate; best option when sufficient time is available before cancer treatment; requires a male partner or sperm donation; requires ovarian stimulation; not applicable for women who have hormone-sensitive cancers; requires outpatient surgical procedure
		Mature oocyte cryopreservation	No ethical problems; no urgent need for sperm; applicable for single women; low pregnancy rate but acceptable fertilization rate; requires ovarian stimulation and delay in cancer treatment; not suitable for PCOS patients because of the high risk of OHSS; requires outpatient surgical procedure
		Immature oocyte cryopreservation*	No delay in cancer treatment; higher fertilization rate compared to the mature oocyte; IVM needed; no ovarian stimulation needed; not expensive; no needed for a partner or sperm donation
		Oophoropexy	No satisfying results; can be performed in all ages; surgical procedures required; ovarian function can be preserved; no ethical problems; spontaneous pregnancy may not be possible
		GnRH analogs	Controversial; not satisfying results in clinical trials; no surgery needed; not expensive and easy to perform; needs more evidence to be applicable; spontaneous pregnancy possible; ovarian function can be preserved
		Cryopreservation of ovarian stem cells*	Further evidence required; highly controversial; outpatient procedures needed

GnRH: Gonadotropin-releasing hormone; IVM: In vitro maturation; OHSS: Ovarian hyperstimulation syndrome; PCOS: Polycystic ovary syndrome; SSC: Spermatogonial stem cell

are mostly in rodents, and it seems unlikely that this method will be available soon in larger animals and humans. The possible strategy involves obtaining multiple ovarian biopsies from young patients through either laparoscopy section or oophorectomy and then isolating follicles from ovarian tissue and cryopreservation. After cancer treatment, follicles will be returned to patients either by auto-transplantation or in vitro maturation to produce a live birth by in vitro fertilization.

Treatment with ovarian stem cells is another novel fertility preservation approach. Considerable controversy exists among reproductive scientists regarding the existence of ovarian stem cells in adolescents and adults. However, if present, ovarian stem cells could potentially be used in the future for fertility preservation purposes (8-10,13,15).

Shielding ovaries is another fertility preservation method, in which ovaries are protected from the side of effects of radiation by surgical transposition (39,40). However, since pelvic irradiation has a destructive effect on the uterus, the probability of a natural pregnancy is significantly reduced (41), even if ovarian function is preserved.

Regarding possible fertility preservation methods in adult women, the most routine and applicable method is embryo preservation, if a partner is available. In the absence of a partner, oocyte freezing can be performed. Most of these methods are expensive, require surgery, and are not as reliable as sperm cryopreservation in males. They are routinely applied based on a patient's marital and economic status, age, time available, and risk of ovarian involvement (39,42).

At the 2012 American Society for Reproductive Medicine (ASRM) meeting, embryo preservation was defined as the only established method for fertility preservation in adult women. The safety and effectiveness of this method have been proven. Now, embryo preservation is a part of routine ART clinics for infertile women, enabling storage of supernumerary embryos. It can also be used for women with ovarian hyperstimulation syndrome or impaired endometrial development, or for impractical embryo transfer (43,44). Recent reports have indicated that oocyte and embryo cryopreservation result in similar pregnancy rates; therefore, the current revised ASRM and American Society of Clinical Oncology guidelines recommend oocyte freezing as an applicable and trusted method for patients for whom a partner is not available (37,45,46). Although embryo cryopreservation is the most established fertility preservation method, recent progress and clinical experiments indicate that the rate of pregnancy after oocyte freezing is increasing dramatically. In addition, the pregnancy rate after the transfer of frozen/thawed embryos is even higher than fresh embryo transfer cycles (47).

Oocytes can be cryopreserved at either the mature or immature status. Single women and those who do not have access to a sperm donor can pursue this option. To avoid any delay in beginning cancer treatment, treatment can be started as soon as possible. During the procedure, the immature oocyte is retrieved from the ovary through ovarian tissue cryobanking or oophorectomy (48). This method might have some advantages over mature oocyte freezing. Some studies showed that immature oocytes are less vulnerable to ultralow temperatures and to cryodamage, due to lack of metaphase spindle and lower cell volume, but the main obstacle is low pregnancy rate and low developmental capacity after fertilization of immature oocytes (49, 50). To our knowledge, there is no report of a live human birth after fertilization with cryopreserved oocytes and transfer of immature oocytes. Additional clinical and experimental studies are necessary before this can become a routine clinical procedure.

Owing to recent significant progress and achievements in humans, cryopreservation and transplantation of ovarian tissue is another promising fertility preservation method that has attracted the attention of reproductive and oncologic scientists (51,52). It has been proven that immature oocytes are more resistant to cryodamage within primordial follicles in ovarian tissue (53). However, the main obstacle to further advances is how to activate quiescent follicles after freezing and thawing procedures. Cryopreserved ovarian tissues can be used by three possible methods: auto-transplantation, xeno-transplantation, and in vitro culture of immature follicles. In this context, auto-transplantation is the only clinically relevant strategy and has led to over 90 live births (54,55). Xeno-transplantation has shown potential to be a promising method in humans and animals; however, it has raised many ethical and legal concerns that need to be fully addressed. Another, much more complicated, method is the in vitro culture of immature follicles. In this method, primordial, primary follicles or even pre-ovulatory follicles are isolated from ovarian fragments and then cultured in the presence of other supplementations and conditions. Later, metaphase I oocytes are retrieved from mature follicles, and through a process called in vitro maturation, oocytes are matured (metaphase II) and fertilized by ICSI or in vitro fertilization. Many remarkable achievements have been made using this method, mostly in rodents and farm animals; however, to be a clinically acceptable method in humans, further studies and investigations are required (56,57). Notably, transplantation of ovarian tissue risks the reintroduction of malignant cells to the patient's body. Thus, before starting the process of transplantation, cancer cells must be absent from ovarian tissue fragments (58,59).

To minimize the deleterious effects of ionizing radiation on the ultrastructure and function of ovarian tissue, particularly in the cases of Hodgkin disease and abdominal surgery, oophoropexy, or ovarian transposition, is another method that is routinely used in clinics (60). Although this method is clinically relevant, the outcomes are not satisfying considering how directly dependent the outcomes are on radiation dose, patient age, whether concomitant chemotherapy is used, and whether the ovaries are shielded (5,61).

There is one final fertility preservation method in which ovaries can be protected from chemotherapy-induced damage (34). In this method, agonists of GnRH are administrated to patients before the onset of chemo/radiotherapy. These agonists increase the probability of spontaneous menstruation within 3-8 months after the termination of chemotherapy. Even though this method is only in clinical trials, its clinical applicability is controversial (62-64).

CONCLUSION

Additional methods for fertility preservation exist. The clinical applicability of these methods depend on the results of ongoing clinical trials, further investigations, and other validation measures. Some approaches, such as sphingosine-1-phosphate, AS101, and imatinib, have demonstrated protective effects on germ cells via suppression of apoptosis pathways in germ cells after the devastating consequences of radio/cytotoxic treatments.

In conclusion, as the number of cancer survivors has increased dramatically over the past few decades, so too has the demand for fertility preservation. Most patients are now aware of the detrimental effects of cancer treatments, and they are seeking a variety of fertility preservation options. In addition, industrialization, the desire for increased socioeconomic status, and the growing demand for employment are other reasons why people postpone childbearing and which have led to more requests for fertility preservation options. Both women and men with cancer benefit from adequate consultation regarding possible fertility preservation options. Providing them and their families with immediate and accurate information helps ensure that the best fertility preservation decisions are made.

CONFLICT OF INTEREST

The authors declare that they have no conflicting financial interests.

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