Creating A Standard of Care for Fertility Preservation

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Abstract: Fertility preservation options for women are currently only routinely offered to patients who face iatrogenic fertility loss, and most options are considered experimental. The most common modalities for female fertility preservation are embryo cryopreservation, oocyte cryopreservation, and ovarian tissue cryopreservation, the latter two of which remain in the experimental arena. Natural fertility loss is affecting women as significantly as premature fertility loss. Increasing cancer survival and the modern reproductive trend of delaying childbearing are indications for the need and demand for fertility preservation. Advances in the field are necessary to respond to this demand and include superior cryopreservation techniques and fertility preservation technologies, customized guidelines, comprehensive care plans, and availability of more cost-efficient procedures. The obstacles to creating a standard of care for fertility preservation are as broad as the field itself. Lack of patient awareness, limited physician experience and knowledge, inadequate counseling, costs, and ethical issues are some examples of the many challenges to establishing a standard of care. With continued research and multidisciplinary collaboration, a higher quality of care may be provided to a larger patient population who wishes to maximize their fertility potential in the future.

Keywords: Fertility preservation, standard of care, treatment options, challenges, assisted reproductive technology (ART), patient expectations.

CURRENT STATUS OF FERTILITY PRESERVATION

The technologies of fertility preservation include all methods and efforts to maintain the ability to reproduce even after natural or iatrogenic loss of fertility. The many methods to preserve fertility for women include gonadal protective measures during potentially harmful therapeutic treatments and cryopreservation of the ovary, oocyte, or embryo. Of the cryopreservation options for females, embryo cryopreservation is the only form currently accepted as an established practice [1]. Oocyte and ovarian tissue cryopreservation are still considered experimental forms of preservation due to the less than satisfactory outcomes of cryopreserved oocytes in assisted reproductive techniques (ARTs) and the short lifespan of ovarian tissue transplantation grafts [2]. Additionally, this option is offered mainly for patients who face iatrogenic loss from treatments related to cancer and other diseases. Fertility preservation is less available for patients who wish to delay their childbearing years at the risk of becoming sterile.

Currently there is an increased demand for a broader range of options and availability of treatment for both cancer survivors and healthy individuals [3, 4]. Translational research and improvements in methods and technologies in the last decade have provided a diversity of potential fertility preservation options; however, at present these options remain limited and suboptimal [5]. Continued research and success present the need to establish standards of care for the many available fertility preservation techniques.

NATURAL AND PREMATURE FERTILITY LOSS

Natural fertility loss occurs for all women with advancing age. For most women, menopause occurs during their mid-50s; however, fecundity occurs some 10 years before the onset of menopause [6]. A natural atresia of oocytes over the years accounts for the decrease in fertility potential. As the quantity and quality of oocytes declines as age advances, the possibility of conceiving a healthy child decreases.

Premature fertility loss occurs before the naturally occurring time and may be induced by gonadotoxic treatments necessary for cancer and other diseases, from genetic causes such as Turner’s syndrome [7], or from environmental hazards. With premature fertility loss women not only lose their reproductive potential, but, in addition, the cessation of ovarian function induces menopause symptoms, including osteoporosis, which may have greater consequences when endured at a younger and more active age [6].

The most common forms of cancer that a female may suffer during her reproductive years that require gonadotoxic treatment are breast and cervical cancer [3, 8]. Most diagnoses of these cancers occur before the age of 35, and many others occur during the prepubertal and adolescent years, including hematologic malignant conditions, sarcomas, central nervous system lesions, renal cancer, and bone cancer [4]. Autoimmune diseases that require similar chemotherapeutic treatments include rheumatoid arthritis, systemic lupus erythematosus, steroid-resistant glomerulonephritis, inflammatory bowel disease, and pemphigus vulgaris [3, 8].

Treatment for these diseases may wreak havoc on the female reproductive system. Chemotherapy, radiation therapy of the pelvic region, gonadotoxic medication, and surgical incisions of or near the gonads or reproductive system...
produce a high risk for induced fertility loss. Among women who undergo combination chemotherapies, 20-50% under the age of 20 and 80-90% over the age of 25 will present with amenorrhea after treatment [9]. Radiation may cause apoptosis to occur, decreasing the amount of primordial follicles available to mature and resulting in premature ovarian failure (POF) [3, 10-12]. Gonadotoxic drugs such as alkylating agents arrest cell proliferation and may also induce POF [3, 9].

**INDICATIONS FOR DEMAND FOR FERTILITY PRESERVATION**

In the last decade cancer treatment and ART have made significant advances and achieved higher success rates than ever [13]. The goal of cancer treatment is first and foremost survival, yet the inevitable gonadotoxicity of the treatment harms the potential for survivors to genetically parent their own children. Until an effective treatment for cancer can be developed to target tumor cells specifically, sterility will remain a possible consequence of successful cancer treatment [14]. Many patients undergoing treatment are nulliparous but desire to have children in the future.

With the increase in cancer survival more attention is being given to the patient’s quality of life post-treatment [15]. Current survival rates for patients with Hodgkin’s disease, lymphoma, and leukemia are as high as 90% [5], and of 10,700 children diagnosed with cancer in 2008, approximately 80% of them were expected to survive [4]. Additionally, the incidence of cancer in the adolescent and young adult population has increased steadily over the last 25 years [13]. Thus, as more patients are undergoing treatment and more of those patients are living longer, fertility preservation must become an integral part of holistic cancer treatment.

Concurrently with increased cancer survival, the modern reproductive trend of delaying childbearing necessitates a greater need for fertility preservation. Women all over the world, especially in developed countries, are choosing to defer pregnancy in pursuit of academic or occupational achievements or for lack of a suitable partner [7, 9, 16, 17]. With advancing reproductive age the ability to conceive greatly decreases due to the naturally accelerating atresia of primordial follicles that occurs in the late 30s and early 40s of a woman’s lifetime [9, 12]. During this time the possibility to spontaneous abortion and aneuploidy increases [9, 12]. Cryopreservation of oocytes at a maternal age of 35 years or younger for fertility preservation may provide the potential for women to reproduce even after the biological clock has run down [17].

The positive risk-benefit ratio for the cryopreservation of oocytes to be electively self-donated to healthy individuals at a later date calls for an increased availability of these services for all women who desire its potential benefits [18]. As oocyte cryopreservation has been considered experimental, the Practice Committee of the American Society for Reproductive Medicine did not recommend it to postpone reproductive aging and asserts that it should be offered only in an experimental setting and with the approval of an institutional review board [2]. The Practice Committee recently purported that oocyte cryopreservation appears promising and may assist in reducing the rising number of cryopreserved em-

**NECESSARY ADVANCES IN THE FIELD**

Fertility preservation strategies emerged from techniques used for infertility treatment, yet the development of specific protocols and technologies is necessary for this advancing and distinct field of medicine [20]. The complexity and broadness of the field of fertility preservation requires that its technology and research be particular and organized. Novel techniques have been developed that are promising, yet challenges remain to applying these techniques routinely and successfully [21]. Research findings must be applied in protocol to improve the efficacy of the current strategies, as well as to develop new methods and tools [15].

For women undergoing cancer treatment, bridging the treatment gap between the oncologists and the fertility specialist is imperative [13]. By establishing a multidisciplinary team that includes oncologists, fertility and oncology nurses, social workers, reproductive endocrinology and infertility specialists, embryologists, and researchers, a specific treatment plan may be established that provides the highest possibility for success [13]. The members of the team that provide fertility preservation care for the female cancer patient must work together and keep the patient and the center of their focus; refer to Fig. (1). The goal is to provide a multidisciplinary treatment plan for the female cancer patient that maintains the greatest survival potential, preserves fertility, and offers the best quality of life with the least long-term suffering post-treatment [4, 22].

![Fig. (1)](Image)

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With a cohesive and knowledgeable team, an individualized care plan based on case-specific motives, situations, age, disease, and other necessary medical treatments can be established for each patient [11, 23]. Counseling is a fundamental aspect of a standard of care because it ensures that the woman may make the most informed decisions based on an
understanding of realistic expectations and after weighing the risk-benefit ratio [2, 9, 10, 24].

An established standard of care may allow more women who might desire the benefits of fertility preservation to utilize the services [5]. The standard must also be flexible to adjust to new technologies and discoveries, as well as to adapt to each patient in her specific socio-economic case. With increased awareness, success, and use of fertility preservation with a standard of care, the different options may become more clinically available and affordable for those who desire to maximize their fertility potential later in life.

MOST COMMON MODALITIES FOR FERTILITY PRESERVATION

1. Embryo Cryopreservation

As the only established form of cryopreservation, embryo cryopreservation is the most commonly utilized option based on its predictable and reproducible success [5, 9, 25, 26]. The human embryo is highly resistant to cryoinjury and thus has a high cryosurvival rate [12]. Cryopreserved embryos produce pregnancy rates similar to those of fresh embryos [3]. With embryo cryopreservation, stimulation is required to retrieve mature oocytes from the woman to be fertilized and then frozen until the embryo is ready to be transferred to the uterus in attempt for pregnancy. The stimulation cycle requires time that may delay cancer treatment and also may induce ovarian hyperstimulation syndrome (OHSS).

Depending on the time allowed for stimulation, multiple cycles may be utilized to preserve many embryos for multiple attempts. The number of oocytes necessary can be estimated based on fertilization, cryosurvival, and implantation rates for the woman’s age, along with consideration of the woman’s desired family size.

From an economic perspective, the most expensive aspect of treatment is the stimulation protocol for retrieval of mature oocytes. The cost of medication may constitute half the total cost and is dependent on age as higher doses of stimulation are required and more attempts are necessary with increasing age [27]. If multiple stimulation cycles are desired to maximize the potential for achieving multiple pregnancies, the costs increase exponentially.

In long-term studies of children born from cryopreserved embryos, no negative effects have been reported on cognitive, psychomotor, or neurodevelopmental outcomes [22].

2. Oocyte Cryopreservation

Oocyte cryopreservation remains in the experimental arena; however, recent promising and repeated successes have moved this method closer to becoming established [17]. Oocytes may be retrieved in the mature or immature stage of development. Hormonal stimulation is required to retrieve mature oocytes. This is the traditional method; however, as one of the largest and most complex human cells, the mature oocyte is particularly susceptible to cryoinjury [7]. Cryopreservation techniques cause a dissemblement of the meiotic spindle, depolymerization of chromosomes, and a hardening of the zona pellucida [12, 25, 26]. With novel techniques such as vitrification to evade ice crystallization and the use of intracytoplasmic sperm injection (ICSI) to bypass a hardened zona pellucida, these complications may be resolved [26].

Immature oocyte retrieval requires little or no stimulation, and the smaller, less developed oocyte is less susceptible to cryoinjury [7, 28]. For fertilization to occur, the immature oocyte must be matured through in vitro maturation (IVM), which unfortunately has low success rates [7, 11, 29]. If optimized, this option would allow immediate retrieval with no delay in treatment and elimination of the risk of OHSS that could be induced through stimulation of mature oocytes [3].

Vitrification of oocytes has been proven to increase success in oocyte cryopreservation, producing reliable results and excellent obstetric and perinatal outcomes over the last decade [30]. Additionally, recent data suggests the repolymization of the meiotic spindle upon thawing of the mature oocyte [7]. No known congenital or developmental deficits were reported from any child born from fertilized cryopreserved oocytes [28].

Utilizing immature oocytes decreases costs by eliminating the need for stimulation [17]. Cryopreservation of oocytes also reduces ethical dilemmas with children and women with no partner at the time of preservation. With improved techniques, this option is likely to become the most routine and reliable fertility preservation method within the next three to five years [25], and a universal vitrification protocol is expected to be established [7].

3. Ovarian Tissue Cryopreservation

Ovarian tissue is the definitive source of female fertility, and the ability to preserve and restore the endocrine and reproductive function of the ovary after removal and cryopreservation would be an ideal option if optimized [3, 31]. Ovarian tissue may be harvested immediately, as no stimulation is required, so cancer treatment would not be delayed [3]. Gonadal tissue may be retrieved and cryopreserved as a whole ovary with its vascular pedicle, as cortical strips, fragments, or as isolated primordial follicles [11, 23]. Primordial follicles in the ovarian cortex are more resistant to cryoinjury than the mature oocyte [12]. The tissue may be autotransplanted to the woman later in either an orthotopic or heterotopic location [1, 9]. Autotransplantation of the whole ovary orthotopically has the advantage of immediately resuming blood flow, thus avoiding ischemic damage; pregnancy also may occur spontaneously with this method [1, 9]. Transplantation to a heterotopic location presents a higher risk of ischemic damage, and this method relies completely on ART to achieve pregnancy [1, 31].

The risks involved with ovarian tissue cryopreservation include the risks of a surgical procedure, as well as the possibility of reintroducing malignant cells upon autotransplantation [11, 25]. This option should not be offered to patients with ovarian cancer [3], and it should be utilized with caution for other cancer patients, especially if the cancer has metastasized [4]. Cancer recurrence as a result of ovarian tissue grafts after autotransplantation has not been reported since the technique’s introduction [32].
Despite current reports of success, evidence of reproducible results is still limited, and a standard protocol has yet to be established [12, 23]. Most cases evidence only a short longevity of the ovarian grafts and produce low success rates [1], and a definitively superior location for autotransplantation has not been decided [33]. Only seven live births have been reported to date [34], yet this still may provide some hope for young girls as this is the only option suitable for pre-pubertal girls undergoing treatment [11, 12, 25].

The most significant advances in cryopreservation over the next several years most likely will occur in ovarian tissue cryopreservation [25]. Advances may result from innovations in surgical technologies and research in tissue engineering to promote better uptake of ovarian grafts and reduced loss of primordial follicles from ischemic damage [11, 23].

**OBSTACLES TO FERTILITY PRESERVATION**

Obstacles to fertility preservation include, but are not limited to, lack of patient awareness, limited physician experience and knowledge, inadequate counseling about fertility preservation options, the costs of the procedures involved, and ethical dilemmas.

The patient’s own lack of awareness of the option for fertility preservation is the first challenge for ensuring fertility preservation for all those who may desire it. For patients who have been told about fertility preservation at the time of diagnosis, looking beyond their own survival can be difficult. These patients may not adequately assess the importance of fertility preservation before treatment, especially if it causes a delay in treatment.

Secondly, the physician’s own lack of knowledge relating to fertility preservation options constitutes another hurdle in the effort to avoid sterility. An oncologist may not refer a patient to a fertility specialist because of the risk of delaying treatment, the patient’s limited resources, or feeling that a discussion of fertility preservation is inappropriate in the midst of fighting a disease [35]. The vast majority of studies examining the discussion and referral of fertility preservation among oncologists and patients indicate that less than half of eligible patients are presented with this information [36].

Discussion is more common than an actual referral to a reproductive endocrinologist, and, according to a survey of oncologists, patients may be willing to sacrifice more in survival than would the physician [37]. A recent study determined that with supportive resources available, the time required for stimulation of mature oocytes for cryopreservation does not significantly extend the period of time between diagnosis and the start of chemotherapy [38].

It is the physician’s role to be knowledgeable about the options and adequately present fair information to the patient or couple, or at least to refer the patient to a more expert specialist [39]. This is often the best solution as many techniques involved in fertility preservation are only performed at specialized centers and the oncologist may have limited access to the most current developments in the field.

Discussion and management of preserving reproductive potential are challenging aspects of care, and inadequate counseling results from the lack of a multidisciplinary approach to providing fertility preservation [40]. Information about actual clinical success rates, outcomes, and risks must be imparted to the patient so that she may make an informed decision founded in practical expectations and an understanding of the risks and benefits [41]. In a study on the experience of receiving fertility preservation options around the time of diagnosis, women were likely to report low levels of comprehension regarding the physiological impact of treatment as well as express distress from lack of services available [40]. The findings of this study suggest that young women may cope with information about fertility preservation alongside cancer diagnosis if there is sufficient professional and familial support [40].

Professional counseling is vital as much of the information that patients may find in the media may be biased or scientifically unfounded [41]. Specifically with healthy women who elect to cryopreserve oocytes, misunderstanding the actual potential can cause emotional devastation if they are unable to conceive later in life [41].

Another significant obstacle to fertility preservation is the high cost of services and the lack of insurance coverage. In the United States, there are currently no states that offer insurance for fertility preservation for cancer patients, although 15 states have laws for insurance coverage of IVF and/or other ART services [35]. Loss of fertility is an inevitable sequela of cancer treatment and as such may justify the coverage of fertility preservation by insurance. Especially with cancer treatment versus normal infertility services, the patient may not have the time to attain the necessary monetary resources required to undergo fertility preservation. The costs may deter both cancer patients and healthy patients alike until these services can be made more affordable.

Many ethical dilemmas currently present obstacles to achieving fertility preservation. For young girls and females without a partner at the time of preservation, embryo cryopreservation may not be an acceptable modality if the female is unwilling to use a donor sperm. In the case of children, it may be difficult to accurately gain informed consent or even for a parent to make an informed decision [22]. The use of oocytes for cryopreservation avoids this ethical issue, yet oocyte cryopreservation remains experimental and is not offered routinely [10]. Ovarian tissue cryopreservation also avoids the dilemma concerning donor sperm, yet it is also experimental, and the faint risk of reintroducing malignant cells should be considered.

In the case of cryopreserved embryos, the future fate of unused embryos presents a dilemma. The options of disposition of the embryo include using all the embryos in an attempt to conceive, donating embryos to another couple or to research, discarding the embryos, and continuing cryopreserved storage indefinitely [26]. Couples often have difficulty resolving this issue before undergoing IVF [42] as the outcome of the treatment is indeterminate.

With optimized outcomes and safe procedures involved with oocyte preservation, arguments against elective self-donation of oocytes are unjustified on clinical or ethical grounds [18, 29]. A person is free to choose when and whether to reproduce if medical and technological means...
exist to execute that choice. With this principal of reproductive autonomy, oocyte cryopreservation for the healthy individual represents a legitimate use of physician and medical resources [41]. Recognizing the medical insufficiencies and the limitations of current fertility preservation technologies, balancing realistic expectations with the desire to conceive and the right to maximize the potential to do so is a wise approach.

EXPERT COMMENTARY

The aim of this article is to elucidate the necessity for and the challenges to establishing a standard of care for fertility preservation. Currently embryo cryopreservation is the only routinely performed procedure for fertility preservation, yet oocyte and ovarian tissue cryopreservation are promising modalities that would increase the ease and availability of fertility preservation for a more diverse patient population. These experimental options have the potential to avoid the risks associated with hormonal stimulation and/or a delay in cancer treatment and to eliminate the ethical dilemmas of embryo cryopreservation, including embryo disposition and use of donor sperm in the case of children or single women. These options also allow healthy patients to maximize their potential to achieve pregnancy later in life. The techniques and methods of fertility preservation evolved from the use of ART for infertile patients, yet the circumstances involved with preservation solicit the need for specific standards, research, and multidisciplinary care. Fertility preservation is emerging as a distinct and specialized field of reproductive medicine, necessitating further research and standards of practice that may lead to better patient care.

FIVE-YEAR REVIEW

Attention to and demand for fertility preservation have increased significantly in the past few years. This was compelled by the increase in cancer survival and the modern reproductive trend of delaying childbearing, and indicated by the boom in research and collaborative efforts. Of specific note, the founding of the International Fertility Preservation Society points to the worldwide importance of preserving the potential to genetically parent one’s own child [20]. This collaborative effort allows clinical and research experts to work together to develop standards of care that provide minimal risk and greater efficiency. In addition, public education should be improved to confer objective and analytical information about current advances in technologies, the lack of evidence of long-term outcomes, and the ethical dilemmas a patient faces [5]. With the advancement of technology and establishment of a standard of care, the cost of procedures and treatment may fall, allowing more patients to take advantage of these benefits with greater ease and accessibility.

KEY POINTS

- Fertility preservation is the preservation of the potential to genetically parent a child beyond natural fertility and despite iatrogenic loss through the means of ART.
- Fertility loss occurs naturally with age or prematurely from gonadotoxic treatment, genetic disorders, or environmental hazards.
- Increased cancer survival and cancer diagnoses in the adolescent and young adult population, as well as the modern reproductive trend of delaying childbearing, indicate a growing need for fertility preservation.
- For women, embryo cryopreservation is the only established technique, and options for oocyte and ovarian tissue cryopreservation are still considered experimental.
- The standardization of oocyte and ovarian tissue modalities of cryopreservation would increase the availability of fertility preservation for a greater patient population while reducing risks and eliminating ethical issues.
- Necessary advances in the field include improved cryopreservation techniques and fertility preservation technologies, comprehensive care plans and customized guidelines, and the availability of more cost-efficient procedures.
- Obstacles to creating a standard of care consist of lack of patient awareness, limited physician experience with new modalities, inadequate counseling, the costs of procedures involved, and ethical dilemmas.
- Continued collaborative efforts among disciplines will assist in greater utilization of research discoveries in clinical applications and support multidisciplinary standards of care for fertility preservation patients.

REFERENCES


