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REVIEW ARTICLE

Medical, ethical, and legal considerations in fertility preservation

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ABSTRACT

The past 2 decades have seen a significant rise in cancer survival rates, and an increasing proportion of survivors at reproductive age are interested in childbearing. Although assisted reproduction provides physicians with an array of potential possibilities to help patients whose fertility is compromised by cancer treatment, there is still a dearth of regulation regarding the application of this technology. The present paper reviews the current options for fertility preservation, with a particular focus on the legal and ethical challenges that confront providers of this type of care.

1. Introduction

The past 2 decades have seen a significant increase in cancer survival rates, particularly for malignancies that commonly affect children and young adults. The 5-year cancer survival rate among children improved from 58% for patients diagnosed between 1975 and 1977 to 81% for those diagnosed between 1999 and 2005 [1]. Survivors of childhood and adolescent cancers now comprise 1 in every 570 individuals between the ages of 20 and 34 years [2]. An increasing proportion of these reproductive-aged survivors are interested in childbearing. Interviews among young survivors suggest the possibility of biologic parenthood after cancer is a powerful stimulus for recovery, and over 70% identify their illness as a life experience that enhances their ability to successfully parent a child [3].

Both the American Society of Clinical Oncology [4] and the American Society for Reproductive Medicine [5] recommend that cancer patients be informed about options for fertility preservation at the time of diagnosis. Studies show, however, that only 50% of childhood cancer survivors had discussed fertility with their physicians, and half of the surveyed oncologists rarely or never raised the issue of fertility preservation with their patients [6].

This paper reviews the current options for fertility preservation with a focus on legal and ethical challenges that confront providers of this type of care.

2. Medical considerations

The level of supporting evidence for treatments for fertility preservation varies considerably, and each modality has distinct advantages and limitations. The most well-established methods include embryo cryopreservation and ovarian transposition in women and sperm cryopreservation in men. Because fertility preservation is an emerging field, most other options remain experimental. The American Society for Reproductive Medicine recommends that methods such as oocyte cryopreservation and ovarian tissue freezing be offered only on an experimental basis under institutional review board (IRB) approval [7].

2.1. Embryo cryopreservation

Embryo cryopreservation is the most established method for female fertility preservation and is routinely used during in vitro fertilization (IVF) cycles for the storage of surplus embryos. The approach involves a 2–3-week delay in cancer treatment to allow time for an IVF cycle, making it unsuitable for patients who require immediate treatment. It also requires a male gamete source, thus precluding its use in children and women without a partner who do not wish to use donor sperm. Finally, there is theoretical concern that the supraphysiologic levels of estradiol present during conventional stimulation protocols may increase the risk of disease recurrence among women with estrogen-sensitive tumors. A prospective trial [8] using aromatase inhibitors in conjunction with gonadotropins to minimize levels of circulating estrogen did not demonstrate an increase in disease recurrence as compared with women who did not undergo a fertility preserving procedure.

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Despite these limitations, embryo cryopreservation remains the most successful method of fertility preservation. Approximately 75% of embryos survive the freeze–thaw process, with reported pregnancy rates of up to 30% per cycle, depending on the woman's age and the total number of embryos transferred [9]. Higher embryo survival rates approaching 90% have been reported after rapid freezing by vitrification [10]. A large retrospective study [11] found live birth rates to be independent of the time the embryos spent in storage—an important factor for young patients who may undergo cryopreservation far in advance of their intended time of family planning.

2.2. Ovarian transposition

The treatment of genital, intestinal, or urinary tract malignancies often involves pelvic radiation. Ovarian transposition (also called oophoropexy or ovarian suspension) involves transposition of the ovaries above the pelvic brim to minimize radiation-inflicted damage. The utero-ovarian ligament and mesovarium are divided, but the fallopian tube is left intact to retain the chance of spontaneous conception.

A 2003 meta-analysis [12] reported that 89% of women under the age of 40 years resumed menstruation after ovarian transposition, although most studies included in the meta-analysis did not address subsequent pregnancy rates. Other studies have demonstrated resumption of menstruation in 16%–90% of women, depending on the age of the patient, the degree of scatter radiation, the radiation dose, and whether the ovaries were shielded [13].

Should these patients require IVF in the future, transvaginal oocyte retrieval may be difficult and an abdominal approach may be required. Moreover, ovarian transposition offers no protection against chemotherapy or whole-body irradiation and should not be used in these situations.

2.3. Sperm cryopreservation

Like embryo cryopreservation, sperm cryopreservation is an established technique that is frequently used as part of an IVF cycle. It should be offered before chemotherapy, radiation, or surgery affecting the male reproductive tract. Traditional recommendations involve banking at least 3 semen samples with a 48-hour abstinence between samples, but fewer specimens are often obtained when there is an urgent need to initiate therapy. Sperm cryopreservation can be used in adult men and pubertal boys. If a young patient is unable to provide a specimen, electroejaculation or surgical sperm extraction can be performed.

Sperm may still be cryopreserved after chemotherapy or radiation prior to the onset of azoospermia, but the effect of these therapies on the reproductive performance of sperm remains unclear. Increased aneuploidy rates have been shown up to 18 months after chemotherapy for testicular cancer [14], prompting the recommendation that men either cryopreserve sperm before chemotherapy or wait 18 months after treatment before pursuing fertility.

2.4. Oocyte cryopreservation

Oocyte cryopreservation, although experimental, is one of the few available options for prepubertal girls and women who do not wish to use donor sperm [15].

Oocytes can be cryopreserved at either the mature or the immature stage. Mature oocytes are halted in metaphase of meiosis II prior to fertilization. Because of their large size, water content, and meiotic spindle, these oocytes are sensitive to cryodamage. The efficiency of this strategy has improved significantly with the use of rapid-freeze methods such as vitrification, which afford survival rates as high as 90%, compared with rates of 50%–60% seen with conventional slow-freeze methods [16]. Despite the concern that damage to the meiotic spindle can increase aneuploidy rates, a study [17] of 200 infants conceived after oocyte vitrification did not identify a higher incidence of congenital abnormalities compared with infants conceived with standard IVF. While experienced centers report delivery rates up to 57% [18], a 2006 meta-analysis reported an overall live birth rate of 21.6% per embryo transfer [19]. It is worth noting that these figures are not yet typical and a more average success rate may be 2–3% per thawed oocyte [20].

Retrieval of immature oocytes with in vitro maturation and subsequent cryopreservation can be done without hormonal stimulation, thus avoiding delays in cancer treatment and the presence of supraphysiologic estradiol levels in women with hormone-sensitive tumors. Immature oocytes are more resistant to injury because they lack a metaphase spindle and contain diffuse chromatin surrounded by a nuclear membrane. Despite the superior survival rate, the inefficiency of in vitro maturation results in a final mature oocyte yield similar to that obtained with cryopreservation of metaphase II oocytes. There are few reported live births among patients treated with oocyte cryopreservation and in vitro maturation [21].

2.5. Ovarian suppression

Suppression of folliculogenesis with gonadotropin-releasing hormone agonists (GnRH-a) for fertility preservation remains controversial. An early animal study [22] indicated that pretreatment with GnRH-a protects against gonadal damage induced by cytotoxic chemotherapy. Although nonrandomized human studies have supported the protective effect of GnRH-a in women with Hodgkin's lymphoma and breast cancer [23], a randomized study [24] of 18 women with Hodgkin's disease failed to demonstrate this effect. Critics of GnRH-a cite a lack of biologic plausibility, because over 90% of the adult ovary is comprised of primordial follicles that are recruited through a follicle-stimulating-hormone-independent mechanism and that are, therefore, unresponsive to GnRH-a [25]. Conserving the remaining 10% of the follicle pool, although possible, is unlikely to significantly impact ovarian reserve. The American Society of Clinical Oncology concludes that “there is insufficient evidence that GnRH-a protects gonadal function from gonadotoxic agents” [4]. Large randomized trials addressing this issue are currently underway.

2.6. Ovarian tissue freezing

Ovarian cryopreservation involves the laparoscopic removal and cryopreservation of ovarian cortical tissue followed by subsequent transplantation at the time of desired conception. The technique offers many advantages: Tissue can be obtained at any point in the menstrual cycle without delay of cancer treatment and no male gamete source is required, making it an option for children or women who do not desire donor sperm. Follicular loss rates of up to 66% secondary to ischemia upon initial transplantation limit the usefulness of this strategy in patients with a diminished ovarian reserve [26]. A second concern is that transplanted tissue may result in the reseeding of cancer. A thorough histologic and immunohistochemical evaluation is therefore recommended before and after ovarian cryopreservation to screen for malignancy.

The ovarian graft can be transplanted to an orthotopic site in the ovarian fossa or to a heterotopic site in the forearm or abdominal wall. Heterotopic transplants do not require general anesthesia but eliminate the chance for a spontaneous pregnancy. A review of the literature [27] identified 13 live births after orthotopic transplantation. Oktay et al. [28] described the development of a 4-cell embryo following stimulation of a heterotopic transplant in a woman with breast cancer, but no ongoing pregnancies have yet been reported.

2.7. Testicular tissue freezing

At present, the only possibility for fertility preservation in prepubertal boys is cryopreservation of spermatogonial stem cells

for subsequent intratesticular stem cell transplantation. Transplanted stem cells recolonize the seminiferous tubules and reinitiate spermatogenesis. This process has resulted in live births in mice [29], but remains theoretical in humans. The efficacy of the freezing protocols, the long-term safety, the reproductive outcomes, the risk of malignant contamination, and the damage to the recipient testes all require further investigation before the technology can be clinically applied.

3. Ethical considerations

3.1. Assisted reproduction in cancer patients

An often cited ethical consideration when treating cancer survivors is whether the act of reproduction poses a risk to the potential offspring, a dilemma that can be simplified to a conflict between patient autonomy and provider non-maleficence [30].

The first issue is whether children of cancer survivors are themselves at increased risk of cancer. The literature does not support an increase in the risk of malignancy among the offspring of cancer survivors [31], and a hereditary cancer risk should therefore not be used as a justification for withholding assisted reproduction from cancer patients.

A second concern is that the premature death of a cancer survivor would unfairly leave a child bereft of a parent. Although some have suggested it unethical to enable reproduction for individuals whose lifespan may be reduced by illness, most ethicists consider this an insufficient argument to deny cancer patients infertility treatment. Given that many children lead meaningful lives despite suffering the loss of a parent, the Ethics Committee of the American Society for Reproductive Medicine concludes that the risks to children from the possibility of being raised by a single parent "are not a sufficient reason to deny cancer patients assistance in reproducing" [5].

This issue is more contentious for single cancer survivors who may leave an orphaned child should they suffer a premature death. A recent series [32] reported that 16 of 35 (37%) female cancer patients were single at the time of fertility preservation, indicating a significant interest in these technologies on the part of single women. A number of arguments can be made for the provision of fertility preservation therapies to single cancer survivors. An individual's relationship status is dynamic—a woman who is single at the time of fertility preservation may be coupled by the time she is ready to procreate. Moreover, a significant self-selection process is likely to occur in that the women who are most likely to return for the use of stored gametes or ovarian tissue are those who are healthy enough to withstand the physiologic demands of pregnancy.

3.2. Resource allocation

A common debate surrounding infertility and fertility preservation is that of access to care: Is prevention of infertility a just and prudent use of resources? The answer depends on the manner in which society views the concept of procreative liberty. As described by John Robertson [33], the right to reproduce has long been considered a "negative right", meaning that the state should not interfere with an individual's ability to reproduce through mandatory sterilization or by denying access to fertility treatment. It has not yet, however, been granted the status of a "positive right", in that the state should provide resources to enable an otherwise infertile individual to procreate. Daniel Brock [34] describes health care as a means to "afford individuals access to the normal range of opportunities in society", whether it be the ability to care for themselves, hold productive employment, or maintain interpersonal relationships. Extending procreative liberty to a "positive right" would require expanding this concept to include the ability to parent a child—an experience that is considered the norm in most societies [35,36]. Backhus and Zoloth [37] suggest that this decision may be clearer in the case of cancer survivors, arguing that "there is a duty to prevent damage to or repair that which is damaged by [cancer] treatment".

A practical extension of this argument is that insurance companies are ethically obligated to cover fertility preservation in cancer patients because of impending iatrogenic damage to the reproductive organs. Unfortunately, insurance coverage for fertility preservation is scarce and there are currently no state or federal mandates in the USA that specifically address the issue. Even in the few states that have mandated coverage for general infertility services, cancer patients are often excluded because they are not technically "infertile" at the time when they seek care [38]. This is inconsistent with existing policies that offer insurance coverage for other types of iatrogenic injury, such as reconstructive breast surgery after mastectomy for breast cancer [39]. There is little ethical justification to withhold insurance coverage for fertility preservation technologies in states that already mandate coverage of infertility services.

4. Legal considerations

4.1. Consent and assent in minors

The first guidelines for the ethical study of drugs in children were published by the American Academy of Pediatrics in 1977 [40]. These guidelines describe the concept of "minimal risk", which is defined as risk similar to that encountered in the child's usual daily life—including interventions such as physical examinations, venipuncture, and urine collection. By this definition, a majority of available fertility preservation procedures are categorized as posing a "greater than minimal risk" given that they involve invasive procedures. Additionally, many currently available options for fertility preservation among minors remain experimental and are therefore only offered under IRB-approved research protocols.

The updated 1995 American Academy of Pediatrics guidelines [41] state that research in children involving greater than minimal risk is permissible so long as: (1) The risks are justified by the anticipated benefits, (2) the anticipated benefit is at least as favorable as that provided by alternatives, and (3) appropriate permission (agreement of a parent to participation of their child in research) and assent (agreement to participate in a procedure by a minor over the age of 7 but not yet qualified to give consent) has been obtained. It is worth noting that by these criteria, a child with the ability to understand and give assent (generally around 8 years of age) can refuse participation in a fertility-sparing procedure regardless of parental wishes.

Many advocate a 2-stage consent process that separates the issue of whether to store gametes from the decision of whether to use the stored gametes. While the first decision must be made at the time of cancer diagnosis, the decision regarding the use of stored gametes can be deferred until the patient has reached adulthood.

4.2. Disposition of gametes

Excepting cases of planned gamete donation, sperm and eggs remain the sole possession of the person from whom they were removed. An embryo, however, could "belong" to both the egg and the sperm donor. Conflict arises when an embryo is created for reproduction and the parties involved subsequently disagree about its use, as in the case of separation, divorce, or death.

The US courts have held that the embryo should not be used for reproduction unless the intent of both parties is that reproduction should occur. In the 2001 divorce case of Davis v. Davis regarding embryo disposition, the court held that "ordinarily, the party wishing to avoid procreation should prevail, assuming that the other party has a reasonable possibility of achieving parenthood by means other than use of the preembryos in question. If no other reasonable alternatives exist, then the argument in favor of using the preembryos to achieve pregnancy should be considered" [42].

The precedent set by Davis v. Davis has been upheld in cases of fertility preservation, both in the USA and abroad. An example is the 2007 case of Natalie Evans, a British woman who had been rendered infertile by cancer treatment and lost her attempt to prevent the destruction of embryos that had been created with her eggs and the sperm of her former partner [43]. The UK's Human Fertilisation and Embryology Authority provides standard consent forms that stipulate the disposition of embryos in the case of death, but without specifying disposition in cases of separation or divorce. The wording of the 1995 Australian Infertility Treatment Act was similarly unclear, allowing gamete donors to withdraw consent before a "procedure" is carried out, without specifying which procedure—fertilization or embryo transfer—was being referred to. A more recent version of the Australian Infertility Treatment Act stipulates that a donor may not withdraw his or her consent once an embryo is formed from donated gametes [44].

As a result of this legal ambiguity, many infertility clinics have created contracts specifying how embryos will be managed if the parties refuse to pay storage fees, disagree on future use, die, or divorce. When such contracts exist, the courts have generally upheld them on the theory that the initial agreement of the parties should be carried out. A 2003 review by Schuster et al. [45] discusses guidelines for contracts addressing disposition of semen and embryos, suggesting that they be unambiguous, consistent with public policy, and clearly state the duration of the agreement, the intents of both parties signing the agreement, and the responsibilities of the cryopreservation center in the storage and disposition of the cryopreserved material.

The relevance of these issues in cancer patients is illustrated by a 2009 study [46] that explored the rates of divorce or separation among couples where 1 partner was affected with cancer. The investigators reported a 6-fold increased risk of separation when the affected spouse was the woman (20.8% versus 2.9%, $P<0.001$). Further confusion may arise in cases where an adolescent woman cryopreserves embryos with sperm from a partner with whom she later parts. Many clinics, including our own, suggest that these young women consider fertilizing half of the embryos with their partner's sperm and the other half with donor sperm to preserve their right to use the embryos regardless of the relationship outcome. Couples who are embarking upon gamete storage should be made aware of these possibilities and referred to legal counsel to create contracts specifying their wishes for gamete disposition.

4.3. Posthumous reproduction

A more controversial legal issue is the use an individual's gametes after their death, also termed posthumous reproduction. There are wide differences in national law concerning this subject, ranging from complete prohibition in some countries to permissive rules in others, often intersecting with religious belief. Roman Catholicism rejects the procedure on the same grounds as its rejection of assisted reproduction technologies: the separation of human reproduction from sexual intercourse. Islam also rejects the procedure because it takes place after the end of the marital term. Jewish law, by contrast, does permit posthumous reproduction [47].

The 2001 case of Woodward v. Commissioner of Social Security was one of the highest-profile legal cases involving posthumous reproduction in the USA. The case was brought by a widow who gave birth to twins by intrauterine insemination with her husband's cryopreserved sperm 2 years after his death from leukemia. When she attempted to file for social security benefits for her children, her claim was rejected on the basis that the children were not heirs. The case was ultimately appealed to the Massachusetts Supreme Court, which determined that even though the plaintiff's husband had frozen his sperm, there was no evidence demonstrating his consent to using the sperm to conceive a child after his death and the children could therefore not be considered heirs [48].

The most rigorous professional guidelines on this topic were published in 2006 by the European Society for Human Reproduction and Embryology [47]. These state that posthumous reproduction is acceptable only if (1) the decision is made by the surviving partner in the relationship, (2) written consent regarding the use of gametes was given by the deceased at the time of storage, and (3) the surviving partner waits a minimum of 1 year to allow time for grieving before using the gametes. If these clauses are met, children born from posthumous reproduction should not be discriminated against as compared with those born prior to the death of a parent.

5. Conclusions

Assisted reproduction has been advancing at an extremely rapid rate, providing physicians with an array of emerging possibilities to help patients whose fertility is compromised by malignancy or cancer treatment. In the face of this rapid progress, however, there is still a dearth of regulation regarding the application of this technology. The implementation of a consistent legal and ethical standard will likely require not only the cooperation of professional organizations and the legal community, but also the input of the patients themselves.

Conflict of interest

The authors have no conflicts of interest.

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