Outlook

Technical and ethical challenges of fertility preservation in young cancer patients

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Abstract

As cancer treatment improves, more young men and women survive, but they suffer from infertility as a major sequel of cancer treatment. Gamete and embryo cryopreservation are the only options available to these patients for preserving their fertility. Although cryopreservation of spermatozoa and embryos are already established, oocyte banking is still experimental. The advent of testicular tissue cryopreservation and spermatogonial stem cell transplantation in men, and ovarian tissue cryopreservation and in-vitro follicular maturation in women, has started a frenzy of experiments worldwide trying to demonstrate their potential use in fertility preservation. Although major improvements have been made in tissue cryobanking in the past decade, there are still many unresolved technical issues related to these procedures. Furthermore, the intersection of cancer and fertility preservation in young patients raises ethical, legal and policy issues for oncologists and cancer survivors. Informed consent of minor patients, legal parentage and medical negligence claims are some of the potential legal challenges faced by society and healthcare providers. This review summarizes the technical and ethical challenges of gamete cryopreservation in young cancer patients.

Keywords: cancer, cryopreservation, ethics, gametes, ovarian tissue, testicular tissue

Introduction

In the past two decades, major strides have been made in the curability of cancers leading to striking improvements in the chances of long-term survival, particularly in young people including children and adolescents. The use of chemotherapeutic and radiotherapeutic interventions has led to 70% survival rates in children with malignancies (Robison, 1996). However, one of the major complications of these advanced treatment modalities is sterility and loss of gonadal function (Mackie et al., 1996). The effects might be transient or permanent depending upon the individual variability in the sensitivity to reproductive damage (Blumenfeld and Haim, 1997). The severity of damage is dependent on the type of chemotherapy or radiotherapy, the treatment protocol and the age and gender of the patients (Howell and Shalet, 1998).

Although, future fertility of young patients is very low on the relative list of quality of life parameters at the time of anti-cancer treatment, infertility becomes an important issue following cure from cancer. According to a recent survey, 51% of men with cancer wanted children in the future, including 77% of men who were childless when their cancer was first diagnosed (Schover et al., 2002). Since it is difficult to predict who will survive or become infertile after anti-cancer treatment, fertility conservation is an important issue for those young cancer patients who have not yet started or completed their family.

Although, fertility preservation in men by sperm cryopreservation is already established, cryopreservation of oocytes is still experimental. There has been tremendous progress in the development of strategies for sperm and
Egg banking. However, before considering these advanced techniques for fertility preservation, there are a number of technical concerns requiring careful evaluation. Moreover, fertility preservation in young patients has raised a host of ethical and legal issues involving the patients, oncologists and fertility specialists. This review familiarizes the readers with various options available for preserving fertility in cancer survivors (Figure 1) and the technical and ethical challenges faced by the healthcare providers while trying to cryopreserve human gametes.

**Fertility preservation in men and its challenges**

Traditionally, sperm banking by cryopreservation of at least three semen samples with an abstinence period of at least 48 h in between the samples has been recommended for adult men desiring to preserve their fertility. However, many young cancer patients, especially those with testicular carcinoma or Hodgkin’s disease already have decreased semen quality at the time of diagnosis and start of anti-cancer therapy (Agarwal et al., 1996). Freezing and thawing semen further reduces sperm count, motility and viability (Gandini et al., 2006). Although, additional samples and longer abstinence periods may be used to achieve higher total sperm counts, the need to initiate lifesaving anti-cancer therapy urgently often becomes a barrier in the process. However, recent advances in assisted reproductive technology, especially the advent of intracytoplasmic sperm injection (ICSI), have made it possible for a man to become a father even if only a few spermatozoa remain alive after cryopreservation (Hallak et al., 1998; Kuczynski et al., 2001).

Semen banking should ideally be done before the start of cancer treatment. Theoretically semen collection and storage is feasible after the initiation of chemotherapy and radiation therapy, at least until azoospermia ensues. However, it is advisable to wait for 12–18 months because of the time taken for the recovery of spermatogenesis and significant increase in the frequency of sperm aneuploidy persisting for 18 months or more after initiation of anti-cancer treatment (De Mas et al., 2001; Howell and Shalet, 2005; Shin et al., 2005). Although post-pubertal men are generally able to ejaculate, some young cancer patients may not be able to produce a sample by masturbation. A strong vibrator or a rectal electric probe can be used to stimulate ejaculation in these boys; however it should be used under anaesthesia to avoid pain. Another concern with electroejaculation is the possible reduction in sperm motility (Ohl et al., 2001). Advanced methods for sperm retrieval include microsurgical epididymal sperm aspiration for patients with unreconstructable obstructive azoospermia (Janzen et al., 2000) and testicular sperm extraction for patients suffering from non-obstructive azoospermia (Devroey et al., 1995; Chan et al., 2001). Although testicular sperm extraction in combination with ICSI has shown some recent promise in patients with post-chemotherapy azoospermia, the long-term potential for genetic risks among children born with this technique are still unknown.

Absence of spermatozoa and spermatids in the testis prevents prepubertal boys from benefiting from the technique of sperm freezing. Although a few spermatids might be present in some seminiferous tubules in the late prepubertal period; such spermatocytes never seem to give rise to spermatozoa (Paniagua and Nistal, 1984). Furthermore, cryopreserved semen samples are a finite source and do not offer the patients a chance to achieve natural fertility. Hence, with the recent advances in assisted reproductive techniques, mature and immature sperm extraction and maturation (Fishel et al., 1995; Hovatta et al., 1996a), focus has been shifted to the possibility of testicular tissue preservation in young cancer patients. The testicular tissue contains testicular precursors called spermatogonial stem cells. These cells are the genuine totipotent population of cells in the adult body and they undergo self-renewal throughout life. These are also more resistant than other testicular cells to a variety of toxic insults (Russell et al., 1990). The spermatogonial stem cells are present in pre-pubertal testicular tissue, and can be isolated and successfully cryopreserved with almost 70% cells surviving freezing and thawing, as demonstrated in animal experiments (Izadyar et al., 2002). These stem cells can be retransplanted autologously into the testis, where they recolonize the seminiferous tubules.

**Figure 1.** Options available to young cancer patients undergoing anti-cancer therapy for fertility preservation.
generating complete spermatogenesis and mature germ cells thus restoring natural fertility (Brinster and Avarbock, 1994; Ogawa et al., 2000; Honaramooz et al., 2003; Ryu et al., 2003; Wyns et al., 2007). The other option is transplantation of testicular tissue pieces to an ectopic site such as under the skin of patients after successful completion of cancer therapy or into animals. The grafted testicular tissue revascularizes in the ectopic site producing complete spermatogenesis, first demonstrated by Brinster and Zimmermann in mice (Brinster and Zimmermann, 1994; Ogawa, 2000).

Although, successful establishment of fertility has been achieved with stem cell transplantation in mice, rats and goats, the technique is still experimental in humans (Brinster and Avarbock, 1994; Ogawa et al., 2000; Honaramooz et al., 2003; Ryu et al., 2003; Wyns et al., 2007). One of the crucial steps for re-fertilization is the safe retrieval of sufficient testicular tissue before the cytotoxic insults of chemotherapy and radiotherapy. However, the presence of low numbers of stem cell spermatogonia in prepubertal testis necessitates the need of an in-vitro culture system to increase the number of stem cells after isolation. Furthermore, due to low numbers of stem cells in prepubertal testis, density gradient and sedimentation techniques are unlikely to be successful in their isolation and purification (Aasmam et al., 1998). It is also impossible to generate haploid male gametes from diploid germ cells with the existing in-vitro approaches as testicular stem cell expansion and meiotic entry appears to be blocked in cultures of testicular cell suspensions (Orwig and Schlatt, 2005). A safe cryopreservation protocol for the spermatogenic stem cells, similar to freezing of human spermatozoa and embryos, is needed. Dimethylsulphoxide (DMSO) as a cryoprotectant has been shown to maintain the structure of testicular tissue, especially the spermatogonia, better than others like propanediol and glycerol. In a study involving 16 infertile men, after freezing with 5% DMSO, 70 ± 6% of seminiferous tubules were found to be good as compared with 37 ± 3% with propanediol (Keros et al., 2005). However, DMSO itself is a potential carcinogen, which restricts its application in clinical practice (Avarbock et al., 1996; Aasmam et al., 2000). Although DMSO is usually used in concentrations of 10–20% (Hovatta et al., 1996b; Jezeck et al., 2002; Shinohara et al., 2002), Keros et al. (2005, 2007) have shown promising results with 5% DMSO in human testicular tissue cryopreservation. Another potential concern is the contamination of spermatogonia with tumour cells leading to retransmission of cancer back to the recipient. Systemic malignancies can metastasize to the testis, and transplantation of testicular cells can re-expose the recipients to the same problem. As of now, no technology is available which can scan and select healthy cells from the cryopreserved ones. Transplantation of human spermatogonial stem cells into animals may introduce animal infectious agents like retroviruses in the human germ line when these cells are used to procure conception (Patience et al., 1997). Some of the other challenges encountered with this technology include the ischaemic damage to the transplanted testicular tissue, in-vitro enrichment of stem cell spermatogonia and non-invasive transfer of germ cell suspensions into the rete testis. Hence, in spite of the latest developments in the field suggesting bright prospects for fertility preservation in young cancer patients who have not achieved puberty, techniques still need to be developed for isolation, storage and re-infusion of spermatogonial stem cells in humans.

Fertility preservation in women and its challenges

In contrast to preservation of male fertility, the techniques to preserve female fertility have only been recently developed. According to the most recent recommendations of the American Society for Reproductive Medicine (ASRM) and the American Society of Clinical Oncology (ASCO), embryo cryopreservation is the only established option for fertility preservation in female cancer patients (American Society for Reproductive Medicine, 2006; Lee et al., 2006). Embryo cryopreservation has high success rates (10–20% per frozen embryo); however it is only available to post-pubertal women who either have a male partner or donor spermatogonia to use.

Cryopreservation of oocytes is an experimental option for female cancer patients who do not have any male partner or who do not want to use a sperm donor. Oocyte quality is a decisive factor for embryo quality. Egg banking is inefficient as the oocytes are sensitive to chilling because: (i) their large size and high water content make them vulnerable to intracellular ice-crystal formation and rupture; (ii) the low surface area to volume ratio leads to limited penetration of cryoprotectant solutions and limited ability of the cell to lose water during cooling leading to intracellular ice formation; (iii) the fully extended delicate spindle apparatus of metaphase II is prone to disassembly at low temperatures, leading to aneuploidy (Cobo et al., 2001; Boiso et al., 2002); and (iv) altered membrane permeability during maturation (Coticchio et al., 2007). It is now believed that altered membrane permeability plays a more decisive role in the post-thaw survival as compared with the physical characteristics of the oocyte (Coticchio et., 2007). Cryoprotective agents such as 1,2-propanediol, ethylene glycol, and DMSO, which are used for cell survival, themselves affect the cytoskeleton and may further aggravate the already high incidence of aneuploidy in human oocytes (Pickering et al., 1990; Vincent et al., 1990). Furthermore, exposure to cryoprotective agents may increase intracellular Ca2+ concentrations, triggering premature exocytosis of cortical granules, which causes enzymatic modification of the zona pellucida and makes it harder for spermatozoa to penetrate (Zona hardening) (Matson et al., 1997; Ghettler et al., 2006; Nottola et al., 2007). However, this problem has already been overcome with the introduction of ICSI in the early 1990s (Palermo et al., 1992). Recently, Larman et al. (2007) demonstrated that use of nominally calcium-free media significantly reduces the detrimental physiological effects in mouse oocytes. Human oocyte spindle has shown the ability to reform after cryopreservation. Stachecki et al. (2004) found that 95.5% of human oocytes (n = 63) repolymerized microtubules following incubation at 37°C for 1 h after thawing. No significant difference was found in the chromosomes aligned along the metaphase spindle equator between cryopreserved (71.2%, n = 47) and non-cryopreserved oocytes (76.7%, n = 23). It has also been shown that slow-freezing protocols using higher sucrose concentrations (0.3 mol/l) in the freezing solution promote the retention of an intact chromosome segregation apparatus comparable to fresh oocytes (Coticchio et al., 2006).

Several protocols have been described for oocyte cryopreservation based on different rates of freezing and thawing and cryoprotectants used (Chen, 1986; Fabbri et al.,
from fresh oocytes (Cobo et al., 2001; Eroglu et al., 2002; Boldt et al., 2006; Bianchi et al., 2007). The most commonly used strategy is slow freeze–rapid thaw. Human oocytes are cooled slowly because of the extremely low membrane permeability to cryoprotective agents and water and thawed rapidly to avoid intracellular ice-crystal formation during temperature reversal. The rate of cooling is critical as too rapid cooling leads to insufficient dehydration and intracellular ice crystallization and too slow cooling may lead to cell damage due to prolonged exposure to cryoprotective agents. Although thawing rapidly leads to osmotic stress, it is preferable to thawing slowly, when the intracellular ice crystals in the oocytes have enough time to grow, thus decreasing cell survival. The most damaging phase of freezing is during cooling between –10°C and –40°C when the liquid phase is supercooled (Gardner et al., 2001). According to a recent meta-analysis, clinical pregnancy and live birth rates per thawed oocyte were 2% and 1.9%, respectively. Live birth rate per injected oocyte and embryo transfer for slow freezing were 3.4% and 21.6%; and for IVF with unfrozen oocytes were 6.6% and 60.4%, respectively. In comparison to IVF with frozen–thawed oocytes by slow freezing, IVF with unfrozen oocytes resulted in significantly better fertilization rate (odds ratio (OR) 2.22; confidence interval (CI) 1.80–2.74), live birth per injected oocyte (OR 1.5; CI 1.26–1.79) and implantation rates (OR 4.66; CI 3.93–5.52) (Oktay et al., 2006). The dismal pregnancy rate with cryopreserved oocytes is related to a number of stressors (changes in temperature, volume, and solute concentrations) that the cells have to undergo during the cryopreservation process. Several studies have shown improved oocyte survival by modifications of cryopreservation techniques such as increasing the sucrose concentration of the cryoprotectant medium (Fabbri et al., 2001), changing the initial temperature of the cryoprotectant (Sathananthan et al., 1988), changing the seeding temperature (Trad et al., 1999), using low sodium medium (Stachecki and Willadsen, 2000) and injecting cryoprotectants such as trehalose directly into the oocyte (Eroglu et al., 2002). Boldt et al. (2006) achieved 60.4% post-thaw oocyte survival rate and an implantation rate of 4.2% per thawed oocyte by using sodium-depleted phosphate-buffered saline and sodium-depleted modified human tubal fluid as culture media. More recently, Bianchi et al. (2007) demonstrated an oocyte survival rate of 75.9% and an implantation rate of 13.5% per embryo transfer using a modified slow-cooling protocol involving 1.5 mol/l propane-1,2-diol and 0.2 mol/l sucrose during dehydration, and decreasing concentrations of 1.5 mol/l propane-1,2-diol and 0.3 mol/l sucrose during rehydration.

An alternative strategy for improving oocyte survival by preventing ice formation during cryopreservation is vitrification (Liebermann et al., 2002). It involves the use of very high concentrations of cryoprotective agents (5–6 mol/l), combined with ultra-rapid cooling to achieve a glassy, solid state without the cells having to undergo during the cryopreservation process. Vitrification does not require a programmable freezer as required by the conventional slow cooling method, and causes ice formation during temperature reversal. The rate of cooling is critical as too rapid cooling leads to insufficient dehydration and intracellular ice crystallization and too slow cooling may lead to cell damage due to prolonged exposure to cryoprotective agents. Although thawing rapidly leads to osmotic stress, it is preferable to thawing slowly, when the intracellular ice crystals in the oocytes have enough time to grow, thus decreasing cell survival. The most damaging phase of freezing is during cooling between –10°C and –40°C when the liquid phase is supercooled (Gardner et al., 2001). According to a recent meta-analysis, clinical pregnancy and live birth rates per thawed oocyte were 2% and 1.9%, respectively. Live birth rate per injected oocyte and embryo transfer for slow freezing were 3.4% and 21.6%; and for IVF with unfrozen oocytes were 6.6% and 60.4%, respectively. In comparison to IVF with frozen–thawed oocytes by slow freezing, IVF with unfrozen oocytes resulted in significantly better fertilization rate (odds ratio (OR) 2.22; confidence interval (CI) 1.80–2.74), live birth per injected oocyte (OR 1.5; CI 1.26–1.79) and implantation rates (OR 4.66; CI 3.93–5.52) (Oktay et al., 2006). The dismal pregnancy rate with cryopreserved oocytes is related to a number of stressors (changes in temperature, volume, and solute concentrations) that the cells have to undergo during the cryopreservation process. Several studies have shown improved oocyte survival by modifications of cryopreservation techniques such as increasing the sucrose concentration of the cryoprotectant medium (Fabbri et al., 2001), changing the initial temperature of the cryoprotectant (Sathananthan et al., 1988), changing the seeding temperature (Trad et al., 1999), using low sodium medium (Stachecki and Willadsen, 2000) and injecting cryoprotectants such as trehalose directly into the oocyte (Eroglu et al., 2002). Boldt et al. (2006) achieved 60.4% post-thaw oocyte survival rate and an implantation rate of 4.2% per thawed oocyte by using sodium-depleted phosphate-buffered saline and sodium-depleted modified human tubal fluid as culture media. More recently, Bianchi et al. (2007) demonstrated an oocyte survival rate of 75.9% and an implantation rate of 13.5% per embryo transfer using a modified slow-cooling protocol involving 1.5 mol/l propane-1,2-diol and 0.2 mol/l sucrose during dehydration, and decreasing concentrations of 1.5 mol/l propane-1,2-diol and 0.3 mol/l sucrose during rehydration.

Immature oocytes are recovered for in-vitro maturation from the ovary by aspiration without flushing at a low pressure. In the germinal vesicle stage of oocytes, the cells are in prophase I with chromatin still diffuse and protected within a nuclear membrane and no delicate spindle apparatus available to be damaged by the effects of cooling and cryoprotectants (Oktay et al., 1998; Kim, 2006). Cryopreservation of immature oocytes is more challenging in terms of in-vitro meiotic maturation of prophase I oocytes to metaphase II stage (Tucker et al., 1998a,b). Moreover, the recovery rate of immature oocytes is lower than that of mature oocytes because of the presence of unmucified cumulus cell mass around them in the absence of any gonadotrophin stimulation. The cumulus–oocyte complex needs to be cultured intact so as to preserve the physiological interactions between the oocyte and its somatic envelope (Downs, 2001; Downs et al., 2001; Ruppert-Lingham et al., 2003). However, it is challenging because of the different optimal times for equilibration for oocytes and cumulus cells. Furthermore, hypertonic cryoprotective agents may cause cell shrinkage, thus disrupting granulosa cell processes and gap junctions between oocytes and cumulus cells that serve as vital communication links for transmitting nutrient and regulatory molecules (Gosden, 2005).

Cryopreservation of ovarian tissue is another experimental option for fertility preservation in prepubertal girls and those who cannot wait for ovarian stimulation. It can be accomplished by freezing either fragments of ovarian cortex or whole ovary along with its vascular pedicle (Bedaiwy et al., 2003; Falcone and Bedaiwy, 2005; Bedaiwy et al., 2006). However, unlike single-cell freezing it is much more challenging to optimize conditions to freeze ovarian tissue due to the presence of multiple cell types. Using modern cryopreservation techniques, viability can be retained in over 70% of the follicles. Most of the surviving ones are primordial follicles, which are smaller, dormant and lesser differentiated cells that lack zona pellucida and cortical granules (Newton et al., 1996; Gook et al., 1999; Kim, 2006). The culture techniques and media presently available are inadequate for the long period (about
12 weeks) necessary for the development of a primordial follicle to produce a fertilizable oocyte (Gougeon, 1986; Kim, 2006). Three different techniques have been reported to obtain mature oocytes from these follicles: (i) retransplantation of the ovarian tissue back to the patient (autografting) either within the pelvis (orthotopic-autografting) (Donnez et al., 2004; Meirow et al., 2005; Demeestere et al., 2006) or subcutaneous tissue of forearm (heterotopic autografting) (Oktay, 2006); (ii) transplantation of human ovarian tissue into immunodeficient animals such as mice (xenografting) (Dolmans et al., 2007); and (iii) in-vitro follicle maturation as described above. Only orthotopic autografting restores hormonal function and natural fertility (Oktay and Karlkaya, 2000). However, live births have been reported with both orthotopic autografting (Donnez et al., 2004; Merirow et al., 2005) and heterotopic ovarian transplantation (Oktay, 2006). Demeestere et al. (2006) also achieved spontaneous ovarian cycles and pregnancy with orthotopic ovarian grafting.

Retransplantation of the primary cancer cells is a major concern related with ovarian autografting. The risk depends on the type and stage of cancer and the number of malignant cells transferred (Sonnez et al., 2005). Although most of the cancers of the reproductive age group do not metastasize to the ovaries, a thorough pathological assessment of the tissue must be performed to exclude the presence of any metastatic disease. Another problem with transplantation of ovarian tissue is the ischaemic tissue damage that occurs while waiting for the revascularization process. In fact, most primordial follicles die of hypoxia rather than freezing and thawing injury (Newton et al., 1996; Baird et al., 1999). Although transplantation of the intact ovary along with its vascular pedicle can be used to prevent ischaemic tissue injury, it is technically challenging and further increases the risk of cancer transmission. With heterotopic ovarian transplantation, the real challenge is obtaining healthy mature oocytes for IVF. Another concern with this technique is the lack of an optimal site for transplantation of ovarian tissue (Kim et al., 2004). Xenografting eliminates the risk of reintroducing primary cancer cells back into the patient and in addition makes animals undergo ovarian stimulation rather than the patients themselves. However, major problems with this technology are the long periods needed to grow human follicles to maturity and the risk of transferring infections like retroviruses and prions from animals to human recipients (Paris et al., 2004) (Figure 1).

Ethical and legal challenges in parenthood after cancer

Preservation of fertility in young cancer patients has raised a host of ethical and legal concerns for oncologists and fertility specialists. While, sperm and embryo cryopreservation have been accepted as established techniques, both the ASRM and ASCO recommends that cryopreservation of oocytes, ovarian and testicular tissue be offered only as a part of an institutional review board-approved protocol (American Society for Reproductive Medicine, 2006; Lee et al., 2006). It is advisable not to advertise or offer these techniques as established procedures.

The question of preserving fertility beyond a cancer patient’s current treatment raises the need for an informed consent. This may be complicated because of the paucity of meaningful options and very little time available to most of the patients for taking any decision. Patients also need to be made aware of the financial costs involved as the insurance companies will not always cover the costs of cryopreservation. The informed consent process for minors needs the involvement of patient’s parents or legal guardians. Assent (permission less than full consent) is required in case of minors who are able to understand the issue, such as post-pubertal boys and girls, together with the parental consent. However, for children too young to give an assent, parents may consent to experimental procedures only if the expected benefits are sufficient to justify the risks involved. In a study done in Netherlands asking the opinion of 318 parents of boys surviving cancer, sperm collection was approved by 70%, whereas spermatogonial stem cell collection by biopsy and hemicastration received approval by 61% and 33%, respectively (Van den Berg et al., 2007). The principles of beneficence and non-maleficence are considered paramount in such cases and often hospital ethics committees are asked to review parental decisions. Failure to offer all the existing methods of fertility preservation and accurately explaining the associated risks with such procedures may give rise to medical malpractice claims against healthcare providers. Hence, it is essential to keep written documentation of such a process (American Academy of Pediatrics, 1995). Discussing fertility preservation with young patients and their families takes patience and sensitivity. In addition to addressing the patient’s own future use of his/her gametes, it also involves the consent for future disposition of that tissue or its use by a specific partner in case of the patient’s death. Because of the important ethical and emotional issues raised, it is advisable to make a bioethicist available to patients along with their families and to formulate institutional policies to provide limits and guidance (Schover et al., 1998). Complicated issues may still arise in situations, such as when the patient dies without banking his semen and the surviving partner requests the healthcare provider for posthumous extraction of spermatozoa (Crockin, 2005).

Although post-pubertal men are ordinarily capable of ejaculation and provide spermatozoa for storage, teenagers may be embarrassed to discuss the option of masturbation in front of their parents. A mental health expert, oncology nurse or a social worker can minimize the embarrassment by discussing it outside the presence of their parents. With parental permission, having some non-violent erotic magazines or videos in the collection room may be helpful. For boys who cannot ejaculate, invasive procedures as described earlier can be done with their assent and parental consent (Schover et al., 1998). Likewise, young women need to agree to undergo a cycle of ovarian stimulation and an invasive procedure to collect the ovarian tissue. If a young teenager objects to any of the above procedures, they should not be done, despite parental wishes (Robertson, 2005).

Challenges may arise with respect to legal parentage of the children resulting from cryopreserved tissues. The need to determine legal paternity arises in context of inheritance and federal benefits. Most courts recognize that if a spouse dies before placement of his/her gametes or embryos, the deceased spouse is not a parent of the child resulting from posthumous assisted reproduction unless he or she consented otherwise. Hence, it is important to include in the informed consent the patient’s intended legal relationship to any resulting child. In addition to paternity, legal complications may arise to establish...
legal maternity for those women who want their frozen gametes or embryos to be transferred to a gestational carrier, as most states presume that a woman who gives birth to a child is the mother of the child. Legal uncertainties may arise even with the established technique of embryo cryopreservation in situations such as when a couple divorces, one partner dies or if the couple was never married (Crockin, 2005).

In a prospective study involving 320 semen samples frozen before antineoplastic treatment, five intratubercine insemination cycles and 30 ICSI cycles were performed on follow-up, resulting in one and 15 pregnancies, respectively (Meseguer et al., 2006). A cause of concern for both fertility specialists and cancer survivors seeking fertility preservation is whether their offspring are at higher risk for physical defects and cancer because of the effects of their disease, anti-cancer therapy and cryopreservation techniques. Children born with disabilities may allege medical negligence in connection with their parent’s fertility preservation during cancer treatment that preserved their life (Crockin, 2005). Some experts have also questioned if it is ethical to enable cancer patients to reproduce, as they face a greatly lowered life span and thus their leaving a minor child bereft of one parent (Robertson, 2004). Furthermore, providers who store human genetic material for future use may face liability for damages in the event of loss or destruction of the cryopreserved tissue (Crockin, 2005).

**Summary and perspective**

Recent advances in medicine have led to an ever increasing number of children and patients in their reproductive ages surviving cancer treatment. This has increased the need to improve the existing technology for cryopreservation of gametes and search for new fertility preservation options. As of today, only sperm and embryo cryopreservation are considered accepted standard clinical practices. Cryopreservation of oocytes, ovarian tissue and testicular tissue should only be offered within institutional review board-approved clinical protocols after thorough counselling of patients and their family members as there are still many unresolved issues related to these technologies.

Preserving the fertility of young cancer patients requires coordinated efforts and attention to a host of ethical and legal issues by oncologists and fertility specialists. Informed consent should be obtained from the patients regarding the type of fertility preservation treatment and legal status of any resulting child. The more specific and comprehensively a written directive is executed by the patient during his or her lifetime, the less likely it will be that disputes will arise regarding future use of the stored genetic material.

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