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ASSISTED REPRODUCTION

Human oocyte and ovarian tissue cryopreservation and its application

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Abstract

Purpose To review the recent progress in human oocyte and ovarian tissue cryopreservation, and in the application of these two technologies for preserving female fertility of patients who are undergoing cancer treatment.

Design The literature on human oocyte and ovarian tissue freezing was searched with PubMed. The scientific background, current developments and potential future applications of these two methods were reviewed.

Results Chemotherapy and/or radiotherapy can induce premature ovarian failure in most of female cancer patients. Consequently, there has been a greater need for options to preserve the reproductive potential of these individuals. However, options are somewhat limited currently, particularly following aggressive chemotherapy and/or radiotherapy treatment protocols. In recent years, there have been considerable advances in the cryopreservation of human oocytes and ovarian tissue. For women facing upcoming cancer therapies, cryopreservation of ovarian tissue and oocytes is a technology that holds promise for banking reproductive potential for the future. Recent laboratory modifications have resulted in improved oocyte survival, oocyte fertilization, and pregnancy rates from frozen–thawed oocytes in IVF. This suggests potential for clinical application.

Conclusions In the case of patients who are facing infertility due to cancer therapy, oocyte cryopreservation may be one of the few options available. Ovarian tissue cryopreservation can only be recommended as an experimental protocol in carefully selected patients. In ovarian tissue transplantation, more research is needed in order to enhance the revascularization process with the goal of reducing the follicular loss that takes place after tissue grafting. These technologies are still investigational, although tremendous progress has been made. The availability of such treatment will potentially lead to its demand not only from patients with cancer but also from healthy women who chose to postpone childbearing until later in life and therefore wish to retain their fertility.

Keywords Oocyte · Ovarian tissue · Cryopreservation · Transplantation

Capsule Cryopreservation of ovarian tissue and oocytes is a technology that holds promise for banking reproductive potential for the future. This paper reviews the scientific background, current developments and potential future applications of two methods for preserving female fertility: ovarian tissue cryopreservation and oocyte cryopreservation. It can help both cancer and fertility specialists in attempts to preserve fertility in young female cancer patients in the future.

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Introduction

As current cancer treatments improve, the survival rate of young female cancer patients has steadily increased [1]. However, ionizing radiation and most of alkylating agents (e.g., busulfan, carboplatin, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, thiotepa) [2] that used for gonadotoxic chemotherapy regimens can often induce premature ovarian failure, rendering the patient infertile [3, 4]. In addition, bone marrow transplantation, which is used in the treatment of cancerous and noncancerous hematologic diseases, also results in ovarian failure because heavy chemotherapy and radiotherapy is utilized to destroy the pre-existing bone marrow [5, 6]. Therefore, the

protection against iatrogenic infertility caused by radiotherapy and/or chemotherapy assumes a greater priority.

Embryo cryopreservation has been a proven method to preserve fertility. However, in nearly all cancers, with the possible exception of breast cancer, chemotherapy is initiated soon after diagnosis. Because preparation and stimulation for oocyte retrieval usually requires 2 to 3 weeks or longer, it is generally not feasible to freeze embryos from an adult female cancer patient for potential future use. Even in breast cancer patients, most would not be candidates for oocyte or embryo freezing due to concerns that high estrogen levels might have detrimental effects on the primary tumor. Additionally, not all patients have partners with whom they can create embryos to cryopreserve. Therefore, most female cancer patients of reproductive age do not have the option of utilizing established assisted reproductive technologies to safeguard their fertility so far.

Oocyte cryopreservation avoids some of the disadvantages of embryo banking, although investigations of the application of this technology have been hampered historically by poor oocyte survival, fertilization, and resulting pregnancy rates. Recently, there have been more encouraging reports on the outcomes of oocyte freezing. Ovarian tissue cryopreservation has been successful in restoring fertility in laboratory animals [7, 8] and in at least one human [9]. Ovarian tissue cryopreservation remains a promising clinical technique because it avoids ovarian stimulation and provides the opportunity for preserving gonadal function in prepubertal, as well as adult patients.

By cryopreserving ovarian tissue or oocytes before these gonadotoxic treatments are initiated, reproductive potential can be preserved. In addition, when an oophorectomy is performed for a benign indication, portions of healthy tissue can be preserved for future use. The ethical basis for performing surgery for elective cryopreservation of ovarian tissue has been debated [10, 11]. However, patients' requests for cryopreserving small ovarian biopsies or oocytes at the time of clinically indicated procedures, for examples, cesarean sections or tubal ligations, can not be denied on ethical grounds. Moreover, none of the ethical or legal problems related to embryo cryopreservation applies to ovarian tissue freezing.

The purpose of this paper is to review scientific background, current methods and future applications of human oocyte and ovarian tissue cryopreservation.

Mechanism of ovarian damage

The mechanism of follicular damage induced by chemotherapy and radiotherapy is not yet understood. Ovarian damage induced by radiotherapy depends on the position of the ovaries within the abdominal radiotherapy field. Exposure to 4 Gy of pelvic irradiation is the lethal dose to oocytes, and 97% of women receiving 5 to 10.5 Gy will subsequently undergo ovarian failure [12]. The combination of chemotherapy and radiotherapy is particularly devastating. However, studies in women who conceived years after their chemotherapy treatment have found no significant increase in congenital malformations or malignant neoplasms in the resulting offspring [13, 14]. One possible explanation is that these drugs cause damage only in growing follicles, and through the hypophysial feedback mechanism, more primordial follicles are recruited to the growing pool. Most of the follicles in the human ovary are inactive primordial follicles and do not undergo mitotic division [15], whereas chemotherapeutic drugs are supposed to affect only dividing cells [16].

There are no human studies that have specifically examined the quality of oocytes and embryos that derived from a prior course of chemotherapy. It is known that chemotherapeutic agents can cause mutations, DNA adducts, and structural breaks, as well as oxidative damage in somatic and germ cells. Fertilization in female mice recently exposed to cyclophosphamide resulted in a higher rate of pregnancy failures and fetal malformations [17]. In vitro studies of rat granulosa cells have shown that these cells are the primary targets for cyclophosphamide-induced ovarian damage [16, 18]. However, cyclophosphamide was also shown to cause damage to oocytes in vitro and in vivo. This is possible due to the fact that the granulosa cells serve as nurturing cells to the oocytes through gap junctions [16].

Cryopreservation of oocyte

Oocyte cryopreservation is an attractive strategy to preserve female fertility as it does not require surgery, and well tested stimulation protocols for IVF can be used. The first birth after human oocyte cryopreservation was reported in 1986 [19]. Until 2004, approximately 100 children had been born from oocyte freezing, but the pregnancy rates were very low (1% to 5%) after transfer of embryos derived from frozen oocytes [20–22]. There were various reasons for this limited success: low oocyte survival rates (25–40%), low fertilizations after traditional in vitro fertilization, a high incidence of polyploidy, and poor developmental ability of the embryos [19, 21, 23, 24]. In addition, chilling also induces premature cortical granule exocytosis that may cause zona hardening [25]. Hardening of the zona pellucida can adversely affect the normal fertilization process [26]. This change halts the sperm penetration of zona and inhibits embryonic hatching, but these problems can be overcome by intracytoplasmic sperm injection and assisted hatching [27–29]. Several studies, however, have recently reported better post-thaw

oocyte survival, fertilization, and pregnancy rates [30, 31]. The incidence of chromosomal abnormalities in human embryos obtained from cryopreserved oocytes was no different from that of control embryos [32]. The fertilization and early developmental ability of cryopreserved human oocytes is comparable to sibling fresh oocytes [33]. The first birth of a baby has been reported in Canada from an egg that had undergone in vitro maturation, vitrification and in vitro fertilization [34, 35]. Recently, the first successful fertility preservation with freezing mature oocytes for a cancer patient has also been reported [36].

Factors affecting oocyte freezing

Several parameters have been taken into account in oocyte cryopreservation: cell characteristics, permeability to the cryoprotectants, toxicity, temperature and time of exposure to the cryoprotectants [37, 38]. Chilling injury is the main obstacle to successful oocyte cryopreservation [38–40]. It has been reported that chilling injury affects the membrane, the microtubules [41], the cytoskeletal organization [42] and the zona pellucida [25]. Chromosome abnormalities also were observed after cryopreservation of human and mouse oocytes [43–45]. Most striking sample is the effects of freezing on the second meiotic spindle where microtubles are disrupted or disassembled because of tubulin depolimerization [46]. Mouse oocytes had abnormal spindles after being exposed to 25°C for only 10 min [47]. The meiotic spindle of the bovine and human oocyte is also sensitive to chilling injury and their incubation at 25°C and 4°C significantly reduces the spindle assembly [48]. Several approaches have been used to overcome the damage caused by chilling injury. Significant improvements have been obtained with rapid cooling throughout the transition phase [49], or by the addition of substance known to stabilize the plasma membrane against the thermal effect of oocytes: such as proteins (linoleic acid–albumin) [50], sugar (sucrose or trehalose) [51, 52] or anti-oxidant (Butylated Hydroxytoluene) [53]. In addition, supplementation of choline [54] and higher sucrose concentration [51] in the freezing solution can promote the retention of an intact chromosome segregation apparatus comparable in incidence to freshly collected oocytes.

Effect of meiotic stage

Metaphase-II oocyte freezing

The meiotic stage seems to influence the survival of oocytes after freezing [45, 46]. Differing sensitivity to the cooling procedures for the oocyte cryopreservation has been related to the cell cycle stage during meiosis [55, 56]. The metaphase-II (MII) oocyte is extremely fragile due to its large size, water content, and chromosomal arrangement. In the mature oocyte, the metaphase chromosomes are lined up by the meiotic spindle along the equatorial plate. Increases in chromosomal aberrations in matured oocytes were observed upon cooling and cryopreservation due to the alteration to the meiotic spindle [57]. It has been well documented that the spindle apparatus is easily damaged by intracellular ice formation during the freezing or thawing process [58, 59]. MII oocytes are susceptible to cryopreservation damage because of disruption of the metaphase spindle microtubule integrity during slow cooling, which may result in aneuploidy after fertilization of thawed oocytes [48]. Variability in survival rates of frozen–thawed MII oocytes may also be partly attributable to the quality of oocytes used, as salvaging of surplus oocytes is attributed to poor implantation rates [60].

Oocyte freezing at the germinal vesicle stage

An alternative to cryopreservation of mature oocyte is to freeze oocyte when they have reached full size and become meiotically competent, but before they resume maturation and proceed to MII. It has been showed that oocytes frozen at the germinal vesicle (GV) stage survive better than those frozen at the metaphase-II stage [61]. Additionally, oocytes frozen at the GV stage have lower rates of abnormalities in the resulting meiotic spindle than oocytes frozen at the MII stage [59]. At this stage the oocyte do not present a chilling-sensitive microtubular or meiotic spindle. Several other reports, however, paradoxically showed that the immature oocytes are more sensitive to freezing than mature oocytes [55, 56, 62], probably due to lower cell membrane stability and a particular cytoskeletal formation [56]. This sensitivity to cryopreservation also seems to be due to the damage or interruption of cumulus cell projections, which may control the intercellular communication between cumulus cells and oocytes during maturation [63]. Even though GV oocytes have a superior thaw survival rate and a lower incidence of meiotic spindle damage, the continued inefficiency of in vitro maturation protocols results in a final yield of mature oocytes that is similar to that obtained with cryopreserved metaphase-II oocytes.

Oocyte freezing techniques

Slow freezing

There have been many attempts to optimize oocyte freezing techniques. One main technique is slow freezing. Slow freezing gives acceptable results for human oocyte recently [30, 31, 64, 65]. A major problem during the procedure of

slow freezing is the time of exposure of oocyte to the cryoprotectants. In fact, the cooling rate should be slow enough to allow dehydration and to avoid intracellular freezing, but fast enough to avoid the toxicity effects of the cryoprotectants. Slow freezing and rapid thawing have been found to minimize intracellular ice formation and subsequent structural damage [66, 67].

Slow freezing method is a standard operating procedure in most IVF centers, but it is a time consuming procedure. Oocyte slow freezing traditionally cooled to −7°C at −1 to −2°C/min, seeded at −7°C, and further cooled to −30°C to −35°C at −0.3°C/min, then free falling to −50°C before plunging into liquid nitrogen, it took about 3 h for the whole freezing procedure. To date, there is no enough evidence to show that such slow cooling is necessary.

Several different solutes have been used to protect human oocytes against freezing damage, including dimethylsulfoxide (DMSO), glycerol, and both ethylene and propylene glycol. Several modifications in the slow freezing methods have been reported to improve the survival rate. These modifications are as follows: 1, Increased oocyte survival rates can be achieved by moderately high sucrose concentrations in the freezing (0.2 mol/l) and thawing solutions (0.3 mol/l). This also ensures elevated success rates in terms of fertilization, embryo development and clinical outcome [68, 69]. 2, By carrying out the cryoprotectant exposure procedure at 37°C, it alleviates potential cooling injury to the oocyte cytoskeleton [70]. 3, Undesirable intracellular ice formation can be prevented and survival rates maximized by raising the seeding temperature as close as possible to the melting point of the solution (−4.5°C) [71]. 4, Reducing the sodium content of the freezing medium to a very low level or eliminating sodium (choline-based freezing medium, with 1.5 M 1,2-propanediol and 0.1 M sucrose) may allow oocytes to be frozen more effectively [72]. 5, Small amounts (0.15 M) of intracellular trehalose in the absence of any other cryoprotectant provide a significant protection against freeze-associated stresses. Trehalose was introduced into oocytes by microinjection [73].

Vitrification

An alternative to slow-freezing procedures is ultra rapid freezing method (vitrification). Vitrification methods are slowly becoming more widely used in IVF facilities. Vitrification uses high concentrations of cryoprotectants (1.0–1.6 mol Ethylene Glycol and DMSO) and rapid cooling (−1,500°C/min) that solidify without the formation of ice crystals. Furthermore, a rapid fall in temperature throughout the transition phase may reduce the thermal stress of the oocyte and consequently decrease chilling injury [74]. For these reasons the latest systems were designed to increase the cooling rate using containers with a reduced volume. They include cooper grids [56, 75, 76]; open pulled straw [77]; glass capillary [78]; cryo-loops [55, 79]. The cryotop technique has been also modified by using a hermetically sealed container for storage to eliminate potential dangers of disease transmission [80]. A major breakthrough occurred when human pregnancies and deliveries from vitrified mature oocytes were obtained [62, 81].

In spite of some progresses on vitrification, little is known about the potentially detrimental effects of this procedure on the oocytes. The high concentrations of cryoprotectants typically used in vitrification, such as ethylene glycol and dimethylsulfoxide, are associated with higher levels of toxicity and osmotic injuries [82, 83]. Different approaches are used to minimize these injuries: using less toxic chemicals, the combination of two or three cryoprotectants, stepwise addition and exposure of cells to precooled concentrated solutions [84].

Cryopreservation of ovarian tissue

Contrary to difficulties with full size oocytes, immature oocytes in primordial follicles that are found in the ovarian cortex are less sensitive to cryopreservation damage because they are small, not well developed, with few organelles, no pellucida, and are relatively metabolically quiescent and undifferentiated [85, 86]. Therefore, cryopreservation of ovarian cortex tissue which is rich in primordial and primary follicles has been suggested as an alternative to ovulation induction and oocyte cryopreservation for preserving fertility [87, 88]. Viable follicles survive after freezing–thawing of human ovaries [89] and ovarian tissue [90–92]. This has aroused interest in this procedure as a potential means of preserving the fecundity of patients at risk of premature ovarian failure [9, 87, 93]. In sheep, autotransplantation of frozen–thawed ovarian cortex [85] and of hemi-ovaries [94] has resulted in pregnancies, deliveries and prolonged hormone production [7, 8]. Nevertheless, in all these cases there was a reduction in the total follicular number due to ischemia, therefore ovarian function was transient [95]. Only eight of 80 human oocytes aspirated from a cryopreserved transplanted ovary were suitable for IVF and only one oocyte fertilized normally [96]. The first human pregnancy by cryopreserved ovarian cortex and transplantation was recently reported [9]. It appears that the main obstacles to successful restoration of fertility from frozen–thawed ovarian cortex are adhesions and the massive ischemic damage to follicles until neovascularization develops [95]. Most follicles which survive cryopreservation undergo ischemic loss during the time required for neovascularization [97].

Ovarian tissue freezing techniques

The freezing and thawing process can damage ovarian tissue possibly by both the formation of intracellular ice and the toxicity of the cryoprotectants. Histological analysis indicated that a proportion of follicles are damaged during the freezing and thawing process in mouse, marmoset, and human ovarian tissue [90, 98, 99]. Nuclear and DNA damage in human and ovine follicles after freezing and thawing has been reported using immunohistochemistry, fluorescent in situ hybridization, and terminal deoxynucleotidyl transferase end labeling [100–102]. Similar to oocyte cryopreservation, there are also two main techniques for freezing ovarian tissues: slow freezing and vitrification.

Slow freezing

The common slow freezing protocol is as follows [85]: after incubation in 1.5 M ethylene glycol and 0.1 M sucrose for 20–30 min, cryovials with ovarian tissue pieces are cooled to −7°C at −2°C/min, seeded, and further cooled to −40°C at −0.3°C/min, then free falling to −100°C before storage in liquid nitrogen. Vials are thawed in a 37°C water bath, and tissue pieces are washed through progressively lower concentrations of cryoprotectant media (1.5, 1.0, 0.5, 0) M ethylene glycol.

Vitrification

Cryopreservation by vitrification involves ultra rapid cooling in which solutions go directly from aqueous phase to the amorphous solid state without exposure to a crystalline state in which damage can occur [46]. Thus, the rapid cooling (1,500°C/min) in the presence of high concentrations of cryoprotectants avoids intracellular ice crystal formation. Vitrification has been used successfully with ovarian tissue with minimal changes in morphology [103, 104], but when transplanted in mice and rats, diminished follicular development and fertility were observed compared with the case of fresh transplants. For examples, the number of antral follicles in cryopreserved grafts was smaller than in the fresh grafts [105]. After grafting, the follicular density was less in frozen/thawed ovarian tissue compared with that in fresh ovarian tissue [106].

Ovarian tissue transplantation

It is noteworthy that the biopsy and transplantation of ovarian tissue involves only a simple and safe laporoscopic operation, without the side effects of hormonal stimulation for IVF [107, 108]. In theory, there are four potential directions for use of frozen ovarian tissue: heterotopic autografting, orthotopic autografting, in vitro maturation, and xenografting.

For research purpose, ovarian tissue is commonly grafted to the kidney capsule because this site favors rapid revascularization due to its rich capillary bed. This is, however, not an ideal site from which to harvest mature oocytes for human IVF. It would be relatively easy to recover oocytes from subcutaneous tissue grafts. However, the revascularization is slow and the follicular survival rate is low. It is reported that oocytes collected from super-ovulated sheep with subcutaneous grafts underwent IVF and, although these oocytes were able to resume meiosis and fertilize, none developed to the morula/blastocyst stage [109]. This may indicate deficient oocyte cytoplasmic maturation due to the freezing damage. Thus, several challenging questions have to be answered before ovarian transplantation can be considered in humans. These questions include whether sufficient primordial and growing follicles survive in the ovaries after subcutaneous transplantation and whether surviving oocytes resume meiosis, fertilize, and develop to blastocyst stage after in vitro maturation and fertilization [109].

Orthotopic autografting

Ovarian tissue could be grafted into the normal site (orthotopic), which would allow the possibility of pregnancy without further medical assistance. Although fresh ovarian transplantation was reported as early as 1906 [110], orthotopic transplantation of previously frozen ovarian tissue had been performed only in animals until 1999. It is this approach that has restored ovarian endocrine function, fertility, and yielded viable offspring in animals [7, 85, 111], and that has been tried recently in the human with limited success [112]. In humans, ovarian stimulation has successfully induced ovulation from transplanted frozen–thawed ovarian cortical tissue [113, 114]. In one individual, transient restoration of spontaneous ovarian follicular development and estrogen production, but not ovulation, was observed after autotransplantation of frozen–thawed ovarian tissue that derived from a cancer patient before chemotherapy and radiation therapy [115]. The first human livebirth after orthotopic transplantation of cryopreserved ovarian tissue has now been reported in a woman previously treated with chemotherapy and radiotherapy for lymphoma [9].

Heterotopic autografting

Heterotopic autografting, followed by in vitro fertilization (IVF), is an alternative to orthotopic autografting that offers a chance of pregnancy to young patients who have been treated with chemotherapy and/or radiotherapy [116]. There have

been several reports regarding the use of heterotopic sites for ovarian transplantation. Utilizing a forearm heterotopic autograft, in which ovarian tissue is grafted into the subcutaneous space above the brachioradialis fascia of the forearm, patients must undergo an IVF–ET procedure to conceive. The forearm transplantation technique does not require general anesthesia or abdominal surgery and allows the ovarian tissue to be closely monitored. If needed, ovarian removal would be less complicated with a forearm heterotopic graft rather than an orthotopic graft. Moreover, the forearm has been successfully used for autografting fresh and frozen–banked parathyroid tissue for many years [117, 118].

A recent primate study has also confirmed the feasibility of the forearm heterotopic approach in restoring menstrual cyclicity and the capacity to produce mature oocytes in response to gonadotropin stimulation [119]. The first live birth in a primate after heterotopic ovarian transplantation has been reported [120]. In human, ovarian function has been restored in two patients for at least 2 years after transplanting ovarian tissue to the forearm. In one of these patients, oocytes were even aspirated percutaneously [121], a morphologically normal embryo was developed and transferred, but no pregnancy resulted [96].

Xenografting

Xenografting of frozen–thawed ovarian tissue to an animal host can provide another possibility to restore fertility for cancer patients, especially the patients with high risk of hyperstimulation syndrome. With this technique, the cancer transmission and relapse can be eliminated because cancer cells cannot penetrate the zona pellucida. In contrast to transplantation of large organs, in which reanastomosis of blood vessels is achieved surgically, transplantation of small ovarian fragments depends on the growth of new blood vessels for restoring adequate perfusion. It has been shown that more follicles die from ischemia during transplantation than from freeze–thaw injury during cryopreservation [91, 122]. However, a recent study suggests that glutathione and uninastatin can improve the survival rate of follicles in cryopreserved human ovarian tissue after transplantation in nod-scid mice, and resting follicles could be recruited into growing follicles without exogenous gonadotrophin [123].

In vitro maturation of primordial follicles

The development of an efficient method to preserve, isolate and culture follicles to maturity in vitro would provide an alternative to the current options for fecundity preservation. Studies in mice and sheep have shown that oocyte–granulose complexes isolated from the frozen–thawed ovarian tissue can grow to antral size [124, 125]. The maturation of primordial follicles in vitro, which are capable of successful fertilization, has been demonstrated in a mouse model [126]. However, even with animal models there has only been one live birth from in vitro maturation (IVM) of a mouse primordial follicle. IVM of human primordial follicles will not be available until we have a full understanding of the signal and control mechanism of follicle growth. Once the technology of in vitro maturation of human unilaminar follicles is established, it will be possible to switch to a revolutionary method of IVF using oocytes that were matured and fertilized in vitro, thus avoiding the dangers of ovarian replantation.

Potential risks to patients

There is a legitimate concern regarding the potential for reseeding cancer cells with ovarian transplantation. It is known that ovarian involvement is extremely rare in Wilms' tumor, lymphomas (with the exception of Burkitt's lymphoma), osteosarcomas, Ewing's sarcoma, and extra-genital rhabdomyosarcomas. Ovarian involvement is also highly unlikely in squamous cell cervical cancers, even in the most advanced stages [64]. However, human frozen/thawed ovarian tissues from patients with Hodgkin's and non-Hodgkin lymphoma could survive and grow to large antral stages after xenografted into immunodeficient mice, and none of the tissues from these patients resulted in cancer recurrence [127, 128]. Although many types of cancer never metastasize to the ovaries, leukemias are systemic in nature and pose a greater risk to the recipient. Neuroblasto-mas and breast cancers are also of moderate risk to metastasize to the ovaries.

Elizuret et al. showed the feasibility and importance of detecting microscopic metastasis in ovarian tissue before transplantation using various methods and cancer markers such as HER2 for breast cancer [129]. To reduce the risk of cryopreserving ovarian tissue with metastasis, a histological evaluation should be performed on multiple tissue samples. In cases of leukemia or lymphoma, chromosomal and other tumor markers can be studied by immunohistochemical or other molecular biological methods to screen for the presence of cancer cells [112]. In the near future, it may be feasible to screen metastatic cancer cells harbored in the stored tissue before transplantation using immunohisto-chemistry, flow cytometry, or molecular genetic techniques such as reverse transcriptase–polymerase chain reaction and fluorescence in situ hybridization [130].

Ethical and legal issues

As some other new reproductive technologies, application of ovarian cryopreservation and transplantation raises a

number of potential legal and ethical issues related to both patient and offspring welfare [10, 131]. It includes clinical indications, issues of experimental vs. established therapies, age limits, time limit for storage, the ability of minors to give consent, tissue custody, the welfare of offspring, and posthumous reproduction. Defining clinical indications and resolving safety issues will be an ongoing effort, along with improvement of the technology.

It would be an ethical dilemma if a woman requesting use of her preserved ovarian tissue has reached the customary age of menopause in her culture or has exceeded a designated age [131]. The important factor in this situation is the health of an old woman requesting autologous replacement or in vitro maturation of her follicles (oocytes) for the purpose of initiating a pregnancy in herself. It is not ethical to establish a pregnancy via these techniques for an old woman if she can not meet the health and responsibility criteria. In addition, is it ethical to harvest and freeze ovarian tissue without a certainty of success in transplantation?

A diagnosis of cancer is a life crisis for any person. In a survey, cancer patients have been showing a strong desire to be informed of available options for fertility preservation and future reproduction [132]. Although cancer patients desperately want to preserve fertility with no other option, it is the responsibility of cancer and fertility specialists to try to prevent misunderstanding and misuse of this new technology. In short, there are many ethic issues to be concerned carefully in developing this technology.

Conclusion

In recent years, there have been considerable advances in the cryopreservation of human oocytes and ovarian tissue. For women facing upcoming cancer therapies, cryopreservation of ovarian tissue and oocytes is a technology that holds promise for banking reproductive potential for the future, because the majority of cancer patients do not have enough time to complete an IVF stimulation cycle before starting cancer treatment.

Recent laboratory modifications have resulted in improved oocyte survival, oocyte fertilization, and pregnancy rates from frozen–thawed oocytes in IVF. This suggests potential for clinical application. In the case of patients who are facing infertility due to cancer therapy, oocyte cryopreservation may be one of the few options available. This option can also be utilized by healthy patients wishing to bank their oocytes for future use. Further research is needed to delineate the current success rates and safety, as well as to improve the efficiency of this procedure.

Currently, ovarian tissue cryopreservation can only be recommended as an experimental protocol in carefully selected patients. Future research should focus on better defining patient suitability, choice of cryoprotectants and cryopreservation methods, and possible in vitro maturation of oocytes from frozen/thawed human ovarian tissue. In addition, research is also needed in order to enhance the revascularization process with the goal of reducing the follicular loss that takes place after tissue grafting.

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