Fertility Preservation Among the Cancer Patients by Ovarian Tissue Cryopreservation, Transplantation, and Follicular Development

Ali Abedelahi[1], Mostafa Rezaei-Tavirani[2], Daryosh Mohammadnejad[1]

Abstract

Ovarian tissue freezing or cryopreservation might be the only acceptable method for preserving the young women fertility, before radiotherapy or chemotherapy. This technology might be used for patients with recurrent ovarian cysts or endometriosis, without ovarian stimulation.

Many efforts have made to improve cryopreservation conditions that should be seriously considered for cancer patients. Vitrification is a process which prevents ovarian tissue from cryo damage, then preserves cell viability. Both methods have used for evaluating not only the follicular development, but also the fertility after freezing and thawing. In this manuscript, we have discussed the techniques of ovarian tissue vitrification, then graft and maturation or follicular development is also mentioned.

Keywords: Ovary; Vitrification; Transplantation; Chemotherapy

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1. Dept. of Anatomical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
2. Proteomics Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author:
Daryosh Mohammadnejad, Ph.D;
Assistant Professor of Histology
Tel: (+98) 411 334 20 86
Email: daryoshm44@yahoo.com
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Introduction

Unfortunately the new cancer cases have increased among the women.

According to the reports, 8% of cancerous women have been 40 years old, or even younger; regarding the population status and geographical distribution even more than that [1-2]. Infertility is one of the major problems after chemotherapy in cancer treatments. The ovaries are very sensitive to chemotherapy agents. Therefore in young patients, chemotherapy agents have affected fertility by influence on ovarian function. On the other hand, the adverse effects of chemotherapeutic agents and irradiation doses, would be ovarian failure induction, then increasing the risk of Premature Ovarian Failure (POF) [3, 4]. In radiotherapy, a dose of 5-20 Gy has been prescribed for ovarian cancer treatment, which has impaired gonadal functions [5].

Recently studies have shown that spermatogenesis and oogenesis, both have influenced by radiotherapy and cancer cytotoxic drugs.

There are 3 ways for fertility preservation in cancerous women and premature ovarian failure: embryo freezing, oocyte freezing and ovarian tissue cryopreservation. Ovarian tissue freezing or cryopreservation might be the only acceptable method for preserving the young women fertility who have received requiring radiotherapy or chemotherapy [6, 7]. This technology might be used for patients with recurrent ovarian cysts or endometriosis that might also be at risk for severe premature menopauses include hormone replacement therapy, but without ovarian stimulation [1, 2, 6, 7].

The major steps in the cryopreservation process could be summarized as follows:

1. Addition of cryo protectant solution to cells or tissues before cooling
2. Freezing the cells or tissue with very low temperature, then stored in liquid nitrogen (-196°C)
3. Warming the cells or tissues
4. Thawing the cells or tissue by removing the cryo protectant solution

For this reason, many investigators might have attention to this technique. Since, only a few pregnancies have been reported after ovarian tissue cryopreservation. Ovarian tissue cryopreservation is more complex than that of oocytes or embryos because of several different cell types and water permeability.

This review has covered current options for ovarian tissue cryopreservation, transplantation and in vitro maturation of follicles and provides a systematic review of the ISI (3%), Scopus (3%) and PubMed (94%) indexed literature within the last 15

years (87 selected articles from 250 assessed articles) (Figure 1). About 8% of these articles have related to essential fertility preservation among the cancerous patients, 5% related to physics of cryopreservation, 10% to cryoprotectant solutions, 20% to cryopreservation methods, 22% to fertility preservation methods in cancer patients, 15% to transplantation, at least 23% have related to in vitro maturation and ovarian follicles culture. The current review is a result of authors' previous studies, then some professional works in this area. In this field, there are some controversial results.

Besides in our country, even regarding the importance of clinical assessment, and "fertility problems solving" before chemotherapy, but we could not find practical strategy in clinics. So, in this paper we have decided to assess deeply between the related works in this field in order to reach a summary of developed countries' experiences, for our clinics usage.

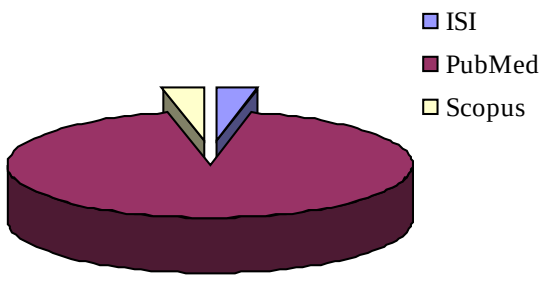

Figure 1. It shows relative contribution of different databases used in current review article.

Physics in Cryopreservation

The intracellular ice formation and osmotic injury are the important biophysical tissue damage reasons during cryopreservation. At subzero temperatures (less than the freezing point of water, 0°C), the water cooling leads to the formation of ice nucleation as the first microscopic ice crystals, which composed of single molecules of water. After formation of ice nucleation, water molecules have connected to the surface of the ice thus achieved greater initial ice crystals, then lead to the macroscopic ice crystals formation. Based on the physics-chemical laws, water temperature reduces in time of formation or melting of ice crystals after addition of cryoprotectant [8-10].

High concentration of cryoprotectant solution in vitrification, have resulted in flow out the water of the cell before cooling period, which intracellular ice crystal formation could not occur [11]. In this study, all simple and complex cells have carried out in liquid nitrogen in -196°C and chemical reaction inside the cells has suppressed at this temperature. Cryodamage injuries of the cells have restricted by controlling the speed of freezing-thawing.

Cryoprotectants

A cryoprotectant is a substance that is used to protect biological tissue from cryoinjuries [12]. The requirements of an optimal cryoprotectant are permeability and low toxicity. Although various cryo protectants have been developed, many of them are toxic to cells [2–5, 9, 11]. The vitrification solutions which have been used in experiments as below:

a) Intracellular (permeating) cryoprotectants such as ethylene glycol, dimethyl sulphoxide and propandiol

b) Extracellular (non-permeating) cryo protectants such as sucrose and threalose

c) Macromolecules such as Raffinose and ficoll [13]

Initial studies have used Glycerol as cryoprotectant solution [14, 15]. Other cryoprotectant solutions such as propylene glycol or Dimethyl Sulfoxide (DMSO) have used in relation with low toxicity [11, 16, 17].

Recently, Ethylene Glycol (EG) is one of the most effective cryoprotectant for vitrification, because of low toxicity, then rapidly penetration from cell membranes. Also EG has used alone or in combination with DMSO [16-18]. These cryoprotectants have used in higher vitrification concentration, in comparison with slow freezing technique. During the equilibrium phase, the cells initially shrink as water flows out, and then swell as water and cryoprotectant agent enter. The addition of sucrose in equilibration and vitrification solution could facilitate the exit of water from the cell and decrease the ice crystal formation, thus it could protect the cells during cooling and warming process [11].

Isachenko et al. cryopreserved human ovarian tissue by direct plunging into liquid nitrogen and has concluded that vitrification could be a useful strategy to preserve ovarian tissue, if we have used only permeable cryoprotectants such as DMSO, glycerol and ethylene glycerol [19]. Abedelahi et al. have shown that EG is an efficient and optimal cryoprotectant for cryopreservation of mice ovarian tissue (Figure 2) [18].

Conventional (Slow) Freezing

In slow freezing, with combination of low concentrations of cryoprotectant solutions around the cell, the water has removed and concentrated within the cell. Water has continued out of the cells during cooling, and ice crystals has formed by cooling the solution outside the cell, thus has prevented the formation of intracellular ice crystals [9]. The slow freezing is a time-consuming procedure and an expensive method because of using the controlled-rate cooling devices. In addition, this procedure could cause damage by intracellular ice crystal formation [20-22]. So, an optimum cooling rate has required for traverse of water out of the cells, then cryoprotectant solution into the cells.

Vitrification

Cryopreservation protocols have depended on many factors such as adequate cryopreservation techniques, type and concentration of cryoprotectant, number of equilibration and warming steps and cryopreservation devices [23-25]. Therefore many attempts have been made to improve cryopreservation conditions by using simple and efficient procedures. For this purpose, a rapid, simple and economical cryopreservation method has applied to ovarian tissues. Vitrification is a rapid cooling cryopreservation technique in which solutions go directly from the aqueous phase to a solid amorphous phase (solidification) without formation of ice crystals, thus reduces the tissues cryodamage , and cells originated from ice formation [13, 18, 26-28]. Vitrification instead of slow-freezing is rapid cooling, time saving and does not require expensive equipment.

Mazoochi et al. has shown cryopreservation of the immature mouse ovary by conventional vitrification has not induced apoptosis just after warming [29] but apoptosis increased after slow freezing-thawing [30]. Also our results demonstrated that human ovarian tissue has vitrified very rapidly, which shown no increase in any tissue Reactive Oxygen Species (ROS) levels after warming [31]. Hani et al. has indicated that cryopreservation of mouse ovaries by vitrification would be a useful method for preservation of female germ cells from mice of various ages [32]. Small volumes of vitrification solution are necessary to achieve rapid freezing. Therefore many devices have used to reduce the volume of vitrification solutions such as grids [33], glass capillaries [20, 29], Open pulled Plastic Straws (OPS) [23], cryovial and cryotube [18], cryoloop [34] and In-Straw Vitrification (ISV) and Solid-Surface Vitrification (SSV) [11, 35]. Chen et al. have designed new vitrification method using less concentrated cryoprotectants and direct application of liquid nitrogen to the ovarian tissue (Direct Cover Vitrification, DCV) [36]. We have shown that DCV has preserved better morphological, viability and ultrastracture of follicles than conventional vitrification (Figure 2, 3) [18]. Despite many attempts on improvement of vitrification procedure, few successes have been reported regarding the non-vitrified groups.

Embryo Cryopreservation

Mammalian embryos have successfully frozen and thawed first in mice in 1972 [37]. Although embryo cryopreservation has become a routine technique in all IVF center, then embryo freezing have been succeed offensive (pregnancy rate were about 15 to 25 percent after 2 or 3 transfers of frozen embryo). However, there would be problems in this area. Obtaining eggs is difficult for fertilization techniques, the limited number of embryos might be used, which need to partner or donor sperm. In addition, there is no time for ovarian stimulation, as well as collection and maturation of oocytes among the women whose started cancer treatment. Also this technique could cause problem among the women with estrogen-sensitive cancers such as breast cancer, ovarian epithelial tumors and severe endometriosis. Finally, this technique is inappropriate for children before puberty [25, 38, 39].

Oocyte Cryopreservation

In 1986, the first pregnancies and live birth after human oocyte cryopreservation has reported [40]. Mature or immature oocytes could be collected and frozen [9, 17, 24, 34, 35, 43]. Cryopreservation of oocyte in metaphase II stage has created a disappointing result due to problems during fertilization and embryo development [41].

The zonapelucida has hardened within the oocyte cryopreservation that impairing sperm penetration, then has shown that "blastocyst hatching rate" has decreased after freezing [42]. Moreover, the chromosome has lined up by the meiotic spindle, and have damaged by intracellular ice formation, then result to aneuploidy [43]. Freezing process has also damaged the cell cytoskeleton by changing in the molecule and organelles structure [44].

Although cryopreservation of oocytes in germinal vesicle stage has not hazarded aneuploidy, but the risk of zonapelucida hardening and the cytoskeleton damaging could not be avoided [45]. Indeed, only a little in vitro maturation of oocyte and pregnancies (1-5%) has reported [41, 46].

Ovarian Tissue Cryopreservation

Cryopreservation of the ovarian tissue is a useful technology for preservation large number of oocyte [18, 19, 22, 28, 29, 36]. Ovarian tissue freezing or cryopreservation might be the only acceptable method for preserving fertility of young women who received requiring radiotherapy or chemotherapy for cancer treatment. This technology might be used for patients with recurrent ovarian cysts or endometriosis that also might be at risk for severe premature menopauses including hormone replacement therapy, without any ovarian stimulation [47, 48].

For this reason, many investigators might attend in this technique. Since, only a few pregnancies have been reported after ovarian tissue cryopreservation [49, 50]. Ovarian tissue cryopreservation is complex because of the different cell types and physical structures in ovarian tissue that require different process for optimal survival. Ovarian tissue could be cryopreserved in various forms, such as fragments, slices, hemi and whole ovaries.

Ovarian tissue cryopreservation unlike oocyte and embryo cryopreservation might be used before or after puberty or at any stage of the life cycle. The earliest successful cryopreservation of ovarian tissue has proposed in 1950 by Deansely and colleagues [9]. In 1953, Parkes and Smith have reported successful cryopreservation of mouse ovarian tissue by using glycerol but shown lower rate of pregnancies after autograft of frozen ovaries [51]. Then Candy and colleagues have frizzed pieces of ovarian tissue using glycerol [52]. They have precisely controlled cooling rate and reported survival rate about 20 percent.

Sheep ovarian tissue cryopreservation has reported for the first time in 1994 by Gosden [20]. Human ovarian tissue cryopreservation has proposed by Zhang in 1995 [53]. Ovarian cortex of young women have contained hundreds to thousands primordial follicles. Even a small piece ($1mm^3$) of them might have several hundred follicles. Human ovarian cortical tissue freezing have grafted in kidney capsule of immunodeficiency mice and has observed normal development of follicles [54]. After one month of transplantation, they have observed that the grafted ovarian cortex has contained grown follicles as well as survived follicles in the phase of scalp tissue. The diameter of follicles have increased from 37 microns to 85 microns, then the number of granulosa cell layers has increased [55].

Transplantation and Follicle Culture

There are two methods including graft of ovarian tissue and in vitro maturation of follicles for obtaining mature oocyte from frozen-thawed ovaries. Once the ovarian tissue is frozen, this could be transplanted autograft or autotransplantation and xenograft or allotransplantation. In autotransplantation, the dissected ovaries grafted into same animal which could performed either orthotopically (graft to its site in ovarian pedicle or bursa) or heterotopically (graft into the nonphysiological region such as subcutaneously or renal subcapsule). Autotransplantation of frozen-thawed ovarian tissue has applied for restoration of endocrine function, fertility in humans [26, 50, 54, 56, 57]. Yang et al. has reported that ovarian tissue transplanted to the kidney capsule were more favorable site than subcutaneous and intraperitoneal grafting and followed by more growing follicles [58]. Recently healthy babies have born following autotransplantation of cryopreserved ovarian tissue [50].

Another type of transplant is xenograft that has transplanted into another animal (same species or different species). In this transplant, the ectomized ovaries grafted into Nude animals (without T lymphocytes) or Severe Combined Immunedeficient (SCID/without B and T lymphocytes) animals [59, 60]. The xenotransplantation, frequently used an experimental model to evaluate oocyte and follicular viability [61, 62]. However, after transplantation of vitrified–warmed mouse ovarian tissue, the primordial and primary follicles were intact but the preantral and antral follicles have lost.

Transplantation after cryopreservation method had two main disadvantages: the first was postgrafting ischemia, then another re-transferring the cancer cells after grafting the ectomized ovaries in young cancer patients. The ischemic injury without vascularization induced the follicular reserve during grafting (about 60-95%) [63, 64]. Therefore revascularization is the key factor for ovarian tissue transplantation. Ovaries have produced factors which facilitate the endothelial cell migration in grafting. The successful autograft of frozen-thawed ovarian tissue has reported in sheep, rabbit and monkey but for human has still remained in experimental stage [65]. Baird and colleagues [66] have observed decreases of primordial follicles after transplantation (65% in non-vitrified ovaries and 72% in vitrified ovaries). They have shown that only 7% of follicular loss is due to the freezing process and others due to ischemia before revascularization. Dissen et al. has detected neovascularization after

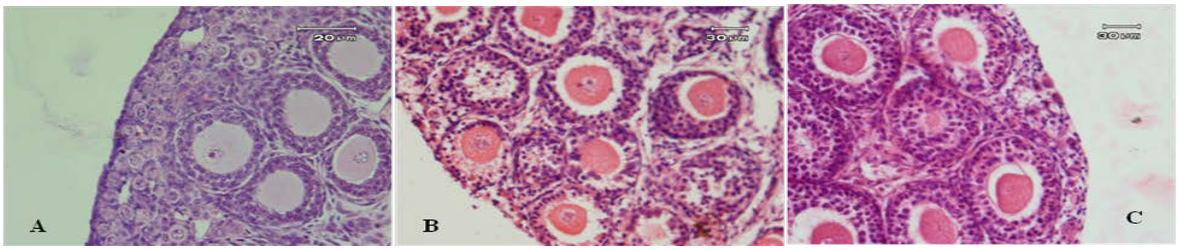

Figure 2. The morphology of follicles after ovarian tissue vitrification: A) non vitrified, B) slow freezing and C) vitrification. No significant differences were observed between the normality of primordial and primary follicles in all groups of study. But slow freezing groups showed more sign of degeneration and cryoinjury in preantral follicles and the disruption of intercellular contacts among innermost granulosa layer and oocyte, nuclear piknosis and cytoplasmic retraction were prominent.

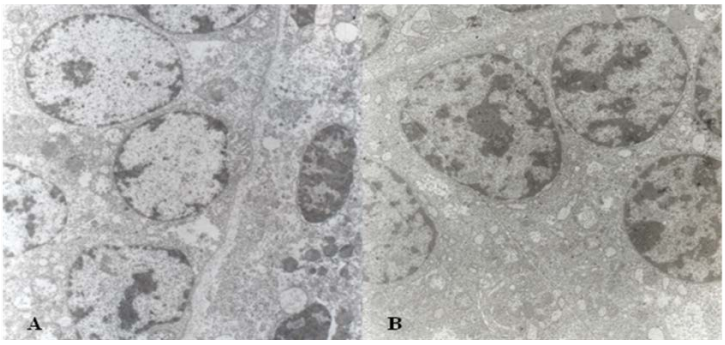

Figure 3. The electron micrograph of granoulosa cells of preantral follicles from conventional vitrification (A) and direct cover vitrification (B). The oocytes were surrounded by two or three layers of cuboidal granulosa cells in preantral follicles. At the periphery, all the follicles from fresh and frozen-thawed tissue were surrounded by a continuous basement membrane and this structure were preserved during both vitrification procedures.

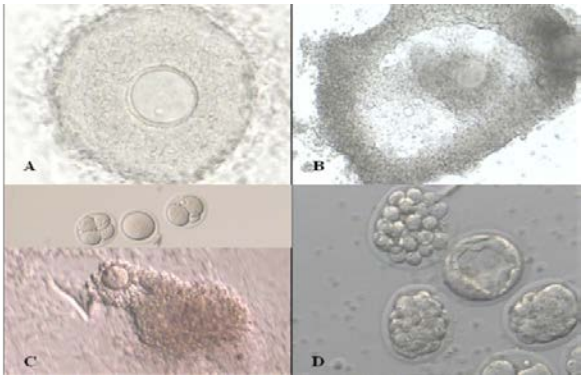

Figure 4. It shows the morphology of mouse preantral follicles during in vitro maturation: the isolated and cultured follicle on day 6 (A); and day 10 (B) of culturing;the oocyte ovulated of cultured preantral follicle, two and four cell embryos(C); and embryos in morolla and blastocyte stages (D).

48 hours, and functional vessels after 1 week in autotransplanted rat ovary [67]. Also Donnez et al. has reported that follicular development occurs 4-5 months after ovarian autografting [68].

Follicular Isolation and Culture System

The different culture systems have designed for in vitro culture of preantral follicles and have a common

step-the isolation of preantral follicles from ovarian tissue [69-71]. Preantral follicles could be isolated either mechanical or enzymatic. Mechanical isolation of follicles has preserved the integrity of the preantral follicle structure, then has allowed being maintained centrally located oocyte, oocyte-granulosa interaction and theca cells that attached to the basal membrane. The limitation of this method is in large mammals and human with high density of the ovarian cortex [69, 70].

In enzymatic isolation of preantral follicles, could be achieved a large number of preantral follicles. This technique facilitates the isolation when present the dense ovarian cortex such as human. However, the integrity of follicles has not preserved and removed the theca cells and degrades the basal membrane because of proteolytic digestion. These changes might be altered the response of follicles to hormonal stimulation [69, 72]. Although, the mechanical method is time consuming and difficult but also the physiological development of the follicle needs the presence of granulosa and theca cells that secrete steroids. Therefore, this method is recommended for the isolation of preantral follicles.

Nagano et al. has reported that mechanically isolated preantral follicles from vitrified ovaries have shown higher survival rate than enzymatically isolated follicles [73].

Optimal in vitro follicular culture models should result in competent mature oocyte that could be fertilized to obtain viable embryos. Isolated follicles have cultured spherical or non-spherical culture system. In spherical culture system, the 3D structure of follicles have preserved and follicle was not adherent to the bottom of the culture dish that accomplished by the hydrophobic membrane as the cell culture support or by moving follicle at each day (Figure 4). In non-spherical culture system, follicular structure has remained intact and by disruption of basement membrane granulosa cells adhering to the bottom of the culture dish [70, 74, 75].

After the enzymatically isolation of follicles, culture systems should be designed that prevents from migration the granulosa cells around the oocyte by facilitating the granulosa cell adhesion. For this reason, some researcher's culture oocyte- granulosa complexes on membrane collagen or culture dishes coated with serum. In this system, the oocyte-granulosa complex loss itself spherical structure and oocytes could be collected directly into medium after in vitro maturation [74, 75].

In another way, the oocyte-granulosa cell complexes have cultured within the collagen matrix. In this culture system, the spherical morphology of follicles remained to the antral stage, but it would be difficult to oocyte collection [76]. In addition to differences in follicle isolation and culture systems, various media and supplements have used in these systems.

In Vitro Maturation of Follicles

Several endocrine and paracrine factors have involved during ovarian follicular growth and development [31, 77-79]. Therefore in vitro follicular systems were useful techniques for identification of these factors, studying the mechanism of folliculogenesis and a good model for studying toxicity and teratogenic effects of compounds, and new drugs on follicular growth.

Another important outcome was preserving the fertility of follicles after frozen-thawed ovarian tissue. In vitro folliculogenesis has defined as the transformation of the primordial follicles (flattened granulosa cells) into primary follicles (cuboidal granulosa cell layer) [74, 80]. The earliest stages of ovarian folliculogenesis were morphologically similar in different mammalian species. Ovarian tissue has cultured and primordial follicles have grown as secondary follicles and then have followed by vitro maturation, fertilization, and finally a live birth [74]. This repeater has shown successful and fully in vitro folliculogenesis.

The folliculogenesis process could be divided to three stages: growth stage, the formation of antral follicles from primary or secondary follicles and finally oocytes maturation to metaphase II oocytes that could be fertilized [81]. The culture of primordial human follicle was more difficult and has taken longer (120 days in human and but 22 days in mice) [81]. The human ovary has different structure and dens stroma that difficult follicle isolation.

The ovarian tissue has composed of follicles in various stages of growth and the selection of growth stage was important to obtain in vitro development, then matured. Primordial follicles were more than 90% of ovarian follicular population and could be the first follicle that formed in the ovarian tissue. This follicle has contained a centrally oocyte that surrounded by a layer of flattened granulosa cells. The primordial follicle could be considered as a reserve follicles and a valuable source of oocyte for clinical, agriculture and animal purposes [81].

Choi et al. after vitrification-warming of ovarian tissue has observed the least damage in the primordial follicle compared to other stages of follicles [82]. In addition, Kim SS et al. have reported primordial follicles to have more potential to repair sublethal damage to organelles and other structures

during their prolonged growth phase [83]. These follicles had a relatively inactive metabolic rate, small size, low number of granulosa cells around the small oocyte, an absence of the zonapellucida and cortical granules [84]. In addition, they have small intracytoplasmic lipid molecule which is sensitive to freeze. The most primordial follicles have remained alive after thawing using vital stain and electron microscopy. The culture of primordial follicles was a real problem. Unfortunately the most isolated primordial follicles were atretic after three weeks in vitro culture but the culture of ovarian cortex has resulted in development of primordial follicles to preantral and early antral follicles due the interaction of follicles-follicles and surrounding stroma in the cultured ovarian tissue [85].

Liu and colleagues has designed a two-step approach that primordial follicles could be matured by combination of in vivo and in vitro techniques [86]. In first step, immature mouse ovarian tissue which contains only primordial follicles transplanted to renal subcapsule of ovary ectomized mice. Two weeks after transplantation has observed that the primordial follicles developed to pre-antral follicles. In next step, the isolated follicles cultured in vitro for 12 days and matured to the MII phase. However, the mechanism involved in the growth of primordial follicles to pre-antral follicles has still unknown and might need to extra ovarian factors.

The pre-antral follicles were other categories of follicles that sensitive to gonadotropin stimulation and have better grown in culture medium contained gonadotropin. In addition, studies have shown that at least follicular atresia or apoptosis has occurred in pre-antral follicles in vivo [77, 79].

In the most advanced culture systems that used from the rodent model. At present, the mouse is the only species for in vitro culture system. Rodent models have several advantages. As in human, the follicular growth includes gonadotropin-independent and dependent periods. Furthermore, ovarian tissue contains a large number of follicles at a similar stage of development. Also the isolation of the follicles was easy because of low density of the cortex and free ovarian fibrosis. Finally, the development of the preantral follicles until the preovulatory stage spreads to 10-12 days (about 85 days in human) that has needed short period of in vitro growth [69, 80].

Medium has generally supplemented with a protein source (serum) to support follicular growth in vitro. Most culture systems have used Fetal Bovine Serum (FBS), Fetal Calf Serum (FCS) and Bovine Serum Albumin (BSA) [31, 70, 71, 78, 79, 87, 97]. Our recently research has shown that FBS could increase the maturation rate of mouse preantral follicles (Figure 4) [70]. The different growth factors and supplements added to the culture system, could be essential for follicular development, were still a challenge in culture systems. Insulin with Transferrin and Selenium (ITS) have usually added to the culture medium as survival factors [31]. The other ingredients have added to the culture medium are the gonadotropins. The gonadotropins-Follicle Stimulating Hormone (FSH) or Luteinizing Hormone (LH) were the major endocrine factors that modulate follicular development. The essential role of FSH on antral follicles could be further growth and differentiation, then role of LH on theca cells, would be final differentiation granulosa cells and the rupture of the follicle walls that lead to ovulation process [29, 31, 70, 77, 79]. In addition, the time that various factors have added to the culture medium could be important. For example, if LH or HCG has added to early stage of culture instead of ovulation duration, it has resulted in low growth rate of follicles and losing the spherical structure.

Conclusion

Advanced fertility preservation techniques could be an essential solution among the young couples who suffered the infertility problems. One of the major causes of infertility is chemotherapy and radiotherapy. The effects of these treatments have based on their antimitotic actions of gonadal cells.

Ovarian tissue cryopreservation might be the only acceptable method for fertility preservation in cancerous patients during the treatment by radiotherapy or chemotherapy. Many researches have focused on preserving ovarian function after freezing-thawing processes but there is still much work to be done. Transplantation and follicular culture are valuable options for follicular development and fertility preservation in cryopreserved ovaries.

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This manuscript just cited selected number of articles. Therefore, I appreciate all researchers in this field. We thank Dr. Hadihasanzadeh for his help in designing and editing the manuscript.

Conflict of Interest

The authors have no conflict of interest.

Authors' Contribution

Ali Abedelahi and Daryosh Mohammad nejad designed the study and wrote the paper. Mostafa

Rezaei-Tavirani helped in writing and overall correction of the manuscript. All authors read and approved the final manuscript.

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