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Mini-Review

Ovarian Tissue Transplantation versus Follicular Culture

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Abstract

The banking of ovarian tissue containing large number of primordial follicles has become widespread as one of the promising fertility preservation options in young cancerous patients. There are substantially three approaches in female fertility restoration including embryo and oocyte freezing as well as ovarian tissue cryopreservation. Two former methods require ovarian hyperstimulation which in turn have their own side effects and limitations. The third option as the only feasible approach in prepubertal girls allows immediate cancer treatment. In third method, two main approaches are proposed. One is ovarian tissue transplantation which may not be an applicable approach for all patients especially where there is a chance of reintroducing malignant cells. The second approach with greater interest is one or two steps ovarian follicular culture followed by in vitro maturation of resulting oocytes and the subsequent IVF and IVC procedures. Among various studies conducted in different species, following follicle culture, the live birth has been achieved only in mouse. In this review various aspects of the studies done in this area would be challenged.

Keywords: Follicle culture; Ovarian tissue culture; Primordial follicle; Autotransplantation; Three dimensional culture

Introduction

Fertility preservation provides the pregnancy chances at the right time in patients or those who want to postpone childbearing for social or financial reasons. The majority of patients who can benefit from fertility preservation techniques are cancerous patients. Irreversible follicular and oocyte damage due to chemotherapy and radiotherapy led to the fertility loss in women so that 50% of primordial follicles could be destroyed following radiation [1]. There are several approaches for fertility preservation in female cancerous patients including oocyte or embryo cryopreservation and ovarian tissue banking followed by tissue transplantation or one or two steps follicular culture [2-4].

Embryo cryopreservation has been widely used in many species [5-8] and the oocytes cryopreservation as an alternative method is accounted for more than 200 live births [9-12]. Application of oocyte cryopreservation, however, needs to be more improved in animal species [13]. In prepubertal girls or cancerous patients where the future fertility is desired, the ovarian tissue cryopreservation is more promising. The human ovarian cortex contains the vast majority of the follicular reserve that is less susceptible to cryodamage. Cortical ovarian tissue can ortotopically or heterotopically be autotransplanted and also can be used for follicle culture. In in vitro culture of follicles both follicle development and oocyte health supported during long-term culture [4].

Considering the importance of female fertility preservation in patients at risk of compromised fertility, this mini-review will discuss two main approaches proposed in cancerous patients.

Transplantation of Ovarian Tissue

Autotransplantation

In cancerous patient, when there is no risk of ovarian metastatic involvement, ovarian tissue can be transplanted otherwise an alternative approach should be considered such as one or two step follicular culture. There are mainly two strategies including transplantation of whole ovary or cortical ovarian tissue reimplantation.

In whole ovary transplantation, despite reduction in ischemia and prolonged graft longevity, there are difficulties in cryopreservation and supplying the required nutrients to deeper parts considering the size of ovary. Nonetheless, transplantation of frozen-thawed whole ovaries in sheep and subsequent oocyte aspiration has resulted in embryo development up to the 8-cell stage [14]. Transplantation of whole cryopreserved ovaries with microanastomosis of the ovarian vascular pedicle resulted in pregnancy and live birth in mouse and sheep [15,16]. The whole human ovary transplantation between monozygotic twins who were discordant for polycystic ovarian failure led to the birth of healthy baby [17].

In second strategy, the cortical ovarian tissue has been successfully transplanted into mouse, sheep, and monkey [18-20]. The first successful human ovarian tissue transplantation was performed between monozygotic twins in 2005 [21]. The results of ovarian cortex reimplantation were more promising as such ovarian activity restoration was observed 3.5 months after reimplantantation and successful pregnancy was achieved 9 month after orthotopic reimplantation of ovarian cortex [22]. Ovarian cortex autotransplantation to a peritoneal pocket in the broad ligament led to ovarian function recovery 24 weeks after transplantation and normal pregnancy following the fifth stimulation attempt [23]. So far, 30 live births have been reported after orthotopic reimplantation of cryopreserved ovarian tissues [24]. On the other side the heterotopic transplantation has resulted in production of a four-cell embryo leading to one pregnancy [25].

Xenotransplantation

Since in human autotransplantation there are some limitations in assessment of physiological aspects of follicular development, xenotransplantation of ovarian tissue to immunodeficient animals

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provides the opportunity to perform such studies on survival, morphology and functional recovery of ovarian follicles.

The oocytes in bovine secondary follicles grown in Severe Combined Immune Deficiency mice (SCID) were able to resume meiosis and progress to the second metaphase [26]. Xenografting of pig vitrified-warmed and fresh ovarian tissues in SCID mice led to primordial follicles development to the secondary and antral stages, respectively, after two months. In between, though the primordial follicles could maintain their developmental competence after vitrification and warming, their developmental rate was slower than that of fresh counterparts [27]. Fresh and frozen-thawed human ovarian tissue xenograft to SCID mice has increased the proportion of growing follicles as well as the growth of follicle to the antral stage. There was, however, no significant difference in oocyte or follicle diameters between fresh and frozen-thawed tissue grafts. Theca layer in antral follicles of frozen-thawed grafted tissue, however, was significantly thinner than fresh tissue [28].

Xenografting of vitrified-warmed bovine follicles into SCID mice has led to the growth of primordial and secondary follicles to the antral stage, indicating the developmental ability of follicles after vitrification [29]. The survival and development of xenografted human follicles into antral stages after six months was indicated the capacity of oocytes to survive for long term [30]. Xenotransplantation of fresh isolated human follicles into nude mice resulted in primordial follicles activation and formation of follicles surrounded by stroma-like tissue of human origin [31]. Bovine isolated preantral follicles embedded in granulosa and stroma cells matrix were able to survive and grow 14 days after renal subcapsular xenotransplantation. This matrix provides an in vivo model to study preantral follicles development [32]. Observation of infiltrating blood capillaries after xenograft of an alginate-matrigel matrix containing isolated ovarian cells was another promising event in developing a biodegradable scaffold [33].

One major limitation in grafted ovarian tissue is a considerable follicles loss. Ischemia and the consequent apoptosis that occurs before efficient revascularization is the cause of this reduction, as >50% of primordial follicles are lost following ovarian transplantation. The loss of follicles may also be due to premature activation of the transplanted follicular pool [31]. Lack of antimullerian hormone in ovarian grafts is proposed for premature follicular activation [34]. Graft pretreatment with vascular endothelial growth factor A (VEGF-A) and vitamin E besides host treatment with vitamin E and gonadotropins could improve the survival of grafted human ovarian tissue by reducing apoptosis [35]. Additionally, the ischemic injury was decreased by sphingosine-1-phosphate supplementation through acceleration of angiogenic process and reduction of tissue hypoxia [36]. VEGF and fibroblast growth factor b (bFGF), especially in combination, through triggering angiogenesis and reducing apoptosis could increase the survival of transplanted human ovarian tissue [37].

Follicle Culture

Ovarian tissue culture

Since the early 1990s, ovarian follicle culture techniques have been developed with the aim of achieving competent oocytes. In some species such as mouse the culture of ovarian follicles in the form of whole ovary culture is executable. Moreover, the small size and soft texture of the ovaries provide the opportunity to achieve intact follicles following enzymatic digestion. In contrast, in human and most domestic species, the ovaries are too large to be organ-cultured, and the toughness of ovarian stroma impairs (compromises) the follicle intactness following enzymatic dissociation. To conquer these problems, an in vitro system was developed for culturing small pieces of ovarian cortex prior to follicle isolation. Cortical pieces were cultured in medium supplemented with serum plus insulin, transferrin, and selenium (ITS) where the primordial follicles were activated to become primary follicles. Though, in ovarian cortical strip culture, the follicles were deprived from the in vivo endocrine and paracrine factors, the follicles were received the effects of follicle-stromal interactions. Removing stromal cells and culturing the flattened tissues led to the greater activation and faster follicles growth [38].

Hormones and growth factors in tissue culture

Studies on animal models considering the effects of hormones and growth factors on follicular development and survival have widely provided a basis for human follicle culture experiments.

In human ovarian tissue culture, ascorbic acid and cyclic adenosine monophosphate have been used to prevent apoptosis [39]. The positive effects of insulin growth factor I and II (IGF-I and II) in reducing atresia, increasing growing follicles and follicular integrity has been established [40]. There are also evidences indicating the promontory effect of FGF on human follicle development as well as the stimulatory effect of growth and differentiation factor 9 (GDF9) on follicle integrity and primordial follicle activation [41,42]. In between, anti mullerian hormone has an inhibitory effect on human ovarian follicular development by suppressing primordial follicle activation [43].

Studies in animal have indicated the positive effect of GDF9 on ultrastructural integrity of goat preantral follicles and primordial follicles activation [44]. The presence of follicle stimulating hormone (FSH) and FGF-2 in ovarian tissue culture has shown the promotory effects of FSH on percentage of the primary follicles. FSH alone or combined with FGF-2 increased the growth and integrity of caprine preantral follicle [45]. In cattle, FSH in combination of GDF-9 or bFGF has increased the rate of normal follicles and decreased the rate of apoptotic cells [46]. Presence of indol acetic acid (IAA), EGF, and FSH has maintained ultrastructural integrity of sheep primordial follicles and oocytes [47]. In mice, culture of prepubertal ovarian explants with R-spondin2, stem cell growth factor, has promoted primary follicles activation [48].

Isolated follicle culture

In culturing ovarian tissues, as the follicles develop to the secondary stage the cortical tissue environment becomes inhibitory to further growth. Therefore, ovarian tissue culture cannot support follicle development to the more advanced stages so that a multi-step culture system is required to support further development. Ovarian follicles can be mechanically or enzymatically isolated from the cortex and then cultured for further development [38]. In human, considering the toughness of ovarian cortex, mechanical isolation of intact primordial follicles is difficult and enzymatic digestion is more appropriate.

For isolated follicles culture, two approaches have been proposed including two- and three-dimensional culture systems. In two-dimensional culture system, referred to attached follicle approach, concurrent with follicular development the proliferating granulosa cells attach to the plate and migrate away from the oocyte. Therefore, the granulose cells are not able to support properly the follicle development because of their spatial disarrangement. In contrast, in three dimensional culture system, the follicle is able to maintain its three-dimensional architecture as the follicular growth occurs radially from the center of the follicle. This structure provides mechanical support which is essential for maintaining cell–cell contacts and paracrine signaling [49].

There are various materials to maintain 3D architecture such as natural (e.g. collagen) and synthetic (e.g. alginate) hydrogels. Alginate encapsulation due to its flexibility and partial rigidity can mimic the extracellular matrix. This 3D architecture besides facilitating molecular exchange between the follicle and the culture medium can provide the proper conditions for cell proliferation and antrum formation [50,51].

Two dimensional follicle culture

Although this system has been successful in production of live murine pups, it has not been successful in bovine, ovine, and human species. In human and large animals to maintain the communication between the oocyte and granulosa cells, which is necessary for follicular development, is more difficult due to considerable size of follicle and the longer time required to culture. Two-dimensional culture of human follicles has shown the high level of follicular atresia due to loss of connections between the oocyte and the granulosa cells [52,53]. In mouse, two-step culture system, including an 8-day culture of whole newborn ovaries followed by culture of isolated secondary follicles and the subsequent culture of obtained oocytes has resulted in production of normal offspring [54].

Three dimensional follicle culture

Experience with primordial and primary follicles: The two-step primordial and primary follicles culture in serum free media covering 6 days culture of human ovarian cortical strip followed by 4 days culture of isolated follicles resulted in formation of antrum in cultured follicles [38].

In 3-dimentional culture system, among different contributing factors, the type and rigidity of follicular extracellular matrix by maintaining the connection between oocyte and granulosa cells and regulation of numerous cellular processes has an important role in follicle development. Seven days culture of frozen-thawed human primordial follicles in alginate hydrogel 1% led to an increase in follicle size with survival rate of 90% [55]. Long term culture of ovine primary follicles in fibronectin-coated wells in serum-free medium resulted in follicular progression to the secondary follicle stage [56]. Encapsulating the macaque primary and secondary follicles in alginate and fibrin alginate promoted the follicle development into antral stage. In between, the culture of secondary follicle in alginate yielded an MII oocyte which after fertilization could further develop to morula stage. Depends on developmental stage of follicle, the type of scaffold has an important effect on subsequent follicle development [57]. Culturing macaque primordial follicles in different concentrations of alginate demonstrated 0.5% alginate could maintain the integrity of cultured follicles for up to 3 days, while the integrity was lost after 6 days. In contrast, follicular integrity could be maintained in 2% alginate up to sixth day. Therefore, in order to culture macaque primordial follicles, a more rigid environment was needed to support follicle growth in vitro [58].

In between, hormones and growth factors through endocrine, paracrine, and autocrine mechanisms have major role in follicle development. In bovine, primary follicles culture in presence of gonadotropins and growth factors during 21 days has optimized the culture system to support follicle growth to antral stage [59]. Considering to the paracrine mechanism, it would be expected that group culture of follicles could better support the follicle growth compared to single culture system. In vitro culture of sheep primordial follicles in higher densities (50 or 100 lectin-aggregated follicles per well) has significantly increased the diameter and survival of oocytes and induced granulosa cell differentiation [60]. In mouse, group culture of primary follicles has increased the growth and survival of follicles leading to antral follicles formation containing meiotically competent oocytes [61].

Any follicular growth system should be able to promote quiescent primordial follicles to grow within ovarian cortical tissue. To this end, and considering the negative regulatory effects of PTEN and FOXO3, as inhibitors of primordial follicle activation, application of their inhibitors may promote the growth of human and mouse follicular reserves [62,63]. It has also been established that inhibition of mTOR, mammalian target of rapamycin, may decrease human primordial follicles activation, leading to oocyte loss in growing follicles [64].

Experience with preantral follicle: Until recently the work has focused on secondary follicles which are less abundant in adult ovaries. Factors controlling in vitro follicular development are including extra cellular matrix (ECM) and culture condition that regulate numerous cellular process.

Structural and biochemical design of the ECM has an influence on growth of follicles. Alginate has been used successfully in preantral follicle culture. Culture of mouse encapsulated secondary follicles within alginate matrix could support follicle development and resulted in oocyte maturation required for fertilization and live birth [65,66]. Antral follicles have also been achieved through 30 days culture of human fresh secondary follicles in alginate in the presence of FSH [50]. Macaque secondary follicle culture in alginate yielded an MII oocyte that following IVF could cleave and reach the morula stage [57].

Fibrin alginate can also be used in preantral follicle culture. As the follicle expands it can produce proteases which in turn through fibrin degradation lead to the reduction of compressive force and support volume increase concurrent with follicular growth. Culture of mouse secondary follicles in alginate and fibrin alginate showed that the rate of meiotically competent oocytes produced by culture in fibrin alginate was greater than alginate alone [51]. The progression of mouse follicles to antral stage in fibrin alginate after aprotinin removal indicate that delay in fibrin degradation by protease inhibitors may be suitable for smaller follilcles that require longer culture time [67]. Semidegradable fibrin-alginate matrices allowed the growth of baboon preantral follicle to the antral stage in an FSH-independent manner [68]. Apart from commonly used matrix (alginate), the application of hyaluronan, in mouse, could increase the survival rate and germinal vesicle breakdown [69].

In follicle culture, the ovarian cycle stages during which follicles are collected as well as the physical properties of the matrix are important. Culture of monkey secondary follicles throughout 30 days showed the higher survival rate and growth rate in follicles obtained from prepubertal and adult monkeys, respectively [70]. In another study in monkey, culture of follicles in alginate scaffold, obtained during early follicular phase had a higher survival rate than those collected during the luteal phase [71]. In mouse, 0.25% and 0.5% alginate could better support the growth of follicles and antrum formation compared to the higher alginate concentrations despite the lack of difference in survival rates and oocyte developmental competence [72].

Hormones and growth factors in preantral follicle culture: Besides the impact of used system on follicular culture, the contents of culture media including gonadotropins and growth factors are effective in follicular development.

Concerning the effects of gonadotropins on follicular culture, 6-days culture of sheep follicles in the presence of FSH and thyroxin has greatly improved the proportion of matured oocyte [73]. In prepubertal monkey, the culture of follicles in presence of LH after 30

days had a positive effect on follicle diameter [70]. Interestingly, while the application of FSH, alone, had a positive effect on follicular growth, medium supplementation with both FSH and LH had a lower effect [71]. No follicles were survived after forty days culture of alginate-encapsulated primate secondary follicles in the absence of rhFSH [74]. In macaque, the highest survival rate of secondary follicles was observed in presence of high or medium FSH concentrations. FSH had different effect on follicular steroidogenesis based on its concentration. While, steroid production by growing follicles was stimulated in the presence of high FSH concentrations, this production at low FSH concentrations was promoted by LH [75]. In baboon, FSH even had a negative influence on preantral follicular health by disrupting the integrity of oocyte and cumulus cells connections so that the growing follicles could produce MII oocytes with normal spindle structure in the absence of FSH [68]. From above, it could be concluded that despite the positive effects of FSH on preantral follicular development, in many species, there is an exception so that in baboon, it had a negative effect on preantral follicular growth.

In caprine, while the growth of both small and large follicles was stimulated by the presence of growth factors, FSH could stimulate only the development of small but not large preantral follicles [76]. The culture of buffalo preantral follicles in the presence of growth factors and FSH resulted in follicle survival for up to 20 days and early antrum formation. In meantime, IGF-I supplementation had a significantly positive effect on growth and survival of cultured follicles. However, the results were inversed when IGF-I was accompanied with bFGF [77]. In sheep, supplementation of preantral follicles culture medium with growth factors and hormones (ITS, IGF-I, insulin and GH) could properly support follicular development so that IGF-I in combination with GH had the best effect. Though, the cultured oocytes in any concentration of TGF failed to develop to MII stage [78]. Human isolated secondary fol¬licles undergo differentiation after a 4 days in vitro culture in the presence of activin [38]. In feline, 14-days culture of follicles in the presence of activin A promoted granulosa cell proliferation and preantral follicles growth and viability whereas no beneficial effects was observed by thyroxin supplementation [79]. There is also evidence indicating the effect of nitric oxide on preantral follicle culture. As shown, nitric oxide depends on its concentration could play a dual role on follicle growth and survival, whereas the lower doses could stimulate the follicle survival, growth, and antrum formation, the higher concentrations had an inhibitory effects [80]. Moreover, group culture of goat preantral follicles, increased the rates of follicular survival and growth as well as the number of grown oocytes and meiosis resumption [81].

Besides the content of culture medium, the culture condition, e.g. oxygen tension, has an effect on follicle development. It was found that 20% O_2 was more efficient than 5% in goat preantral follicular survival and growth and resumption of oocyte meiosis throughout 30 days culture [82]. In macaque, the effects of various concentrations of fetuin and O_2 on encapsulated secondary follicle showed the highest follicular survival rate in the presence of 1 mg/ml fetuin at 5% O_2 [75].

Follicle co-culture

Co-culturing of buffalo preantral follicles with somatic cells led to the higher growth rate and survivability [83]. In mouse, follicles co cultured with stormal cells grew more with the greater survival rate [84]. Co-culture of mouse alginate encapsulated follicles with mouse embryonic fibroblast (MEF) promoted the growth of secondary and primary follicles to antral stage after 14 days while the follicles were degenerated, within 6-10 days, in the absence of fibroblasts. In between, survival rate of 100-µm follicles was significantly higher than 70-µm follicles [85]. The presence of MEF and media supplementation with activin A especially when used together had a positive effect on growth, survivability, and hormonal production of preantral follicles. However, no significant differences were observed in antrum formation, ovulation rate, and subsequent embryonic development [86].

Follicle development evaluations: There are numerous criteria which might be considered in assessment of follicular development including follicule survival and growth, steroidogenesis, production of paracrine/autocrine factors, the ability of oocyte to mature, and the pattern of genes expression. Follicle survivability can be identified through assessment of basement membrane intactness, presence of granulosa cells, and the presence of round and centrally located oocyte with a visible zona pellucida. The in vitro follicular production of endocrine factors such as progesterone (P4), androstenedione (A4), and estradiol (E2), as well as paracrine/autocrine factors, such as anti-Müllerian hormone (AMH) and vascular endothelial growth factor (VEGF) that positively correlates with follicle growth and development, might be considered as other criteria. The nuclear maturational status of oocytes derived from in vitro antral follicles following 34 h hCG treatment can be considered as another criterion. In performed studies, no difference was observed in gene expression between the in vitro and in vivo-developed antral follicles in major steroidogenic enzymes except for the upregulation of low density lipoprotein receptor gene that might be related to the prolonged exposure to exogenous FSH. TheVEGF downregulation and anti-apoptotic factors upregulation in in vitro-developed primate antral follicles compared to in vivo-derived ones might indicate the influence of culture conditions on gene expression [87].

Conclusion

The application of ovarian tissue grafting or culture of isolated follicles followed by in vitro production of embryos has their own benefits and defects. Nonetheless, autotransplantation of thawed ovarian tissue has been the only method that resulted in birth of healthy baby. The major drawback of this method, probable re-introduction of cancer cells, has forced the investigators to think of other methods such as multi-steps ovarian follicular culture. In this method despite the remarkable reduction in risk of cancer cells transmission, because of our inadequate knowledge about follicular development and its complexity, no proper system has been fully optimized to meet all challenges posed to extended human follicle growth in vitro. Therefore an introduction of a practical and reliable method has remained to be further investigated.

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