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The Beneficial Effect on Improving the in Vitro Maturation of Immature Oocytes Using 3D Scaffolds

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ABSTRACT: The procedure of developing and maturing immature eggs outside of the body is named in vitro maturation. It is a different way to stimulate hormones. 3D scaffolds are principally essential becautilize they provide oocyte culture a three-dimensional shape that makes the microenvironment more resemble what arises in the body. 3D scaffold-based IVM is a safer method to keep your fertility that helps individuals with cancer and other illnesses that impair the ovaries. Finding out more about how 3D scaffolds impact the growth of oocytes may make ART treatments like in vitro fertilization (IVF) operate better. Reducing risks by lessening the risks of ovarian hyperstimulation syndrome (OHSS), this technique makes ART therapies safer. Utilizing 3D scaffolds is a novel method in reproductive medicine that might transform the way oocytes are grown and kept. This review investigates new concepts in assisted reproductive technology that might transform how we maintain people fertile and make fertility treatments better.

KEYWORDS: In vitro maturation, immature oocytes, 3D scaffolds, assisted reproductive techniques.

INTRODUCTION

1. In vitro maturation of oocytes

Controlled ovarian stimulation (COS) and later in vitro fertilization (IVF) are the furthermost common ways to develop oocytes in assisted reproductive procedures. The controlled ovarian stimulation approach is based on hormonal stimulation (1). This treatment offers a woman hormones such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) to help a lot of ovarian follicles develop at once. We employ hormone level testing and ultrasound imaging to keep a close check on how the patient's ovaries are doing. Dose of human chorionic gonadotropin (hCG) is administered after the follicles are completely developed, This starts the latter stage of oocyte maturation. Then, a little operation termed transvaginal oocyte extraction is done to obtain the mature eggs (2).

In the lab, sperm fertilizes the developed oocytes. This may be done by traditional IVF, where sperm and eggs are mixed in a dish, or using intracytoplasmic sperm injection (ICSI), when a single sperm is injected directly into an egg. In the lab, fertilized eggs turn into embryos instead. The best embryos are chosen and put into the woman's uterus, where they may implant and start a pregnancy (3, 4), In reality, the conventional way of maturing oocytes has its own problems, such as the danger of ovarian hyperstimulation syndrome (OHSS). Hormonal stimulation in COS may cautilize OHSS, a serious and perhaps life-threatening illness that cautilize s the ovaries to swell, fluid to build up, and pain in the abdomen. This danger is particularly significant for women whose ovaries are very sensitive (4, 5). Second the COS may be stressful on both the body and psyche since it needs daily hormone injections, numerous monitoring sessions, and an intrusive surgery to extract the eggs (6). Third standard IVF with COS is too expensive for some individuals since it includes drugs, monitoring, and lab testing. Fourth, typical ways of maturing oocytes and preserving fertility may not work for cancer patients who require therapy right immediately becautilize they take too long to get the ovaries going. Finally with conventional IVF, the quality of the embryos might be different, which can make it less likely to work and lead to multiple pregnancies if more than one embryo is transplanted (7).

1.1. Methods to enhance maturation and development of immature oocytes

Maturation and development of immature oocytes are crucial parts of ART and maintaining your fertility. There have been a number of ways to speed up the growth, and maturity of immature oocytes, which has improved outcomes in reproductive medicine (8).

1.1.1. In vitro maturation (IVM)

IVM is a typical way to cultivate immature oocytes in a lab until they are ready to be utilized. This method minimizes the requirement for hormonal stimulation which lowers the chance of opposing effects and problems that might emerge with standard

superovulation treatments (9). IVM is particularly relevant for persons with polycystic ovarian syndrome (PCOS) or cancer when the hazards of hormonal stimulation are a worry (10). IVM, is a means to assist immature oocytes grow up and become ready for fertilization in a controlled lab environment by pulling them out of tiny antral follicles at the pre-selection stage. The best thing about IVM is that it helps people keep their fertility, IVM could help individuals stay fertile which is one of its finest features (11). People with cancer or other circumstances where utilizing hormones to develop oocytes may not be safe might utilize IVM instead. You may harvest immature oocytes and grow them in a controlled lab environment, which retains them viable for later utilize (12). Also typical ovarian stimulation for in vitro fertilization (IVF) may trigger OHSS, which is a dangerous disorder that makes the ovaries enlarge and fluid build up. IVM eliminates the requirement for high-dose hormone stimulation, which minimizes the risk of OHSS and related problems. IVM may also cost less than traditional IVF. It is simpler for more folks to receive since it doesn't need as many drugs and checkups (13). IVM typically has a shorter treatment cycle than standard IVF since it doesn't include the extended period of hormonal stimulation. This may benefit people who wish to get to fertility therapy quicker (14). IVM on the other hand, has a huge problem: it doesn't work as well. IVM has a big problem: it doesn't work as well as regular IVF. In a controlled lab environment the maturation procedure may produce the oocytes of inferior quality which might make it less probable that fertilization and pregnancy would happen.

Researchers are currently researching at the long-term consequences of IVM since it is a novel procedure and there isn't a lot of clinical experience with it now. Becautilize of this, some individuals may not always be sure how secure and utilize ful IVM , it's vital to remember that IVM may not work for everyone. It depends on variables like the patient's age and the quality of the immature oocytes that were obtained. It might be hard to foresee what will happen (15).

1.1.2. Follicle culture

In human follicle culture, immature eggs are cultured within their follicles. This approach helps oocytes grow in a way that is comparable to the way they would in a normal ovarian microenvironment (16). Follicle culture is a new way of doing things in reproductive biology, and ART that helps preserve fertility, learn more about how the ovaries operate, and make infertility therapy better (17). In a lab this new approach grows ovarian follicles, which are the tiny fluid-filled structures in the ovary that store immature eggs. Follicle culture lets scientists and clinicians analyze and manipulate the intricate processes of oocyte growth, maturation, and fertilization in a manner that is always changing. Follicle culture is quite popular now since it could be able to aid with a lot of reproductive issues (18). It appears like it might help women with poor ovarian reserve or cancer patients who are having chemotherapy or radiation treatment for example, whose ovarian function may be at danger. It is feasible to maintain these important reproductive cells for later utilize by growing and developing oocytes in a controlled environment outside of the body. Follicle culture also helps scientists understand more about how the ovaries work which is quite intricate (19). It tells us how oocyte development is regulated, what follicular cells do, and what makes oocytes less healthy. This information is incredibly helpful for making IVF and other fertility therapies better and for finding novel methods to treat infertility and reproductive problems. Follicle culture, like any new procedure has its advantages and downsides that must be carefully considered about while trying to become pregnant and keep your fertility (20). One good thing about follicular culture is that it helps keep people fertile. Follicle culture is great becautilize it can help keep individuals pregnant, particularly women who are having treatments like chemotherapy or radiation that might harm their ovaries. Patients may still have biological children in the future by cultivating and developing oocytes in vitro (21). Follicle culture is also a great tool for scientists to understand about the complex processes that take place when oocytes grow and mature. We could learn more about how the ovaries operate from this research, and it might even lead to novel ways to help individuals become pregnant (22,23). Follicle culture also makes it possible to make reproductive treatments more individualized. It helps clinicians come up with individualized treatment approaches for infertility based on the patient's specific ovarian physiology and reproductive problems (24, 25). Even if it has a lot of wonderful things about it, there are some drawbacks with it. For example, follicle cultivation is a difficult and time-consuming procedure. It costs a lot since you require certain instruments and know-how. Becautilize of the expense, some people may not be able to acquire this. Follicle culture may also work at various levels, and not all cultivated follicles become mature oocytes that can be fertilized (26). The patient's age and the amount of eggs they have remaining are two elements that affect their odds of success. Follicle culture also brings up crucial moral considerations that need to be carefully thought about, such as the utilize of young oocytes and the prospective repercussions on human cloning, Follicle culture isn't accessible at most reproductive clinics which makes it challenging for many patients who may benefit from this procedure to acquire it (27–32).

1.2. Bioprinting-based methods

Bioprinting-based approaches for three-dimensional (3D) in vitro maturation are a brand new topic in the fields of assisted reproductive technology and fertility preservation. This novel procedure utilize s 3D bioprinting technology, which is very precise, and, the process of oocyte maturation, which is quite complicated. It could make in vitro maturation (IVM) more successful and transform the area of reproductive medicine (33–38). In the past, conventional ways of maturing oocytes, which is an essential aspect of reproductive therapies, have been employed. However, these strategies don't always provide the optimal microenvironment for the development of oocytes (39,41). Bioprinting-based approaches come into play, which let you make complicated 3D structures

exactly and over and over again. Researchers and surgeons may utilize this technology to make unique scaffolds and habitats that are quite similar to the natural ovarian microenvironment. This makes the process of maturing much faster (42). Using bioprinting to do 3D in vitro maturation has a lot of advantages. It offers the cumulus-oocyte complex a safe and regulated place to develop which helps the oocyte grow in the best manner possible. This strategy seeks to make oocytes better and speed up the maturation process by mimicking the physiological signals and interactions that happen in the follicular environment (43). This new approach might also help us understand more about the difficult process of oocyte formation and make it easier to keep people from losing their fertility. Bioprinting technology may help researchers find new techniques to understand more about the processes that influence the maturation of oocytes, over time this will lead to greater success in assisted reproduction and maintaining fertility (44). But, like any new technology, it has its own good and bad points that you should think about carefully. Bioprinting lets you create 3D microenvironments for oocyte maturation that are incredibly precise and can be changed to fit your needs. This degree of precision lets researchers better copy the natural environment of the ovaries. This might make maturation go better (45). Bioprinting can create the physiological signals and interactions that occurs in the follicular environment. Bioprinting-based methods try to make oocytes better. This might make oocytes better so that they can be fertilized and utilized to make embryos. 3D in vitro maturation based on bioprinting is another fantastic technique to learn about the difficult process of oocyte development. It lets scientists study the laws that govern maturation, which helps them understand more about how reproduction works (46). But bioprinting-based methods have their limits, which are shown by bioprinting-based methods. People who work in bioprinting need to know a lot about both biology and engineering. It may be hard and require a lot of resources to set up and maintain bioprinting technology functioning. Also the equipment and materials needed for bioprinting might be highly costly. This could make it tougher for certain clinics or research organizations to access this technology (47). Also like with any new technology, there are ethical issues with bioprinting-based methods, especially when it comes to reproductive medicine. These include questions about how bioprinted structures will be utilize d and what might happen that wasn't planned. Ensuring the safety and long-term effects of bioprinted structures in reproductive utilize s is also an ongoing challenge. There is still a lot of new information coming out about how safe and effective these procedures are (48).

1.3. Three-dimensional (3D) scaffolds

IVM of immature oocytes using 3D scaffolds is a new and exciting method in the field of ART that has a lot of potential benefits (49). This new method utilize s a three-dimensional framework to grow and mature immature oocytes outside of the human body. Using 3D scaffolds to mature oocytes may have a number of advantages over more traditional methods (50–51). IVF usually utilize s hormones to mature oocytes, but IVM with 3D scaffolds is a different way to do it. This method could lower the risks that come with hormonal stimulation, like ovarian hyperstimulation syndrome (OHSS) (52–54). It also opens up new ways to keep fertility, especially for cancer patients and people with conditions that affect ovarian function. Over the years the field of assisted reproduction and fertility preservation has changed a lot. This is becautilize people want methods that are safer, more effective, and more focutilize d on the patient (55–56). One thing that really interests me is how IVM can help immature oocytes mature outside of the body. This method has shown a lot of promise in solving a lot of the problems that come up with traditional IVF methods (56,57). The utilize of 3D scaffolds (58) is a revolutionary new development in the field of IVM that has come about in the last few years. These three-dimensional architectural structures have gotten a lot of attention as a new and very creative way to help immature oocytes grow up. Three-dimensional scaffolds create a microenvironment that closely resembles the complex structure of natural ovarian tissue unlike traditional two-dimensional culture systems. The move from two-dimensional to three-dimensional culture systems has created new ways to make IVM procedures safer, more efficient, and more patient-friendly (59,60).

This article will look closely at the different types of 3D scaffolds that could be utilize d to help immature oocytes mature in vitro. It will also talk about how important this new method is, what benefits it could have and, what it means for the future of assisted reproduction and fertility preservation. We can learn more about how this cutting-edge technology is changing the field of reproductive medicine by looking into the principles and benefits of 3D scaffold-based IVM.

1.4. Types of 3D scaffolds

The utilize of polymer biomaterials has gotten a lot of attention and looks like it could be utilize ful in a number of reproductive settings. Biocompatible and versatile polymer biomaterials are natural or man-made polymers that have been designed to be these things (61,62). Researchers are looking into their ability to help ovarian follicles grow and develop outside of the body. Ovarian follicles are very important for female fertility becautilize they hold immature eggs. The ability to culture these follicles in vitro opens up new ways to deal with infertility and keep fertility (63). Polymer biomaterials can be utilize d in in vitro follicle culture systems in many ways such as making three-dimensional environments that look like the natural ovarian microenvironment. These biomaterials can act as scaffolds to help follicles grow, oocytes mature, and women who are getting medical treatments that might hurt their ability to have children stay fertile (64). This new method not only shows promise for treating infertility but it also helps us learn more about how follicles develop and how reproduction works. The utilize of polymer biomaterials in in vitro follicle culture systems is a dynamic and growing area of research that could change the face of reproductive medicine and give new hope to people who are having trouble getting pregnant (65). In this context we will look at the benefits and utilize s of different types of

polymer biomaterials for in vitro follicle culture systems. We will also talk about the research that is still going on and what it means for preserving and treating fertility.

1.4.1. Natural polymers

1.4.1.1. Alginate

Alginate (ALG) is currently the most popular biomaterial for growing follicles in a lab. ALG is a linear polysaccharide that comes from bacteria or brown algae. It is known for being very hydrophilic, biocompatible, and not harmful to cells. Its flexibility to take various forms, such as microspheres, sponges, foams, elastomers, and hydrogels, has significantly broadened its application in tissue and regeneration engineering (65,66). When cross-linked with calcium ALG creates hydrogels and gives the support for pre antral follicles of all mammals' structural. Due to this criterion of ALG the follicles can easily become implanted under physiological settings. In order to preserve the three-dimensional structure of the follicles, a hydrogel's scaffold in a three-dimensional system needs to be both strong and flexible enough to encourage the creation of oocytes, the proliferation of somatic cells, and the production of antrums (67-70).

Different concentrations of ALG, ranging from 0.125% to 3%, have distinct impacts on in vitro moutilize follicle culture. Research findings indicate that higher ALG concentrations are favorable for maintaining the 3D morphology and structure of follicles, while lower concentrations of ALG hydrogels are more supportive of follicle growth and development. Additionally, lower ALG concentrations facilitate the production of progesterone and estradiol (71,72). promotes the growth and development of follicles, Dorati et al. (2016) identified the optimal approach by combining 100 mM CaCl2 with 0.25% ALG through cross-linking (73). Xu et al. showed in 2009 that it was possible to grow secondary primate follicles in vitro within a three-dimensional matrix. This, was the first time the ALG method was utilize d to protect primate tissue architecture (74). Hornick et al. say that primate follicles grown in 2% ALG had better shape and survival rates than those grown in 0.5% ALG. Studies have also shown that adding androgens and follicle-stimulating hormone (FSH) to the 0.25% ALG hydrogel system has made primate follicles more likely to survive and grow (74–77). Despite its potential for 3D culture ALG exhibits limited matrix angiogenesis capability and insufficient biological viscosity. Mainigi et al. observed disrupted meiotic spindle assembly and poor developmental capacity in oocytes derived from the ALG system, to address these challenges, some researchers propose enhancing follicle growth and overall survival rates by incorporating cell adhesion molecules like arginine-glycine-aspartic acid, fibronectin, and laminin. This addition is recommended during the establishment of an in vitro culture system to counteract the biological inertia of ALG hydrogel, which may otherwise hinder cell adhesion and proliferation (78).

Xu et al. discovered that 1,25-dihydroxy vitamin D3 (VD3) is beneficial for primate follicular development within the 0.25% ALG hydrogel system. Lower doses of VD3 were observed to enhance the survival of preantral follicles and sustain Anti-Mullerian Hormone production in antral follicles. Conversely, higher doses of VD3 were found to promote the growth of antral follicles (77). Studies have also shown that adding hesperidin (Hesp), Panax ginseng extract (PGE), vascular endothelial growth factor (VEGF), mesenchymal stem cells (MSCs), platelet-rich plasma (PRP), adipose-derived stem cells (ADSCs), bone morphogenetic protein-4 (BMP-4), and other things to the ALG hydrogel system helps moutilize follicles grow. In short, the development of follicles depends on more than just the concentration, viscosity, hardness, and density of ALG. It also depends on the nutrients that are in the ALG hydrogel system (79).

1.4.1.2. Extracellular matrix

Collagen, non-collagen, elastin, aminoglycan, proteoglycan, and other things make up the extracellular matrix (ECM). Synthetic ECM has the potential to be a utilize ful material in tissue engineering (80). The hardness of the extracellular matrix (ECM) affects how well oocytes mature and how long follicles live. Optimal conditions for the 3D culture of follicles, as well as efficient hormone and nutrition exchange are achieved with a low-hardness ECM. In terms of hardness the ECM hydrogel exhibits lower mechanical strength (MS) and storage modulus (SM) compared to the ALG hydrogel (81). Kim et al. found that, based on the mechanical characteristics of the extracellular matrix (ECM), the ECM hydrogel outperforms ALG in mice regarding preantral follicular antrum formation, oocyte maturation, chromosome/spindle formation and, hormone secretion (82). Sadr et al. found that ECM-ALG composite scaffolds, abundant in ECM components and closely resembling the physiological conditions of the ovary exhibit superior follicular survival and maturation rates compared to FIB-ALG composite scaffolds. This is attributed to their ability to establish a more favorable environment for follicular development (83). Pors et al. demonstrated, for the initial time the viability of isolated human follicles within a decellularized human scaffold. Their success in grafting reached a 25% rate three weeks post-procedure (84). The applications of ECM components in in vitro culture of immature oocytes are outlined below.

1.4.1.3. Collagen

Collagen (COL) possesses unique mechanical, biological, and physicochemical characteristics, making it the predominant and extensively distributed protein in mammals. Widely employed in biomedicine, COL serves as an elastic biomolecule within the extracellular matrix (ECM) featuring a triple helix structure (85). COL hydrogel exhibits minimal immunogenicity and participates in diverse cellular biological processes. An exceptional characteristic of this hydrogel is its transparency enabling the observation of the complete follicular growth process through an inverted phase-contrast microscope (86). Following a 12-day in vitro culture

of moutilize preantral follicles using 1-7% COL hydrogel, Joo et al. investigated parameters such as follicular survival rate, estradiol and progesterone secretion, and oocyte meiosis. Their findings indicated that the optimal concentration for follicle 3D culture is within the range of 3-5% COL (87). Although the incorporation of MSCs into the COL hydrogel enhances follicular survival and promotes oocyte maturation, it proves ineffective in preserving the three-dimensional architecture of follicles and preventing the migration of cumulus cells (88). In a groundbreaking discovery. Su et al. revealed that the incorporation of adipose-derived stem cells (ADSCs) into soluble COL scaffolds stimulates follicular development and hormone secretion. This presents an innovative therapeutic approach for addressing premature ovarian failure (89). Following the transplantation of soluble collagen (COL) scaffolds containing umbilical cord mesenchymal stem cells (UC-MSCs) into mice with ovariectomies, several outcomes were observed. These, included the activation of the PI3K-AKT pathway, phosphorylation of FOXO3a and FOXO1, activation of primordial follicles, an elevation in estradiol concentration, and an increase in the number of antral follicles. But for in vitro culture it is important to take follicles out of the COL hydrogel so they can be looked at more closely. This step could hurt the follicles, so more research is needed to find a workable solution (90).

1.4.1.4. Hyaluronic acid

Hyaluronic acid (HA) which is an important part of the extracellular matrix (ECM), could be a good biomaterial for growing follicles in a lab. This is becautilize it works well with living tissues, breaks down naturally and has an amazing ability to regenerate blood vessels. The HA hydrogel is a flexible scaffold in the field of tissue engineering. It is utilize d in cell cultures that include mesenchymal and hematopoietic stem cells, which shows that it can be utilize d in a variety of ways and is effective at supporting different cellular processes (91). It is the best biomaterial for tissue engineering becautilize it helps mesenchymal and epithelial cells move and become specialized. These cellular processes are very important for putting on bandages and fixing tissues in general (92). Desai et al. made a groundbreaking discovery they found that using HA hydrogel is effective for growing follicles in a 3D environment. They discovered that a concentration of 3 mg/ml of HA creates the best conditions for follicles which helps keep their complex three-dimensional structure (93).

1.4.1.5. Fibrin

Thrombin and fibrinogen combine to make fibrin (FIB), a natural polymer with a molecular weight of 360 kD. It has a lot of elasticity and viscosity, breaks down easily, can help new blood vessels grow, and has a mild inflammatory response. Due to its distinctive porous structure, the fibrin scaffold proves optimal for supporting cell adhesion, proliferation, and differentiation (94). It can function as a system for releasing growth factors, rendering it an excellent choice for tissue engineering. The fibrinogen hydrogel-wrapped follicles, through the action of proteolytic enzymes, can degrade the matrix and extricate the follicles. Consequently fibrinogen is generally not exclusively employed for in vitro follicle culture (95). Creating a transplanted artificial ovary with fibrin, Luyckx et al. observed, for the first time, the successful survival and development of moutilize preantral follicles after transplantation. This occurred within a matrix featuring reduced concentrations of fibrinogen and thrombin (96). Studies investigating the influence of the FIB matrix on primate primary follicles cultured separately have documented the in vitro growth and maturation of these follicles. Notably, the FIB matrix was found to enhance the development of macaque primary follicles specifically during encapsulated 3D culture (97). In 2016, Paulini et al. conducted research indicating that fibrin holds potential as a favorable substance for crafting artificial ovaries, fostering the viability and growth of human follicles (98). The Chiti group conducted research to explore the optimal ratio of fibrinogen to thrombin. The F50/T50 ratio (fibrinogen 50 mg/ml, thrombin 50 IU/ml) emerged as the most closely resembling the ultrastructure and hardness of the human ovarian cortex among various fibrin matrix concentrations. This ratio was identified as the optimal concentration for in vitro follicle culture (99). Enhancing the FIB hydrogel system with platelet lysate (PL) has the potential to elevate both graft vascularization and the survival rate of follicles (100). Following brief transplantation, preantral follicles have the ability to persist and undergo maturation into antral follicles. This capability arises from the complete embedding of moutilize preantral follicles within the FIB matrix, offering a conducive and natural milieu for the survival of the follicles (101). Despite the FIB matrix exhibiting low matrix hardness and suboptimal preservation of follicle 3D structure a combined system of FIB and ALG proves more effective in producing fertile oocytes than a singular ALG system. This is achieved by providing follicles with a dynamic mechanical environment (102).

1.4.2. Synthetic polymers

Due to their distinctive properties, natural polymers pose specific difficulties in biomedical applications, notwithstanding their potential advantages in fostering cell adhesion and proliferation. For example, controlling the mechanical attributes and degradation rate of natural polymers is challenging, potentially leading to an immunological response (103,104). Synthetic polymers can be more readily altered to exhibit a broader spectrum of mechanical and chemical characteristics compared to natural polymers (105). Artificial polymers boast extended durability and the capacity for mass production in a single batch. On the other hand, natural polymers, while lacking crucial cell adhesion molecules, are bioactive substances that are easily integrated (106).

Nevertheless the presence of organic solvents in certain synthetic polymers can lead to transplant rejection due to their inability to mimic the natural polymer's capacity in supporting cell adhesion migration, proliferation, and differentiation. Presently, poly ethylene glycol (PEG) serves as the synthetic matrix employed in 3D follicular culture, with its hydrogel being extensively

researched and recognized as the most effective synthetic matrix for this purpose (106, 107). Due to its infrequent tendency to cautilize inflammation and possessing a low inflammatory index, PEG stands out as a commonly utilized material in islet immune isolation therapy. Its applications extend beyond stabilizing blood sugar levels, also prolonging the survival time of islet grafts by mitigating the immune response to the graft. PEG-encapsulated immunoimmunization capsules offer a potential solution for implantation in cancer patients. This approach aims to prevent the reimplantation of tumor cells during tissue transplantation while simultaneously restoring ovarian endocrine function (108, 109).

Kim and colleagues made a groundbreaking observation, marking the first instance where they identified the capability of PEG hydrogel to serve as a framework for the three-dimensional (3D) cultivation of follicles. This novel finding highlights PEG hydrogel's ability to maintain the structural integrity of both somatic and oocyte components, simultaneously fostering the growth of follicles (110). Nam and colleagues found that manipulating both the concentration and molecular weight of PEG enables the control of stress relaxation in the ALG-PEG hydrogel when PEG is linked to ALG. This suggests that altering the PEG parameters influences the stress relaxation properties of the hydroge (111).

CONCLUSION

The primary goal of the 3D follicle culture system is to promote follicular development and generate mature follicles, serving as a foundation for research in follicular toxicology, restoring fertility in cancer patients, and enhancing the well-being and life expectancy of women with ovarian aging. Additionally this system finds applications in follicular biology research, wildlife conservation, and evaluating the effects of isolation and cold preservation on follicular survival. To improve in vitro culture outcomes, further consideration should be given to understanding the fundamental processes governing oocyte maturation both in vivo and in vitro, aiming to yield fertilizable oocytes.

Enhancements in in vitro culture, including the incorporation of nutritional components, oocyte- and somatic cell-secreted cytokines, and the selection of scaffolds mimicking natural architecture, are expected to boost current culture results. Several issues in 3D follicular culture remain unresolved, including the need for comparative research on preservation techniques' effects on follicle quality and addressing ethical concerns surrounding artificial ovaries due to the distinct genetic traits of oocytes. Moreover, the polymer biomaterials in the 3D culture system should preserve physiological structure exhibit favorable histocompatibility, minimal inflammatory response, and neovascularization. Emerging technologies like 3D printing and creatively patterned fibrous scaffolds offer promising matrices for follicle growth. As we explore new biomaterials and hybrid in vitro culture systems, future challenges will emerge.

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