A review on biomaterials for ovarian tissue engineering

Arezoo Dadashzadeh[1,∫], Saeid Moghassemi[1,ƒ], Amin Shavandi[2,ǂ], Christiani A. Amorim[1,*]

[1]Pôle de Recherche en Gynécologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Avenue Mounier 52, Bte. B1.52.02, 1200 Brussels, Belgium

[2]BioMatter Unit-Biomass Transformation Lab (BTL), École Polytechnique de Bruxelles, Université Libre de Bruxelles, Campus du Solbosch - CP 165/61 Avenue F.D. Roosevelt, 50 1050 Brussels, Belgium

∫arezoo.dadashzadeh@uclouvain.be

ƒsaeid.moghassemi@uclouvain.be

ǂamin.shavandi@ulb.be

*Corresponding author:

Prof. Christiani A. Amorim

Pôle de Recherche en Gynécologie

Institut de Recherche Expérimentale et Clinique

Université Catholique de Louvain

Avenue Mounier 52, bte B1.52.02, 1200 Brussels, Belgium

E-mail: christiani.amorim@uclouvain.be

Tel: +32 (0)2 764 5287

Abstract

Considerable challenges in engineering the female reproductive tissue are the follicle's unique architecture, the need to recapitulate the extracellular matrix, and tissue vascularization. Over the years, various strategies have been developed for preserving fertility in women diagnosed with cancer, such as embryo, oocyte, or ovarian tissue cryopreservation. While autotransplantation of cryopreserved ovarian tissue is a viable choice to restore fertility in prepubertal girls and women who need to begin chemo- or radiotherapy soon after the cancer diagnosis, it is not suitable for all patients due to the risk of having malignant cells present in the ovarian fragments in some types of cancer. Advances in tissue engineering such as 3D printing and ovary-on-a-chip technologies have the potential to be a translational strategy for precisely recapitulating normal tissue in terms of physical structure, vascularization, and molecular and cellular spatial distribution. This review first introduces the ovarian tissue structure, describes suitable properties of biomaterials for ovarian tissue engineering, and highlights recent advances in tissue engineering for developing an artificial ovary.

Keywords

Ovarian tissue engineering; follicle; *in vitro* culture; 3D printing; ovary-on-a-chip

1 Introduction

Ovarian follicles are the mammalian ovary's functional units, consisting of an oocyte surrounded by granulosa cells and different types of extracellular matrices (zona pellucida, antrum, basement membrane, and theca matrix) [1, 2]. The firmly connected granulosa cells surrounding the oocyte are responsible for its nourishment and development and mediate the external signals during its maturation process [3]. Consequently, the 3D architecture of follicles with tight maintenance of granulosa cell and oocyte interactions is crucial for successful oocyte growth and maturation [4, 5].

In the 90s, *in vitro* culture of rodent ovarian follicles [6] established the framework for the possible *ex vivo* follicle development, which could aid women or girls with fertility-threatening diseases or treatments [7]. However, the conventional 2D culture systems showed to be inefficient in preserving the 3D spatial arrangement required by human follicles. The 2D culture resulted in immature oocytes, as the follicles adhered to the flat plastic bottom of the culture dish and lost their 3D structure and the connections between granulosa cells and oocytes [8, 9]. For follicles from large mammalian species and humans, the 3D cell culture systems revealed a better choice to preserve cell-cell and cell-matrix interactions and maintain the spherical shape of follicles [10, 11], and provide proper steroid production [12, 13].

Tissue engineering offers a multitude of 3D cell-seeded/encapsulated scaffolds for *in vitro* culture. Some of these 3D scaffolds can also be implanted into the target site to restore function, repair, or replace the damaged tissue or organ [14-16]. In this aspect, the ovarian tissue engineering concept presents a 3D system for folliculogenesis resumption, supporting follicle survival and growth [17]. An engineered ovary can be fabricated by encapsulating

ovarian follicles and cells into a 3D biomaterial (Fig. 1). In addition to the general requirement of biomaterials, which should be biocompatibility, biodegradability, and being able to exchange nutrients and waste, the biomaterial for ovarian tissue engineering needs to have a right balance between rigidity and elasticity to maintain follicle spherical shape and provide an appropriate substrate for its radial growth [18]. Indeed, when the diameter of follicles increases, they receive compressive forces from the biomaterial surrounding them that the magnitude of the forces depends on the elasticity of the biomaterials and the follicle size changes. For example, when the diameter of murine secondary follicles changes from 120 μm to 400 μm, their volume increases 37-fold. This volume alteration is much more in human follicles, increasing 4.7 million-fold volume when they develop from secondary (120 μm) to the pre-ovulatory stage (20 mm) [19]. The shear stiffness (G') of the normal human ovary could be around 1-2.5 KPa [20], and they have an average strain of 23.05 με (± 10.74) in the response of axial compression of a square wave (500 Hz, 50% duty) [21]. Therefore, recapitulating the natural ovary's mechanical properties is crucial when developing a suitable scaffold for the survival and development of follicles.

The conventional tissue engineering methods such as seeding cells in decellularized scaffolds, nanofibers, or encapsulating them in hydrogels have been somewhat able to mimic biological tissues. However, precisely recapitulation of the natural tissue complexities, cellular architecture, mass transfer, and oxygen diffusion remains a challenge for the traditional scaffold fabricating methods [22-24]. Nowadays, 3D biofabrication methods have been developed to construct complex biomimetic structures with high control over the geometry, ability to pattern biomolecular cues, and suitable mechanical properties [25, 26], overcoming tissue engineering challenges, such as vascularization [22] and spatiotemporal

control of cell-cell and cell-extracellular matrix (ECM) interactions [27]. This article aims to review natural and synthetic biomaterials used to promote ovarian follicle growth and describe recent advances in ovarian tissue engineering in terms of the 3D printing approach, microfluidics for encapsulation of follicles, and ovary-on-a-chip.

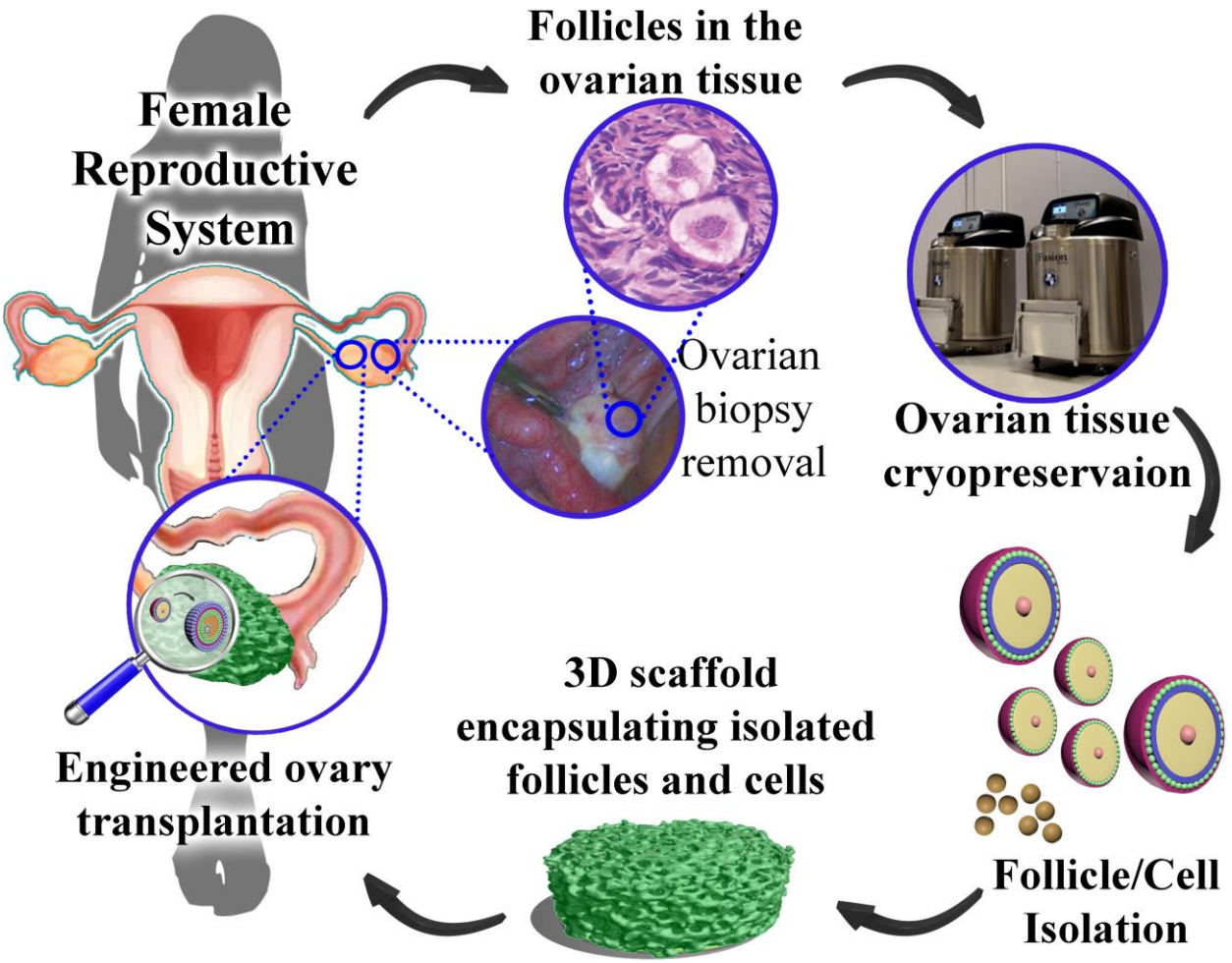


Figure 1. A schematic illustration of the fertility preservation strategy using ovarian tissue cryopreservation and ovarian tissue engineering. Before chemo- or radiotherapy, the ovarian tissue is removed and cryopreserved. Once the patient is cured, the tissue

fragments are thawed, and their follicles and cells are isolated and seeded/encapsulated in a 3D bioengineered scaffold. Finally, the construct is orthotopically transplanted.

2 The ovary

Ovaries are reproductive glands located beside the uterus. They are responsible for gamete production and hormone secretion [28, 29]. The ovary consists of four layers from the outer to the central section, respectively: the germinal epithelium layer, the collagenous connective tissue, the cortex containing preantral follicles, the medulla containing loose connective tissue, blood vessels, and large follicles [30]. Follicles are the primary units of ovaries that consist of an oocyte surrounded by granulosa cells. A basal lamina separates granulosa cells from stromal cells in primordial and primary follicles or from the theca cells in the secondary and antral-staged ones [31, 32]. Follicle development can be affected by bidirectional signaling between the oocyte and granulosa cells, the granulosa and theca cells, and their interactions with the ECM and growth factors [31]. Moreover, one of the requirements for folliculogenesis is the presence of interactions between the oocyte and somatic cells [33], which mediate the action of external signals and nourish the oocyte during the maturation process [3]. Folliculogenesis (Fig. 2) is the process of follicle development from the primordial stage to either ovulation or death by atresia [34]. The growing of follicles occurs in two stages: the first slow stage that takes weeks in small rodents and months in large mammalian species is characterized by proliferation of granulosa cells and an increase in follicles and oocyte diameter; in the second stage, the follicle is responsive to follicle-stimulating (FSH) and luteinizing hormones (LH), forms antrum cavity, synthesizes steroid hormones and reaches the pre-ovulatory step [9].

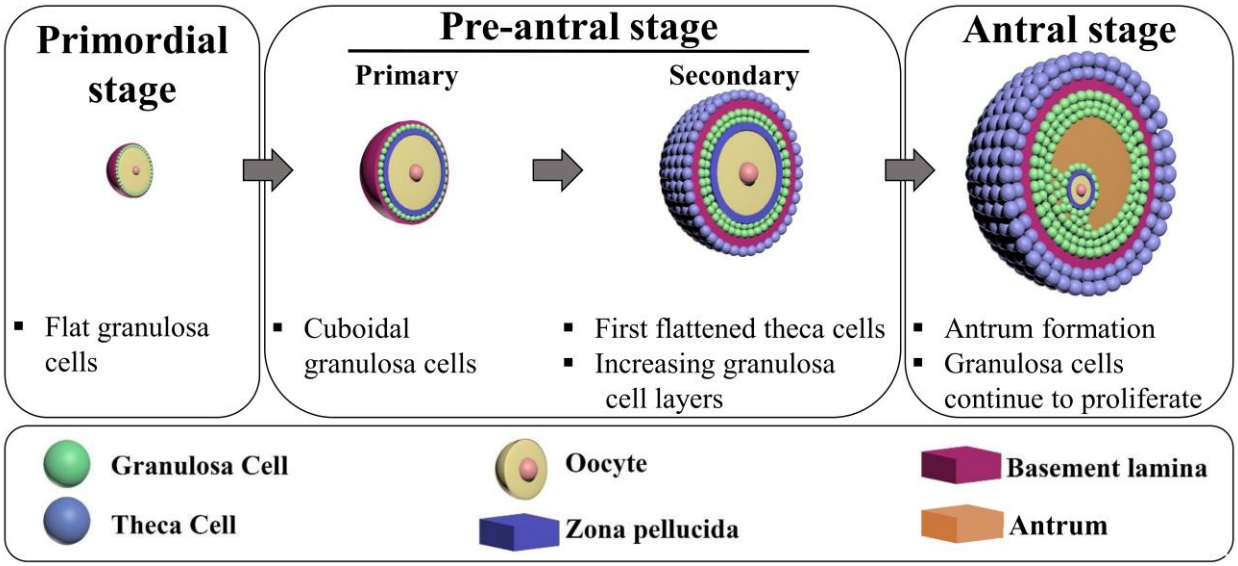


Figure 2. A schematic of follicle development from the primordial to the antral stage.

3 Cryopreservation as a strategy to safeguard ovarian function and fertility

Ovarian tissue cryopreservation and transplantation is the main alternative to preserve fertility for prepubertal girls and women who need to start their treatment as soon as they are diagnosed with cancer. This alternative has been shown to restore ovarian function in more than 90% of the transplanted patients [35]. Up to now, more than 200 live births have been reported worldwide after cryopreservation and transplantation of ovarian tissue [36]. Despite the new methods described for ovarian tissue cryopreservation [37-39], conventional freezing using low concentrations of penetrating cryoprotectant, such as dimethylsulfoxide (DMSO) or ethylene glycol combined with a slow cooling curve in a controlled programmed freezing machine remains the method of choice [40]. Such a procedure has also been shown to successfully cryopreserve isolated human preantral follicles [41, 42].

While cryopreservation of ovarian tissue can be advised to girls and women in need to preserve their fertility, transplantation is not allowed to patients diagnosed with tumors at high risk of ovarian metastasis, such as leukemia, neuroblastoma, and Burkitt lymphoma, due to the risk of reintroducing malignant cells present in the cryopreserved ovarian tissue. This could potentially cause the recurrence of the primary disease [43, 44]. To preserve fertility in these patients, researchers have been attempting to develop follicles in vitro or transplant them after isolation from malignant cells [44, 45].

Regarding the in vitro growth of ovarian follicles, it is important to bear in mind that folliculogenesis is a long process in humans, taking at least six months, and not yet fully understood. While short-term in vitro culture of follicles can be used as an evaluation tool for toxicity tests, recreating the optimal conditions or media required for these follicles to grow in vitro over a long period of time remains a challenge. Additionally, the lengthy in vitro culture could interfere with epigenetic mechanisms, and particularly genomic imprinting.

Transplantation of ovarian follicles could be an alternative to this problem, but these structures must be entirely isolated from surrounding cancer cells to ensure the safety of this procedure. Soares et al. [46] developed a simple purging step to separate malignant cells from preantral follicles after their isolation. They also reported that even if a small number of leukemia cells were accidentally grafted, they could not induce tumor mass formation after 20 weeks of xenografting [47].

Ovarian cells can be added to the isolated follicles to support their development during in vitro culture or transplantation. These cells secrete autocrine/paracrine factors involved in folliculogenesis [44], and some of them will be recruited by growing follicles to differentiate into theca cells [48]. Moreover, to improve follicle survival, one could play with the biomaterial used as a scaffold, its porosity, mechanical strength, and bioactive sites, as well as the addition of hormones, growth factors, etc. [8, 11, 49-53]. For instance, to enhance vascularization, follicles could be encapsulated in biomaterials with sustained release of vascular endothelial growth factor (VEGF) [54] or basic fibroblast growth factor (bFGF) [55].

4 Development of follicle culture systems

The 2D *in vitro* system has been routinely used for follicle' *in vitro* culture [56-61]. Several approaches, such as multi-well plates, cell culture dishes, or coverslips coated by gels or ECM proteins such as collagen, fibronectin, and laminin, have been used in this procedure [3, 33, 62]. When isolated follicles are attached to a 2D culture surface, the somatic cells migrate to the bottom of the well, gradually losing their interaction with the oocyte, and consequently, the follicle 3D structure is destroyed [7]. Indeed, 2D culture systems are different from *in vivo* microenvironment conditions, where cells and tissues have complex connections with different adherent ligands in the 3D ECM [63]. Cell-cell and cell-matrix interactions are essential for follicle and oocyte development [64], and therefore, 3D culture approaches have been developed to maintain the original follicle structure **(Table1)** [3, 49, 65].

In 3D systems, it is possible to preserve follicle architecture, which has positively impacted morphological follicle integrity, diameter [66], and oocyte maturation [7]. The 3D follicle

culture systems have been demonstrated to yield higher follicle survival and growth rates, preserve follicle morphology, and reduce oocyte maturation genes' expression than 2D strategies. Moreover, using a 3D culture, it is possible to co-culture multiple types of cells to better mimic *in vivo* conditions [67]. Although the 3D culture systems have been widely investigated, there are still many challenges such as reproducibility, hypoxia probability, and insufficient nutrient supplying that must be overcome before its clinical applications [68]. **Indeed, poor reproducibility in engineered scaffolds could be observed because of lot-to-lot variations of biological materials, reagents, animal-derived media [69], and different microarchitectures of scaffolds [70], as well as discrepancies in the quality and quantity of isolated cells from human sources [71]. Moreover, oxygen could only diffuse around a few hundred micrometers inside the scaffolds, and the cells located in the central part of the construct would be found in hypoxic conditions [72]. This leads to a gradient in the 3D scaffold in terms of quality from the periphery to the center [73], as hypoxia is a potential cause of cellular damage and decreased regeneration [74]. Therefore, vascularization is essential for scaffolds bigger than 1 mm^3 as this is the only means to supply cells with the required oxygen and nutritional and metabolic molecules [75, 76]. To this end, angiogenic factors, such as VEGF, bFGF, and epidermal growth factor (EGF), could be added to the scaffold to promote neovascularization by attracting endothelial cells existing in the surrounding tissue [77]. Other alternatives to overcome hypoxia and shortage of nutrients are the encapsulation of endothelial cells in 3D scaffolds [78, 79] or 3D printing of vascular networks [80, 81].**

Table 1. Some studies on follicle development in 2D and 3D systems.

Biomaterial	Culture system	Suppl.	Species	Follicle class	Culture duration	Main results	Ref.
-	2D	r-FSH	Mouse	Early preantral follicles	16 days	Follicles attached to the culture surface lost their spherical structure and developed antral-like cavities	[56]
Alginate (3D)	2D/3D	-	Goat	Secondary follicles	36 days	Successful antrum formation in both systems	[66]
Alginate (3D)	2D/3D	KL	Mouse	Preantral follicles	12 days	3D culture supported higher rates of follicles maturation, survival, and steroidogenesis. KL increased follicular function and development in both 2D and 3D culture systems	[8]
Alginate (3D)	2D/3D	VEGF and IGF-1	Bovine	Secondary follicles	32 days	VEGF treatment affected on the follicular growth and antrum formation in 2D culture system	[11]
Tyramine-based HA hydrogel (3D)	2D/3D	-	Mouse	Preantral follicles	12 days	Follicles maintain their architecture only in 3D *in vitro* culture	[33]
Collagen (3D)	2D/3D	FSH	Mouse	Preantral follicles	6 days	2D culture caused a distortion of follicle morphology, 3D culture systems maintained follicular structure and increased follicle growth, particularly in presence of FSH	[1]
Alginate	3D	-	Human	Preantral follicles	7 days	High follicle survival rate with increasing size in the spherical shape	[4]

Fibrin and alginate	**3D**	**FSH**	**Macaque**	**Primary and secondary follicles**	**5 (fibrin) or 13 weeks (alginate)**	**Primary and secondary follicles grew to form an antrum at weeks 9 and 3, respectively. Development of primary follicles was higher in fibrin than alginate**	**[82]**
Alginate and collagen	**3D**	**EGF and LH**	**Deer mouse**	**Early secondary preantral follicles**	**13 days**	**Biomimetic ovarian microtissue enabled follicle growth to antral stage and led to ovulation in the absence of EGF and LH**	**[50]**
Fibrin-alginate	**3D**	**LH and FSH**	**Dog**	**Secondary follicles**	**12 days**	**Fibrin-alginate hydrogel improved follicle development compared to alginate hydrogels**	**[51]**
Alginate-Matrigel	**3D**	**-**	**Human**	**Secondary follicles**	**30 days**	**Follicles showed steroidogenically activity and developed to antral stage**	**[83]**
Alginate-Matrigel	**3D**	**-**	**Human**	**Preantral follicles**	**7 days**	**Increasing follicle size and preservation of its viability**	**[42]**
Fibrin- or Matrigel-alginate	**3D**	**-**	**Mouse**	**Preantral follicles**	**12 days**	**Higher follicle survival and growth in Matrigel-alginate hydrogel**	**[84]**

205 **Suppl.: supplementation; Ref.: reference; KL: kit ligand; IGF-1: insulin-like growth factor-1; HA: hyaluronan.**

5 Biomaterials used in ovarian tissue engineering

Compared to synthetic polymers, naturally-derived biomaterials have an interdependence of mechanical and biological properties. For instance, increasing collagen concentration alters the integrin-binding and protease-sensitive sites, which has been indicated by cell proliferation and mitochondrial activity and changes the mechanical behavior of this protein [85, 86]. On the other hand, polyethylene glycol (PEG) as an inert polymer has tunable physical properties independent of its bioactivity [85, 86]. Therefore, the combination of required biological (such as providing a substrate for cell attachment, differentiation, migration, remodeling, etc.) and mechanical properties resembling the natural organ or tissue is essential when choosing a biomaterial for ovarian tissue engineering [19, 86-88]. Biomaterials employed for this strategy (Fig. 3) must have a certain amount of elasticity (storage modulus between 1 and 2.5 KPa), as this is an essential requirement for granulosa expansion during follicular growth while supporting the spherical shape of follicles. Furthermore, comparing the development of follicles encapsulated in biomaterials with different stiffness could give an insight into finding the proper scaffold rigidity for follicle encapsulation.

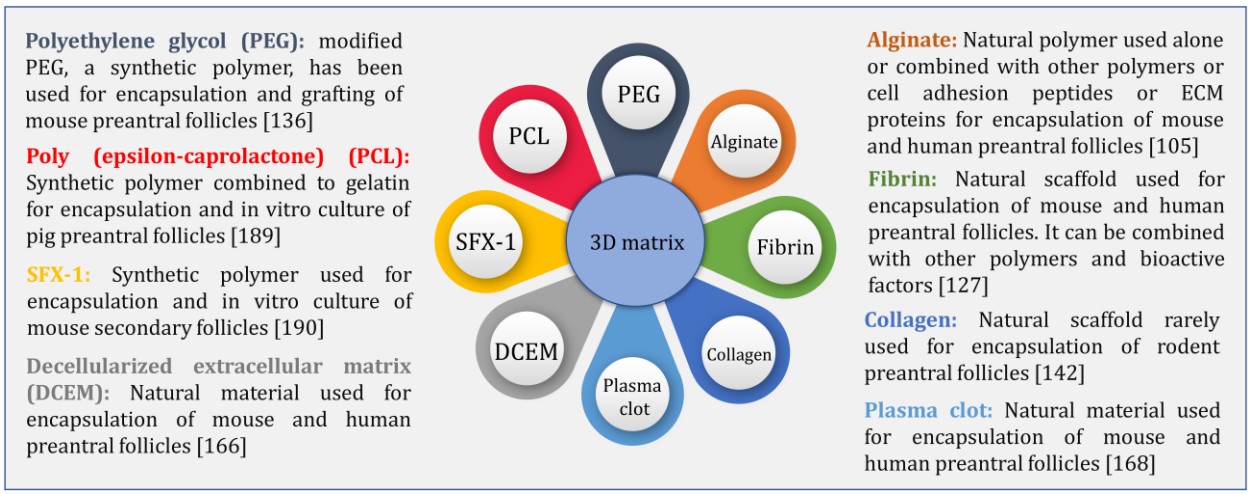


Figure 3. Biomaterials used for ovarian tissue engineering.

5.1 Natural polymers for ovarian tissue engineering

5.1.1 Alginate

Alginate is a linear polysaccharide derived from algae with biocompatible, readily available, bio-inactive, biodegradable, and non-immunogenic properties [89, 90]. It has FDA approval for clinical use [91] and has been widely used in tissue engineering applications [89-94]. Mechanical strength and gelation properties of alginate can be affected by its molecular weight, crosslinking degree, and the percentage of guluronic acids units available in its backbone [91, 95].

Alginate is the most used polymer for *in vitro* culture of isolated preantral follicles [4, 28, 41, 42, 66, 67, 83, 96-102]. It has been applied as a matrix to promote follicle development *in vitro* and a tool to learn about folliculogenesis and test the impact of cryopreservation and chemotherapy on follicle population [4, 41, 42, 100, 103, 104]. The effect of different bioactive factors, such as VEGF [11], kit ligand [8], LH, and EGF [50], on follicle survival and development, has also been assessed with the aid of the alginate. Similarly, the effect of

preantral follicle density on its growth and survival was evaluated using alginate [105]. Different numbers of mouse follicles (1, 5, and 10) were encapsulated in 0.5% alginate beads. A positive correlation was found between follicle development and their density in the alginate bead, demonstrating that crosstalk among follicles is necessary for their survival and growth [105].

Alginate was also applied to graft isolated follicles. Vanacker et al. [106] allografted mouse preantral follicles and ovarian cells encapsulated in 1% alginate. The results showed that alginate beads could successfully support the survival and development of follicles and the viability and proliferation of ovarian cells after one week of transplantation [106].

While several studies reported alginate as a suitable polymer for encapsulation of ovarian follicles [41, 97, 106], controlling the degradation rate of the alginate hydrogel to match with the follicle growth is challenging, and the polymer rigidity can negatively affect further development of the follicles [90]. For instance, mouse preantral follicles encapsulated in 0.125% alginate showed better follicle survival and antral formation than their counterparts encapsulated in 0.25% alginate [107]. Similarly, West-Farrell et al. [52] compared two different alginate concentrations (0.5 and 1.5%) to *in vitro* culture mouse secondary follicles and reported that the softer hydrogel could better support their development. On the other hand, in large animal species, the results were the opposite: compared to 1%, 2% alginate showed a better influence on the diameter of sheep primordial and primary follicles [53]. Such discrepancy among mammalian species could be due to the different follicle mechanical properties requirements. For instance, as regards the shear modulus of 1.5% alginate (approximately 1500 Pa) is much more than the alginate 0.5% (around 121 Pa) [52], it seems

that the follicles isolated from the mouse compared to the human isolated follicles prefer to be encapsulated in a softer biomaterial.

Alginate is inert and does not have cell-binding sites. However, the cell adhesion property of the alginate can be enhanced through the binding of cell adhesion peptides, such as the RGD (arginine-glycine-aspartic acid) sequence [90]. Indeed, Kreeger et al. [108] modified alginate with ECM proteins or RGD to encapsulate secondary follicles and showed that the modified alginate improved follicle development. Combining alginate with other polymers such as fibrin [109, 110], Matrigel [101], and gelatin [89] is another way to enhance its cell attachment properties and biodegradation rate. Jin et al. [7] encapsulated isolated mouse secondary follicles in a fibrin-alginate matrix, which proved to be superior to alginate alone to improve follicle growth and oocyte diameter, antrum formation, and increasing the percentage of competent oocytes for fertilization. On the other hand, Jamalzaei et al. [111] showed that alginate/hyaluronic acid hydrogel was superior to fibrin/alginate hydrogels for the *in vitro* culture of mouse preantral follicles, improving their development up to the antral stage, yielding metaphase II oocytes and higher expression of growth and differentiation genes.

5.1.2 Fibrin

Fibrin is the major component in blood coagulation, playing a temporary matrix role in supporting fibroblast and endothelial cell invasion [112]. FDA has approved commercial fibrin sealants, such as Tisseel®, EvicelTM, and CrossealTM, which have different compositions, methods of production, and formulations [17] for numerous clinical applications [113].

Fibrin is a biocompatible [114] and biodegradable biomaterial [115, 116], which has been studied as a cell carrier, drug delivery system, and scaffold [117]. It provides a biomimetic ECM for cells, improving their interaction with scaffolds [118], adhesion, and proliferation [115, 119, 120]. Moreover, fibrin has been shown to support the formation of the capillary network *in vitro* [121].

Activated thrombin cleaves fibrinogen peptides A and B from the central domain of fibrinogen (named E domain). Then, the central domain of cleaved fibrinogen is linked to the end group (named D domain) of other cleaved fibrinogen, which this end group has an interaction with another end group (D-D). Then, the formed fibers are covalently linked by fibrin stabilizing factor (FXIII) to generate a stabilized fibrin network [17]. Combinations of different concentrations of fibrinogen and thrombin result in fibrin matrices with wide varieties of morphology and rigidity [122], which affect cell behavior. For instance, decreasing fibrinogen concentration from 50 mg/ml to 5 mg/ml changes human mesenchymal stem cells morphology from round to spindle-like shape and their higher proliferation was observed in dilute fibrinogen solutions. The spindle shape morphology, establishing cytoplasmic projections, and increasing cell proliferation allow the cells to form a 3D cellular structure [123]. On the other hand, changing thrombin concentration can affect fibrin mechanical strength and cell activity [122, 124]. Taking advantage of this plasticity, Luyckx et al. [122] encapsulated human isolated ovarian cells in nine combinations of fibrinogen (F; mg/ml) and thrombin (T; IU/mL) (F1/T4, F12.5/T1, F12.5/T20, F25/T0.1, F25/T4, F25/T500, F50/T1, F50/T20, and F100/T4) to report the best combinations to support cell proliferation and viability. They showed that two fibrin formulations (F12.5/T1 and F25/T4) yielded positive effects on cell density dynamic, which ranged from 94.0% to

96.6% and 94.2% to 98.9% with high proliferation indexes 4.45 ± 2.34 and 4.38 ± 4.81, respectively. Then, Luyckx et al. [125] used these two fibrin formulations to encapsulate and auto-transplant isolated mouse preantral follicles. Both matrices were able to successfully support follicle survival and development up to the antral stage. However, when tested with isolated human preantral follicles, the follicles showed a recovery rate of approximately 2%. Hypothesizing that this may be due to the lack of rigidity of these matrices, Paulini et al. [126] increased both fibrinogen and thrombin concentrations (F50/T10), obtaining a stiffer fibrin matrix to graft isolated human preantral follicles. Their results showed a follicle recovery rate of 22% after one week of xenografting in immunodeficient mice [126]. Such results were comparable to Nisolle et al. [127] after xenotransplantation of human ovarian tissue during the same period.

Aiming to optimize fibrin matrix to transplant isolated human ovarian follicles, Chiti et al. [128] investigated four different fibrin formulations (F12.5/T1, F30/T50, F50/T50, and F75/T75). They observed that fibrin formulations of F50/T50, and F75/T75 yielded fiber thickness similar to the human ovarian cortex, which varied between 61.3 to 72.4 nm. Also, increasing fibrinogen and thrombin concentrations augmented G', and F50/T50 yielded a G' similar to the natural human ovary. Therefore, they concluded that F50/T50 could closely mimic natural human ovary properties in terms of mechanical properties and fiber thickness [128].

In another study, Chiti et al. [129] used fibrin hydrogel to investigate the correlation between the stages of mouse follicle development on its survival and matrix vascularization after grafting. They reported that secondary follicles had higher survival and recovery rates than primordial and primary ones. Also, a superior number of vessels was found in clots

containing secondary follicles. It appears that the higher survival rate of these larger follicles may be due to their spatial distribution in fibrin and the larger vascularization observed in this group. Another fibrin formulation (20mg/ml fibrinogen and 50 IU/ml thrombin) also showed to support mouse follicle development after transplantation, as observed by the increase in follicular diameter and restoration of hormone cyclicity [130].

Fibrin can also be enriched with bioactive factors to enhance its biological properties. For instance, fibrin was supplemented with VEGF for transplantation of mouse preantral follicles, resulting in resumption of estrous cycling in the mice and offsprings [131]. Also, Rajabzadeh et al. [132] used fibrin hydrogel enriched with different human platelet lysate concentrations (5, 10, 15, 20%) to transplant murine preantral follicles. They showed that fibrin plus 15% platelet lysate yielded a higher follicle recovery rate, indicating the positive effects of the growth factors of platelet lysate on follicle survival. In another study [133], this group showed that this fibrin supplemented with 15% platelet lysate increased vascularization and follicle survival and development compared to the fibrin matrix alone.

While fibrin is a promising hydrogel for ovarian tissue engineering [17, 125, 126, 129, 134], this matrix has rapid degradation and intrinsic instability, which leads to loss of implant volume within days and, consequently, loss of the physical protection of follicles and stromal cells [113, 116, 135-138]. However, the fibrin degradation rate can be controlled by combining fibrinogen with natural or synthetic polymers such as alginate [109, 110] or using enzyme inhibitors such as aprotinin [116, 139, 140]. In a fibrin-alginate matrix, fibrin provides cell adhesion properties, while alginate supports matrix stability. This hybrid hydrogel is an example of a dynamic construct for embedding follicles, allowing follicle growth while decreasing the tension of the scaffold on the follicles during *in vitro* culture

[12]. The fibrin-alginate hybrid hydrogel has been shown to enhance follicle development [86, 88, 141]. Shikanov et al. [140] introduced the fibrin-alginate interpenetrating network as a dynamic mechanical scaffold whose stiffness changes according to fibrin degradation during *in vitro* culture. This network could allow follicle expanding by the degradation of fibrin and decreasing the concentration of alginate from 0.5 % to below 0.25%. Moreover, they reported that for extending the mechanical gradient of the scaffold, different concentrations of aprotinin as a protease inhibitor could be added to the culture medium to change the fibrin degradation rate. Xu et al. [82] investigated a matrix containing 25 mg/ml fibrinogen, 50 IU/ml thrombin, and 0.25% alginate to encapsulate macaque primary and secondary follicles. The results indicated that the fibrin improved primary follicle development and had no effect on secondary follicles, in contrast to the alginate hydrogels. In another study, Xu et al. [142] tested a matrix containing 50 mg/ml fibrinogen, 50 IU/ml thrombin, 0.5% alginate, and Matrigel for culturing isolated baboon preantral follicles. They showed that this hydrogel yielded metaphase II oocytes.

5.1.3 Collagen

Collagen is the most widely distributed type of protein in the human body and the first natural matrix used to graft isolated preantral follicles [143]. Collagen possesses several advantages: biodegradability, biocompatibility, and great versatility [44, 144]. Torrance et al. [143] showed that collagen is a promising hydrogel for encapsulation and *in vitro* culture of mouse preantral follicles. Telfer et al. [145] encapsulated mouse follicles in collagen and *in vitro* culture them for five days before transplantation to mouse kidney capsule for a period between 2 and 21 days. Although they reported a suitable survival rate of the follicles

after transplantation, they also observed oocyte atresia in antral follicles, and granulosa cell luteinization [145]. Recently, Joo et al. [146] studied cell survival, follicle growth, hormone production, and oocyte maturation in rat ovarian follicles encapsulated in type I collagen hydrogels as a 3D culture system. The results demonstrated that varying collagen hydrogel density and elasticity could significantly affect follicle development regarding their phenotype, hormone secretion, and maturation. In another study, the transplantation of adipose-derived stem cells on soluble collagen scaffolds showed to contribute to long-term restoration of ovarian function and the fertility of rats after tripterygium glycosides-induced ovarian damage [147].

Beyond the excellent biological properties of collagen, such as biocompatibility, biodegradability, and support of cellular growth, migration, and differentiation, this biomaterial has poor mechanical properties and structural stability that limit its application in tissue engineering [148]. To overcome this limitation, collagen could be combined with other biomaterials such as alginate[149], silk [150], chitosan [151], PLGA [152], and heparin sulfate [153]. It could also be enhanced with a chemical reaction such as using glutaraldehyde [154] or PEGylation [155] or physical modifications such as gamma radiation [156]. However, it is important to stress that although gamma radiation or glutaraldehyde improve collagen mechanical strength, these strategies decrease the stability or biocompatibility of modified collagen [148]. Regrettably, collagen blended biomaterials and chemically/physically modified collagen have not been investigating extensively for the ovarian tissue engineering concept, and we do not know their effect on follicle survival and development.

5.1.4 Plasma clots

Plasma clot is an autologous material with high biocompatibility and rich in growth factors [43]. It has been successfully used for culturing different types of cells such as human mesenchymal stromal cells [157, 158], chondrocytes [159], carcinoma cells [160], and monocytes [161], as well as follicle encapsulation [162-165]. Compared to purified fibrinogen, plasma clots are stiffer primarily due to the platelet, which can be increased to enhance the matrix rigidity [166]. The use of autologous plasma clots to encapsulate isolated follicles was first reported in the 1990s. After transplantation of mouse ovarian follicles and cells in plasma clots, animals could ovulate and deliver normal offspring [162, 163]. Following these successful results, Dolmans et al. [164, 165] encapsulated freshly isolated human follicles in autologous plasma clots and xenografted them to the ovarian bursa of immunodeficient mice. Although the results demonstrated follicle development up to the secondary stage after one week and even finding antral follicles after five months [165], plasma clots degraded rapidly, which could have led to follicle loss [43]. **An alternative could be the use of fibrin-based hydrogels, as discussed above.**

5.1.5 Decellularized extracellular matrix

In tissue engineering, decellularized extracellular matrix (DECM) has been shown considerable potential to promote regeneration in various organs, such as the kidney, liver, and heart. DECM from ovarian tissue for ovarian tissue engineering has also yielded promising outcomes in isolated follicle transplantation. Recently, Pors et al. studied human preantral follicles seeded in DECM from ovarian tissue [167]. The results indicated a high survival rate of follicles injected with Matrigel after three weeks of xenografting to mice

[167]. Hassanpour et al. [168] evaluated bioengineered ovary construction using a 3D scaffold based on a sodium lauryl ester sulfate-treated DECM protocol. After 14-day transplantation in rats, the results showed that DECM could be an ideal scaffold for this regard due to the great bioactivity and viability of primary ovarian cells and the ability to reconstruct the primordial or primary follicle-like structures. Laronda et al. [169] decellularized bovine and human ovaries with sodium dodecyl sulfate and recellullarized them with primary ovarian cells. They reported that the decellularized scaffolds could preserve ovarian microstructure and provide estradiol hormone production *in vitro*. Recently, Alshaikh et al. [170] investigated the decellularization of mouse ovarian tissue using two different types of detergents: 0.5% sodium dodecyl sulfate and 2% sodium deoxycholate. While both protocols showed high biocompatibility, the latter produced DECM that appeared to be slightly more advantageous due to a higher recellularization efficiency. Moreover, Eivazkhani et al. [171] studied the effects of two different treatments of sodium dodecyl sulfate and NaOH for the decellularization of the mouse, sheep, and human ovaries. The scaffolds created by using NaOH demonstrated better decellularization and support cell growth than sodium dodecyl sulfate. Liu et al. [172] used physical, chemical, and enzymatical treatments for decellularization of the porcine ovary to shorten the sodium dodecyl sulfate treatment time and consequently reduce its damaging effect on the tissues. They showed that the three steps of decellularization (using Triton X-100, SDS, and DNAase I) could successfully remove cell components, and the decellularized scaffolds were biocompatible with minimum host immune responses, supported cell penetration, and enhanced the estradiol production.

DECM of ovarian tissue for seeding isolated follicles is in its infancy despite the exhaustive investigation of this strategy for other tissues [173-175]. It is important to bear in mind that while the optimal DECM source is the human ovary itself, the amount of tissue required to prepare the scaffold renders this option unrealistic. An alternative could be the use of ovaries from mono-ovulating species, as they seem to be comparable in composition. However, it is known that collagen fibers from different mono-ovulating species can induce allergic reactions [176, 177], which may decrease the number of patients that would benefit from this strategy. Moreover, it is vital to consider the possible challenges for developing an appropriate DECM for ovarian tissue engineering, such as optimization of decellularization method [178], improving weak mechanical properties, and fast degradation of DECM [179-181]. Finally, regarding the necessity of using a high number of cells for suitable recellularization of DECM [182] and the limited number of isolated follicles from human frozen-thawed ovaries, it is necessary to find an appropriate technique for the efficient seeding of follicles and cells in the ovarian DECM.

5.2 Synthetic hydrogels for ovarian tissue engineering

5.2.1 Polyethylene glycol (PEG)

PEG is a synthetic biocompatible polymer [183-185]. It is FDA-approved [25, 183] and widely used in tissue engineering and regenerative medicine [183]. Pure PEG is biologically inert and unable to support cell adhesion and proliferation [183]. However, it can be modified with Arg-Gly-Asp (RGD) peptides for encouraging cell attachment using Michael-type addition (MTA) chemistry. When crosslinked by protease-sensitive peptides, it can

induce cell migration and proliferation [86, 186-190]. Kim et al. [137] used PEG hydrogel modified with RGD and crosslinked with matrix metalloproteinase-sensitive tri-functional crosslinking peptides for ovarian tissue engineering and implanted it to mice for *in vivo* culture. Their results demonstrated that this synthetic matrix could support the survival and development of early-stage follicles in addition to graft remodeling and revascularization [137]. This approach demonstrated the ability of scaffold engineering by adding susceptible protease peptides to the PEG backbone to achieve the goal of synchronizing biodegradation, which occurs in response to cell-associated proteolytic activities, with ECM remodeling and supporting the tissue regeneration [191]. Furthermore, 8-Arm PEG-vinyl sulfone (PEG-VS) supplemented with the MMP- and plasmin-sensitive crosslinker was investigated by Tomaszewski et al. [192] for encapsulating follicles with or without adipose-derived stem cells to evaluate their effect on follicles. They reported that this biomimetic matrix preserved multipotency of the cells and induced them to produce paracrine factors beneficial for enhancing follicle viability and development.

Recently, Tomaszewski et al. [193] modified PEG with the ECM-sequestering peptides, Heparin-binding peptide (HBP), ECM-binding region of placental growth factor 2 (RRR), laminin-derived peptide (AG73), and basement membrane binder (BMB) to mimic the natural ovarian ECM. They used two types of crosslinkers: fast-degrading GCYKNRGCYKNRCG (YKNR) and slow-degrading GCYKNSGCYKNSCG (YKNS) to optimize the proteolytic degradation of hydrogels. They encapsulated single isolated murine follicles in each hydrogel and showed that these modified hydrogels improved follicle viability, development, and maturation and caused the recreation of ECM molecules in terms of laminin, fibronectin, perlecan, and collagen I [193].

5.3 Other natural and synthetic scaffolds

Synthetic polymers have been widely used for tissue engineering and regenerative medicine applications, but they have been poorly explored in ovarian tissue engineering. Poly(epsilon-caprolactone) (PCL) is one of the most biodegradable and biocompatible polyesters with many applications in tissue engineering [147, 194]. Gelatin/PCL electrospun fibrous 3D scaffold [195] was studied for seeding isolated porcine preantral follicles. Gelatin, as a natural polymer, was used to enhance cell-biomaterial interactions, improving cell adhesion, migration, and differentiation. The gelatin/PCL scaffold was demonstrated to preserve follicles morphology, increase their adhesion. Moreover, the amount of estradiol and progesterone produced by follicles seeded in gelatin/PCL was higher than PCL samples, which indicated better follicle growth in this scaffold. SFX-1, a synthetic polymer, which was produced from N-isopropylacrylamide (NIPAM) monomer, has also been used for ovarian tissue engineering [196]. Murine secondary follicles were encapsulated in the 30 mg/ml SFX-1 and *in vitro* cultured for two days. Although the results demonstrated an increase in follicles diameter from 153 ± 28 μm to 201 ± 38, only 12.5% of follicles maintained their morphological integrity [196].

Synthetic polymers are chemically defined materials that allow the synthesis of reproducible scaffolds with tunable properties to guide cellular behavior. They could easily be functionalized by crosslinking biological materials and bioactive molecules and present dynamic scaffolds that can change their properties based on the engineered design [197]. Indeed, dynamic scaffolds could be a good strategy to utilize for follicle encapsulation. Since follicles significantly increase in diameter during

folliculogenesis, they require a change in scaffold stiffness [140], which could be modulated employing synthetic materials that are chemically functionalized [137, 192, 193, 198] or incorporated with natural polymers [195, 199, 200]. This could potentially be a framework to develop a dynamic matrix for supporting follicle growth.

6 Recent trends

The 3D biofabrication strategies can manufacture complex cellular environments to recapitulate natural tissues by precise control of material geometry and properties and spatially molecular concentration [25]. Indeed, computer-aided technologies have been altering the concept of manufacturing in both industry and human life [201], such as 3D printing systems that aim to fabricate viable constructs by the following biomimicry, autonomous self-assembly, and mini-tissue approaches [202, 203]. The 3D printing technology can be an alternative for tissue engineering and regenerative medicine challenges [204-207], fabricating functional tissues by controlling precise cellular and biomaterial spatial distribution [208, 209] and recapitulating microstructures [210]. Despite the promising results, this technology is in the early stage of development, and only simple tissue constructs have been fabricated by the current 3D printers [209]. On the other hand, *in vitro* growth of ovarian follicles from large mammalian species remains a challenge because of the long-term culture necessity and follicle size, which exponentially increases during folliculogenesis, and their complex metabolic conditions.

The innovative ovary-on-a-chip platforms using dynamic systems may overcome these difficulties. They can be a strategy to restore fertility in cancer patients and a valuable tool

for preserving endangered mammalian species [211]. In the mouse model, Xiao et al. [212] showed that organ-on-a-chip platforms using microfluidic technology could maintain ovarian endocrine function, mimic menstrual cycle, and provide high stability and controllability of flow patterns for approximately 100 days. This study opened a door for improving investigations about tissue-tissue interactions, biological and pharmacological research by producing organs-on-a-chip models consisting of the ovary, fallopian tube, uterus, cervix, and liver for representing the human reproductive tract. Overall, organ-on-a-chip systems can replicate the natural structure and functions of organs and their dynamic flow conditions via controllable microfluidic fluids [213].

6.1 3D printing

Three-dimensional printing fabricates 3D complex tissue constructs mimicking natural tissues using robotic additive manufacturing technologies [204, 214, 215]. Three different types of 3D printing approaches have been developed: laser, inkjet, and extrusion-based 3D printing [203, 204, 216, 217] (Fig. 4), which provide cell viability of 95%, >85%, and 80%, respectively [203]. Different natural, synthetic, and hybrid biomaterials have been studied as 3D printing materials for encapsulating cells [209, 214]. In general, 3D printing materials include cell aggregates, cells encapsulated in hydrogels, viscous fluids, and microcarriers involving cells [214]. They must also have printability, biocompatibility, biodegradability, biological activity, and appropriate physical, chemical, and mechanical properties [209].

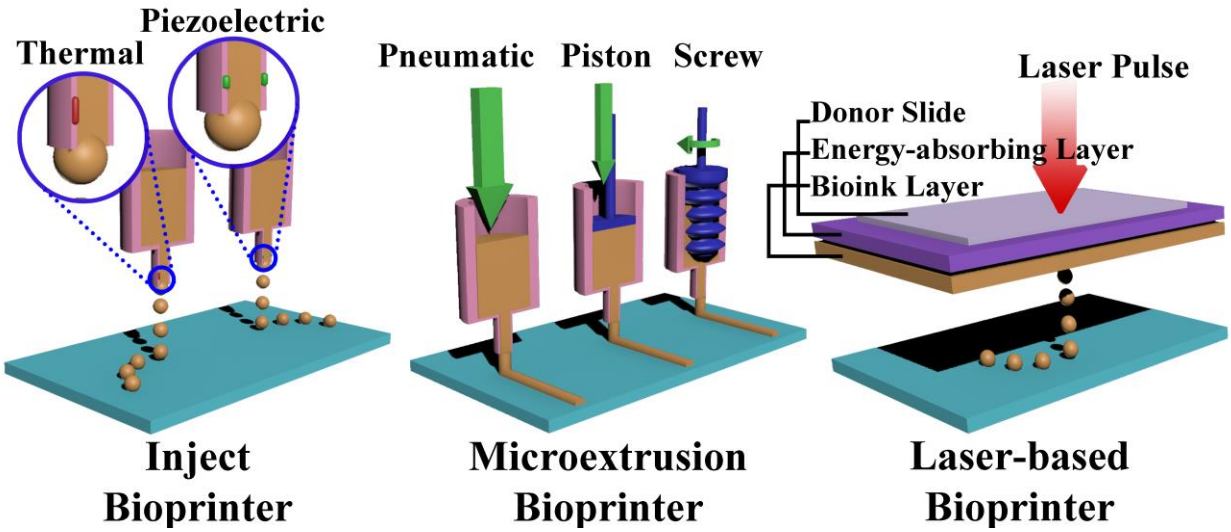


Figure 4. Classification of 3D printing technologies. Inkjet 3D printers are divide into thermal and piezoelectric setups, which use heat or mechanical stimulation, respectively, to generate droplets. Extrusion-based 3D printers extrude bioink using pneumatic, piston, or screw dispensing systems. In laser-based 3D printers, a laser pulse focuses on the donor slide coated by an absorbing layer and induces a vapor bubble that ejects the droplet onto the collection substrate.

Several functional tissues have been developed using this emerging technology, such as cartilage [215, 218-221], skin [222-226], vascular system [227-231], and liver [232-234]. However, ovary 3D printing is still in its infancy. Laronda et al. [235] developed a functional 3D printed follicle-seeded ovarian scaffold. In this study, by altering the orientation of printed layers, the authors assessed the effect of pore geometry on follicle viability. Interestingly, they found a positive correlation between the number of interactions between scaffold and follicles and their survival rate. The follicles seeded in these partially crosslinked gelatin 3D-printed platforms accounted for increasing vascularization and restoring ovarian function in surgically sterilized mice and yielded healthy pups (Fig. 5) [235].

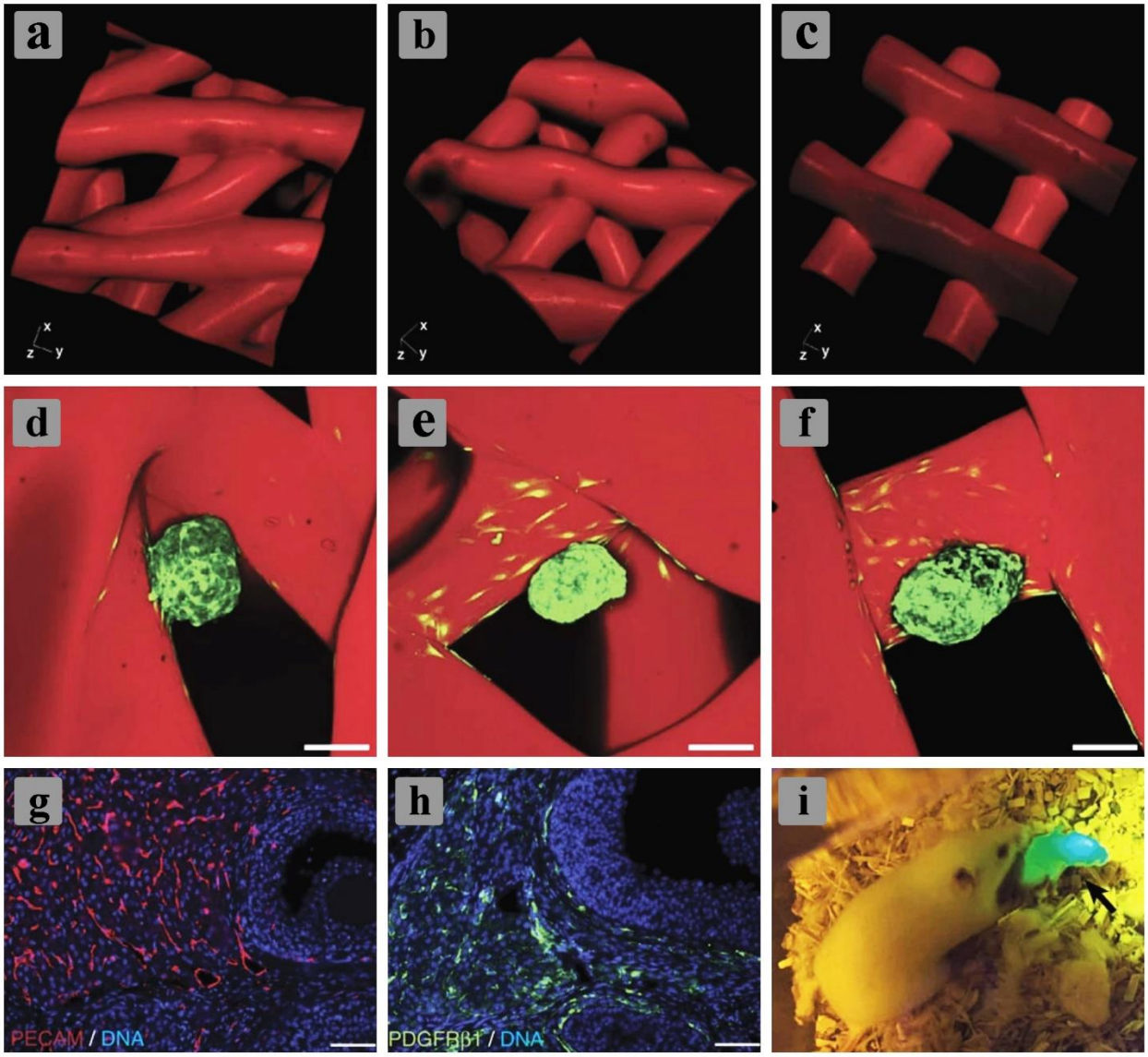


Figure 5. 3D printed construct for isolated follicles. (a-c) 3D reconstructions of confocal fluorescence images of 30°, 60°, and 90° angle 3D printed scaffolds (a, b and c, respectively). (d-f) green fluorescent protein-positive (GFP+) follicles seeded in pores after two days in culture. Follicles in 30° and 60° pores (d and e, respectively) often resided in corners, whereas they tended to be on one strut in 90° pores. (g and h) vascularization in 60° angle 3D printed scaffold with immunostaining for endothelial marker platelet endothelial cell

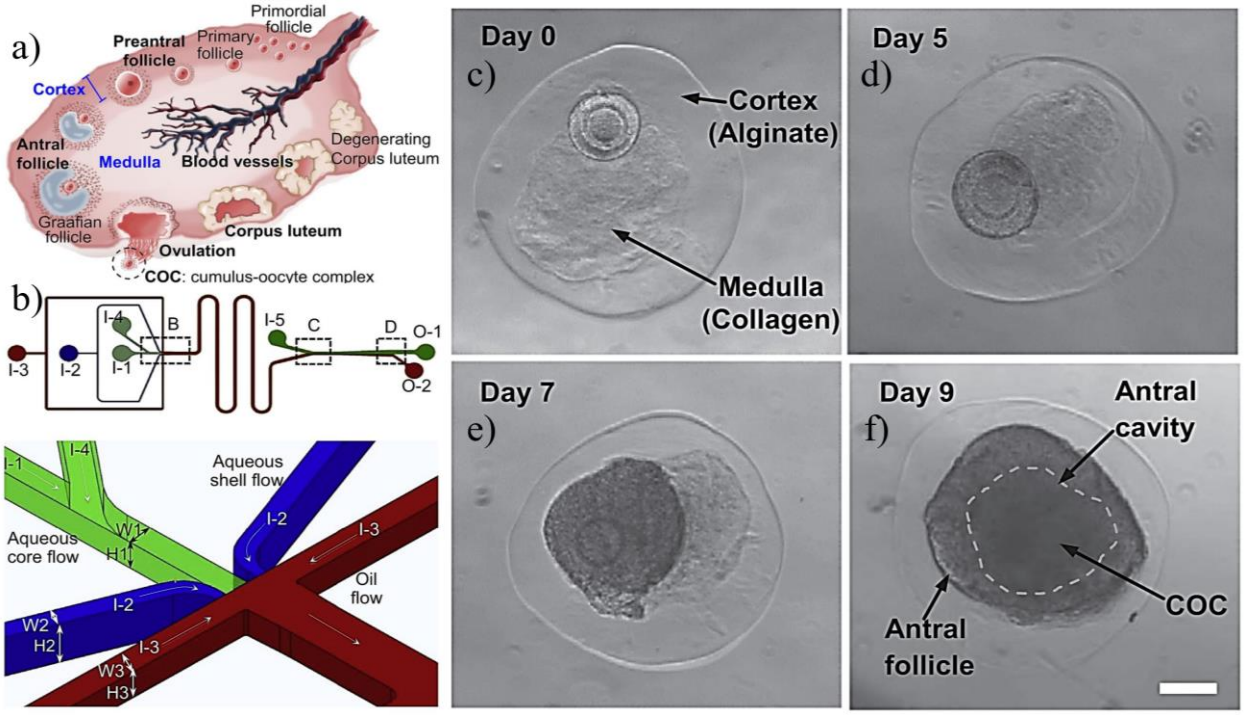
adhesion molecule (PECAM) (red) or pericyte marker PDGFR β1 (green) and DNA (blue) in corpus luteum, antral follicles and interstitial space of bioprosthetic ovary removed after 8-10 weeks. (i) a healthy pup after mating transplanted animals [235]. Reprinted with permission from [235] © Springer Nature (2021).

Wu et al. [236] investigated the gelatin-methacryloyl for 3D printing of ovarian tissue and reported that the isolated primary stromal cells lost their viability after printing, indicating more vulnerability of the primary cells to the printing process than ovarian tumor cell lines (COV434, KGN, ID8). Then, the authors evaluated isolated murine follicles seeded in scaffolds with 60° or 90° angles between the adjacent upper and lower strands. They observed that while 60° constructs successfully supported follicle viability (84%) after seven days of *in vitro* culture, most follicles in 90° constructs fell into the bottom of the culture plate and a few numbers of them attached to the strands [236].

6.2 Microfluidics for follicle encapsulation

A mammalian ovary is divided into stiffer and softer sections regarding the mechanical and structural properties, which are defined as cortex and medulla, respectively. Recapitulation of the ovary's mechanical heterogeneity has an essential role in folliculogenesis [237]. However, it is also important to take into account that the length of oxygen and nutrients penetration is less than 200 μm, and therefore thin microtissues should be constructed to prevent cell death in the core of the substrates [63]. As one of the microfluidics technology applications is fabricating shape-controlled microgels [238], Choi et al. [50] simulated ovarian biomechanical structure by using two different hydrogels (alginate and collagen as

hard and soft segments of the ovary, respectively) and microfluidics for encapsulating mouse early secondary preantral follicles into the microcapsules. They successfully biofabricated a core shell biomimetic ovary prototypes, in which alginate was placed in the shell and collagen in the core section. This biomimetic microtissue led to follicle development up to the antral stage after nine days of *in vitro* culture (Fig. 6). In another study [63], this group encapsulated mouse embryonic stem cells (mESCs) and ovarian preantral follicles in the core (collagen I at different concentrations containing 1% sodium carboxymethyl cellulose)-shell (alginate) microcapsules to evaluate cell proliferation and follicle development. To improve mechanical properties, 5 mg/ml alginate was added to some samples. Although the elastic modulus of microtissues had an increasing trend in cores from 0.5 to 3 mg/ml collagen, the expression of pluripotency genes from mESCs embedded in these microcapsules was decreased, which indicated the possibility of better E-cadherin mediated interactions between cells in a softer microenvironment [63]. Moreover, constructs with softer core (1 mg/ml collagen I) showed a significantly lower proportion of antral follicles compared to counterparts with the higher collagen concentration (5 mg/ml), which also produced higher estradiol concentrations (around 3 ng/ml at day 10). Interestingly, when stiffer cores contained additional alginate concentration (5 mg/ml), the proportion of antral follicles augmented but remained lower than those stiffer microgels without alginate.



626

627 **Figure 6. Design and materials of biomimetic ovarian microtissue**. (a) Ovary anatomy
628 with two distinct layers: a more rigid cortex and softer medulla. (b) A schematic view of
629 microchannels system for encapsulating follicles (top) developed by Choi et al. [50] together
630 with a zoom-in view of the nonplanar design of the flow-focusing junction (bottom) where
631 W1= 200, H1=200, W2= 80, H2=300, W3=200, and H3=400 μm. c-f) follicle growth in the
632 engineered microtissue on days 0, 5, 7, and 9, in which antral cavity and a cumulus-oocyte
633 complex (COC) were observed on day 9 [50]. Reprinted and adapted from [50] © Elsevier
634 (2021).

635

636 6.3 Organ-on-a-chip

637 The organ-on-a-chip system converges two research areas (tissue engineering and
638 microfluidic technologies) to emulate key characteristics of a specific living organ, such as
639 extracellular microenvironments and cell-cell interactions. The main goal of developing

organ-on-a-chip systems is to use them as a replacement for animal tests. They have numerous applications, including creating *in vitro* healthy/diseased models for tissue development studies, drug discovery and development, and evaluating the efficiency and safety of drugs [239-241].

An organ-on-a-chip platform can mimic the critical environment multifunction of a specific organ on a single chip. Its fabrication consists of designing a microchannel network, which allows for controlled loading, placement, diffusion, and permeation of microfluidic, a cell chamber to replicate the microenvironment of the organ, and a cell-retention filter that can also be used in connection sites with external tubing [242-244]. Despite the wide variety of organ-on-a-chip platforms, such as liver [245-250], lung [251-254], vessel [255-258], and kidney [259-262], which have been developed to improve studies on functional human organs, only a few studies are aiming to create the ovary-on-a-chip.

The first studies using the ovary-on-a-chip technology have shown promising results supporting follicle development [211, 212, 263, 264]. It has also been successfully applied to monitor ovotoxicity induced by microcystins [263], study anti-cancer drugs effects on ovarian follicles growth and function [265], and as a model for ovarian cancer [213, 266, 267] and a tool to characterize oocyte quality [268, 269]. However, this approach is still in its infancy, and it will surely be explored in the following years.

7 Perspectives and outlooks

Ovarian engineered tissue could be a promising strategy for patients who can not use the current strategies for preserving their fertility. Although, several offspring reports have been published from the encapsulated mouse follicles [65, 99, 131, 162, 163],

supporting the development of isolated human follicles still need in-depth investigations due to differences between the mouse and human ovaries in terms of physicochemical structures [270-272]. Therefore, choosing a suitable biomaterial that could resemble a human ovary in terms of dynamic physiologic conditions, mechanical strength, and proteomic compositions is an essential step for creating an engineered human ovary. Moreover, more investigations are expected in 3D printing and microfluidics technologies to get the benefit of precisely mimicking the human ovarian structure.

On the other hand, similar to other tissues that have been investigating in the tissue engineering field, it seems overcoming ischemia is another area for improvement since the final goal of the engineered ovary is grafting to the patient. Different approaches such as 3D printing of vasculature in the ovarian scaffold containing follicles and cells [273-275], using oxygen releasing scaffolds [276-279], or incorporation of growth factors in scaffolds for encouraging vascularizations [280-282] could be objectives for further investigations to improve follicle survival after transplanting ovarian engineered scaffold to the body.

8 Conclusion

In this review, we have summarized the biomaterial requirements for ovarian tissue engineering and the 2D and 3D culture systems for follicle development. Moreover, we have discussed innovative biofabrication methods that have been employed for creating ovarian tissue. The 3D printing and organ-on-a-chip technologies, as biofabrication techniques,

endeavor to recapitulate the complexity of natural organs and be a solution for convenient tissue engineering challenges. Indeed, they have the potential to create biomimetic functional systems, which can be used for tissue engineering and regenerative medicine applications. These emerging strategies can help the ovarian tissue engineering concept by precisely mimicking the ovarian microenvironment. This can allow follicle development to restore fertility in cancer patients and analyze and monitor the effects of biological and chemical agents such as hormones, growth factors, and drugs on folliculogenesis.

Credit author statement

Arezoo Dadashzadeh drafted the initial version of the manuscript together with Saeid Moghassemi. Amin Shavandi and Christiani A. Amorim reviewed and agreed on the final version of the manuscript.

Data availability

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study was supported by grants from the Fonds National de la Recherche Scientifique de Belgique (the Excellence of Science (FNRS-EOS), number 30443682 (PhD scholarship awarded to S.M.)) and and Fondation Louvain (PhD scholarship awarded to A.D.).

9 References

[1] J.E. Gomes, S.C. Correia, A. Gouveia-Oliveira, A.J. Cidadão, C.E. Plancha, Three-dimensional environments preserve extracellular matrix compartments of ovarian follicles and increase FSH-dependent growth, Molecular Reproduction and Development: Incorporating Gamete Research 54(2) (1999) 163-172.

[2] X. He, T.L. Toth, In vitro culture of ovarian follicles from Peromyscus, Seminars in cell & developmental biology, Elsevier, 2017, pp. 140-149.

[3] M. Belli, G. Vigone, V. Merico, C.A. Redi, M. Zuccotti, S. Garagna, Towards a 3D culture of mouse ovarian follicles, International Journal of Developmental Biology 56(10-11-12) (2013) 931-937.

[4] C.A. Amorim, A. Van Langendonckt, A. David, M.-M. Dolmans, J. Donnez, Survival of human pre-antral follicles after cryopreservation of ovarian tissue, follicular isolation and in vitro culture in a calcium alginate matrix, Human Reproduction 24(1) (2009) 92-99.

[5] T.K. Woodruff, L.D. Shea, The role of the extracellular matrix in ovarian follicle development, Reproductive sciences 14(8_suppl) (2007) 6-10.

[6] J.J. Eppig, M.J. O'Brien, Development in vitro of mouse oocytes from primordial follicles, Biology of reproduction 54(1) (1996) 197-207.

[7] S.Y. Jin, L. Lei, A. Shikanov, L.D. Shea, T.K. Woodruff, A novel two-step strategy for in vitro culture of early-stage ovarian follicles in the mouse, Fertility and sterility 93(8) (2010) 2633-2639.

[8] S. Abdi, M. Salehnia, S. Hosseinkhani, Quality of oocytes derived from vitrified ovarian follicles cultured in two-and three-dimensional culture system in the presence and absence of kit ligand, Biopreservation and biobanking 14(4) (2016) 279-288.

[9] N. Desai, A. Alex, F. AbdelHafez, A. Calabro, J. Goldfarb, A. Fleischman, T. Falcone, Three-dimensional in vitro follicle growth: overview of culture models, biomaterials, design parameters and future directions, Reproductive Biology and Endocrinology 8(1) (2010) 119.

[10] D.F. Albertini, G. Akkoyunlu, Ovarian follicle culture systems for mammals, Methods in enzymology, Elsevier2010, pp. 107-121.

[11] V. Araújo, M. Gastal, A. Wischral, J. Figueiredo, E. Gastal, In vitro development of bovine secondary follicles in two-and three-dimensional culture systems using vascular endothelial growth factor, insulin-like growth factor-1, and growth hormone, Theriogenology 82(9) (2014) 1246-1253.

[12] A. Shikanov, M. Xu, T.K. Woodruff, L.D. Shea, Interpenetrating fibrin–alginate matrices for in vitro ovarian follicle development, Biomaterials 30(29) (2009) 5476-5485.

[13] A.E. Drummond, The role of steroids in follicular growth, Reprod Biol Endocrinol 4 (2006) 16.

[14] R. Obregón, J. Ramón-Azcón, S. Ahadian, Nanofiber composites in blood vessel tissue engineering, Nanofiber composites for biomedical applications, Elsevier2017, pp. 483-506.
[15] A. Boccaccini, J. Gough, Tissue engineering usin g ceramics and polymers. 2007, Woodhead Publishing Limited.
[16] F.J. O'brien, Biomaterials & scaffolds for tissue engineering, Materials today 14(3) (2011) 88-95.
[17] M.C. Chiti, M.-M. Dolmans, J. Donnez, C. Amorim, Fibrin in reproductive tissue engineering: a review on its application as a biomaterial for fertility preservation, Annals of biomedical engineering 45(7) (2017) 1650-1663.
[18] M.C. Chiti, C.A. Amorim, M.-M. Dolmans, A fibrin-based artificial ovary prototype: from animal models to human clinical application, Current trends in clinical embryology (2018).
[19] R.M. Smith, T.K. Woodruff, L.D. Shea, Designing follicle–environment interactions with biomaterials, Oncofertility, Springer2010, pp. 11-24.
[20] C.D. Wood, M. Vijayvergia, F.H. Miller, T. Carroll, C. Fasanati, L.D. Shea, L.C. Brinson, T.K. Woodruff, Multi-modal magnetic resonance elastography for noninvasive assessment of ovarian tissue rigidity in vivo, Acta biomaterialia 13 (2015) 295-300.
[21] S. Nandy, H.S. Salehi, T. Wang, X. Wang, M. Sanders, A. Kueck, M. Brewer, Q. Zhu, Correlating optical coherence elastography based strain measurements with collagen content of the human ovarian tissue, Biomedical optics express 6(10) (2015) 3806-3811.
[22] R.D. Pedde, B. Mirani, A. Navaei, T. Styan, S. Wong, M. Mehrali, A. Thakur, N.K. Mohtaram, A. Bayati, A. Dolatshahi-Pirouz, Emerging biofabrication strategies for engineering complex tissue constructs, Advanced Materials 29(19) (2017) 1606061.
[23] J.K. Tessmar, A.M. Göpferich, Customized PEG-derived copolymers for tissue-engineering applications, Macromolecular bioscience 7(1) (2007) 23-39.
[24] M. Qasim, F. Haq, M.-H. Kang, J.-H. Kim, 3D printing approaches for cardiac tissue engineering and role of immune modulation in tissue regeneration, International journal of nanomedicine 14 (2019) 1311.
[25] P. Bajaj, R.M. Schweller, A. Khademhosseini, J.L. West, R. Bashir, 3D biofabrication strategies for tissue engineering and regenerative medicine, Annual review of biomedical engineering 16 (2014) 247-276.
[26] R.F. Pereira, C.C. Barrias, P.L. Granja, P.J. Bartolo, Advanced biofabrication strategies for skin regeneration and repair, Nanomedicine 8(4) (2013) 603-621.
[27] L. Moroni, J.A. Burdick, C. Highley, S.J. Lee, Y. Morimoto, S. Takeuchi, J.J. Yoo, Biofabrication strategies for 3D in vitro models and regenerative medicine, Nature Reviews Materials 3(5) (2018) 21-37.
[28] M. Heise, R. Koepsel, A.J. Russell, E.A. McGee, Calcium alginate microencapsulation of ovarian follicles impacts FSH delivery and follicle morphology, Reproductive Biology and Endocrinology 3(1) (2005) 47.
[29] A. Blaustein, Anatomy and histology of the human ovary, Pathology of the female genital tract, Springer1982, pp. 416-441.
[30] E. Gibson, H. Mahdy, Anatomy, Abdomen and Pelvis, Ovary, StatPearls [Internet] (2020).
[31] O. Oktem, K. Oktay, The ovary: anatomy and function throughout human life, Annals of the New York Academy of Sciences 1127(1) (2008) 1-9.
[32] H.F. Irving-Rodgers, S. Morris, R.A. Collett, T.T. Peura, M. Davy, J.G. Thompson, H.D. Mason, R.J. Rodgers, Phenotypes of the ovarian follicular basal lamina predict developmental competence of oocytes, Human Reproduction 24(4) (2009) 936-944.
[33] N. Desai, F. Abdelhafez, A. Calabro, T. Falcone, Three dimensional culture of fresh and vitrified mouse pre-antral follicles in a hyaluronan-based hydrogel: a preliminary investigation of a novel biomaterial for in vitro follicle maturation, Reproductive Biology and Endocrinology 10(1) (2012) 29.

[34] N.M. Orsi, N.E. Baskind, M. Cummings, Anatomy, Development, Histology, and Normal Function of the Ovary, Pathology of the Ovary, Fallopian Tube and Peritoneum, Springer2014, pp. 1-32.
[35] J. Donnez, M.-M. Dolmans, Fertility preservation in women, Nature Reviews Endocrinology 9(12) (2013) 735-749.
[36] M.-M. Dolmans, J. Donnez, L. Cacciottola, Fertility preservation: the challenge of freezing and transplanting ovarian tissue, Trends in Molecular Medicine (2020).
[37] S. Silber, Chapter 13 Human Ovarian Tissue Vitrification, Methods Mol Biol 1568 (2017) 177-194.
[38] S. Lierman, A. Bus, S. Andries, E. Trias, P.E.J. Bols, K. Tilleman, Passive slow freezing is an efficacious and cost-effective alternative to controlled slow freezing for ovarian tissue cryopreservation, Cryobiology 100 (2021) 164-172.
[39] Z. Xiao, Z.Y. Huang, Y.Y. Zhang, W. Fan, Q. Chen, Hyaluronidase Pretreatment Improves the Cryopreservation of Human Ovarian Tissue, Cryo Letters 40(3) (2019) 139-144.
[40] E.C. Rivas Leonel, C.M. Lucci, C.A. Amorim, Cryopreservation of Human Ovarian Tissue: A Review, Transfus Med Hemother 46(3) (2019) 173-181.
[41] A. Camboni, A. Van Langendonckt, J. Donnez, J. Vanacker, M.-M. Dolmans, C. Amorim, Alginate beads as a tool to handle, cryopreserve and culture isolated human primordial/primary follicles, Cryobiology 67(1) (2013) 64-69.
[42] J. Vanacker, V. Luyckx, C. Amorim, M.-M. Dolmans, A. Van Langendonckt, J. Donnez, A. Camboni, Should we isolate human preantral follicles before or after cryopreservation of ovarian tissue?, Fertility and sterility 99(5) (2013) 1363-1368. e2.
[43] C.A. Amorim, A. Shikanov, The artificial ovary: current status and future perspectives, Future oncology 12(19) (2016) 2323-2332.
[44] M.-M. Dolmans, C.A. Amorim, Fertility preservation: construction and use of artificial ovaries, Reproduction 158(5) (2019) F15-F25.
[45] E.E. Telfer, FERTILITY PRESERVATION: Progress and prospects for developing human immature oocytes in vitro, Reproduction 158(5) (2019) F45-F54.
[46] M. Soares, K. Sahrari, C.A. Amorim, P. Saussoy, J. Donnez, M.-M. Dolmans, Evaluation of a human ovarian follicle isolation technique to obtain disease-free follicle suspensions before safely grafting to cancer patients, Fertility and sterility 104(3) (2015) 672-680. e2.
[47] M. Soares, P. Saussoy, K. Sahrari, C.A. Amorim, J. Donnez, M.-M. Dolmans, Is transplantation of a few leukemic cells inside an artificial ovary able to induce leukemia in an experimental model?, Journal of assisted reproduction and genetics 32(4) (2015) 597-606.
[48] P. Asiabi, M.-M. Dolmans, J. Ambroise, A. Camboni, C. Amorim, In vitro differentiation of theca cells from ovarian cells isolated from postmenopausal women, Human Reproduction 35(12) (2020) 2793-2807.
[49] I.R. Brito, I.M. Lima, M. Xu, L.D. Shea, T.K. Woodruff, J.R. Figueiredo, Three-dimensional systems for in vitro follicular culture: overview of alginate-based matrices, Reproduction, Fertility and Development 26(7) (2014) 915-930.
[50] J.K. Choi, P. Agarwal, H. Huang, S. Zhao, X. He, The crucial role of mechanical heterogeneity in regulating follicle development and ovulation with engineered ovarian microtissue, Biomaterials 35(19) (2014) 5122-5128.
[51] N. Songsasen, C. Guzy, D. Wildt, 121 Alginate-fibrin gel matrix promotes in vitro growth of dog secondary follicles, Reproduction, Fertility and Development 24(1) (2011) 173-173.
[52] E.R. West-Farrell, M. Xu, M.A. Gomberg, Y.H. Chow, T.K. Woodruff, L.D. Shea, The mouse follicle microenvironment regulates antrum formation and steroid production: alterations in gene expression profiles, Biology of reproduction 80(3) (2009) 432-439.
[53] S. Sadeghnia, M.M. Akhondi, G. Hossein, S. Mobini, L. Hosseini, M.M. Naderi, S.B. Boroujeni, A. Sarvari, B. Behzadi, A. Shirazi, Development of sheep primordial follicles encapsulated in alginate or in ovarian tissue in fresh and vitrified samples, Cryobiology 72(2) (2016) 100-105.

[54] L. Wu, Y. Gu, L. Liu, J. Tang, J. Mao, K. Xi, Z. Jiang, Y. Zhou, Y. Xu, L. Deng, Hierarchical micro/nanofibrous membranes of sustained releasing VEGF for periosteal regeneration, Biomaterials 227 (2020) 119555.
[55] S. Moghassemi, A. Hadjizadeh, A. Hakamivala, K. Omidfar, Growth factor-loaded nano-niosomal gel formulation and characterization, AAPS PharmSciTech 18(1) (2017) 34-41.
[56] R. Cortvrindt, J. Smitz, A. Van Steirteghem, Ovary and ovulation: In-vitro maturation, fertilization and embryo development of immature oocytes from early preantral follicles from prepuberal mice in a simplified culture system, Human Reproduction 11(12) (1996) 2656-2666.
[57] N. Boland, P. Humpherson, H. Leese, R. Gosden, Pattern of lactate production and steroidogenesis during growth and maturation of mouse ovarian follicles in vitro, Biology of reproduction 48(4) (1993) 798-806.
[58] J. Carroll, D. Whittingham, M. Wood, Effect of dibutyryl cyclic adenosine monophosphate on granulosa cell proliferation, oocyte growth and meiotic maturation in isolated mouse primary ovarian follicles cultured in collagen gels, Reproduction 92(1) (1991) 197-207.
[59] S.A. Daniel, D.T. Armstrong, R.E. Gore-Langton, Growth and development of rat oocytes in vitro, Gamete research 24(1) (1989) 109-121.
[60] K. Das, W.R. Phipps, H.C. Hensleigh, G.E. Tagatz, Epidermal growth factor in human follicular fluid stimulates mouse oocyte maturation in vitro, Fertility and sterility 57(4) (1992) 895-901.
[61] J.J. Eppig, M. Hosoe, M.J. O'Brien, F.M. Pendola, A. Requena, S. Watanabe, Conditions that affect acquisition of developmental competence by mouse oocytes in vitro: FSH, insulin, glucose and ascorbic acid, Molecular and cellular endocrinology 163(1-2) (2000) 109-116.
[62] O. Oktem, K. Oktay, The role of extracellular matrix and activin-A in in vitro growth and survival of murine preantral follicles, Reproductive Sciences 14(4) (2007) 358-366.
[63] P. Agarwal, J.K. Choi, H. Huang, S. Zhao, J. Dumbleton, J. Li, X. He, A biomimetic core–shell platform for miniaturized 3D cell and tissue engineering, Particle & Particle Systems Characterization 32(8) (2015) 809-816.
[64] E.R. West, L.D. Shea, T.K. Woodruff, Engineering the follicle microenvironment, Seminars in reproductive medicine, Copyright© 2007 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New …, 2007, pp. 287-299.
[65] C.M. Higuchi, Y. Maeda, T. Horiuchi, Y. Yamazaki, A simplified method for three-dimensional (3-D) ovarian tissue culture yielding oocytes competent to produce full-term offspring in mice, PloS one 10(11) (2015).
[66] A. Pessoa, R. Rocha, I. Brito, G. Silva, R. Chaves, D. Magalhães-Padilha, C. Campello, A. Rodrigues, D. Nunes-Pinheiro, J. Figueiredo, Effect of morphological integrity, period, and type of culture system on the in vitro development of isolated caprine preantral follicles, Theriogenology 82(2) (2014) 312-317.
[67] S.Z. Sadr, B. Ebrahimi, M. Shahhoseini, R. Fatehi, R. Favaedi, Mouse preantral follicle development in two-dimensional and three-dimensional culture systems after ovarian tissue vitrification, European Journal of Obstetrics & Gynecology and Reproductive Biology 194 (2015) 206-211.
[68] R. Edmondson, J.J. Broglie, A.F. Adcock, L. Yang, Three-dimensional cell culture systems and their applications in drug discovery and cell-based biosensors, Assay and drug development technologies 12(4) (2014) 207-218.
[69] C. McKee, G.R. Chaudhry, Advances and challenges in stem cell culture, Colloids and surfaces B: Biointerfaces 159 (2017) 62-77.
[70] R. Nigam, B. Mahanta, An overview of various biomimetic scaffolds: Challenges and applications in tissue engineering, Journal of Tissue Science & Engineering 5(2) (2014) 1.
[71] K.M. Panchalingam, S. Jung, L. Rosenberg, L.A. Behie, Bioprocessing strategies for the large-scale production of human mesenchymal stem cells: a review, Stem cell research & therapy 6(1) (2015) 1-10.

[72] L.G. Griffith, G. Naughton, Tissue engineering--current challenges and expanding opportunities, science 295(5557) (2002) 1009-1014.
[73] E. Volkmer, I. Drosse, S. Otto, A. Stangelmayer, M. Stengele, B.C. Kallukalam, W. Mutschler, M. Schieker, Hypoxia in static and dynamic 3D culture systems for tissue engineering of bone, Tissue Engineering Part A 14(8) (2008) 1331-1340.
[74] T. Agarwal, S. Kazemi, M. Costantini, F. Perfeito, C.R. Correia, V. Gaspar, L. Montazeri, C. De Maria, J.F. Mano, M. Vosough, Oxygen releasing materials: towards addressing the hypoxia-related issues in tissue engineering, Materials Science and Engineering: C (2021) 111896.
[75] M.S. Chapekar, Tissue engineering: challenges and opportunities, Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 53(6) (2000) 617-620.
[76] Y. Ikada, Challenges in tissue engineering, Journal of the Royal Society Interface 3(10) (2006) 589-601.
[77] W.-Y. Yeong, C.-K. Chua, K.-F. Leong, M. Chandrasekaran, Rapid prototyping in tissue engineering: challenges and potential, TRENDS in Biotechnology 22(12) (2004) 643-652.
[78] W.D. Holder Jr, H.E. Gruber, W.D. Roland, A.L. Moore, C.R. Culberson, A.B. Loebsack, K.J. Burg, D.J. Mooney, Increased vascularization and heterogeneity of vascular structures occurring in polyglycolide matrices containing aortic endothelial cells implanted in the rat, Tissue Engineering 3(2) (1997) 149-160.
[79] W. Zhang, L.S. Wray, J. Rnjak-Kovacina, L. Xu, D. Zou, S. Wang, M. Zhang, J. Dong, G. Li, D.L. Kaplan, Vascularization of hollow channel-modified porous silk scaffolds with endothelial cells for tissue regeneration, Biomaterials 56 (2015) 68-77.
[80] S.Y. Hann, H. Cui, T. Esworthy, S. Miao, X. Zhou, S.-j. Lee, J.P. Fisher, L.G. Zhang, Recent advances in 3D printing: vascular network for tissue and organ regeneration, Translational Research 211 (2019) 46-63.
[81] A. Ekinci, X. Han, R. Bibb, R. Harris, Optimised Vascular Network for Skin Tissue Engineering by Additive Manufacturing, Virtual Prototyping & Bio Manufacturing in Medical Applications, Springer2021, pp. 1-20.
[82] J. Xu, M. Lawson, R. Yeoman, T. Molskness, A. Ting, R. Stouffer, M. Zelinski, Fibrin promotes development and function of macaque primary follicles during encapsulated three-dimensional culture, Human Reproduction 28(8) (2013) 2187-2200.
[83] M. Xu, S.L. Barrett, E. West-Farrell, L.A. Kondapalli, S.E. Kiesewetter, L.D. Shea, T.K. Woodruff, In vitro grown human ovarian follicles from cancer patients support oocyte growth, Human Reproduction 24(10) (2009) 2531-2540.
[84] S.Z. Sadr, R. Fatehi, S. Maroufizadeh, C.A. Amorim, B. Ebrahimi, Utilizing fibrin-alginate and matrigel-alginate for mouse follicle development in three-dimensional culture systems, Biopreservation and biobanking 16(2) (2018) 120-127.
[85] E. Suesca, A. Dias, M. Braga, H. De Sousa, M. Fontanilla, Multifactor analysis on the effect of collagen concentration, cross-linking and fiber/pore orientation on chemical, microstructural, mechanical and biological properties of collagen type I scaffolds, Materials Science and Engineering: C 77 (2017) 333-341.
[86] J. Kim, Y.P. Kong, S.M. Niedzielski, R.K. Singh, A.J. Putnam, A. Shikanov, Characterization of the crosslinking kinetics of multi-arm poly (ethylene glycol) hydrogels formed via Michael-type addition, Soft matter 12(7) (2016) 2076-2085.
[87] C.P. Laurent, C. Vaquette, X. Liu, J.-F. Schmitt, R. Rahouadj, Suitability of a PLCL fibrous scaffold for soft tissue engineering applications: A combined biological and mechanical characterisation, Journal of biomaterials applications 32(9) (2018) 1276-1288.

[88] E.J. Kim, C. Yang, J. Lee, H.W. Youm, J.R. Lee, C.S. Suh, S.H. Kim, The new biocompatible material for mouse ovarian follicle development in three-dimensional in vitro culture systems, Theriogenology 144 (2020) 33-40.
[89] A. Dadashzadeh, R. Imani, S. Moghassemi, K. Omidfar, N. Abolfathi, Study of hybrid alginate/gelatin hydrogel-incorporated niosomal Aloe vera capable of sustained release of Aloe vera as potential skin wound dressing, Polymer Bulletin 77(1) (2020) 387-403.
[90] J. Vanacker, C.A. Amorim, Alginate: A versatile biomaterial to encapsulate isolated ovarian follicles, Annals of biomedical engineering 45(7) (2017) 1633-1649.
[91] H. Wen, W. Xiao, S. Biswas, Z.-Q. Cong, X.-M. Liu, K.S. Lam, Y.-H. Liao, W. Deng, Alginate hydrogel modified with a ligand interacting with α3β1 integrin receptor promotes the differentiation of 3D neural spheroids toward oligodendrocytes in vitro, ACS applied materials & interfaces 11(6) (2019) 5821-5833.
[92] S.J. Bidarra, C.C. Barrias, P.L. Granja, Injectable alginate hydrogels for cell delivery in tissue engineering, Acta biomaterialia 10(4) (2014) 1646-1662.
[93] B. Christensen, Alginates as biomaterials in tissue engineering, Carbohydrate chemistry: chemical and biological approaches 37 (2011) 227-258.
[94] J.L. Drury, D.J. Mooney, Hydrogels for tissue engineering: scaffold design variables and applications, Biomaterials 24(24) (2003) 4337-4351.
[95] J. Sun, H. Tan, Alginate-based biomaterials for regenerative medicine applications, Materials 6(4) (2013) 1285-1309.
[96] S.A. Pangas, H. Saudye, L.D. Shea, T.K. Woodruff, Novel approach for the three-dimensional culture of granulosa cell–oocyte complexes, Tissue engineering 9(5) (2003) 1013-1021.
[97] P.K. Kreeger, N.N. Fernandes, T.K. Woodruff, L.D. Shea, Regulation of mouse follicle development by follicle-stimulating hormone in a three-dimensional in vitro culture system is dependent on follicle stage and dose, Biology of reproduction 73(5) (2005) 942-950.
[98] E.R. West, M. Xu, T.K. Woodruff, L.D. Shea, Physical properties of alginate hydrogels and their effects on in vitro follicle development, Biomaterials 28(30) (2007) 4439-4448.
[99] M. Xu, P.K. Kreeger, L.D. Shea, T.K. Woodruff, Tissue-engineered follicles produce live, fertile offspring, Tissue engineering 12(10) (2006) 2739-2746.
[100] M. Xu, A. Banc, T.K. Woodruff, L.D. Shea, Secondary follicle growth and oocyte maturation by culture in alginate hydrogel following cryopreservation of the ovary or individual follicles, Biotechnology and bioengineering 103(2) (2009) 378-386.
[101] J. Vanacker, V. Luyckx, M.-M. Dolmans, A. Des Rieux, J. Jaeger, A. Van Langendonckt, J. Donnez, C.A. Amorim, Transplantation of an alginate–matrigel matrix containing isolated ovarian cells: first step in developing a biodegradable scaffold to transplant isolated preantral follicles and ovarian cells, Biomaterials 33(26) (2012) 6079-6085.
[102] J. Nagashima, D.E. Wildt, A.J. Travis, N. Songsasen, Follicular size and stage and gonadotropin concentration affect alginate-encapsulated in vitro growth and survival of pre-and early antral dog follicles, Reproduction, Fertility and Development 29(2) (2017) 262-273.
[103] M.M. Laronda, F.E. Duncan, J.E. Hornick, M. Xu, J.E. Pahnke, K.A. Whelan, L.D. Shea, T.K. Woodruff, Alginate encapsulation supports the growth and differentiation of human primordial follicles within ovarian cortical tissue, Journal of assisted reproduction and genetics 31(8) (2014) 1013-1028.
[104] L. Hosseini, A. Shirazi, M.M. Naderi, N. Shams-Esfandabadi, S.B. Boroujeni, A. Sarvari, S. Sadeghnia, B. Behzadi, M.M. Akhondi, Platelet-rich plasma promotes the development of isolated human primordial and primary follicles to the preantral stage, Reproductive BioMedicine Online 35(4) (2017) 343-350.
[105] J.E. Hornick, F.E. Duncan, L. Shea, T.K. Woodruff, Multiple follicle culture supports primary follicle growth through paracrine-acting signals, Reproduction (Cambridge, England) 145(1) (2013).

[106] J. Vanacker, M.-M. Dolmans, V. Luyckx, J. Donnez, C.A. Amorim, First transplantation of isolated murine follicles in alginate, Regenerative medicine 9(5) (2014) 609-619.
[107] K.E. Park, Y.Y. Kim, S.-Y. Ku, S.M. Baek, Y. Huh, Y.J. Kim, S.H. Kim, Y.M. Choi, S.Y. Moon, Effects of alginate hydrogels on in vitro maturation outcome of mouse preantral follicles, Tissue Engineering and Regenerative Medicine 9(3) (2012) 170-174.
[108] P.K. Kreeger, J.W. Deck, T.K. Woodruff, L.D. Shea, The in vitro regulation of ovarian follicle development using alginate-extracellular matrix gels, Biomaterials 27(5) (2006) 714-723.
[109] W. Chen, H. Zhou, M.D. Weir, C. Bao, H.H. Xu, Umbilical cord stem cells released from alginate–fibrin microbeads inside macroporous and biofunctionalized calcium phosphate cement for bone regeneration, Acta biomaterialia 8(6) (2012) 2297-2306.
[110] J.B. Nagashima, D.E. Wildt, A.J. Travis, N. Songsasen, Activin promotes growth and antral cavity expansion in the dog ovarian follicle, Theriogenology 129 (2019) 168-177.
[111] P. Jamalzaei, M.R. Valojerdi, L. Montazeri, H. Baharvand, Applicability of Hyaluronic Acid-Alginate Hydrogel and Ovarian Cells for In Vitro Development of Mouse Preantral Follicles, Cell Journal (Yakhteh) 22(Suppl 1) (2020) 49.
[112] B. Bujoli, J.-C. Scimeca, E. Verron, Fibrin as a Multipurpose Physiological Platform for Bone Tissue Engineering and Targeted Delivery of Bioactive Compounds, Pharmaceutics 11(11) (2019) 556.
[113] T.A. Ahmed, E.V. Dare, M. Hincke, Fibrin: a versatile scaffold for tissue engineering applications, Tissue Engineering Part B: Reviews 14(2) (2008) 199-215.
[114] C.R. Lee, S. Grad, K. Gorna, S. Gogolewski, A. Goessl, M. Alini, Fibrin–polyurethane composites for articular cartilage tissue engineering: a preliminary analysis, Tissue engineering 11(9-10) (2005) 1562-1573.
[115] Y. Li, H. Meng, Y. Liu, B.P. Lee, Fibrin gel as an injectable biodegradable scaffold and cell carrier for tissue engineering, The Scientific World Journal 2015 (2015).
[116] F.M. Shaikh, A. Callanan, E.G. Kavanagh, P.E. Burke, P.A. Grace, T.M. McGloughlin, Fibrin: a natural biodegradable scaffold in vascular tissue engineering, Cells Tissues Organs 188(4) (2008) 333-346.
[117] E. Malikmammadov, T.E. Tanir, A. Kiziltay, N. Hasirci, Preparation and characterization of poly (ε-caprolactone) scaffolds modified with cell-loaded fibrin gel, International journal of biological macromolecules 125 (2019) 683-689.
[118] T. Al Kayal, P. Losi, S. Pierozzi, G. Soldani, A new Method for fibrin-Based Electrospun/Sprayed Scaffold fabrication, Scientific Reports 10(1) (2020) 1-4.
[119] B. Nazari, M. Kazemi, A. Kamyab, B. Nazari, S. Ebrahimi-Barough, M. Hadjighassem, A. Norouzi-Javidan, A. Ai, A. Ahmadi, J. Ai, Fibrin hydrogel as a scaffold for differentiation of induced pluripotent stem cells into oligodendrocytes, Journal of Biomedical Materials Research Part B: Applied Biomaterials 108(1) (2020) 192-200.
[120] C.-m. Han, L.-p. Zhang, J.-z. Sun, H.-f. Shi, J. Zhou, C.-y. Gao, Application of collagen-chitosan/fibrin glue asymmetric scaffolds in skin tissue engineering, Journal of Zhejiang University Science B 11(7) (2010) 524-530.
[121] D.N. Heo, M. Hospodiuk, I.T. Ozbolat, Synergistic interplay between human MSCs and HUVECs in 3D spheroids laden in collagen/fibrin hydrogels for bone tissue engineering, Acta biomaterialia 95 (2019) 348-356.
[122] V. Luyckx, M.-M. Dolmans, J. Vanacker, S.R. Scalercio, J. Donnez, C.A. Amorim, First step in developing a 3D biodegradable fibrin scaffold for an artificial ovary, Journal of ovarian research 6(1) (2013) 83.
[123] W. Ho, B. Tawil, J.C. Dunn, B.M. Wu, The behavior of human mesenchymal stem cells in 3D fibrin clots: dependence on fibrinogen concentration and clot structure, Tissue Engineering 12(6) (2006) 1587-1595.

[124] S.L. Rowe, S. Lee, J.P. Stegemann, Influence of thrombin concentration on the mechanical and morphological properties of cell-seeded fibrin hydrogels, Acta biomaterialia 3(1) (2007) 59-67.
[125] V. Luyckx, M.-M. Dolmans, J. Vanacker, C. Legat, C.F. Moya, J. Donnez, C.A. Amorim, A new step toward the artificial ovary: survival and proliferation of isolated murine follicles after autologous transplantation in a fibrin scaffold, Fertility and sterility 101(4) (2014) 1149-1156.
[126] F. Paulini, J.M. Vilela, M.C. Chiti, J. Donnez, P. Jadoul, M.-M. Dolmans, C.A. Amorim, Survival and growth of human preantral follicles after cryopreservation of ovarian tissue, follicle isolation and short-term xenografting, Reproductive biomedicine online 33(3) (2016) 425-432.
[127] M. Nisolle, F. Casanas-Roux, J. Qu, P. Motta, J. Donnez, Histologic and ultrastructural evaluation of fresh and frozen-thawed human ovarian xenografts in nude mice, Fertility and sterility 74(1) (2000) 122-129.
[128] M.C. Chiti, M.-M. Dolmans, L. Mortiaux, F. Zhuge, E. Ouni, P.A.K. Shahri, E. Van Ruymbeke, S.-D. Champagne, J. Donnez, C.A. Amorim, A novel fibrin-based artificial ovary prototype resembling human ovarian tissue in terms of architecture and rigidity, Journal of assisted reproduction and genetics 35(1) (2018) 41-48.
[129] M.C. Chiti, M.-M. Dolmans, C. Lucci, F. Paulini, J. Donnez, C. Amorim, Further insights into the impact of mouse follicle stage on graft outcome in an artificial ovary environment, MHR: Basic science of reproductive medicine 23(6) (2017) 381-392.
[130] R.M. Smith, A. Shikanov, E. Kniazeva, D. Ramadurai, T.K. Woodruff, L.D. Shea, Fibrin-mediated delivery of an ovarian follicle pool in a mouse model of infertility, Tissue Engineering Part A 20(21-22) (2014) 3021-3030.
[131] E. Kniazeva, A. Hardy, S. Boukaidi, T. Woodruff, J. Jeruss, L. Shea, Primordial follicle transplantation within designer biomaterial grafts produce live births in a mouse infertility model, Scientific reports 5 (2015) 17709.
[132] A.R. Rajabzadeh, H. Eimani, H.M. Koochesfahani, A.-H. Shahvardi, R. Fathi, Morphological study of isolated ovarian preantral follicles using fibrin gel plus platelet lysate after subcutaneous transplantation, Cell Journal (Yakhteh) 17(1) (2015) 145.
[133] A. Rajabzadeh, F. Jahanpeyma, A. Talebi, F. Moradi, H. Eimani, Fibrin Scaffold Incorporating Platelet Lysate Enhance Follicle Survival and Angiogenesis in Cryopreserved Preantral Follicle Transplantation, Galen medical journal 9 (2020) 1558.
[134] M.C. Chiti, M.-M. Dolmans, R. Orellana, M. Soares, F. Paulini, J. Donnez, C. Amorim, Influence of follicle stage on artificial ovary outcome using fibrin as a matrix, Human Reproduction 31(2) (2016) 427-435.
[135] O.M. Benavides, J.P. Quinn, S. Pok, J. Petsche Connell, R. Ruano, J.G. Jacot, Capillary-like network formation by human amniotic fluid-derived stem cells within fibrin/poly (ethylene glycol) hydrogels, Tissue Engineering Part A 21(7-8) (2015) 1185-1194.
[136] K.M. Galler, A.C. Cavender, U. Koeklue, L.J. Suggs, G. Schmalz, R.N. D'Souza, Bioengineering of dental stem cells in a PEGylated fibrin gel, Regenerative medicine 6(2) (2011) 191-200.
[137] J. Kim, A.S. Perez, J. Claflin, A. David, H. Zhou, A. Shikanov, Synthetic hydrogel supports the function and regeneration of artificial ovarian tissue in mice, NPJ Regenerative medicine 1(1) (2016) 1-8.
[138] C.A. Amorim, Artificial ovary, Gonadal tissue cryopreservation in fertility preservation, Springer2016, pp. 175-192.
[139] A.C. Brown, T.H. Barker, Fibrin-based biomaterials: modulation of macroscopic properties through rational design at the molecular level, Acta biomaterialia 10(4) (2014) 1502-1514.
[140] A. Shikanov, M. Xu, T.K. Woodruff, L.D. Shea, A method for ovarian follicle encapsulation and culture in a proteolytically degradable 3 dimensional system, JoVE (Journal of Visualized Experiments) (49) (2011) e2695.
[141] I. Brito, G. Silva, A. Sales, C. Lobo, G. Rodrigues, R. Sousa, A. Moura, C. Calderón, M. Bertolini, C. Campello, Fibrin–alginate hydrogel supports steroidogenesis, in vitro maturation of oocytes and

parthenotes production from caprine preantral follicles cultured in group, Reproduction in Domestic Animals 51(6) (2016) 997-1009.
[142] M. Xu, A.T. Fazleabas, A. Shikanov, E. Jackson, S.L. Barrett, J. Hirshfeld-Cytron, S.E. Kiesewetter, L.D. Shea, T.K. Woodruff, In vitro oocyte maturation and preantral follicle culture from the luteal-phase baboon ovary produce mature oocytes, Biology of reproduction 84(4) (2011) 689-697.
[143] C. Torrance, E. Telfer, R. Gosden, Quantitative study of the development of isolated mouse pre-antral follicles in collagen gel culture, Reproduction 87(1) (1989) 367-374.
[144] R. Parenteau-Bareil, R. Gauvin, F. Berthod, Collagen-based biomaterials for tissue engineering applications, Materials 3(3) (2010) 1863-1887.
[145] E. Telfer, C. Torrance, R. Gosden, Morphological study of cultured preantral ovarian follicles of mice after transplantation under the kidney capsule, Reproduction 89(2) (1990) 565-571.
[146] S. Joo, S.-H. Oh, S. Sittadjody, E.C. Opara, J.D. Jackson, S.J. Lee, J.J. Yoo, A. Atala, The effect of collagen hydrogel on 3D culture of ovarian follicles, Biomedical Materials 11(6) (2016) 065009.
[147] D. Mondal, M. Griffith, S.S. Venkatraman, Polycaprolactone-based biomaterials for tissue engineering and drug delivery: Current scenario and challenges, International Journal of Polymeric Materials and Polymeric Biomaterials 65(5) (2016) 255-265.
[148] C. Dong, Y. Lv, Application of collagen scaffold in tissue engineering: recent advances and new perspectives, Polymers 8(2) (2016) 42.
[149] S. Ma, J. Zhou, T. Huang, Z. Zhang, Q. Xing, X. Zhou, K. Zhang, M. Yao, T. Cheng, X. Wang, Sodium alginate/collagen/stromal cell-derived factor-1 neural scaffold loaded with BMSCs promotes neurological function recovery after traumatic brain injury, Acta Biomaterialia (2021).
[150] J.-P. Jiang, X.-Y. Liu, F. Zhao, X. Zhu, X.-Y. Li, X.-G. Niu, Z.-T. Yao, C. Dai, H.-Y. Xu, K. Ma, Three-dimensional bioprinting collagen/silk fibroin scaffold combined with neural stem cells promotes nerve regeneration after spinal cord injury, Neural regeneration research 15(5) (2020) 959.
[151] M. Rezaii, S. Oryan, A. Javeri, Curcumin nanoparticles incorporated collagen-chitosan scaffold promotes cutaneous wound healing through regulation of TGF-β1/Smad7 gene expression, Materials Science and Engineering: C 98 (2019) 347-357.
[152] M.V. Jose, V. Thomas, D.R. Dean, E. Nyairo, Fabrication and characterization of aligned nanofibrous PLGA/Collagen blends as bone tissue scaffolds, Polymer 50(15) (2009) 3778-3785.
[153] C. Chen, M.l. Zhao, R.k. Zhang, G. Lu, C.y. Zhao, F. Fu, H.t. Sun, S. Zhang, Y. Tu, X.h. Li, Collagen/heparin sulfate scaffolds fabricated by a 3D bioprinter improved mechanical properties and neurological function after spinal cord injury in rats, Journal of Biomedical Materials Research Part A 105(5) (2017) 1324-1332.
[154] Y.Y. Peng, V. Glattauer, J.A. Ramshaw, Stabilisation of collagen sponges by glutaraldehyde vapour crosslinking, International journal of biomaterials 2017 (2017).
[155] R.K. Singh, D. Seliktar, A.J. Putnam, Capillary morphogenesis in PEG-collagen hydrogels, Biomaterials 34(37) (2013) 9331-9340.
[156] T. Takitoh, M. Bessho, M. Hirose, H. Ohgushi, H. Mori, M. Hara, Gamma-cross-linked nonfibrillar collagen gel as a scaffold for osteogenic differentiation of mesenchymal stem cells, Journal of bioscience and bioengineering 119(2) (2015) 217-225.
[157] D. Seybold, T.A. Schildhauer, J. Geßmann, G. Muhr, M. Köller, B. Roetman, Osteogenic differentiation of human mesenchymal stromal cells is promoted by a leukocytes containing fibrin matrix, Langenbeck's archives of surgery 395(6) (2010) 719-726.
[158] A. Arora, M. Sriram, A. Kothari, D.S. Katti, Co-culture of infrapatellar fat pad–derived mesenchymal stromal cells and articular chondrocytes in plasma clot for cartilage tissue engineering, Cytotherapy 19(7) (2017) 881-894.
[159] R.M. Schulz, M. Haberhauer, G. Zernia, C. Pösel, C. Thümmler, J.S. Somerson, D. Huster, Comprehensive characterization of chondrocyte cultures in plasma and whole blood biomatrices for cartilage tissue engineering, Journal of tissue engineering and regenerative medicine 8(7) (2014) 566-577.

[160] R.F. Nicosia, R. Tchao, J. Leighton, Interactions between newly formed endothelial channels and carcinoma cells in plasma clot culture, Clinical & experimental metastasis 4(2) (1986) 91-104.
[161] C.C. Mouline, D. Quincey, J.-P. Laugier, G.F. Carle, J.-M. Bouler, N. Rochet, J.-C. Scimeca, Osteoclastic differentiation of mouse and human monocytes in a plasma clot/biphasic calcium phosphate microparticles composite, Eur Cell Mater 20 (2010) 379-392.
[162] R. Gosden, Restitution of fertility in sterilized mice by transferring primordial ovarian follicles, Human Reproduction 5(2) (1990) 117-122.
[163] J. Carroll, R.G. Gosden, Transplantation of frozen-thawed mouse primordial follicles, Hum Reprod 8(8) (1993) 1163-7.
[164] M.-M. Dolmans, B. Martinez-Madrid, E. Gadisseux, Y. Guiot, W.Y. Yuan, A. Torre, A. Camboni, A. Van Langendonckt, J. Donnez, Short-term transplantation of isolated human ovarian follicles and cortical tissue into nude mice, Reproduction 134(2) (2007) 253-262.
[165] M.-M. Dolmans, W.Y. Yuan, A. Camboni, A. Torre, A. Van Langendonckt, B. Martinez-Madrid, J. Donnez, Development of antral follicles after xenografting of isolated small human preantral follicles, Reproductive biomedicine online 16(5) (2008) 705-711.
[166] J.V. Shah, P.A. Janmey, Strain hardening of fibrin gels and plasma clots, Rheologica Acta 36(3) (1997) 262-268.
[167] S. Pors, M. Ramløse, D. Nikiforov, K. Lundsgaard, J. Cheng, C.Y. Andersen, S. Kristensen, Initial steps in reconstruction of the human ovary: survival of pre-antral stage follicles in a decellularized human ovarian scaffold, Human Reproduction 34(8) (2019) 1523-1535.
[168] A. Hassanpour, T. Talaei-Khozani, E. Kargar-Abarghouei, V. Razban, Z. Vojdani, Decellularized human ovarian scaffold based on a sodium lauryl ester sulfate (SLES)-treated protocol, as a natural three-dimensional scaffold for construction of bioengineered ovaries, Stem cell research & therapy 9(1) (2018) 1-13.
[169] M.M. Laronda, A.E. Jakus, K.A. Whelan, J.A. Wertheim, R.N. Shah, T.K. Woodruff, Initiation of puberty in mice following decellularized ovary transplant, Biomaterials 50 (2015) 20-29.
[170] A.B. Alshaikh, A.M. Padma, M. Dehlin, R. Akouri, M.J. Song, M. Brännström, M. Hellström, Decellularization and recellularization of the ovary for bioengineering applications; studies in the mouse, Reproductive Biology and Endocrinology 18(1) (2020) 1-10.
[171] F. Eivazkhani, N.S. Abtahi, S. Tavana, L. Mirzaeian, F. Abedi, B. Ebrahimi, L. Montazeri, M.R. Valojerdi, R. Fathi, Evaluating two ovarian decellularization methods in three species, Materials Science and Engineering: C 102 (2019) 670-682.
[172] W.-Y. Liu, S.-G. Lin, R.-Y. Zhuo, Y.-Y. Xie, W. Pan, X.-F. Lin, F.-X. Shen, Xenogeneic decellularized scaffold: a novel platform for ovary regeneration, Tissue Engineering Part C: Methods 23(2) (2017) 61-71.
[173] S.F. Badylak, Decellularized allogeneic and xenogeneic tissue as a bioscaffold for regenerative medicine: factors that influence the host response, Ann Biomed Eng 42(7) (2014) 1517-27.
[174] L.T. Saldin, M.C. Cramer, S.S. Velankar, L.J. White, S.F. Badylak, Extracellular matrix hydrogels from decellularized tissues: Structure and function, Acta Biomater 49 (2017) 1-15.
[175] T.K. Rajab, T.J. O'Malley, V. Tchantchaleishvili, Decellularized scaffolds for tissue engineering: Current status and future perspective, Artif Organs 44(10) (2020) 1031-1043.
[176] M.L. Wong, L.G. Griffiths, Immunogenicity in xenogeneic scaffold generation: antigen removal vs. decellularization, Acta Biomater 10(5) (2014) 1806-16.
[177] U. Boeer, F.F. Buettner, M. Klingenberg, G.C. Antonopoulos, H. Meyer, A. Haverich, M. Wilhelmi, Immunogenicity of intensively decellularized equine carotid arteries is conferred by the extracellular matrix protein collagen type VI, PLoS One 9(8) (2014) e105964.
[178] D. Choudhury, M. Yee, Z.L.J. Sheng, A. Amirul, M.W. Naing, Decellularization Systems and Devices: State-of-the-art Review, Acta Biomaterialia (2020).

[179] Q. Yao, Y.-W. Zheng, H.-L. Lin, Q.-H. Lan, Z.-W. Huang, L.-F. Wang, R. Chen, J. Xiao, L. Kou, H.-L. Xu, Exploiting crosslinked decellularized matrix to achieve uterus regeneration and construction, Artificial cells, nanomedicine, and biotechnology 48(1) (2020) 218-229.
[180] B.S. Kim, H. Kim, G. Gao, J. Jang, D.-W. Cho, Decellularized extracellular matrix: a step towards the next generation source for bioink manufacturing, Biofabrication 9(3) (2017) 034104.
[181] E. Lih, K.W. Park, S.Y. Chun, H. Kim, T.G. Kwon, Y.K. Joung, D.K. Han, Biomimetic porous PLGA scaffolds incorporating decellularized extracellular matrix for kidney tissue regeneration, ACS applied materials & interfaces 8(33) (2016) 21145-21154.
[182] Z. Huang, O. Godkin, G. Schulze-Tanzil, The challenge in using mesenchymal stromal cells for recellularization of decellularized cartilage, Stem cell reviews and reports 13(1) (2017) 50-67.
[183] Y.-H. Tsou, J. Khoneisser, P.-C. Huang, X. Xu, Hydrogel as a bioactive material to regulate stem cell fate, Bioactive materials 1(1) (2016) 39-55.
[184] H. Wang, Y. Feng, Z. Fang, W. Yuan, M. Khan, Co-electrospun blends of PU and PEG as potential biocompatible scaffolds for small-diameter vascular tissue engineering, Materials Science and Engineering: C 32(8) (2012) 2306-2315.
[185] S.R. Bhattarai, N. Bhattarai, H.K. Yi, P.H. Hwang, D.I. Cha, H.Y. Kim, Novel biodegradable electrospun membrane: scaffold for tissue engineering, Biomaterials 25(13) (2004) 2595-2602.
[186] M. Fittkau, P. Zilla, D. Bezuidenhout, M. Lutolf, P. Human, J.A. Hubbell, N. Davies, The selective modulation of endothelial cell mobility on RGD peptide containing surfaces by YIGSR peptides, Biomaterials 26(2) (2005) 167-174.
[187] W. Celentano, J. Battistella, I.P. Silvestri, R. Bruni, X. Huang, M. Li, P. Messa, S. Ordanini, F. Cellesi, Engineered polyester-PEG nanoparticles prepared through a “grafting through” strategy and post-functionalization via Michael type addition, Reactive and Functional Polymers 131 (2018) 164-173.
[188] D. Guarnieri, A. De Capua, M. Ventre, A. Borzacchiello, C. Pedone, D. Marasco, M. Ruvo, P. Netti, Covalently immobilized RGD gradient on PEG hydrogel scaffold influences cell migration parameters, Acta biomaterialia 6(7) (2010) 2532-2539.
[189] M. Lutolf, J. Hubbell, Synthesis and physicochemical characterization of end-linked poly (ethylene glycol)-co-peptide hydrogels formed by Michael-type addition, Biomacromolecules 4(3) (2003) 713-722.
[190] M. Vigen, J. Ceccarelli, A.J. Putnam, Protease-sensitive PEG hydrogels regulate vascularization in vitro and in vivo, Macromolecular bioscience 14(10) (2014) 1368-1379.
[191] Y. Luo, G. Engelmayr, D.T. Auguste, L. da Silva Ferreira, J.M. Karp, R. Saigal, R. Langer, 3D Scaffolds, Principles of Tissue Engineering, Elsevier2014, pp. 475-494.
[192] C.E. Tomaszewski, E. Constance, M.M. Lemke, H. Zhou, V. Padmanabhan, K.B. Arnold, A. Shikanov, Adipose-derived stem cell-secreted factors promote early stage follicle development in a biomimetic matrix, Biomaterials science 7(2) (2019) 571-580.
[193] C.E. Tomaszewski, K.M. DiLillo, B.M. Baker, K.B. Arnold, A. Shikanov, Sequestered cell-secreted extracellular matrix proteins improve murine folliculogenesis and oocyte maturation for fertility preservation, Acta Biomater (2021).
[194] C.R. Reed, L. Han, A. Andrady, M. Caballero, M.C. Jack, J.B. Collins, S.C. Saba, E.G. Loboa, B.A. Cairns, J.A. van Aalst, Composite tissue engineering on polycaprolactone nanofiber scaffolds, Annals of plastic surgery 62(5) (2009) 505-512.
[195] L. Liverani, N. Raffel, A. Fattahi, A. Preis, I. Hoffmann, A.R. Boccaccini, M.W. Beckmann, R. Dittrich, Electrospun patterned porous scaffolds for the support of ovarian follicles growth: a feasibility study, Scientific reports 9(1) (2019) 1-14.
[196] M. Asaduzzman, X. Cui, H. Zhang, F. Young, Three dimensional in vitro culture of murine secondary follicles in a defined synthetic matrix, Journal of Biomaterials and Nanobiotechnology 9(03) (2018) 244.

[197] M.J. Kratochvil, A.J. Seymour, T.L. Li, S.P. Paşca, C.J. Kuo, S.C. Heilshorn, Engineered materials for organoid systems, Nature Reviews Materials 4(9) (2019) 606-622.
[198] N. Gjorevski, N. Sachs, A. Manfrin, S. Giger, M.E. Bragina, P. Ordóñez-Morán, H. Clevers, M.P. Lutolf, Designer matrices for intestinal stem cell and organoid culture, Nature 539(7630) (2016) 560-564.
[199] M. Norouzi, I. Shabani, H.H. Ahvaz, M. Soleimani, PLGA/gelatin hybrid nanofibrous scaffolds encapsulating EGF for skin regeneration, Journal of biomedical materials research Part A 103(7) (2015) 2225-2235.
[200] L. Zhao, X. Li, L. Yang, L. Sun, S. Mu, H. Zong, Q. Li, F. Wang, S. Song, C. Yang, Evaluation of remodeling and regeneration of electrospun PCL/fibrin vascular grafts in vivo, Materials Science and Engineering: C 118 (2021) 111441.
[201] M. Nakamura, S. Iwanaga, K. Arai, H. Toda, G. Capi, T. Nikaido, Computer-Assisted Biofabrication: The challenges on manufacturing 3-D biological tissues for tissue and organ engineering, 2011 Symposium on VLSI Technology-Digest of Technical Papers, IEEE, 2011, pp. 2-5.
[202] S.V. Murphy, A. Atala, 3D bioprinting of tissues and organs, Nature biotechnology 32(8) (2014) 773.
[203] A. Dhawan, P.M. Kennedy, E.B. Rizk, I.T. Ozbolat, Three-dimensional bioprinting for bone and cartilage restoration in orthopaedic surgery, JAAOS-Journal of the American Academy of Orthopaedic Surgeons 27(5) (2019) e215-e226.
[204] A. Arslan-Yildiz, R. El Assal, P. Chen, S. Guven, F. Inci, U. Demirci, Towards artificial tissue models: past, present, and future of 3D bioprinting, Biofabrication 8(1) (2016) 014103.
[205] B. Derby, Printing and prototyping of tissues and scaffolds, Science 338(6109) (2012) 921-926.
[206] V. Mironov, N. Reis, B. Derby, Bioprinting: a beginning, Tissue engineering 12(4) (2006) 631-634.
[207] T. Billiet, M. Vandenhaute, J. Schelfhout, S. Van Vlierberghe, P. Dubruel, A review of trends and limitations in hydrogel-rapid prototyping for tissue engineering, Biomaterials 33(26) (2012) 6020-6041.
[208] Y.-J. Seol, H.-W. Kang, S.J. Lee, A. Atala, J.J. Yoo, Bioprinting technology and its applications, European Journal of Cardio-Thoracic Surgery 46(3) (2014) 342-348.
[209] Y. Wang, Application of 3D bioprinting in cartilage tissue, AIP Conference Proceedings, AIP Publishing LLC, 2019, p. 020047.
[210] M.K. DeBari, M.N. Keyser, M.A. Bai, R.D. Abbott, 3D printing with silk: considerations and applications, Connective tissue research 61(2) (2020) 163-173.
[211] J.B. Nagashima, R. El Assal, N. Songsasen, U. Demirci, Evaluation of an ovary-on-a-chip in large mammalian models: Species specificity and influence of follicle isolation status, Journal of tissue engineering and regenerative medicine 12(4) (2018) e1926-e1935.
[212] S. Xiao, J.R. Coppeta, H.B. Rogers, B.C. Isenberg, J. Zhu, S.A. Olalekan, K.E. McKinnon, D. Dokic, A.S. Rashedi, D.J. Haisenleder, A microfluidic culture model of the human reproductive tract and 28-day menstrual cycle, Nature communications 8 (2017) 14584.
[213] J. Nawroth, J. Rogal, M. Weiss, S.Y. Brucker, P. Loskill, Organ-on-a-Chip Systems for Women's Health Applications, Advanced healthcare materials 7(2) (2018) 1700550.
[214] A. Skardal, A. Atala, Biomaterials for integration with 3-D bioprinting, Annals of biomedical engineering 43(3) (2015) 730-746.
[215] K. Markstedt, A. Mantas, I. Tournier, H.c. Martínez Ávila, D. Hagg, P. Gatenholm, 3D bioprinting human chondrocytes with nanocellulose–alginate bioink for cartilage tissue engineering applications, Biomacromolecules 16(5) (2015) 1489-1496.
[216] S. Vijayavenkataraman, J.Y. Fuh, W.F. Lu, 3D printing and 3D bioprinting in pediatrics, Bioengineering 4(3) (2017) 63.

[217] N. Ashammakhi, A. Hasan, O. Kaarela, B. Byambaa, A. Sheikhi, A.K. Gaharwar, A. Khademhosseini, Advancing frontiers in bone bioprinting, Advanced healthcare materials 8(7) (2019) 1801048.
[218] X. Cui, K. Breitenkamp, M. Finn, M. Lotz, D.D. D'Lima, Direct human cartilage repair using three-dimensional bioprinting technology, Tissue Engineering Part A 18(11-12) (2012) 1304-1312.
[219] V.H. Mouser, F.P. Melchels, J. Visser, W.J. Dhert, D. Gawlitta, J. Malda, Yield stress determines bioprintability of hydrogels based on gelatin-methacryloyl and gellan gum for cartilage bioprinting, Biofabrication 8(3) (2016) 035003.
[220] D. Nguyen, D.A. Hägg, A. Forsman, J. Ekholm, P. Nimkingratana, C. Brantsing, T. Kalogeropoulos, S. Zaunz, S. Concaro, M. Brittberg, Cartilage tissue engineering by the 3D bioprinting of iPS cells in a nanocellulose/alginate bioink, Scientific reports 7(1) (2017) 1-10.
[221] G. Gao, K. Hubbell, A.F. Schilling, G. Dai, X. Cui, Bioprinting cartilage tissue from mesenchymal stem cells and PEG hydrogel, 3D Cell Culture, Springer2017, pp. 391-398.
[222] W.L. Ng, W.Y. Yeong, M.W. Naing, Development of polyelectrolyte chitosan-gelatin hydrogels for skin bioprinting, Procedia CIRP 49 (2016) 105-12.
[223] L.J. Pourchet, A. Thepot, M. Albouy, E.J. Courtial, A. Boher, L.J. Blum, C.A. Marquette, Human skin 3D bioprinting using scaffold-free approach, Advanced healthcare materials 6(4) (2017) 1601101.
[224] D. Min, W. Lee, I.H. Bae, T.R. Lee, P. Croce, S.S. Yoo, Bioprinting of biomimetic skin containing melanocytes, Experimental dermatology 27(5) (2018) 453-459.
[225] P. He, J. Zhao, J. Zhang, B. Li, Z. Gou, M. Gou, X. Li, Bioprinting of skin constructs for wound healing, Burns & trauma 6(1) (2018).
[226] T. Baltazar, J. Merola, C. Catarino, C.B. Xie, N.C. Kirkiles-Smith, V. Lee, S. Hotta, G. Dai, X. Xu, F.C. Ferreira, Three Dimensional Bioprinting of a Vascularized and Perfusable Skin Graft Using Human Keratinocytes, Fibroblasts, Pericytes, and Endothelial Cells, Tissue Engineering Part A 26(5-6) (2020) 227-238.
[227] A.K. Miri, A. Khalilpour, B. Cecen, S. Maharjan, S.R. Shin, A. Khademhosseini, Multiscale bioprinting of vascularized models, Biomaterials 198 (2019) 204-216.
[228] D.B. Kolesky, R.L. Truby, A.S. Gladman, T.A. Busbee, K.A. Homan, J.A. Lewis, 3D bioprinting of vascularized, heterogeneous cell-laden tissue constructs, Advanced materials 26(19) (2014) 3124-3130.
[229] C. Norotte, F.S. Marga, L.E. Niklason, G. Forgacs, Scaffold-free vascular tissue engineering using bioprinting, Biomaterials 30(30) (2009) 5910-5917.
[230] P. Datta, B. Ayan, I.T. Ozbolat, Bioprinting for vascular and vascularized tissue biofabrication, Acta biomaterialia 51 (2017) 1-20.
[231] V.K. Lee, A.M. Lanzi, H. Ngo, S.-S. Yoo, P.A. Vincent, G. Dai, Generation of multi-scale vascular network system within 3D hydrogel using 3D bio-printing technology, Cellular and molecular bioengineering 7(3) (2014) 460-472.
[232] Y. Wu, Z.Y.W. Lin, A.C. Wenger, K.C. Tam, X.S. Tang, 3D bioprinting of liver-mimetic construct with alginate/cellulose nanocrystal hybrid bioink, Bioprinting 9 (2018) 1-6.
[233] C. Zhong, H.-Y. Xie, L. Zhou, X. Xu, S.-S. Zheng, Human hepatocytes loaded in 3D bioprinting generate mini-liver, Hepatobiliary & Pancreatic Diseases International 15(5) (2016) 512-518.
[234] Q. Mao, Y. Wang, Y. Li, S. Juengpanich, W. Li, M. Chen, J. Yin, J. Fu, X. Cai, Fabrication of liver microtissue with liver decellularized extracellular matrix (dECM) bioink by digital light processing (DLP) bioprinting, Materials Science and Engineering: C (2020) 110625.
[235] M.M. Laronda, A.L. Rutz, S. Xiao, K.A. Whelan, F.E. Duncan, E.W. Roth, T.K. Woodruff, R.N. Shah, A bioprosthetic ovary created using 3D printed microporous scaffolds restores ovarian function in sterilized mice, Nature communications 8(1) (2017) 1-10.

[236] T. Wu, Y.Y. Gao, J. Su, X.N. Tang, Q. Chen, L.W. Ma, J.J. Zhang, J.M. Wu, S.X. Wang, Three-dimensional bioprinting of artificial ovaries by an extrusion-based method using gelatin-methacryloyl bioink, Climacteric (2021) 1-9.
[237] X. He, Microfluidic encapsulation of ovarian follicles for 3D culture, Annals of biomedical engineering 45(7) (2017) 1676-1684.
[238] B.G. Chung, K.-H. Lee, A. Khademhosseini, S.-H. Lee, Microfluidic fabrication of microengineered hydrogels and their application in tissue engineering, Lab on a Chip 12(1) (2012) 45-59.
[239] F. Zheng, F. Fu, Y. Cheng, C. Wang, Y. Zhao, Z. Gu, Organ-on-a-Chip Systems: microengineering to biomimic living systems, Small 12(17) (2016) 2253-2282.
[240] B. Zhang, M. Radisic, Organ-on-a-chip devices advance to market, Lab on a Chip 17(14) (2017) 2395-2420.
[241] B. Zhang, A. Korolj, B.F.L. Lai, M. Radisic, Advances in organ-on-a-chip engineering, Nature Reviews Materials 3(8) (2018) 257-278.
[242] D.E. Ingber, Developmentally inspired human 'organs on chips', Development 145(16) (2018) dev156125.
[243] N. Kashaninejad, M.J.A. Shiddiky, N.T. Nguyen, Advances in Microfluidics-Based Assisted Reproductive Technology: From Sperm Sorter to Reproductive System-on-a-Chip, Advanced Biosystems 2(3) (2018) 1700197.
[244] Y.S. Choi, I.D. Kim, Y.J. Seol, M.J. Jeon, J. Jackson*, J. Yoo, A. Atala, MP38-04 BIOPRINTED OVARY-ON-A-CHIP PLATFORM AS A MODEL OF OVARIAN PHYSIOLOGY AND DISEASE, The Journal of Urology 203(Supplement 4) (2020) e570-e570.
[245] C.-T. Ho, R.-Z. Lin, W.-Y. Chang, H.-Y. Chang, C.-H. Liu, Rapid heterogeneous liver-cell on-chip patterning via the enhanced field-induced dielectrophoresis trap, Lab on a Chip 6(6) (2006) 724-734.
[246] N.S. Bhise, V. Manoharan, S. Massa, A. Tamayol, M. Ghaderi, M. Miscuglio, Q. Lang, Y.S. Zhang, S.R. Shin, G. Calzone, A liver-on-a-chip platform with bioprinted hepatic spheroids, Biofabrication 8(1) (2016) 014101.
[247] K.-H. Lee, J. Lee, S.-H. Lee, 3D liver models on a microplatform: well-defined culture, engineering of liver tissue and liver-on-a-chip, Lab on a Chip 15(19) (2015) 3822-3837.
[248] S. Knowlton, S. Tasoglu, A bioprinted liver-on-a-chip for drug screening applications, Trends in biotechnology 34(9) (2016) 681-682.
[249] H. Lee, S. Chae, J.Y. Kim, W. Han, J. Kim, Y. Choi, D.-W. Cho, Cell-printed 3D liver-on-a-chip possessing a liver microenvironment and biliary system, Biofabrication 11(2) (2019) 025001.
[250] S. Lasli, H.J. Kim, K. Lee, C.A.E. Suurmond, M. Goudie, P. Bandaru, W. Sun, S. Zhang, N. Zhang, S. Ahadian, A Human Liver-on-a-Chip Platform for Modeling Nonalcoholic Fatty Liver Disease, Advanced Biosystems 3(8) (2019) 1900104.
[251] D. Huh, D.C. Leslie, B.D. Matthews, J.P. Fraser, S. Jurek, G.A. Hamilton, K.S. Thorneloe, M.A. McAlexander, D.E. Ingber, A human disease model of drug toxicity–induced pulmonary edema in a lung-on-a-chip microdevice, Science translational medicine 4(159) (2012) 159ra147-159ra147.
[252] A.O. Stucki, J.D. Stucki, S.R. Hall, M. Felder, Y. Mermoud, R.A. Schmid, T. Geiser, O.T. Guenat, A lung-on-a-chip array with an integrated bio-inspired respiration mechanism, Lab on a Chip 15(5) (2015) 1302-1310.
[253] D. Huh, A human breathing lung-on-a-chip, Annals of the American Thoracic Society 12(Supplement 1) (2015) S42-S44.
[254] X. Yang, K. Li, X. Zhang, C. Liu, B. Guo, W. Wen, X. Gao, Nanofiber membrane supported lung-on-a-chip microdevice for anti-cancer drug testing, Lab on a Chip 18(3) (2018) 486-495.
[255] J. Nie, Q. Gao, Y. Wang, J. Zeng, H. Zhao, Y. Sun, J. Shen, H. Ramezani, Z. Fu, Z. Liu, Vessel-on-a-chip with Hydrogel-based Microfluidics, Small 14(45) (2018) 1802368.

[256] I. Beekers, T. van Rooij, M.D. Verweij, M. Versluis, N. de Jong, S.J. Trietsch, K. Kooiman, Acoustic characterization of a vessel-on-a-chip microfluidic system for ultrasound-mediated drug delivery, IEEE transactions on ultrasonics, ferroelectrics, and frequency control 65(4) (2018) 570-581.
[257] Y. Li, K. Zhu, X. Liu, Y.S. Zhang, Blood-Vessel-on-a-Chip Platforms for Evaluating Nanoparticle Drug Delivery Systems, Current drug metabolism 19(2) (2018) 100-109.
[258] R. De Luca, G. Silvani, C. Scognamiglio, G. Sinibaldi, G. Peruzzi, M. Chinappi, M. Kiani, C. Casciola, Towards cavitation-enhanced permeability in blood vessel on a chip, AIP Conference Proceedings, AIP Publishing LLC, 2017, p. 020010.
[259] M.J. Wilmer, C.P. Ng, H.L. Lanz, P. Vulto, L. Suter-Dick, R. Masereeuw, Kidney-on-a-chip technology for drug-induced nephrotoxicity screening, Trends in biotechnology 34(2) (2016) 156-170.
[260] T.T. Nieskens, M.J. Wilmer, Kidney-on-a-chip technology for renal proximal tubule tissue reconstruction, European journal of pharmacology 790 (2016) 46-56.
[261] R.D. Sochol, N.R. Gupta, J.V. Bonventre, A role for 3D printing in kidney-on-a-chip platforms, Current transplantation reports 3(1) (2016) 82-92.
[262] E.J. Weber, K.A. Lidberg, L. Wang, T.K. Bammler, J.W. MacDonald, M.J. Li, M. Redhair, W.M. Atkins, C. Tran, K.M. Hines, Human kidney on a chip assessment of polymyxin antibiotic nephrotoxicity, JCI insight 3(24) (2018).
[263] S. Xiao, J. Xu, Y. Wang, B. Brooks, S. Chatterjee, G. Scott, Use of a novel ovary-on-a-chip to screen for female reproductive toxicity of microcystins, Ocean Sciences Meeting 2020, AGU, 2020.
[264] A.U.R. Aziz, M. Fu, J. Deng, C. Geng, Y. Luo, B. Lin, X. Yu, B. Liu, A microfluidic device for culturing an encapsulated ovarian follicle, Micromachines 8(11) (2017) 335.
[265] X. Yu, Q. Jiang, Y. Zhao, S. Deng, K. Qin, H. Wang, B. Liu, Doxorubicin-induced toxicity to 3D-cultured rat ovarian follicles on a microfluidic chip, Toxicology in Vitro 62 (2020) 104677.
[266] B. Patra, E. Carmona, M. Lateef, J. Kendall-Dupont, B. Peant, D. Provencher, A. Mes-Masson, T. Gervais, Are 3D spheroids always more resistant to chemotherapy than 2D cultures? A chip-based survey using ovarian cancer cell lines, Proceedings of the 20th International Conference on Miniaturized Systems in Chemistry and the Life Sciences, 2016, pp. 1555-1556.
[267] B. Saha, J. Bui, P. Biswas, A.K. Sood, V. Afshar-Khargan, A. Jain, Dissecting Vascular and Platelet Function in Ovarian Cancer With Organ-on-a-chip Methodology, Arteriosclerosis, Thrombosis, and Vascular Biology 39(Suppl_1) (2019) A554-A554.
[268] P. ŚNIADEK, R. WALCZAK, J. Dziuban, M. Jackowska, P. ANTOSIK, J. JAŚKOWSKI, B. Kempisty, Lab-on-a-chip for quality classification of pig oocytes, Optica Applicata 41(2) (2011).
[269] B. Kempisty, R. Walczak, P. Antosik, P. Sniadek, M. Rybska, H. Piotrowska, D. Bukowska, J. Dziuban, M. Nowicki, J.M. Jaśkowski, Microfluidic method of pig oocyte quality assessment in relation to different follicular size based on lab-on-chip technology, BioMed research international 2014 (2014).
[270] M.C. Chiti, C.A. Amorim, M.-M. Dolmans, A fibrin-based artificial ovary prototype: from animal models to human clinical application, (2018).
[271] E. Ouni, D. Vertommen, M.C. Chiti, M.-M. Dolmans, C.A. Amorim, A draft map of the human ovarian proteome for tissue engineering and clinical applications, Molecular & Cellular Proteomics 18 (2019) S159-S173.
[272] E. Ouni, C. Bouzin, M. Dolmans, E. Marbaix, S. Pyr dit Ruys, D. Vertommen, C. Amorim, Spatiotemporal changes in mechanical matrisome components of the human ovary from prepuberty to menopause, Human Reproduction 35(6) (2020) 1391-1410.
[273] M. Sarker, S. Naghieh, N. Sharma, L. Ning, X. Chen, Bioprinting of vascularized tissue scaffolds: influence of biopolymer, cells, growth factors, and gene delivery, Journal of healthcare engineering 2019 (2019).

[274] D. Lei, Y. Yang, Z. Liu, B. Yang, W. Gong, S. Chen, S. Wang, L. Sun, B. Song, H. Xuan, 3D printing of biomimetic vasculature for tissue regeneration, Materials Horizons 6(6) (2019) 1197-1206.
[275] R. Suntornnond, E.Y.S. Tan, J. An, C.K. Chua, A highly printable and biocompatible hydrogel composite for direct printing of soft and perfusable vasculature-like structures, Scientific reports 7(1) (2017) 1-11.
[276] T. Abudula, K. Gauthaman, A.H. Hammad, K. Joshi Navare, A.A. Alshahrie, S.A. Bencherif, A. Tamayol, A. Memic, Oxygen-releasing antibacterial nanofibrous scaffolds for tissue engineering applications, Polymers 12(6) (2020) 1233.
[277] H. Steg, A.T. Buizer, W. Woudstra, A.G. Veldhuizen, S.K. Bulstra, D.W. Grijpma, R. Kuijer, Oxygen-releasing poly (trimethylene carbonate) microspheres for tissue engineering applications, Polymers for advanced technologies 28(10) (2017) 1252-1257.
[278] P.A. Shiekh, A. Singh, A. Kumar, Oxygen-releasing antioxidant cryogel scaffolds with sustained oxygen delivery for tissue engineering applications, ACS applied materials & interfaces 10(22) (2018) 18458-18469.
[279] C.Y.C. Montesdeoca, S. Afewerki, T.D. Stocco, M.A.F. Corat, M.M.M. de Paula, F.R. Marciano, A.O. Lobo, Oxygen-generating smart hydrogels supporting chondrocytes survival in oxygen-free environments, Colloids and Surfaces B: Biointerfaces 194 (2020) 111192.
[280] M.R. Casanova, C. Oliveira, E.M. Fernandes, R.L. Reis, T.H. Silva, A. Martins, N.M. Neves, Spatial immobilization of endogenous growth factors to control vascularization in bone tissue engineering, Biomaterials science 8(9) (2020) 2577-2589.
[281] R. Gianni-Barrera, N. Di Maggio, L. Melly, M.G. Burger, E. Mujagic, L. Gürke, D.J. Schaefer, A. Banfi, Therapeutic vascularization in regenerative medicine, Stem cells translational medicine 9(4) (2020) 433-444.
[282] S. Minardi, L. Pandolfi, F. Taraballi, X. Wang, E. De Rosa, Z.D. Mills, X. Liu, M. Ferrari, E. Tasciotti, Enhancing vascularization through the controlled release of platelet-derived growth factor-BB, ACS applied materials & interfaces 9(17) (2017) 14566-14575.

Figure captions

Figure 1. A schematic illustration of the fertility preservation strategy using ovarian tissue cryopreservation and ovarian tissue engineering. Before chemo- or radiotherapy, the ovarian tissue is removed and cryopreserved. Once the patient is cured, the tissue fragments are thawed, and their follicles and cells are isolated and seeded/encapsulated in a 3D bioengineered scaffold. Finally, the construct is orthotopically transplanted.

Figure 2. A schematic of follicle development from the primordial to the antral stage.

Figure 3. Biomaterials used for ovarian tissue engineering.

Figure 4. Classification of 3D printing technologies. Inkjet 3D printers are divide into thermal and piezoelectric setups, which use heat or mechanical stimulation, respectively, to generate droplets. Extrusion-based 3D printers extrude bioink using pneumatic, piston, or screw dispensing systems. In laser-based 3D printers, a laser pulse focuses on the donor slide coated by an absorbing layer and induces a vapor bubble that ejects the droplet onto the collection substrate.

Figure 5. 3D printed construct for isolated follicles. (a-c) 3D reconstructions of confocal fluorescence images of 30°, 60°, and 90° angle 3D printed scaffolds (a, b and c, respectively). (d-f) green fluorescent protein-positive (GFP+) follicles seeded in pores after two days in culture. Follicles in 30° and 60° pores (d and e, respectively) often resided in corners, whereas they tended to be on one strut in 90° pores. (g and h) vascularization in 60° angle 3D printed scaffold with immunostaining for endothelial marker platelet endothelial cell adhesion molecule (PECAM) (red) or pericyte marker PDGFR β1 (green) and DNA (blue) in corpus luteum, antral follicles and interstitial space of bioprosthetic ovary removed after 8-10 weeks. i) a healthy pup after mating transplanted animals [235]. Reprinted with permission from [235] © Springer Nature (2021).

Figure 6. Design and materials of biomimetic ovarian microtissue. (a) Ovary anatomy with two distinct layers: a more rigid cortex and softer medulla. (b) A schematic view of microchannels system for encapsulating follicles (top) developed by Choi et al. [50] together with a zoom-in view of the nonplanar design of the flow-focusing junction (bottom) where W1= 200, H1=200, W2= 80, H2=300, W3=200, and H3=400 μm. (c-f) follicle growth in the engineered microtissue on days 0, 5, 7, and 9, in which antral cavity and a cumulus-oocyte

complex (COC) were observed on day 9 [506]. Reprinted and adapted from [50] © Elsevier (2021).

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: