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From lab to life: Advances in tissue engineering and 3D bioprinting for regenerative female reproductive health

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Abstract

Introduction: Infertility affects millions of women worldwide, and despite current treatment options, definitive therapies remain limited. Emerging regenerative medicine strategies, particularly stem cell therapy and three- dimensional (3D) bioprinting, offer significant potential to repair and regenerate female reproductive tissues.

Methods: In this scoping review, 199 studies, including in vitro experiments, animal models, and early-stage clinical investigations, were analyzed to evaluate scientific advancements and translational potential in female reproductive tissue engineering. The focus was on stem cell sources, the development of bioinks, and the applications of 3D bioprinting to reconstruct the endometrium, ovary, cervix, and vagina.

Results: Stem cells derived from bone marrow, adipose tissue, and menstrual blood improved ovarian function and endometrial regeneration, with several animal studies reporting successful pregnancies. Concurrently, 3D bioprinting technologies enabled the creation of cell-laden scaffolds with promising potential for tissue reconstruction. Remaining challenges include the development of biocompatible bioinks, formation of functional vascular networks, and accurate recreation of extracellular matrix microenvironments. Most current approaches remain at the preclinical stage; however, the growing body of experimental evidence and early clinical investigations indicate promising translational potential and gradual progress toward future clinical application in female reproductive medicine.

Discussion/Conclusion: Although most advances remain at the preclinical stage, the integration of stem cell therapy and 3D bioprinting demonstrates increasing translational readiness and a clear pathway toward future clinical applications. This review highlights the

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current progress, existing barriers, and essential research directions for advancing regenerative strategies in female reproductive health.

Keywords: Bioprinting; Cell-laden scaffolds; Ovary; Stem cells; Uterus; Vaginal substitutes

1. Introduction

According to the World Health Organization (WHO), infertility is a major global health challenge affecting approximately 17.5% of the adult population worldwide, equivalent to nearly one in six individuals during their reproductive lifetime (Liang et al., 2025). Despite its high prevalence and substantial psychosocial and economic burden, access to fertility care remains limited in many regions due to financial, social, and healthcare barriers. These challenges underscore the urgent need for innovative regenerative approaches aimed at restoring reproductive function and improving fertility outcomes (Agarwal et al., 2021; Mancini and Pensabene, 2019; Rosner et al., 2024; Yi et al., 2025). Despite advances in assisted reproductive technologies, effective treatments for ovarian and endometrial dysfunction remain limited, and many causes of female infertility, such as ovarian insufficiency, endometrial damage, and uterine tissue loss, still lack effective regenerative options. This highlights a critical translational gap between current clinical practice and emerging regenerative medicine approaches (Chen et al., 2025; Vaˇskova et al., 2023´). This study is designed as a scoping review aimed at systematically mapping the contemporary landscape of stem cell-based therapies and three-dimensional (3D) bioprinting technologies in female reproductive health. The objectives of this review are to identify key cell sources suitable for reproductive tissue engineering, evaluate the most relevant studies on bioinks and 3D bioprinting for treating female infertility, and highlight remaining challenges and future

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directions. Unlike previous reviews, which have typically addressed stem cell therapies and bioprinting strategies separately, this review provides an integrated perspective by highlighting recent advances in bioinks, stem cell niche engineering, and the integration of 3D bioprinting with organoid technologies for female reproductive tissue engineering. The review work intends to answer the following research questions: "What are the cells/ stem cells for use in female reproductive system tissue engineering? What are the most relevant works on bioinks and 3D printing to treat female infertility?" (Fig. 1). Specifically, the work provides an updated synthesis of newer bioinks, novel stem cell niches, and the emerging convergence of 3D bioprinting with reproductive organoid technologies, offering a comprehensive translational perspective on the current opportunities and obstacles in the field. Tissue engineering and 3D bioprinting offer promising strategies to address these clinical gaps by providing the potential to restore or replace damaged reproductive tissues. Stem cell-based therapies have shown significant potential in improving ovarian function and endometrial regeneration (He and Li, 2025). Stem cells derived from bone marrow, adipose tissue, and menstrual blood have been demonstrated in vivo to enhance hormonal profiles and even lead to successful pregnancies (Dinsdale and Crespi, 2021; Mohamed et al., 2018; Su et al., 2016; Wang et al., 2025). Endometrial stem cells, capable of self-renewal and differentiation, as well as Leucine-rich repeat-containing G-protein-coupled receptor 5 cells, LGR5(+) cells, have been identified as key contributors to tissue maintenance and regeneration, although challenges remain for their clinical application (Franks and Hardy, 2020; Gargett et al., 2016; Saremi et al., 2023). The bioprinting of female reproductive tissues has emerged as a complementary approach that can create cell-laden scaffolds mimicking native tissue architecture. However, several obstacles must be overcome, including the development of bioinks that balance printability and

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biocompatibility, formation of functional vascular networks to deliver nutrients and remove waste, and replication of the extracellular matrix (ECM) to support cell growth (Li et al., 2025; Unagolla and Jayasuriya, 2020; Vermeulen et al., 2019). Furthermore, optimization of cell sources, hydrogels, and bioreactors is critical to achieve viable and functional bioprinted tissues. Addressing these challenges is essential for translating regenerative strategies into clinical practice (Huang and Ye, 2025; Sen et al., 2024).

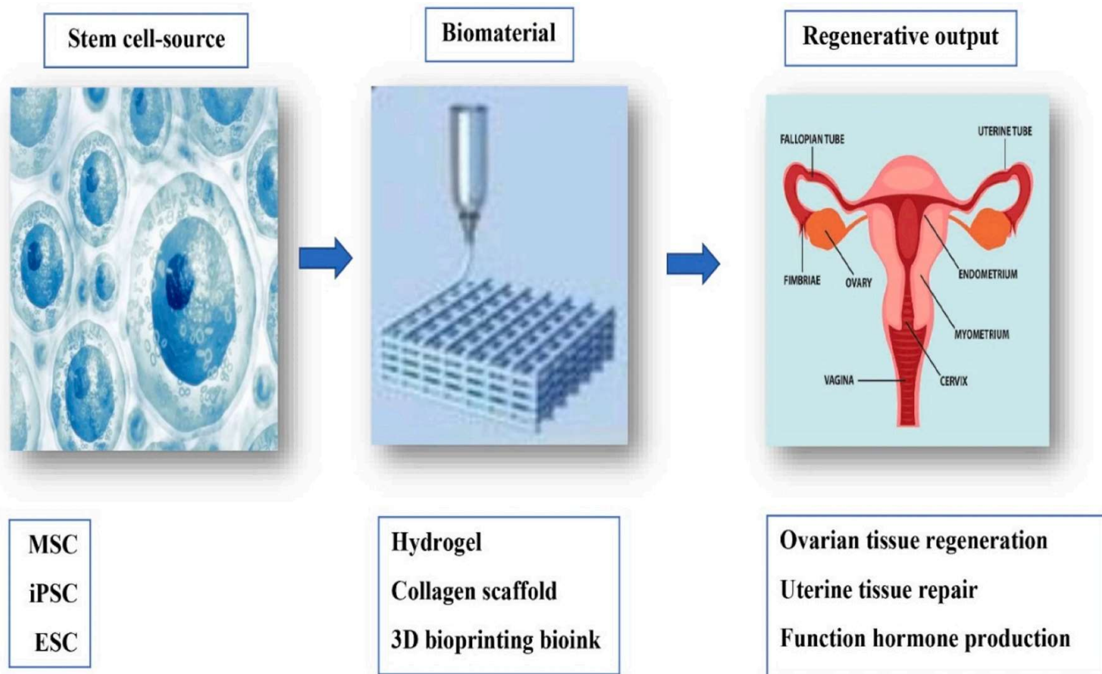

Fig. 1. *Overview of the main research questions addressed in this scoping review.*

2. Materials and methods/search strategy

This scoping review was conducted to systematically map the current landscape of stem cell-based therapies and 3D bioprinting in female reproductive health. A predefined review

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framework, including the search strategy, eligibility criteria, and thematic data extraction approach, was developed by the authors before conducting the literature search. No formal review protocol was registered. A comprehensive literature search was performed in PubMed, Web of Science, and Google Scholar for studies published between January 2010 and September 2025 to capture the most relevant and up-to-date studies. Keywords and search terms included combinations of terms related to female reproductive organs, infertility, stem cells, and bioprinting. Representative search terms included ("ovary" OR "endometrium" OR "cervix" OR "vagina" OR "female infertility") AND ("stem cells" OR "mesenchymal stem cells" OR "induced pluripotent stem cells" OR "3D bioprinting" OR "bioinks"). Boolean operators (AND, OR) were used to optimize the search strategy and maximize retrieval of relevant studies. Inclusion criteria encompassed original research, reviews, and empirical studies focusing on strategies for reconstructing female reproductive tissues using stem cells or 3D bioprinting. Studies addressing ovarian, endometrial, or other reproductive tract tissue regeneration, stem cell applications, or bioink/scaffold development for 3D printing were included. Both in vitro and in vivo studies were considered. Exclusion criteria included non-English publications, studies unrelated to female reproductive health, articles lacking sufficient methodological detail, and case reports, letters, or conference abstracts without full texts. Study quality and relevance were assessed by considering publication in peer- reviewed journals, the recency of publication, study type (human vs. animal models), and the methodological rigor described. A total of 199 articles met these criteria and were included in the review. The study selection process, including identification, screening, eligibility assessment, and final inclusion of studies, is summarized in the PRISMA-style flow diagram (Fig. 2). To synthesize the

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findings, the included studies were thematically categorized according to the specific cell type, target tissue, and the 3D bioprinting approach employed.

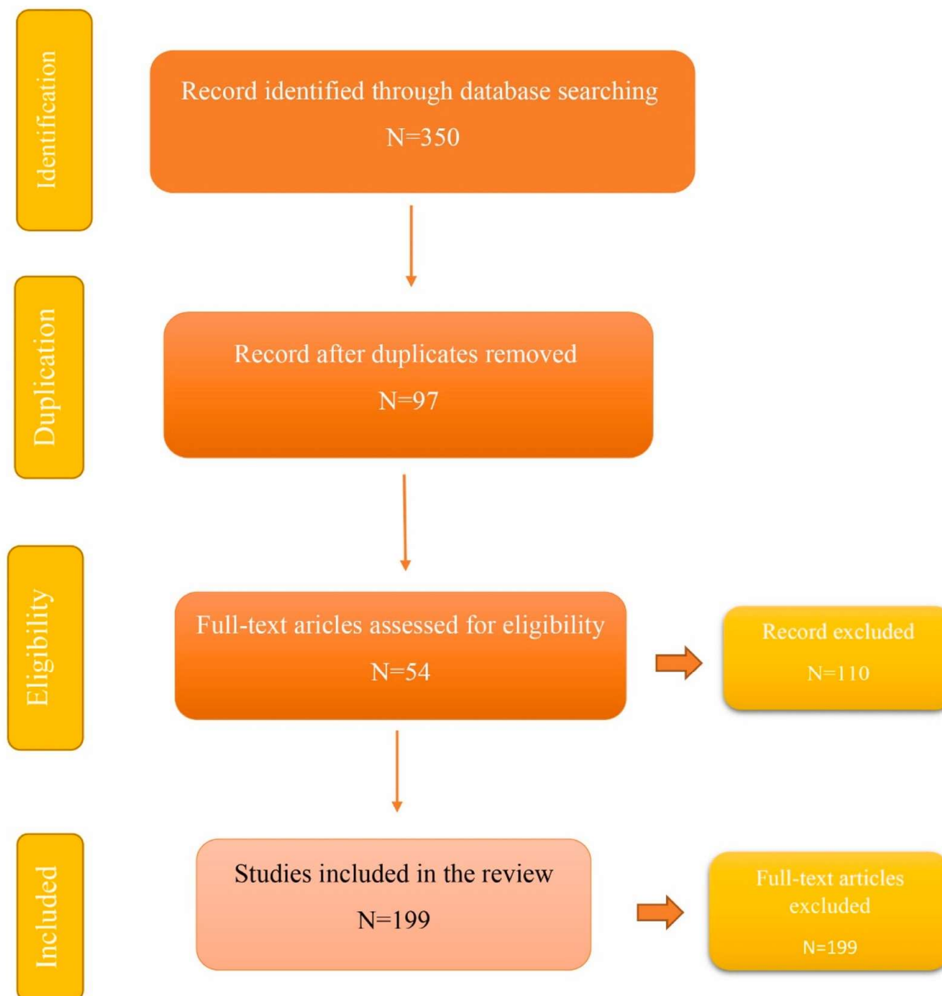

Fig. 2. *PRISMA flow diagram of the study selection process.*

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3. Results

3.1. Tissue engineering and infertility

3.1.1. Cells/stem cells for use in female reproductive system tissue engineering

The female reproductive system is negatively impacted by some toxins, such as: metals like lead, cadmium and mercury, pesticides and radiation. These toxins can directly affect the organ system or indirectly through hormonal disturbances, molecular changes, oxidative stress and DNA methylation (Fig. 3a). Numerous studies have demonstrated that various types of stem cells, including somatic stem cells (SSCs), bone marrow stem cells (BMScs), adipose-derived stem cells (ADSCs), umbilical cord mesenchymal cells (UC-MSCs), amniotic mesenchymal stem cells (hAMSCs), and menstrual blood stem cells (MenSCs), can help restore ovarian function and improve fertility outcomes in animal models of premature ovarian failure (POF) (Chen et al., 2025) (Fig. 3b). In one case, a patient with POF underwent a stem cell transplant, which not only improved their hormonal profile but also led to the return of menstruation, followed by a successful pregnancy and delivery of a healthy baby (Chen et al., 2018). In an animal model of early ovarian failure, Chen et al. found that autologous MSCs transplantation significantly enhanced ovarian function. These cells are believed to be effective partly due to their ability to produce cytokines such as TGF-β and interleukin− 10, which play a role in regulating the immune system (English et al., 2010). SSCs, in contrast to embryonic stem cells (ESCs), have a lower differentiation capacity. SSCs are found in mature tissues like mesenchymal, hematopoietic, nervous, and digestive tissues, with mesenchymal, hematopoietic, and bone marrow-derived stem cells being among the most common (Kim et al., 2005).

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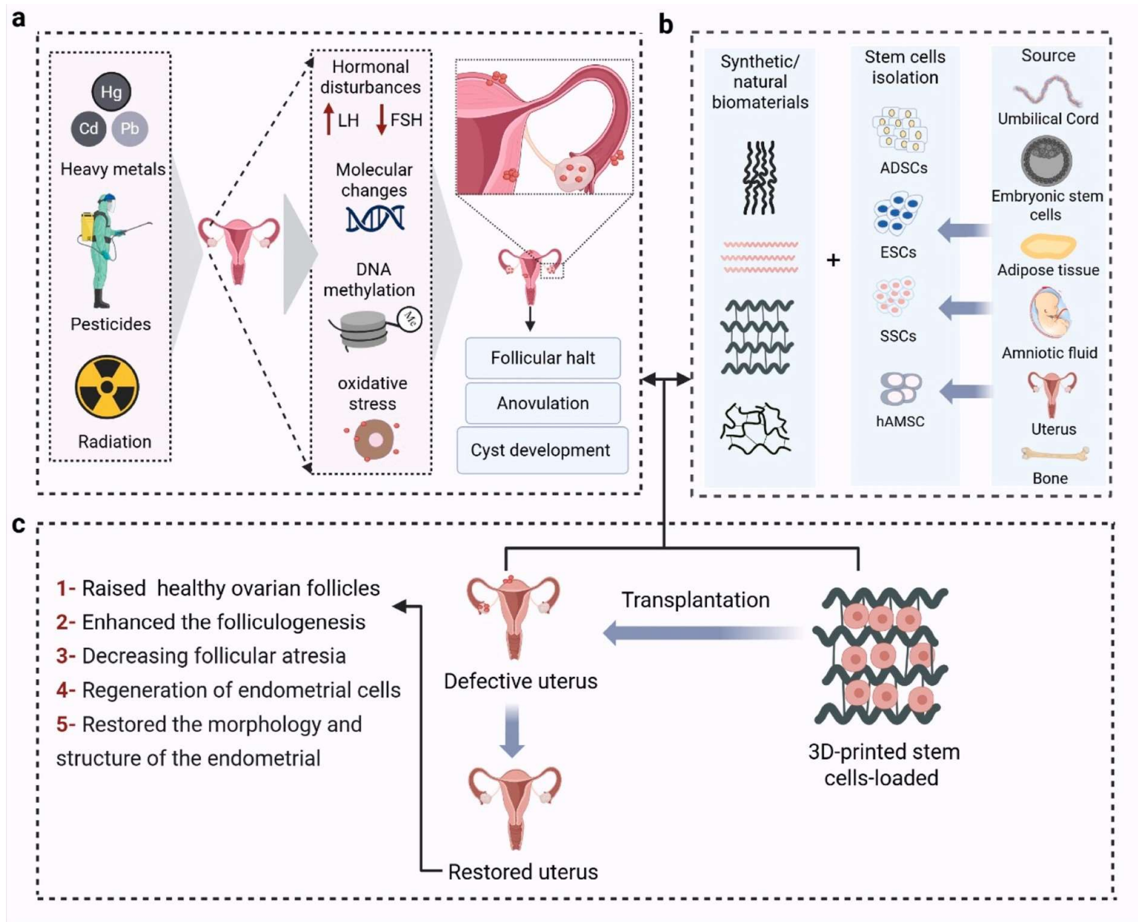

Fig. 3. Schematic overview of reproductive toxicity factors, stem cell sources, therapeutic outcomes, and associated complications in ovarian and endometrial regeneration. (a) *External environmental and physical stressors, including heavy metals, pesticides, and radiation, affecting the female reproductive system. Pathophysiological disturbances and clinical challenges encompass hormonal imbalances, molecular alterations leading to ovarian dysfunction (follicular arrest, anovulation, cystogenesis).* ***(b)*** *Diverse sources of stem cells and biomaterials utilized for tissue engineering and regenerative therapies.* ***(c)*** *Beneficial effects observed following treatment, such as increased healthy ovarian follicles, enhanced folliculogenesis, reduced follicular atresia, endometrial cell regeneration, and restored endometrial morphology and structure. Created with BioRender.com.*

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MSCs, derived from bone marrow, BMSCs, can differentiate into mesodermal tissues such as cartilage, bone, adipose tissue, muscle, and tendons in vitro (Zhang et al., 2017). For instance, a study by Mohamed et al. showed that adult female rats who underwent chemotherapy exhibited improved fertility after receiving a bone marrow transplant (Mohamed et al., 2018).

Stem cells derived from menstrual blood, MenSCs, have self-renewal and differentiation capabilities. When cultured under appropriate laboratory conditions, these cells can differentiate into various somatic cell types, including fat, osteoblasts, cartilage, lung epithelial cells, liver cells, cardiomyocytes, and insulin-producing cells. These stem cells show considerable potential for repairing early ovarian failure and may differentiate into ovarian-like tissue (Liu et al., 2014; Meng et al., 2007).

ESCs, first identified by Martin et al. in 1981 (Gr, 1981). are pluripotent cells with an unlimited capacity for self-renewal due to the production of telomerase. They are derived from the inner cell mass of blastocysts. ESCs can form embryoid bodies (EBs) and differentiate into primordial germ cells (PGCs), a process that has implications for creating primordial follicles and advancing regenerative medicine (Ji et al., 2020). However, due to ethical concerns, the use of ESCs is heavily restricted in both research and clinical settings (Thomson et al., 1998). Induced pluripotent stem cells (iPSCs), generated by reprogramming somatic cells like skin fibroblasts to a pluripotent state, offer an alternative to ESCs. iPSCs share similar differentiation potential to ESCs but lack the ethical and immunogenic concerns, making them more clinically viable. One study demonstrated that iPSCs, derived from mesenchymal cells,

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were used on a scaffold for endometrial regeneration, improving endometrial structure and preserving fertility (Yu et al., 2014).

In 2007, it was discovered that human amniotic fluid contains both adult stem cell and embryonic-like properties, making it a more ethically acceptable alternative to fetal stem cells. The collection of hAMSCs from the amnion, a waste product of pregnancy, is non-invasive and free from ethical issues (De Coppi et al., 2007).

These cells exhibit strong self-renewal capabilities and can differentiate into multiple cell types, including bone, cartilage, fat, and neuronal lineages. They also express markers specific to both mesenchymal and germ cells (e.g., DAZI, STELLA). Research has shown that hAMSCs have minimal teratogenic potential and do not form teratomas when injected into immunocompromised mice. Additionally, hAMSCs have shown promise in treating conditions such as myocardial infarction, Alzheimer's disease, heart failure, and spinal cord injury. In one study, using amniotic fluid stem cells in a mouse model of ovarian failure increased healthy ovarian follicles, improved folliculogenesis, and reduced follicular atresia. Granulosa cells in healthy ovaries were also significantly increased (Xiao et al., 2014). These cells have also been found to boost transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF) levels while decreasing follicular cell death. However, few studies have investigated their role in restoring ovarian function in chemotherapy-induced POF (Chang et al., 2013; Liu et al., 2019).

ADSCs have also been explored as a viable option for treating POF. Clinical trials have demonstrated that these stem cells can promote ovarian function recovery. In one study, after transplantation into POF mice, adipose-derived stem cells differentiated into oocytes or granulosa cells, leading to increased estradiol levels and granulosa cell proliferation, both of

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which are critical for restoring ovarian function. Additionally, adipose-derived stem cells have been shown to form the theca layer, support granulosa cell proliferation, and enhance angiogenesis (Su et al., 2016). A clinical trial using adipose-derived stem cells in collagen scaffolds for POF patients resulted in an increase in antral follicles, enhanced TGF-β1, VEGF, Hepatocyte Growth Factor (HGF), and Fibroblast Growth Factor 2 (FGF2) expression, improved granulosa cell proliferation, and elevated estradiol levels, all contributing to the production of higher-quality oocytes (Boccafoschi et al., 2005).

3.1.2. Stem cells in endometrial regeneration

Under the influence of estrogen and progesterone, the human endometrium, which lines the uterine cavity, is a highly regenerative tissue that undergoes periodic cycles of reproduction, differentiation, and shedding over more than 400 cycles during a woman's reproductive life (Masuda et al., 2010; Gargett et al., 2008). The coordinated actions of progesterone and estrogen regulate these remodeling processes, preparing the endometrium for potential blastocyst implantation each month (Gargett et al., 2012; Gargett and Ye, 2012). Research suggests that mature stem and progenitor cells are likely responsible for the regeneration of the endometrium (Lv et al., 2021; Gargett, 2007). The human endometrial mucosa consists of two main layers with distinct structural and functional properties. The functional layer, which makes up the upper two-thirds, includes glands covered by surface epithelium and a loose stromal matrix. This layer sheds during menstruation and is subsequently replaced in the next cycle. New functional tissue is generated from cells in the basal layer, which surrounds the endometrial glands and supports their development (Padykula, 1989; Spencer et al., 2005).

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Within 48 h of complete shedding, the endometrium begins to re-epithelialize and heal in a rapid, scar-free manner. In addition to stromal cells transitioning from a mesenchymal to an epithelial state, surviving glandular epithelial cells contribute to the formation of new luminal epithelial cells. During the early proliferative phase after menstruation, the endometrium regenerates quickly, and progenitor cells in the basal layer help produce the new functional layer. Elevated estrogen levels stimulate angiogenesis to provide oxygen to the growing tissue and promote stromal growth, while also encouraging the proliferation of glandular epithelial cells. During the secretory phase, progesterone supports the synthesis of secretory molecules and induces the decidualization of stromal cells, preparing the glands for blastocyst implantation. If no blastocyst implants, progesterone levels drop, leading to menstruation and the death of endometrial cells. Stem and progenitor cells in the basal layer play a major role in endometrial regeneration, supporting the repair and growth of both stromal and epithelial cells (Gargett, 2007; Jahanbani et al., 2020). Several genes associated with endometrial stem cells have been identified, but specific markers for these cells remain unknown. These genes include Musashi− 1, OCT4, c-kit (CD177), and CD34 (Yin et al., 2019).

Asherman syndrome (AS) encompasses a group of disorders characterized by irregular menstruation, infertility, recurrent miscarriages, and other issues, often caused by endometrial injury (Nagori et al., 2011). Cancer treatments can also significantly disrupt endometrial function, but studies have shown that stem cells may play a role in endometrial regeneration and repair. In models of AS, non-endometrial stem cells, such as those derived from umbilical cords and bone marrow, have been shown to aid in the restoration of damaged endometrial tissue, both autologously and allogeneically (Fig. 3c). These findings suggest that stem cell therapies may improve reproductive outcomes for patients with cancer or AS (Al-Inany, 2001).

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In 2013, bone marrow-derived MSCs were used to regenerate the endometrium in rats. Bone marrow is a key source of pluripotent MSCs capable of differentiating into various cell types. Additionally, clinical trials using umbilical cord-derived MSCs with collagen scaffolds to treat endometrial injury began in 2018. Endometrial damage is known to significantly impair fertility in women (Jahanbani et al., 2020). Recurrent miscarriages, abortions, and intrauterine infections can lead to the collapse of the uterine cavity or cervical canal, either partially or fully. Studies show that about 68% of AS patients experience menstrual problems such as hypomenorrhea or severe amenorrhea due to restricted menstrual flow, and 43% of these individuals also face infertility (Cousins and Gargett, 2018). Even patients with mild adhesions may become pregnant, but they remain at high risk for miscarriage due to intrinsic defects in the endometrium and its vascularization, which is essential for implantation. AS is also associated with higher risks of premature birth, placenta accreta, and postpartum hemorrhage. Histologically, the endometrial tissue in AS is replaced by cuboidal or columnar epithelium that is insensitive to hormones, while the stroma is largely substituted by fibrous and glandular tissue (Gargett et al., 2016). Currently, repairing this damaged endometrium remains a significant clinical and scientific challenge. Another rare condition, endometrial atrophy (EA), causes the endometrium to be too thin to less than 5 mm in thickness. Long-term use of tamoxifen, oral contraceptives, and other unidentified factors can contribute to EA. Women with this condition often have poor reproductive outcomes, and despite various treatments, none have proven consistently effective. Research has shown that BMSCs are vital in the restoration and regeneration of several tissues and organs (Gargett et al., 2012). Clinical trials using CD133 + BMSCs in regenerative medicine have demonstrated their ability to support

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neoangiogenesis in wound healing, organ ischemia, arteriosclerosis, myocardial infarction recovery, lymphatic organ neovascularization, and tumor growth (Maruyama et al., 2010).

3.1.3. Stem cells in the endometrium and the origin of endometrial stem cells

In 1987, Prianishnikov made the initial finding that stem cells are present within the endometrium (Gargett et al., 2016). A small population of human stromal cells (1.25%) and endometrial epithelial cells (22–52%) was first identified, grown, and generated colony forming units (CFU), which are responsible for regeneration, in 2004 (Chan et al., 2004). Recent studies have shown that endometrial side population (SP) cells are a stem/progenitor cells population. A substantial amount of SP cells were initially derived from hematopoietic stem cells. Actually, SP cells are a group of stem cell populations that do not have surface markers. These indicators are seen in many other adult organs, like skin, liver, brain, kidney and heart (Cervello et al., 2017´). When endometrial SP cells were first identified in 2007, it was found that they were mostly concentrated in the endometrial stroma, especially around the end of the menstrual cycle. These cells are identified by their potent capacities for differentiation, self-renewal, and proliferation (Kato et al., 2007). Research indicates that one popular method for identifying adult stem cells is identifying SP cells, which rapidly remove the crucial Hoechst 33342 DNA binding dye. Using dual-color flow cytometry, SP cells generate a distinct fluorescent profile, allowing for their isolation and subsequent downstream analyses. Short-term cultures of human endometrial cells that were recently isolated revealed the presence of SP cells (0–5%). Though greater numbers were observed in the proliferative and menstrual periods, SP cells vary greatly amongst groups (Gargett et al., 2016).

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3.1.4. The role of bone marrow-derived cells in endometrial regeneration

The bone marrow houses various stem cell types, including endothelial progenitor cells, MSCs, and hematopoietic stem cells. These cells migrate to injured areas, embed within the organ, differentiate into new tissue cells, and contribute to angiogenesis. When BMSCs are injected intravenously into injured tissues (such as an ischemic heart), endogenous stem/progenitor cell activation, immune response regulation, and the release of nutritional elements that support angiogenesis are all observed. All these things cause tissue repair. Myeloid cells from the bone marrow have been found to penetrate organs and differentiate into host tissues, including the endometrium. BMSCs have been identified as an external source of endometrial stem cells. Studies have demonstrated that in humans, BMSCs comprise about 52% of the stromal tissue and 48% of the epithelial tissue (Gargett et al., 2008). The majority of data derived from mice models demonstrate that BMSCs can develop into stromal and epithelial lineages (Cousins et al., 2022). The transdifferentiation of bone marrow to various nonhematopoietic cells, including hepatocytes, endothelial cells, neurons, cardiomyocytes, skin, and gastrointestinal epithelial cells, has been well-established for a considerable amount of time (Simon, 2012´). However, Taylor's study from 2004 describing the presence of BMSCs in human endometrial following transplantation of bone marrow from a mismatched donor was the first publication of proof of this phenomenon in human endometrium. Between 0.2% and 52% of the endometrial tissue's cells were found to have a notable chimerism in four of the patients' endometrial cell origins (Taylor, 2004). The discovery of donor cells in the endometrium of women who had previously received bone marrow transplants from male donors has recently led to a greater knowledge of endometrial physiology and suggests a potential hematopoietic source of stem cells capable of endometrial regeneration. Taken

together, the results raise the prospect that human endometrial regeneration may be facilitated by an external source (nonspecific resident tissue cells) (Ikoma et al., 2009).

3.1.5. Endometrial LGR5(+) cells

The first evidence of LGR5(+) cells in the human endometrium was found in 2007. Furthermore, it has been shown that these cells are crucial for Wnt/βcatenin signaling as well as stromal cell maintenance and self-renewal. Strong expression of LGR5(+) is seen in the uterine epithelium (Sun et al., 2009). In one study, the deficient endometrium recovered after transplanting human stromal/endometrial-derived LGR5(+) cells into immunocompromised people's kidney capsules. Additionally, transcriptional profiling revealed that LGR5(+) cells most likely have hematopoietic origins (Cervello et al., 2017´). The unusual population known as LGR5(+) cells have a phenotype similar to macrophages and the capacity to create tissue resembling the endometrium. Research indicates that these cells are only involved in the process of endometrial regeneration beginning (Zhu et al., 2019).

3.1.6. Menstrual Stem Cells (MenSCs)

MenSCs, also termed endometrial repair cells (ERC), are a subpopulation of endometrial mesenchymal stem cells (EMS) that exhibit robust proliferative activity in vitro. They display a stable diploid karyotype, maintain a characteristic fibroblast-like morphology, and demonstrate high clonogenic potential. Notably, MenSCs/ERCs show multilineage differentiation capacity, with the ability to give rise to myogenic, osteogenic, chondrogenic,

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adipogenic, neurogenic (ectodermal), and mesodermal cell types under appropriate inductive conditions (Meng et al., 2007).

3.2. Cell-laden bioprinting and 3D printing

3.2.1. Basic principles of constructing tissue and organs with 3D printing

A significant challenge in modern medicine is the scarcity of organs available for transplantation and the difficulties associated with organ and cell transplants at the highest medical levels. The number of patients awaiting transplants continues to rise daily due to these issues. Recently, advances in tissue engineering, particularly through 3D bioprinting technology, have greatly contributed to the regeneration of tissues and organs (Parihar et al., 2022). What is the difference between 3D printing and bioprinting? 3D printers and 3D bioprinters are similar to each other, but 3D printers are designed to print solid materials, while 3D bioprinters are designed to print liquid or gel. 3D bioprinters are also designed to handle sensitive material that contains living cells, without creating too much damage on the end result (Fig. 4).

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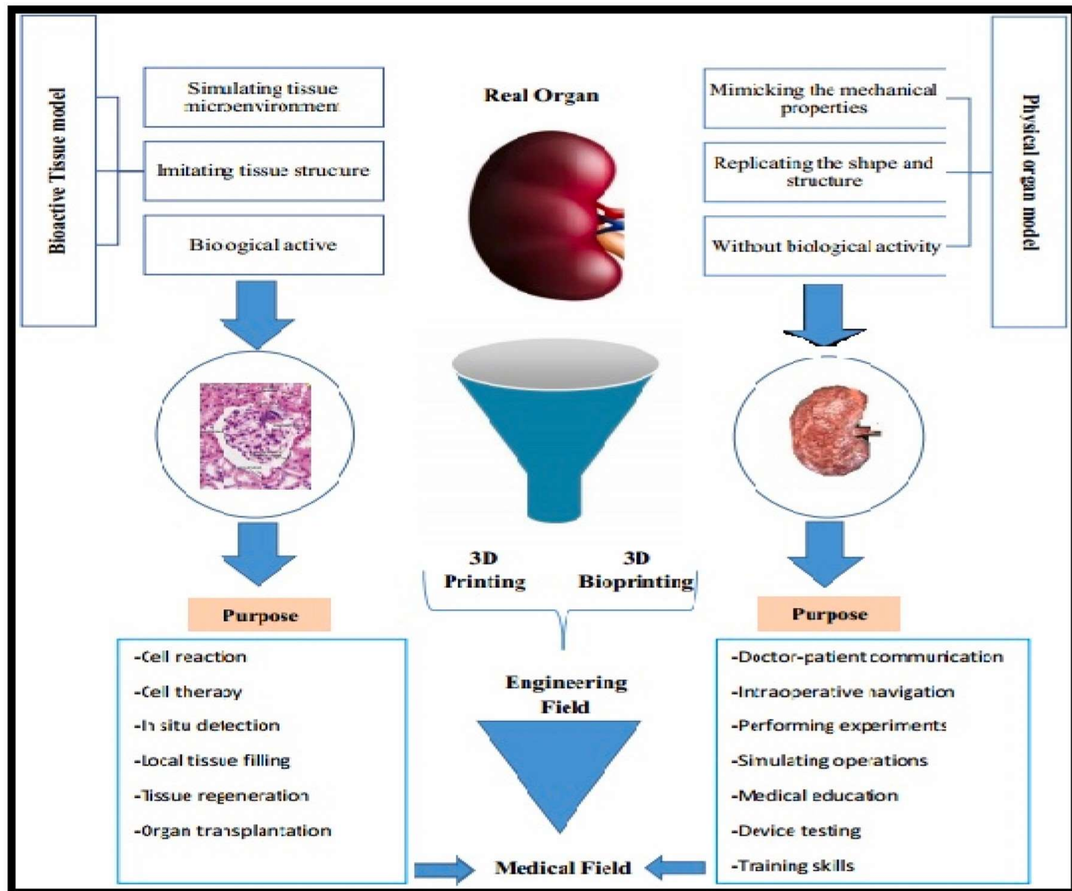

Fig. 4. *3D printing and 3D Bioprinting Model.*

The 3D bioprinting technique has proven useful for tissue regeneration by creating scaffolds using biomaterials, stem cells, and growth factors. This technology builds structures layer by layer, enabling the creation of complex 3D shapes (Rajan et al., 2016). As an industrial manufacturing technology, also known as additive manufacturing (AM), it allows for rapid and large-scale production of parts. Computer software generates precise instructions for creating tissues or organs using 3D printing technology. However, a primary limitation of this approach

is the low resolution of printed structures, despite the many advantages and flexibility in printing various 3D forms (Parihar et al., 2022). Reports suggest that while conventional 2D culture and animal models are useful alternatives for in vitro 3D tissue models, an increasing number of 3D models are now being utilized to evaluate new therapies and enhance understanding of tissue development (Pati et al., 2016).

Compared to 2D models, in vitro 3D tissue models more accurately reflect the chemical and spatial complexity of living tissues. These models have proven more effective than 2D cultures in researching molecular mechanisms of tissue function, signaling pathways, and drug responsiveness (Fulcher and Randell, 2012; Lancaster et al., 2013). The technique of 3D bioprinting allows for the simultaneous printing of various cell types, proteins, and biomaterials into biological structures ranging from millimeters to centimeters. This technology enables the creation of 3D models of real tissues or organs that closely replicate their natural cellular structure (Yan et al., 2018; Seol et al., 2014). Developing 3D tissue models of human cells in vitro that mimic the in vivo behavior has led to reduced drug discovery costs and more accurate predictions of therapeutic and toxic responses (Zhu et al., 2022). Additionally, by engineering structures with diseased or dysfunctional human cells, scientists can explore tissue pathology and investigate new treatment options. These in vitro disease and cancer models may provide valuable platforms for studying pathological conditions and testing new therapies (Gargus et al., 2020).

Recent advancements in bioengineering have significantly boosted the development of novel 3D tissue models for preclinical drug testing, toxicity research, and physiological studies (Dadashzadeh et al., 2021; Zubizarreta and Xiao, 2020). Commonly referred to as AM technology, 3D printing techniques have gained widespread popularity in the past decade,

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especially in the medical field for creating complex material structures. Currently, advances in 3D printing have enabled the production of functional tissues that can be used to replace damaged or diseased human tissue (Mancini and Pensabene, 2019). The Food and Drug Administration (FDA) has approved the long-standing use of 3D printing in the industry. However, despite promising results, this technology is still in its early stages, and the 3D printers available today can only produce basic tissue shapes (Sittadjody et al., 2021). Creating reproductive organs, such as the female reproductive system, remains particularly challenging due to the need for prolonged culture, the rapid growth of follicles during folliculogenesis, and their complex metabolic demands (Sittadjody et al., 2021; Wang, 2019).

For developing effective scaffolds for tissue regeneration, several key factors must be considered, including biocompatibility, biodegradability, porosity, and structural support (Skardal and Atala, 2015). Various techniques, such as phase separation, gas foaming, particulate leaching, and solvent casting, can be used to produce necessary structures. However, these methods do not provide the appropriate pore size, microarchitecture, or pore connectivity required for cell survival, including the efficient transfer of nutrients and oxygen. Furthermore, residual organic solvents used in the treatment of biomaterials may remain in the structures and pose risks to cells (Gargus et al., 2020). As a result, many researchers have turned to AM technology to overcome the limitations of traditional scaffold production techniques. Medical imaging technologies, like magnetic resonance imaging (MRI) and computed tomography (CT), when integrated with computer-assisted design and manufacturing (CAD-CAM) systems, can generate 3D models, enabling the use of AM technology to create these structures (Zhu et al., 2022).

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3.3.Bioink or biological inks

A bioink is commonly considered any biomaterial's solution or hydrogel suitably loaded with cells of different sources. For a successful bioprinting of tissue structures and organs, bioinks are crucial. Indeed, they represent the basic building block of printed structures, and therefore, several criteria should be considered for their perfect design. To support the growth of cells and tissues, bioink must mimic the characteristics of the ECM, including cell adhesion, proliferation, differentiation, tissue growth, and tissue function. To create the final structure, bioink must to be able to crosslink or stabilize during or right after bioprinting (Petta et al., 2020). Several studies in the realm of regenerative medicine and tissue engineering have extensively classified hydrogels for 3D bioprinting (Chen et al., 2022b; Raucci et al., 2020; Szychlinska et al., 2022). Hydrogels are a popular carrier for embedding cells because of their hydrophilic properties. Evidence suggests that an ideal cell-laden hydrogel should be printable and capable of producing 3D scaffolds with high integrity. Other characteristics of hydrogels, in vitro and in vivo, include degradability, adequate mechanical strength, the capacity to develop encapsulated stem cells, and bioactivity (Ozbolat et al., 2016; Gungor-Ozkerim et al., 2018). Cell density is one of the key factors that must be taken into account in connection to the cellular components of bioinks, because it is important that after the printing process there are enough living cells. According to different reports, this method involves the application of forces to the cells therein, which may cause some degree of necrosis (Petta et al., 2020). Research suggests that print resolution is mainly affected by material parameters (such as wettability, surface tension, rheological behavior, and cell density) and device features (such as nozzle diameter, print speed, and flow rate) (Xu et al., 2005). Effective resolution of the relevant structure is also significantly influenced by crosslinking techniques and

environmental factors. Controlled and accurate deposition of different cells in the 3D structure is possible with 3D cell printing devices (Catros et al., 2011). It is crucial to use materials in 3D bioprinting that are compatible with both the mechanical and functional characteristics of the target tissue and the printing process (Murphy and Atala, 2014). Hydrogel bioinks, as todays' most trendy 3D cell embedding biomaterials, must flow through the nozzle during printing and maintain their shape after deposition. Also, these biological materials must support the connection, proliferation and function of cells. Based on their capacity to protect living cells, hydrogels have reportedly been employed broadly as bioinks (Shao et al., 2020). Nevertheless, these cell-containing bioinks face challenges in printing due to their poor crosslinking and liquid-like rheology (Unagolla and Jayasuriya, 2020). The ability of hydrogel materials (i.e., collagen, gelatin, and alginate) to encapsulate cells and their printability have made them widely used for bioinks in 3D cell printing systems (Blaeser et al., 2017). (Fig. 5a). Tissue engineering hydrogels are mostly composed of synthetic molecules like polyvinyl alcohol (PVA), polyethylene glycol (PEG), polylactic acid (PLA), and polycaprolactone (PCL) as well as naturally occurring polymers including gelatin, collagen, agarose, alginate, polylactic-co-glycolic acid (PLGA), and other substances (Fig. 5a). The similarity to natural ECM is one of the advantages of natural polymers. Collagen-based hydrogels, in particular, are among the synthetic and natural materials that are frequently utilized to regenerate certain tissues, including the skin, blood vessels, bones, liver, and nerves. The primary component of the natural ECM that can provide an optimal microenvironment is collagen, which is the most common naturally occurring polymer in mammalian tissue (Carracciuolo and D'Amora, 2024). However, because these hydrogels vary from batch to batch, their printing ability varies, and as cells are sensitive to these changes, implanting them for the purpose of replicating

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structures can be challenging (Fig. 5b). The hydrophilicity and absorbance of synthetic polymers facilitate the gaseous and nutritional exchange. These polymers can also be modified to have physical characteristics that are appropriate for 3D bioprinting (Matai et al., 2020). It is possible to easily change the mechanical properties of these polymers depending on the structure of macromolecules, the method and degree of their crosslinker (Negro et al., 2018). Materials containing cells can be crosslinked chemically, physically, or by combining the two techniques. Chemical techniques rely on the formation of covalent and chemical bonds, whereas physical techniques depend on reversible interactions such as hydrogen bonds and ionic interactions. According to reports, the crosslinkers' network provides the hydrogel greater flexibility and stability, both of which are critical for encapsulating cells (Wu et al., 2016). Reduction of mechanical properties and reduction of biocompatibility are the drawbacks of synthetic polymers compared to natural derived polymers. According to reports, one way to increase the hydrophilicity and bioactivity of thermoplastic polymers is by including inorganic components such as calcium phosphate, tricalcium phosphate β (TCP-β), hydroxyapatite (HA), graphene, and graphene oxide (GO). Furthermore, several candidates with concentration-dependent reversible gelation capabilities have been also identified, including polyethylene oxide, pluronic F127 and polypropylene oxide (Gungor-Ozkerim et al., 2018). The bioprinting process is essentially divided into three steps. 1. Pre-processing: CAD software is used in this stage to prepare the bioink. 2. Processing: The printed structure is grown in a bioreactor following the creation of the 3D structure 3. The post-processing phase essentially aims to stimulate the printed structure's maturation and transform it into a functional tissue (Tabriz et al., 2015; Munoz-Abraham et al., 2016). (Fig. 5c). A general overview of the most common AM techniques is reported in the following paragraphs.

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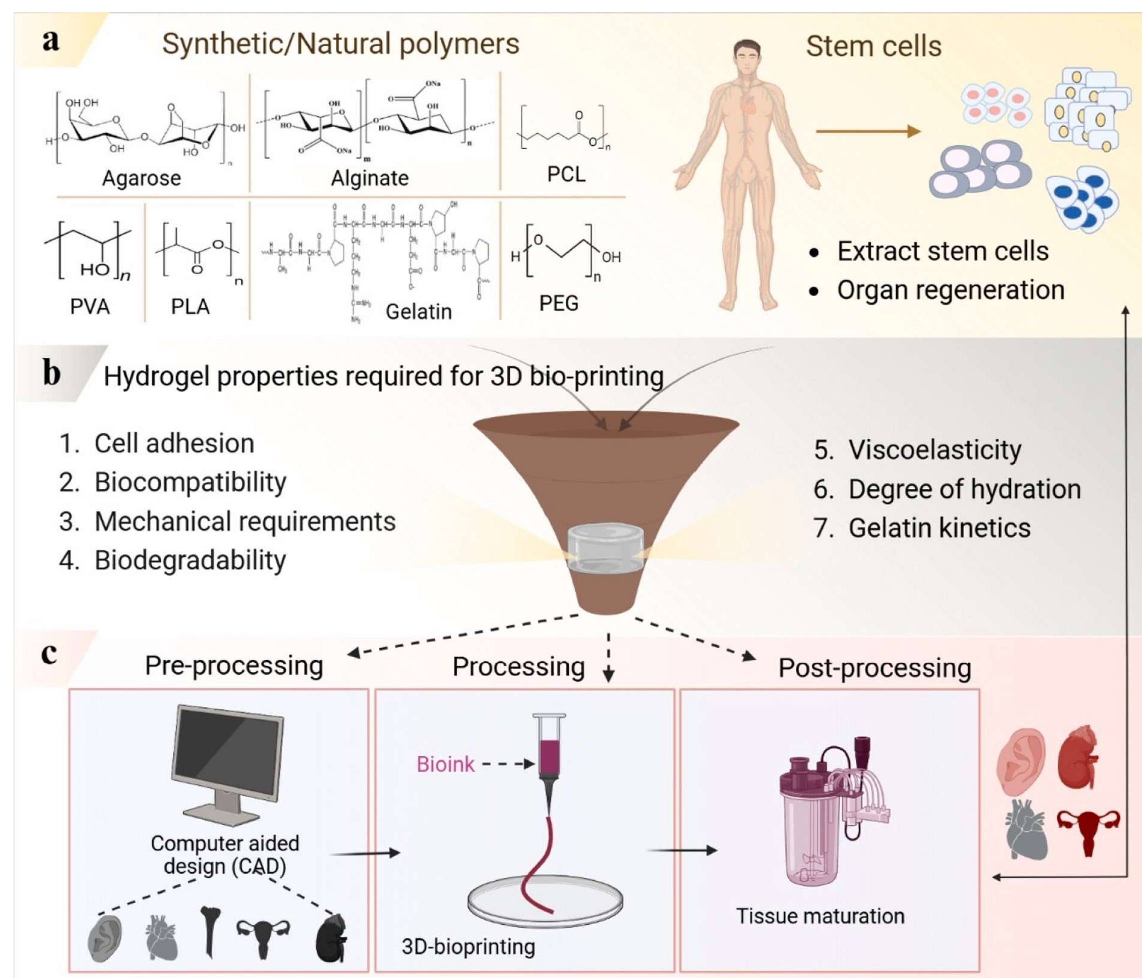

***Fig. 5. (a)** Structure of synthetic/natural polymers that are used for 3D bioprinting. **(b)** Characteristics of hydrogels used in 3D bioprinting. **(c)** Three main processes in organs: 3D bioprinting technology. Created with BioRender.com.*

3.3.1. Stereolithography

Stereolithography, invented by Charles Hull in the 1980s, gave rise to 3D printing. In stereolithography, a polymer material that is extruded from a needle is solidified using a laser

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to create a solid 3D structure (Munoz-Abraham et al., 2016). Building on this foundational technology, three distinct approaches to 3D bioprinting have been developed: extrusion-based, inkjet-based and laser-based. These methods yield cell survival rates of 95%, 85%, and 80%, respectively (Mandrycky et al., 2016). As previously mentioned, various kinds of synthetic, natural, and hybrid biomaterials have been studied for use as cell encapsulation materials in 3D printing. Cell masses, hydrogel-encased cells, viscous liquids, and cell-containing microcarriers are examples of bioinks components commonly used in 3D printing. It should be stated that the physical, chemical, mechanical, biological activity, printability, biocompatibility, and biodegradability of these materials are specific requirements (Skardal and Atala, 2015).

3.3.2. Microextrusion printing

One of the most popular techniques for precisely controlling the deposit of cell-laden hydrogels at the micrometer scale in a particular form is extrusion-based bioprinting (Gokyurek et al., 2020). (Fig. 6a). Microextrusion printing is actually the most widely used and least expensive process for printing non-biological materials. Using a software program, the microextrusion head moves along the z-axis to form a layer that provides the basis for the second layer. The materials are continuously pushed out of this printer by applying pressure, placing them on a substrate in two dimensions. The drive-mechanism components of pneumatic dispensing systems are simpler (Gündogan). One of the major advantages of extrusion-based printing is its ability to print viscous polymer solutions with a wide range of cell densities (up to 10^7 cells per mL), closely mimicking physiological conditions (Munoz-

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Abraham et al., 2016). During the extrusion-based bioprinting process, printed cells may experience mechanical stress as they are deposited through a tiny nozzle. This stress can lead to a loss of cell viability or cause phenotypic alterations. Cell viability actually reduces when shear stress is applied to cells in viscous materials. Under shear stress, a material's tendency to change shape occurs (Kim et al., 2016a). Parameters like nozzle diameter and distribution pressure have an impact on cell viability, which is critical to a tissue's ability to function. Biocompatible materials may maintain the cell's vitality and functionality. Aortic valves, cancers, and in vitro pharmacokinetic models have all been extensively recreated using microextrusion bioprinting technology (Sorkio et al., 2018).

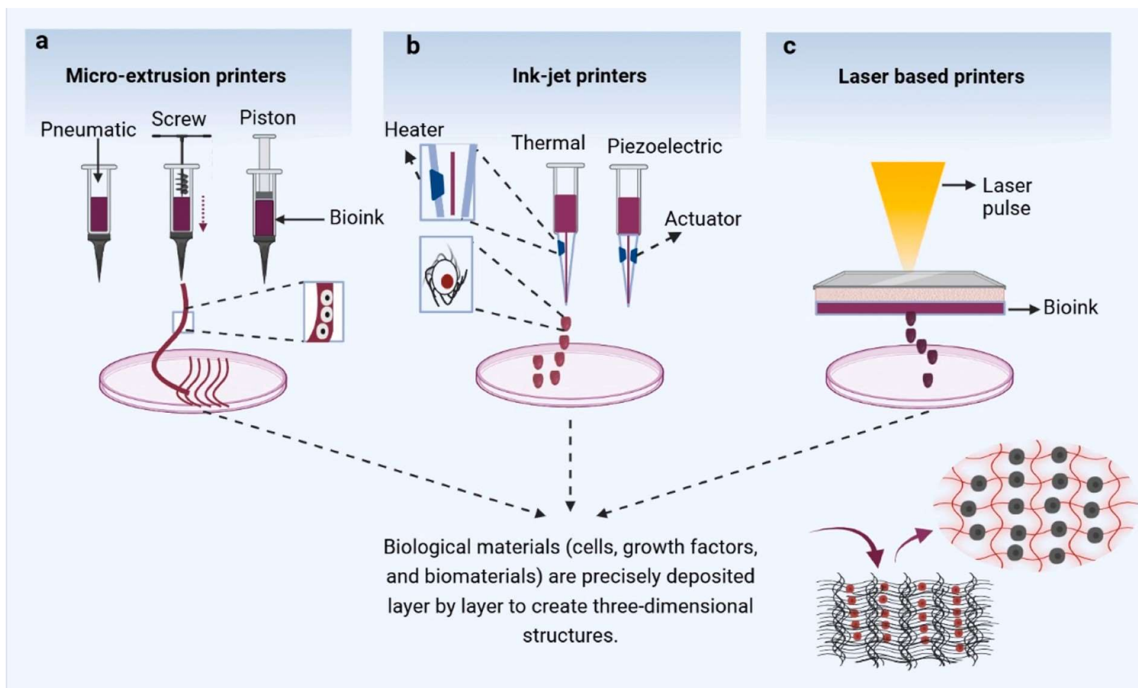

Fig. 6. *Different types of 3D-bioprinters,* ***(a)*** *Micro-extrusion printers,* ***(b)*** *Inkjet-printers and* ***(c)*** *Laser based printers. Created with BioRender.com.*

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3.3.3. Inkjet printer

Inkjet printing has been widely considered as a promising strategy for patterning hydrogels and living cells into 3D structures that are similar in structure to our body tissues. This technique is based on 2D printers based on the heating principle (Negro et al., 2018). In this technique, a piezoelectric stimulant vaporizes the cell suspension and transforms it into bubbles that can be ejected through a nozzle (Fig. 6b). This technique has a high printing speed, but due to the use of a piezoelectric actuator, direct contact of cells with heat can lead to damage to the cell membrane and cell lysis (Ning et al., 2019). Another name for inkjet bioprinters is drop-on-demand bioprinters (Park et al., 2020). Inkjet (thermal, piezo-electric, or electrostatic) bioprinters, micro-valve bioprinting, acoustic droplet election, and electro-hydrodynamic jetting are the four types into which these drop-on-demand bioprinters have been further divided based on their droplet generation techniques, recently (Filardo et al., 2019; Gungor-Ozkerim et al., 2018). There has been significant success in the invention of bio-based inks and bio-based papers suitable for inkjet printers. This technology has provided the possibility of printing organs and complex tissues using cells as biological ink. Also, this technique provides the possibility of better adjustment of the geometry and size of the 3D bioprinted structures. Another advantage of this technique is its commercial availability, cost-effectiveness and versatility. Limitations such as lack of proper innervation and vascularization cause challenges in printing large organs properly with the help of this technique (Chahal et al., 2012). Also, size of the drops cannot be controlled. In addition, the diameter of the opening of this printer causes it to clog during bioprinting and block its flow. However, because this technique increases the resolution of the droplets and increases cell viability, it is superior to the microextrusion technique. The method's limitations additionally include clogging of the

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nozzle and cell settling during operation. Although it is difficult to integrate vascularization features in bioprinted tissues, novel bioprinting methods could be able to solve this issue (Pereira et al., 2017).

3.3.4. Laser-based printers

In this printing technique, a laser is used to design the texture architecture (Fig. 6c). This technique is more advantageous compared to microextrusion and inkjet printers, because less power is used and minimum heat is applied to cells. In bioprinting with the help of a laser, volume of the printed droplets can be from 10 to 700 pL due to viscosity adjustment along with high cell density. Also, through this method, it is possible to process very viscous hydrogels, while in inkjet printing, designing these hydrogels is challenging. However, the use of laser light in this technique can lead to damage to the cell structure (Munoz-Abraham et al., 2016).

3.4. Biomaterials for use in tissue engineering and cell-laden bioprinting technology

The use of tissue-engineering scaffolds holds significant therapeutic promise and offers a novel approach to treating female infertility (Jahanbani et al., 2020). Scaffolds not only function as ECMs in tissue engineering, but they also serve as a substrate for cell implantation and proliferation, providing an ideal environment for the support of blood and lymphatic vessels (Bruˇzauskaite et al., 2016˙). Various biomaterials are employed for tissue repair in engineering applications (Hubbell, 1995). Depending on the regeneration needs, these biomaterials can be either natural or synthetic (Laurencin and Deng, 2014; Hicks et al., 2010;

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Kim et al., 2014a; Sionkowska, 2011). To date, several polymers have been used in infertility-related tissue engineering, including gelatine (Tamadon et al., 2016), collagen (Song et al., 2015), agarose (Tamadon et al., 2016), alginate (Kuo et al., 2017), Matrigel (Zhou et al., 2021), silk fibroin (Liu et al., 2022), Poly-L-lactic acid (PLLA) (Chen et al., 2022a), PLGA (Liu et al., 2022), and PEG. In one study, researchers utilized cell-laden bioinks, specifically gelatin-methacryloyl (GelMA), as the polymer for 3D printing, combined with various cell lines, such as the ID8 mouse ovarian surface epithelial cell line, KGN steroidogenic human granulosa-like tumor cell line (which expresses functional follicle-stimulating hormone receptors), COV434 human ovarian cancer cell line, and ovarian somatic cells. This research demonstrated the potential of GelMA and other natural polymers as effective materials for 3D bioprinting. The scaffolds created using this technique not only showed good performance in terms of moisture retention, degradation rates, and shape integrity but also provided a suitable microenvironment for ovarian follicles, enabling them to develop and ovulate successfully within the scaffolds (Di Nisio et al., 2025).

A stable, long-term 3D model of human ovarian primary cells grown on Biosilk scaffolds, known as Silk-Ovarioids, was created by Di Nisio et al. (Di Nisio et al., 2025). The model was able to keep the cells alive and growing for more than 42 days without showing signs of cell death. In contrast, other models such as Matrix-Free Ovarian Spheroids (MFOS) and 3-Layered Gel/Matrigel Spheroids (3LGS) were unable to survive for more than 15 days and form stable structures. Silk-Ovarioids contain major ovarian cell types such as granulosa, stromal, endothelial and perivascular cells, and their existence was confirmed using advanced genomic, proteomic and immunostaining methods. The model showed a hypoxic core, whose low-oxygen environment stimulated the growth of new vessels, the formation of vessel-like

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structures and the production of ECM, pro-angiogenic cytokines and steroids. These features make Silk-Ovarioids biologically similar to real ovaries, making them highly suitable for studying angiogenesis, folliculogenesis, cellular response to drugs, and toxicology studies. In addition, Silk-Ovarioids are highly stable and reproducible, and can be used as a basis for the development of patient-specific artificial ovaries (Di Nisio et al., 2025).

A bioprinted model of human pregnant uterine myometrium tissue that reproduces the structural, functional, and molecular features of normal pregnant uterine tissue, was also successfully obtained (Ulrich et al., 2025). The model was made using primary human uterine smooth muscle cells, and more than 75% of the cells in the printed tissue survived and maintained their natural elongated and elongated muscle shape. Immunofluorescence studies showed that smooth muscle cell-specific markers such as caldesmon, smooth muscle α-actin, and smooth muscle myosin were naturally expressed. In addition, contraction-related proteins including oxytocin receptor, prostaglandin receptors, connexin 43, and steroid hormone receptors such as estrogen and progesterone receptors were also present in the model. The bioprinted tissue responded to physiological stimuli; it contracted in response to oxytocin and prostaglandins F2α and E2 and expanded in the presence of nitric oxide donors such as S-nitrosoglutathione. These responses indicate that the model, in addition to maintaining cellular structure, has contractile function similar to that of the normal uterus. Further development of this model could provide a uniform and abundant source of myometrial tissue and have important applications in studying the complex mechanisms of labor, evaluating new drugs, and better understanding factors affecting labor and treating disorders related to uterine contraction (Ulrich et al., 2025). In one study, Di Berardino et al. used electrospun scaffolds inspired by the structure of the ovary and made of PCL to investigate the growth of preantral

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follicles (PA). In this study, PA isolated from lamb ovaries were cultured on PCL bioengineered 3D artificial ovary (AO) scaffolds and their growth was evaluated as single follicles or as multifollicular models, simulating an artificial ovary with 5 or 10 follicles. Long-term culture was continued for 14–18 days to determine the suitability of the scaffold microenvironment for folliculogenesis and oogenesis in terms of morphological and functional parameters. The results showed that the PCL scaffold provided a tissue-like environment to support the growth of PA and their transition to the early antral stage, and also enhanced steroidogenic activity. Under multifollicular and long-term culture conditions, the AO10PA model showed the highest percentage of specialized gamete production, and the ability of follicles to enter meiosis, extensive chromatin rearrangement, and parenchymal development were significantly enhanced. This study provides a valuable proof-of-concept demonstrating that PCL scaffolds can play a key role in developing an artificial ovary that can be transplanted with autologous primordial follicles and advancing in vitro folliculogenesis methods using simulated 3D matrices and long-term multifollicular protocols, paving the way for the next generation of assisted reproductive technologies (ART) (Di Berardino et al., 2024). A summary of other bioinks used in infertility treatments is presented in Tables 1 and 2 below.

Table 1. Bioinks for treatment of infertility.

Proposed Bio-ink	Compatible Cell	Target Tissue	Cell culture time	Previous Experiences
Gelatin with Alginate	Induced pluripotent stem cell (iPSC)-derived mesenchymal stem cells (MSCs)	Endometrium and Myometrium	9–15 days	The 3D-printed cell loaded scaffold enhanced the restoration of endometrial histomorphology, including the regeneration of endometrial tissue and glands. It also stimulated the regeneration of stromal and epithelial endometrial cells as well as endothelial cells. Additionally,

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				it improved functional indicators of endometrial receptivity, such as pinopode formation, leukemia inhibitory factor production, and αvβ3 expression (Ji et al., 2020)
Collagen	Umbilical Cord - Derived MSCs (UC-MSCs)	Endometrium and Myometrium	8–14 days	The scaffold/UC-MSCs system can aid in breaking down collagen in uterine scars by upregulating matrix metalloproteinase− 9 (MMP− 9), which is predominantly produced by the transplanted UC-MSCs. Additionally, this system encouraged the regeneration of the endometrium, myometrium, and blood vessels within the scarred areas (Xu et al., 2017)
Sodium Alginate-Hyaluronic acid	Endometrial Stromal Cells	Endometrium	3–6 days	The 3D scaffold effectively reconstructed the endometrial wall's morphology and structure, including the organized luminal and glandular epithelium, stroma, vasculature, and smooth muscle layer. Additionally, it notably improved reproductive outcomes in the area where it was implanted (Nie et al., 2023)
Collagen + Hyaluornic acid + agar	Endometrial Stem Cells, Stromal Cells, Vessel Cells	Endometrium	5–8 days	Biological characteristics, including steroid hormone responsiveness and the viability of encapsulated endometrial cells, are relatively well preserved. Transplanting the artificial endometrium led to a successful pregnancy and subsequent live birth, with no morphological or chromosomal abnormalities observed (Park et al., 2021)
Gelatin-Methacryloyl (GelMA)	Ovarian somatic cells	Ovary	6–8 days	GelMA scaffolds performed well in terms of hygroscopicity, degradation kinetics and shape fidelity and provided an appropriate microenvironment for ovarian follicles, which successfully grew and ovulated in the scaffolds (Wu et al., 2022)
Pig Gelatin	Secondary Follicles	Ovary	8 days	30° and 60° scaffolds compared to 90° provided corners that surround follicles on multiple sides. As the amount of scaffold interaction increases, follicle spreading is limited and survival increases; and follicle-seeded scaffolds become highly vascularized (Laronda et al., 2017)
Chitosan-Silk Fibroin	Human Ovarian Stromal Cells	Ovary	7–10 days	Increasing the proliferation of ovarian cells up to 167%, improving the flexibility and strength of the regenerated tissue (Jafari et al., 2021)

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Polyurethane	Human umbilical vein endothelial cells (HUVEC)	Fallopian tube	3–5 days	Polyurethane ensures proper mechanical properties compared to the physiological tissue of the cervix. The 3D-printed cervical scaffold promoted cell adhesion and growth. Implants with adjustable pore sizes could enable precise management of the loading and release of anti-human papillomavirus (anti-HPV) protein (Zhao et al., 2020)
Acellular vagina matrix + Gelatin + Sodium alginate	Bone Marrow Mesenchymal Stem Cells (BMSCs)	Fallopian tube	8–15 days	The 3D scaffold containing BMSCs had a substantial impact on the vascularization and epithelialization of the printed vaginal tissue. The BMSCs were able to adopt the characteristics of vaginal epithelial and endothelial-like cells (Hou et al., 2021)
Alginate	Human fallopian tube epithelium (FTE) and Secondary Follicles	Fallopian tube	13–15 days	The cultured fallopian tube epithelium exhibited responsiveness to a reproductive cycle mimetic produced by murine follicles. The interaction between ovarian and fallopian tissues augmented progesterone production by the corpus luteum (Zhu et al., 2016)

Table 2. Comparative summary of stem cells, scaffolds/bioinks and outcomes in reproductive tissue engineering studies.

N◦	Cell Type	Scaffold	Bioink Composition	Target Tissue	Main Outcomes	Ref.
1	Primary mouse ovarian cells	Decellularized ovarian extracellular matrix (ECM)	ECM-based bioink	Ovary	Restored ovarian function in mouse model; supported follicle survival	(Zheng et al., 2022).
2	Porcine ovarian cells	Decellularized whole-ovary scaffold	ECM-based hydrogel	Ovary	Maintained structural integrity; supported cell adhesion and proliferation	(Pennarossa et al., 2020).
3	Ovarian granulosa cells	Decellularized ovarian ECM	ECM hydrogel	Ovary	Enhanced cell viability and follicle growth in vitro	(Wu et al., 2023).
4	Human ovarian cells	Human decellularized ovarian ECM	ECM hydrogel	Ovary	Preserved ECM architecture; potential for autologous cell repopulation	(Hosseinpour et al., 2025).
5	Follicles (human)	Wharton's jelly hydrogel	Wharton's jelly + alginate	Ovary	Improved follicle survival; supported	(Tajbakhsh et al., 2025).

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					hormone production	
	Mouse primordial follicles	Electrospun polycaprolactone (PCL) scaffold	PCL + ECM coating	Ovary	Long-term maintenance of follicle viability; partial maturation	(Di Berardino et al., 2024).
6	Endometrial epithelial + stromal cells	Collagen-based scaffold	Alginate + hyaluronic acid	Endometrium	Reconstructed full-thickness endometrial tissue; restored fertility in mouse model	(Nie et al., 2023).
7	Equine endometrial cells	Genipin-crosslinked collagen	Collagen hydrogel	Endometrium	Two-layer endometrial construct maintained morphology and function	(Santiviparat et al., 2025).
8	Human ovarian cells	Decellularized ovarian ECM	ECM hydrogel	Ovary	Supported follicle development; suitable for tissue engineering	(Wu et al., 2023).
9	Ovarian and endometrial cells	3D bioprinted hybrid scaffold	ECM + synthetic polymer bioink	Ovary + Endometrium	Restored tissue-specific structure and function in vitro	(Sen et al., 2024).

3.5. Applications of cell-laden bioprinting technology in reproductive sciences

The reproductive system plays a critical role in species survival, yet 14% of couples reaching reproductive age experience infertility. A variety of disorders can contribute to infertility in both men and women, including congenital conditions such as hypospadias, epispadias, ambiguous genitalia, or penile abnormalities like penile cancer (Atala, 2004). In women, infertility is commonly caused by uterine abnormalities resulting from endocrine disorders, structural issues, chemotherapy, fallopian tube obstructions, uterine trauma, severe intrauterine adhesions, and hysterectomy. A major challenge in treating these genital organ abnormalities is the limited availability of autologous tissue for reconstructive surgeries. Tissue engineering and biological bioprinting offer alternative approaches to address this issue. Through advanced

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3D printing technology, it is possible to create biomimetic, multi-scale, multi-cellular tissues that are suitable for complex tissue microenvironments. While fully engineered reproductive organs have not yet been developed, there have been successful reports of creating tissue constructs made from porous scaffolds and decellularized ECM (dECM) loaded with cells. Bioengineering of uterine, ovarian, and cervical tissues has also been explored (Vijayavenkataraman et al., 2018).

The uterus, a pear-shaped organ, consists of three layers: the myometrium (smooth muscle), the endometrium (epithelial tissue), and the outer connective tissue layer (Campo et al., 2017). Various uterine components have been engineered using traditional tissue engineering methods. For example, Bentin-Ley et al. produced the first in vitro endometrium by creating a three-layered endometrial construct from stromal and epithelial cells derived from human endometrial biopsies, suspended in a collagen-Matrigel hydrogel (Bentin-Ley et al., 1994). Engineered uterine tissues have been utilized in research to explore potential substitutes for small intestine submucosa (SIS). Studies have investigated the use of autologous cells implanted on different scaffolds, such as electrospun polyglycolic acid (PGA) scaffolds, silk protein sponges, fibrin-agarose matrices, Matrigel-collagen matrices, and dECM (Vijayavenkataraman et al., 2018). Matrix-bound growth factors, including collagen-bound vascular endothelial growth factor (CB-VEGF) and basic fibroblast growth factor (b-FGF), have been identified as potential agents to promote tissue healing. Since female infertility is often caused by ovarian failure, the creation of synthetic ovarian tissues has become a key area of research (Li et al., 2011; Lin et al., 2012). One study involved constructing ovarian tissue by implanting ovarian follicles, ovarian cells, and oocytes from humans or animals onto ECM

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or encapsulating them in hydrogels like agarose and alginate, yielding promising results (Ding et al., 2014a).

Similarly, cervical tissue constructs have been developed using comparable methods. For example, cervical cells have been implanted on dECM scaffolds or pig SIS, resulting in successful cervical tissue formation (Ding et al., 2014a; Xu et al., 2006). In a study involving vaginal tissue engineering, an 8-year evaluation of a vaginal construct created by implanting autologous muscle and epithelial cells onto a human-prepared PLGA scaffold showed that the tissue functioned normally. The use of 3D printing technology in the biological field was further demonstrated when 3D constructs of vaginal tissues were observed to help form missing or damaged tissue, with normal Female Sexual Function Index (FSFI) scores (Raya-Rivera et al., 2014). In 1999, Dr. Atala's team successfully created a biodegradable 3D scaffold for the human bladder using autologous urine and muscle cells with 3D printing techniques, highlighting the potential for bioengineering the female reproductive system due to the similarities between the bladder and reproductive organs (Al-Hendy and Ku, 2021).

In another study, ovarian cancer cells and normal fibroblasts were printed using a 3D printer and deposited in a Matrigel substrate in a controlled microenvironment. The analysis revealed that these models formed spherical and acinar structures, simulating the morphology of cervical tumors and ovarian cancer (Yan et al., 2018). Similarly, the implantation of mouse follicles into 3D printed gelatin scaffolds maintained the survival and functionality of the follicles. Additionally, promising results were reported with GelMA hydrogels packed with human trophoblasts created through 3D printing (Seol et al., 2014). Herold et al. bioprinted 3D cylindrical silicone scaffolds to study the long-term effects of extreme environments on release kinetics and mechanical integrity. Their study showed that the 3D printed silicone scaffolds

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could release metronidazole continuously for 14 days, maintaining optimal compressive strength and release kinetics (Mandrycky et al., 2016).

In ovarian tissue engineering, Laronda et al. developed an ovarian scaffold for creating functional tissue by growing follicles on it. This study explored whether a biodegradable scaffold made from a dECM could restore fertility. By altering the printed layer orientation, the researchers found that the geometry of the pores in the scaffold directly impacted follicle survival. Follicles implanted onto gelatin scaffolds with transverse grafts promoted blood vessel formation and restored ovarian functionality in surgically sterilized mice, leading to the birth of healthy offspring (Laronda et al., 2015).

Recent advancements also include the development of engineered cell sheets for endometrial regeneration. These sheets rely on the implantation of specific cells into biodegradable polymer scaffolds. One study demonstrated the creation of 3D-constructed endometrial structures when rabbit endometrial cells were implanted into liquid collagen Matrigel. Immunohistochemical analysis revealed the formation of a columnar epithelium, resembling the lumen epithelium in the body. The reconstructed endometrium significantly enhanced embryo growth compared to control structures (Gargett et al., 2012, 2016).

In another study, endometrial regeneration was achieved by implanting iPSCs onto a scaffold made of sodium alginate and gelatin hydrogel created through 3D printing. This structure supported the regeneration of endothelial, epithelial, and stromal cells and enhanced the histomorphology of the endometrium. Following transplantation, the structure maintained fertility (Ji et al., 2020). Xenograft models were also used to show the potential of endometrial stem/progenitor cells to regenerate human endometrium. Transplanted human endometrial epithelial and stromal cells generated endometrial and myometrial layers in ovariectomized

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NOG mice, mimicking the human menstrual cycle in response to hormonal stimulation (Gargett et al., 2016).

Lastly, a study using bioinks integrated with acellular matrix from pigs successfully constructed a cell-free vaginal matrix based on gelatin/ alginate hydrogel. The results showed that the vaginal tissue exhibited good differentiation, vascularization, and epithelialization. The BMSCs used in the study were also viable, with no immunohistological abnormalities observed after 8 weeks (Mandrycky et al., 2016).

3.6. Cell-laden bioprinting technology for infertility

Studies have shown that infertility poses a significant threat to both the mental and physical well-being of individuals, as well as to the social stability of young couples. While infertility may not always be viewed as a critical medical condition, its impact on various aspects of life, both social and personal, is clear. Couples facing infertility often experience psychological challenges such as anxiety, depression, low self-esteem, and dissatisfaction with their quality of life. Infertile couples face a range of psychological and physical challenges that can affect their marriage and social standing (Jahanbani et al., 2020). These issues also extend to the patient's relationships with their spouse, friends, and colleagues. Infertility can result from trauma or disease, which may lead to anatomical abnormalities in the male and female reproductive systems (Hutmacher, 2001). Additionally, certain specialized treatments, especially those for cancer, can have infertility as a side effect. However, scaffolds have shown promise as a potential treatment for these reproductive system anomalies in regenerative

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medicine. To promote cell migration, adhesion, proliferation, metabolism, and to ensure efficient nutrient and waste exchange, scaffolds used for treatment must be biodegradable, biocompatible, and possess suitable mechanical properties (Roether et al., 2018).

In one study, researchers used an alginate hydrogel matrix as a scaffold to create a 3D environment for oocytes. The hydrogel encapsulated immature mouse follicles, while the alginate matrix provided essential support. Hormonal functions were assessed using immunoassay kits, demonstrating the successful in vitro culture of alginate- encapsulated follicles, which showed normal growth and development in the hydrogel-based 3D culture system. This method suggested potential for infertility treatment. In another study, a bioprosthetic ovary was created using 3D printed hydrogel scaffolds in combination with murine ovarian follicles. The researchers tested different pore geometries of the scaffold to assess their effect on cell survival and behavior. Various microporous scaffolds were seeded with follicles and implanted into mice for in vivo experiments. The results showed that the scaffold's pore structure and design were critical for the survival of cells, underlining the importance of scaffold architecture in the development of functional ovarian implants (Laronda et al., 2017).

In a further study, theca and granulosa cells were seeded into micro- molded agarose gels to address ovarian failure. Researchers aimed to develop a 3D artificial human ovary. Cells isolated from women of reproductive age were seeded into the gels, where they self-assembled into 3D microtissues. Immunohistochemical tests and live-dead staining were used to assess the identity and viability of the cells. The study concluded that self-assembled microtissues could be used to construct an artificial ovary in vitro (Laronda et al., 2017). In another study, Wu and colleagues designed a scaffold using GelMA and alginate combined with tumor cells

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(COV434, KGN, ID8) and ovarian somatic cells, employing 3D printing. The results indicated that ovarian follicles implanted in the scaffold grew and matured over time. The study suggested that the scaffold provided a suitable microenvironment for follicular growth, marking an important step toward the clinical application of this technology in treating female reproductive disorders and offering a novel approach to in vitro follicle cultivation (Wu et al., 2022).

3.7. Tissue engineering of specific structures in the female reproductive tract

In the past decades, reproductive medicine has made significant progress with the progress of assisted reproductive technologies such as in vitro fertilization and molecular and genetic approaches, and in this way, it has greatly contributed to the treatment of infertility in couples. In fact, in addition to using the 3D printing technique, tissue engineering has contributed a lot to this field through the integration of biomaterials, cells and growth factors.

As mentioned, severe damage to the uterine endometrium causes scarring and dysfunction, ultimately leading to infertility or pregnancy complications. There is no effective treatment for these injuries. In a study, Nie et al. used extrusion 3D printing to fabricate a two-layer endometrium on an alginate-hyaluronic acid hydrogel; the upper layer was composed of epithelial cells and the lower layer was composed of stromal cells. After transplantation in a rat model with partial endometrial resection, the normal structure and morphology of the endometrium were restored, and the fertility rate increased by 75% (12 out of 16 animals). These results suggest that 3D printed endometrium could be an effective strategy for the reconstruction of damaged endometrium (Nie et al., 2023). In another study by Wu et al., using

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GelMA-based 3D printing, ovarian cell lines including COV434, KGN, and ID8 were cultured in the printed scaffolds. The results of MTT assay and live/dead staining showed that these cells survived in the 3D environment and their proliferation rate almost doubled within five days. However, primary cells extracted from ovarian tissue were severely damaged when passing through the nozzle and applying extrusion force; about 90% of them were killed. Terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay also confirmed this finding by showing the activation of the apoptosis pathway. Next, mouse follicles were cultured in GelMA scaffolds without cell implantation. After seven days, about 84% of the follicles were alive and the live/dead ratio was approximately 5-fold. The size of the small follicles did not change during this period, but the larger follicles grew significantly over five days. Finally, the extracted oocytes reached metaphase II after in vitro maturation (IVM) and were evaluated for their fertility and potential for clinical applications (Wu et al., 2022).

Laronda and colleagues designed microporous ovarian hydrogel scaffolds using 3D printing and investigated the effect of the layering angle (30°, 60°, and 90°) on follicle survival. Evaluations performed with (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) (MTT) assay and live/dead staining showed that follicles in scaffolds with 30° and 60° architectures had higher survival rates, while scaffolds with 90° angle, due to limited structural interaction with follicles, showed the lowest survival rates. After transplantation of cultured follicles into sterile mice, the scaffolds experienced significant vascularization and ovarian function was fully restored. Mice receiving these scaffolds were able to conceive normally, and the resulting pups developed normally, indicating successful restoration of physiological ovarian function. These findings emphasize that the pore architecture and scaffold layering

angle are key factors in supporting follicle survival and the ultimate function of ovarian tissue in 3D bioprinted systems (Laronda et al., 2017).

Luyckx et al. evaluated different fibrinogen/thrombin (F/T) combinations to create a suitable matrix for artificial ovary construction and found that the two ratios F12.5/T1 and F25/T4 offered the best biological and mechanical properties. The results of quantitative tests showed that the cell density increased from 94.2% to 98.9% in the F25/ T4 combination and from 94.0% to 96.6% in F12.5/T1 after seven days of culture; this is confirmed by the high MTT values. The Ki67 proliferation index was reported to be about 1.35 ± 1.24% in the F50/T1 matrix and about 5.10 ± 3.40% in F100/T4. Also, the apoptosis index in the F25/T4 composite was 26.99 ± 23.45% and for F12.5/T1 it had a wide range from 0.9% to 75.6%. Scanning electron micrscopy (SEM) studies showed that the fibrin network in these composites remained intact, maintained its regular pores, and human stromal cells within the structure not only survived, but also proliferated and established close cell connections with each other. These results collectively indicate that the F25/T4 and F12.5/T1 composites provide a biocompatible environment with high survival and favorable proliferation for human stromal cells and are considered suitable options for the development of artificial ovary matrices (Luyckx et al., 2013). Zheng and colleagues printed 3D constructs loaded with primary ovarian cells (POCs) using a bioink derived from porcine ovarian dECM. Live/dead assay results showed that more than 95% of the cells were viable on the first day after printing. This rate remained around 90% after 14 days of culture in the 3D construct, indicating long-term maintenance of cell viability in the printed environment. Functional evaluations showed that the printed scaffolds containing POC exhibited significant advantages in terms of vascularization, cell proliferation, and sex hormone secretion compared with acellular scaffolds and unprinted hydrogels. Histological

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and immunohistochemical analyses also confirmed the regular distribution of cells in the dECM network and the restoration of key ovarian functions (Zheng et al., 2022).

Anvari-Yazdi et al. designed 3D support scaffolds using a hybrid hydrogel based on decellularized porcine uterine ECM (dUECM) and alginate (3% Alg + 1.5% dUECM). The results of the MTT assay showed that immortalized Human Myometrial Cell Line (hTERT-HM) cells proliferated significantly on this substrate, reaching 258.14 ± 12.83% by day 7; this was significantly higher than the control group containing pure alginate. Evaluation with the Live/Dead assay also showed that more than 90% of the cells survived after seven days, indicating the long-term survival of the cells and the high biocompatibility of the dUECM hydrogel. In addition to preserving the cells, this hydrogel also provided proper cell attachment to the matrix and uniform cell distribution. The printed scaffold exhibited favorable mechanical properties, including stable swelling of approximately 47 ± 12%, high resistance to degradation up to day 14 (94 ± 18%), and good retention of Young's modulus. These findings indicate that the dUECM hydrogel not only provides adequate mechanical support but also provides an ideal environment for cell survival, proliferation, and cellular interaction (Anvari-Yazdi et al., 2025).

Khazaei et al. performed decellularization of sheep ovaries using 1% sodium dodecyl sulfate (SDS) and 1–5% Acanthophyllum (ACP) and examined the DNA content of the tissues to confirm cell removal. In normal tissue, the DNA content was 907.33 ng/mg, while after decellularization, the DNA content decreased in the groups as follows: 1% ACP = 102.73 ng/mg, 2.5% ACP = 76.28 ng/mg, 5% ACP = 37.31 ng/ mg, and 1% SDS = 37.05 ng/mg. The highest DNA removal was observed with 5% ACP and 1% SDS (<50 ng/mg), indicating effective cell removal. Furthermore, the MTT assay showed that more than 90% of cells remained viable in all groups, and the highest biocompatibility was observed in the 5% ACP

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group (Khazaei et al., 2025). Hosseinpour et al. prepared a decellularized human ovary scaffold using supercritical CO_2 ($scCO_2$) and 1% SDS pretreatment. The results showed that tissue DNA was effectively removed while the ECM structure and glycosaminoglycans (GAGs) were well preserved, indicating that important tissue properties were maintained. The MTT assay results showed that the scaffold was biocompatible and cells were able to survive and proliferate on it. This protocol provides optimal conditions for ovarian decellularization without damaging the ECM and is considered a promising strategy for ovarian tissue engineering and related clinical applications (Hosseinpour et al., 2025). Further studies are reported in Table 3.

***Table 3**. Summary of key findings from previous studies on stem cell sources, scaffolds, bioinks, and regenerative outcomes in female reproductive tissue engineering.*

1	follicles	Embedding primordial follicles from human ovaries under in vitro culture conditions for 7 days in alginate matrix and grafting alginate matrigel matrix in mice	Fertilization of cultured eggs and vascularization with less inflammatory response were observed after heterotypic transplantation	(Camboni et al., 2013; Tagler et al., 2014; Hornick et al., 2013)
2	Eggs	The use of an alginate-based system for the growth of oocytes and granulosa cells of mice	The use of the mentioned system led to the maturation of eggs in conditions in vitro, as well as the live birth of embryos from in vitro fertilization	(Park et al., 2012; Kim et al., 2016b)
3	Mouse follicles	Encapsulation of mouse follicles in 0.5% alginate beads	A positive relationship between follicle growth and their density was observed in alginate beads	(Hornick et al., 2013)
4	Mouse follicles	Encapsulation of mouse preantral follicles and ovarian cells in 1% alginate	Survival, development and viability of ovarian cells were observed one week after transplantation	(Vanacker et al., 2014)
5	Secondary follicles of the mouse	Encapsulation in a fibrin-alginate matrix	The results showed improvement in follicle growth and egg diameter	(Jin et al., 2010)

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6	ovary	The use of porous alginate scaffolds with bone morphogenic protein 4 (BMP4)	Pig primordial follicle culture up to preantral stage and maintenance of hormone secretion function after transplantation in immunodeficient mice were observed	(Chen et al., 2022b)
7	Preantral follicles	The use of fibrin hydrogel enriched by different concentrations of human platelets (5%, 10%, 15%, 20%)	Fibrin with 15% platelet content resulted in a higher follicular recovery rate	(Rajabzadeh et al., 2020)
8	ovary	Encapsulation of ovarian stromal cells in a fibrin clot	Favorable results were observed	(Rajabzadeh et al., 2020)
9	Preantral follicles of mice	Encapsulation of mouse preantral follicles together with ovarian cells in fibrinogen and thrombin	After one week, the angiogenesis and follicle development rate was reported to be 31%	(Rajabzadeh et al., 2020)
10	ovary	Using polyethylene glycol (PEG) hydrogel modified by Arginylglycylaspartic acid (RGD) motif and with the help of crosslinker (trifunctional peptides sensitive to metalloproteinase)	The survival and development of follicles in the early stages and also the formation of new vessels were observed	(Kim et al., 2016b)
11	Follicles	Encapsulation of follicles with adipose-derived stem cells and polyethylene glycol/vinyl sulfone (8 branches) modified by crosslinker matrix metalloproteinase (MMP) and plasmin	The production of useful paracrine factors and follicle growth were observed	(Tomaszewski et al., 2021)
12	Follicles	Encapsulation of ovarian cells in polyethylene glycol- fibrinogen hydrogels	An increase in the growth of primordial follicles and a decrease in atretic follicles were observed	(Tomaszewski et al., 2021; Tsou et al., 2016)
13	Ovaries of mice	Using a 3D collagen type 1 scaffold for granulosa cells culture	The development of steroidogenesis process was observed in antral follicles of mice	(Kossowska-Tomaszczuk et al., 2010)
14	ovary	Encapsulating ovarian follicles in collagen type 1 hydrogels	Cell survival, follicle growth, hormone production and oocyte maturation were observed	(Joo et al., 2016)
15	ovary	Cultivation of adipose-derived stem cells (ADSCs) on collagen scaffolds	Long-term recovery of ovarian function and fertility of mice was observed	(Mondal et al., 2016; Su et al., 2016)
16	ovary	Transplantation of autograft ovarian tissue fragments in fibrin and collagen	Survival and improvement of ovarian function were observed	(Joo et al., 2016)
17	ovary	Encapsulation of mouse ovarian cells in plasma clots	After transplantation, the animals were able to ovulate and give birth to normal children	(Carroll and Gosden, 1993)
18	ovary	The use of 3D electrospun gelatin/polycaprolactone (PCL) scaffold for implantation of isolated porcine preantral follicles	Preservation of the morphology and increase in adhesion of the follicles were observed	(Liverani et al., 2019)
19	ovary	Encapsulation of ovarian cells in silica matrices	The encapsulated follicles survived and maintained their cell structure and steroid function	(Catalano et al., 2012)

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20	ovary	Encapsulation of mouse secondary follicles in 30 mg/mL N-Isopropylacrylamide (SFX− 1) polymer	The diameter of the follicles increased from 153 ± 28 µm to 201 ± 38 µm	(Asaduzzaman et al., 2018)
21	ovary	Encapsulation of ovarian follicles in hyaluronic acid hydrogel	The evaluation of the results indicated development and escalation of survival rate for ovarian follicles	(Kim et al., 2014b; Desai et al., 2012)
22	ovary	Cultivation of human preantral follicles in decellularized ovarian tissue	The evaluation of the outcomes showed a high survival rate of follicles	(Pors et al., 2019)
23	ovary	Culture of primary cells on ovaries decellularized by sodium dodecyl sulfate	The decellularized scaffolds were able to maintain the microstructure of the ovary and the production of estradiol hormone	(Laronda et al., 2015)
24	uterus	Replacement of mouse uterine horn by collagen with a size of 15 x 35 mm	90 days after the transplant, there was an increase in the inner vessels of the endometrium and a slight growth of the smooth muscle bundles	(Song et al., 2015)
25	uterus	Capsule transplantation enriched with peritoneal derived myofibroblasts with polyethylene	After transplant, pregnancy occurred in the uterus	(Campbell et al., 2008)
26	uterus	Implantation of mouse uterine cells and mesenchymal stem cells on decellularized uterus by sodium dodecyl sulfate detergent or hydrostatic pressure	Three-layer reconstruction was performed 30 days after transplantation	(Atala, 2012)
27	uterus	Encapsulation of endometrial, myometrial and epithelial cells in a mixture of collagen and Matrigel	The mouse embryos developed much better than the control group	(Lü et al., 2009)
28	uterus	Implantation of bone marrow stem cells (BMSCs) on collagen scaffolds	Full-thickness repair of the uterine wall was performed also 30 and 90 days after the transplantation of endometrial cells, muscle cells and reconstruction of small vessels	(Ding et al., 2014b)
29	uterus	Transplantation of submucosal small intestine to uterine horn of rabbit	After 28 days, 3 out of 6 rabbits became pregnant	
30	uterus	Preparation of artificial uterus consisting of polydimethylsiloxane (first layer), porous polycarbonate membrane with gelatin and endometrial cells (second layer) and polydimethylsiloxane (third layer)	The resulting artificial uterus worked well for up to 8	
31	vagina	Reconstruction of vaginal tissue by autologous muscles or epithelial cells	Creation of vascular vaginal tissues *in vivo* had analogous phenotypic and functional characteristics to ordinary vaginal tissues	(Oberpenning et al., 1999; Raya-Rivera et al., 2014)

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32	vagina	Implantation of vaginal cells on polyglycolic acid (PGA) polymer scaffold	Vaginal epithelial cells and smooth muscles were able to multiply and survive for long periods	(De Filippo et al., 2003)
33	vagina	Implantation of embryonic stem cells and somatic cells on Poly(L-lactide-co-ε-caprolactone) (PLCL) scaffolds	The cells were able to multiply on the mentioned scaffolds	(De Philippo et al., 2008; Sartoneva et al., 2018)
34	Cervix	The use of silk-coated collagen scaffolds	The strength of the scaffolds increased significantly during an 8-week period	(House et al., 2010)
35	egg	Implantation of immature mouse oocyte-granulosa cells in 3D alginate systems	Live births of the embryos obtained from in vitro fertilization were observed	(Pangas et al., 2003)
36	Mouse follicles	Cultivation of mouse follicles on 3-dimensional gelatin scaffolds	The follicles maintained their survival, function and especially the ability to produce hormones	(Kreeger et al., 2005)

4. Discussion

In the last few years, a number of promising results have been published in the highly active field of 3D bioprinting of organ and tissue models. Real representations of tissues and organs have been created through bioprinting technology (Shokri et al., 2022). Because stem cells have a vast ability to build complex structures, they are crucial to the development of 3D tissues (Ferreira-Faria et al., 2022; Pati et al., 2016; Vijayavenkataraman et al., 2018). However, before applying stem cells, a number of problems need to be solved, including improving the cell environment to promote cell adhesion, cell stimulation, and mechanical-structural consistency to replicate the in vivo situation (Wüst et al., 2011). Furthermore, research has demonstrated that the production of oxygen-producing and replaceable dynamic hydrogels, among other recent developments in hydrogel science, has helped in the development of the most efficient techniques for regulating the cellular microenvironment (Gillette et al., 2010). Additional techniques are required to refine the bioprinting microenvironment, including improvements in precipitate prototyping, printing rate, hydrogel physicochemical properties,

incubation and preparation durations for both cells and hydrogels, tissue vascularization and innervation, particularly the establishment of vascular networks within bulky tissues to support nutrient and oxygen delivery as well as metabolic waste removal, and the ability to dynamically adjust scaffold properties in response to specific demands and the stage of cell maturation. Even though 3D bioprinting technology has been applied extensively in drug screening, diseases research, tissue engineering, and numerous other fields that require attention, hurdles in bioprinting, bioink, and vascularization techniques have to be addressed. Current bioprinting methods face with challenges related to printing speed, resolution, and biomaterial compatibility, which prevent them from fully meeting the demands of fabricating simulative tissues or organs-on-chips (de Barros et al., 2025; Harrison et al., 2007).

As mentioned earlier, the commercialization of bioprinting techniques has the potential to revolutionize medical science. This technology can provide scaffolds for drug screening, regenerative medicine, and organ and tissue transplantation (Fleischer et al., 2017). Even with all the advancements, creating complex tissues and designing appropriate bioinks remain difficult tasks. Novel bioink formulations, reliable cell sources, and sophisticated print methods are needed are needed to preserve cell viability and protect encapsulated cells from damage during the printing process. Therefore, the need of new methods for quality control and standardization arise (Lv et al., 2015; Zhang et al., 2021). The primary issue in the development of bioink involves a balance between processability and biocompatibility. Controllable printing speed is necessary to optimize the production of implantable devices in clinically relevant sizes (Townsend et al., 2019; Zhang et al., 2016). This balance can typically be achieved by using easily processed, strong mechanical materials as structural supports, and biocompatible hydrogels as ECM components. Nonetheless, there is a perceived necessity for quick switching

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between various printing components. The successful optimization of various bioink functions for 3D bioprinting also requires standardized bioink characterization and testing methods. The most crucial thing to do is to verify biomaterial degradation. Indeed, once the printed tissue is implanted, the biomaterial needs to be strong enough to hold the embedding cells in place at first and break down gradually without releasing any toxic byproducts (Townsend et al., 2019). Developing biomaterials with optimum chemical and functional characteristics, like printability, biocompatibility, biodegradability, and cell life preservation, remains difficult. Natural biomaterials may not be the most suitable choice for 3D bioprinting due to specific characteristics. As for example, natural alginate is not strong enough mechanically but is biocompatible and biodegradable. Blending different polymers, such as alginate and gelatin, could be useful in these situations. Indeed, after crosslinking with calcium ions (Ca^{2+}), alginate hydrogel may maintain its long-term strength, but early on, gelatin can solidify its 3D structure. Owing to their superior biocompatibility and enhanced mechanical properties, alginate-gelatin hydrogels have been extensively employed in tissue engineering applications. Similarly, according to reports, adding collagen type 1 to agarose greatly promotes cell differentiation and expansion (Yang et al., 2022).

To successfully mimic natural tissues or organs, it is crucial to accurately reproduce cells and bioactive substances. For this purpose, suitable cell materials for specific tissues should be selected. To maintain the survival and functionality of cells, permeable bioreactors should also be constructed with appropriate cell spaces and chemical or physical stimulation. The biological function and structure of ECM is actually difficult to mimic in the lab due to its complexity (Yongnian et al., 2010). The challenges of oxygen delivery and cell nourishment for large scaffolds cannot be resolved by current technologies that produce hydrogels including

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cells. Furthermore, additional constraints including cell survival, growth, and differentiation must be taken into account. A promising avenue for future research lies in the development of novel fabrication platforms capable of producing scaffolds with even higher precision and controlled porosity. Furthermore, it is crucial to investigate high-performance materials for different 3D printing processes, develop integrated standards for 3D printing scaffolds, bolster market surveillance to optimize implants for clinical use, and set up a 3D printing platform to facilitate greater communication between healthcare facilities, businesses, and research institutes. The intrinsic advantages of hydrogels in bioprinting methods sometimes result in printed objects lacking mechanical strength and integrity, which is a typical issue (Nair et al., 2009; Unagolla and Jayasuriya, 2020). After planting, printed structures require to be strong enough to maintain their shape and resist outside pressures. Hydrogels with low mechanical characteristics are mostly utilized in bioprinting systems. The clinical design of bioprinting structures is usually difficult since bioink needs to have a low viscosity to avoid clogging the nozzles. To preserve the integrity of the structures, new biocompatible materials must be developed (Gaebel et al., 2011; Ning et al., 2019). Indeed, hydrogel materials that are compatible with the printing process and have appropriate mechanical, diffusion, and biocompatibility characteristics are essential for the long-term viability of bioprinting platforms. 3D bioprinting may benefit from the encapsulation of cells in gel phase materials to create bioink. Although 3D bioprinting has become a viable technique for cell patterning, the lack of appropriate bioink materials continues to limit its capacity to fabricate tissue-like and bioactive structures. While viscous polymers have been previously employed in 3D printing, these materials frequently exhibit poor biological functionality and inadequate cell compatibility (Hull et al., 2022). Hydrogels have been reported to be excellent candidates for

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fulfilling the biological requirements of encapsulated cells and for protecting them during the extrusion process. These materials are composed of crosslinked, water-swollen polymer networks that can provide an aqueous environment suitable for 3D cell culture. Their physical state can be modulated by the degree of crosslinking; with minimal crosslinking, they behave as viscous liquids, whereas increased crosslinking renders them more solid-like. Studies have shown that hydrogels are frequently employed both as inks for 3D bioprinting and as gel-phase support materials. In addition, they are widely used in 3D cell culture due to their ability to replicate key mechanical and metabolic features of native tissues within an aqueous environment (Mooney et al., 2012). These hydrogels' high-water content and high permeability make it simple for waste products and nutrients to diffuse into and out of the enclosed cells. They can also deliver a variety of signals that are necessary for cell growth, migration, differentiation, and phenotype regulation (Hsiao et al., 2013).

The structure and biological requirements of complex tissue-like scaffolds that imitate in vivo structures can be met by engineering hydrogels, which have been widely employed for tissue engineering applications. Research has shown that hydrogels can achieve a homogenous cell suspension in the bioprinting process by limiting cell deposition. Hydrogels may also protect cells from shear forces during printing, which could cause damage to the cell membrane and threaten cell viability (Zhang et al., 2021). According to reports, around 40% of cells are unable to survive extrusion because the cell membrane is damaged. In addition to directly causing damage to the cell membrane, shear stresses have also been shown to have an impact on gene and protein expression, cytoskeleton organization, and cell shape (Yang et al., 2025). For this reason, further development of these hydrogel systems is imperative, and research is ongoing to address current limitations and expand their biomedical applicability.

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In summary, the literature reviewed in this work provides clear guidance regarding the two central questions posed at the beginning of this review, namely, the optimal stem cell sources for female reproductive tissue engineering and the most promising bioinks and bioprinting strategies for infertility treatment. Among the various cell candidates, MSCs, endometrial stem/progenitor cells, and iPSCs emerge as the most potent due to their high proliferative capacity, immunomodulatory effects, and demonstrated ability to regenerate endometrial, ovarian, and oviductal tissues. MSCs in particular have repeatedly shown effectiveness in restoring endometrial thickness, enhancing angiogenesis, and improving implantation potential. Regarding bioprinting strategies, hydrogel-based bioinks such as alginate-gelatin composites, GelMA, collagen-based matrices, and ECM-derived hydrogels appear most suitable because they support cell viability, allow fine deposition, and mimic the native reproductive microenvironment. Extrusion-based and inkjet bioprinting technologies are currently the leading printable modalities for reproductive tissues, given their compatibility with cell-laden hydrogels and their capacity for constructing layered, hormonally responsive structures. Overall, the collective findings indicate that the combination of stem-cell–laden hydrogels and advanced extrusion bioprinting systems holds the greatest promise for future regenerative therapies aimed at restoring fertility in women.

5. Future perspectives: challenges and opportunities

Despite significant advances in 3D bioprinting of reproductive tissues, significant obstacles remain that require careful consideration. One of the greatest challenges is inadequate vascularization of printed constructs, as the lack of an effective vascular network can lead to

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oxygen and nutrient deprivation and ultimately cell death in bulky tissues. There is also the potential for immunogenicity, particularly when molecules or remnants of decellularization stimulate an immune response. From an ethical perspective, the use of human cells, patient-derived organoids, and decellularized ECM in personalized reproductive models raises specific ethical sensitivities and obligations (Mir et al., 2023; Grover et al., 2018).

To address these challenges, future research should move towards organoid-based bioprinting approaches to produce structures with more natural complexity and architecture. Integrating microfluidic systems with printed tissues can also more accurately simulate nutrition, fluid flow, and physiological pressure application, and facilitate vascular perfusion. Also, the development of personalized models using patient- derived cells such as stem cells or autologous organoids can lead to safer and more precise therapies (de Barros et al., 2025). To achieve clinical applications, standardization of protocols in bioink composition, printing technique, and decellularization methods is essential, and preclinical evaluations with animal models and organ-on-a-chip systems should be rigorously conducted. Ultimately, the combination of these strategies could pave the way for the development of clinically acceptable reproductive tissue regeneration solutions (Chen et al., 2025). The construction of ovarian organoids involves the induction of iPSCs and the creation of a suitable ECM. These cells are capable of generating granulosa cells, epithelial cells, and germ cells, but the induction of theca cells and the initiation of meiosis remains challenging, thus further studies in the field of development and epigenetics are needed. Coordinated induction of multiple cell types is essential for the generation of functional organoids. Stimulation of ovarian hormone production in vitro is also important for the formation of mature and stable follicles. Common matrices such as Matrigel have limitations due to their tumor origin, and the development of

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more biocompatible matrices with optimized mechanical and biochemical properties is still needed. The main goal is to create a stable and large-scale reproducible matrix that can support follicle growth and cellular interactions (Zhao et al., 2021). Advances such as CRISPR-Cas9, a revolutionary gene-editing technology that acts as molecular scissors, and 3D printing could improve organoid technology and increase the safety of iPSCs, providing better outcomes for women with genetic disorders. Increased attention to women's reproductive health has also fueled the demand for ovarian organoids. Future developments will focus on organ-on-a-chip platforms, automation of multipotent systems, and the creation of organoid banks for mass production of in vitro models. Despite advances, there are still challenges in generating ovarian cell types from iPSCs and regenerating ovarian-specific ECM, but with continued progress, there is hope for effective treatment of ovarian disorders, preservation of fertility, and restoration of ovarian function (Zhao et al., 2021; He et al., 2023).

Bioprinting technology also has great potential for reconstructing the female reproductive system, but insufficient vascularization and structural and functional differences from natural tissue remain important challenges. Addressing these problems requires improving printing techniques, selecting biocompatible materials, and identifying appropriate cells and factors. 3D printing can provide a suitable environment for stem cell growth and facilitate their interaction with the environment. The use of new printing materials such as dECM creates more specific physiological conditions and increases adhesion, proliferation, and guided differentiation of stem cells (Zhang et al., 2024). This will also allow to obtain 3D printed tumor models for cervical and ovarian cancers, as valuable tools for studying pathogenesis and drug evaluation. Furthermore, organ-on-a-chip technology should be used to more accurately simulate the body environment. The integration of 3D printing with microfluidics will create

more accurate structures and models that are closer to real-world conditions. From an application perspective, 3D printing could play an important role in preserving female fertility, such as fabricating hybrid implants containing immature oocytes to increase the likelihood of maturation and natural fertilization, or improving the survival of primordial follicles in frozen ovarian tissue (Chen et al., 2025). However, challenges remain, such as cost, scalability, and ethical issues related to cell sourcing and clinical applications. Therefore, the development of low-cost hardware, facilitating access to equipment, and the integration of innovative bioinformatics approaches will be essential to advance this technology (Yang et al., 2025).

6. Conclusion

In summary, stem cells derived from ovarian tissue, bone marrow, adipose tissue, and menstrual blood, combined with bioinks such as ECM-based hydrogels, decellularized ECM, and hybrid polymer-based scaffolds, show the greatest potential for regenerative applications in female reproductive health. Despite significant advances, major barriers remain, including insufficient vascularization, immunogenic responses, standardization of mechanical and bioreactor protocols, and ethical considerations in the use of human-derived materials. Future studies should prioritize the development of vascularized endometrial and ovarian constructs, standardization of mechanical and biofabrication protocols, and optimization of bioink formulations to better mimic native tissue architecture. Additionally, integrating organoid-on-chip platforms, artificial intelligence–assisted biofabrication, and patient- specific cells will be crucial to enhance translational applicability. Moving forward, preclinical studies in appropriate animal models and organoid systems are essential to validate functional outcomes

and safety. With continued progress, these strategies may pave the way toward first-in-human trials, offering promising avenues for fertility preservation and restoration of reproductive function.

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