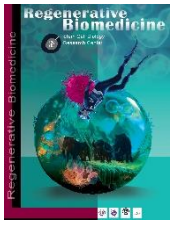

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Review Article

Tissue Engineering Approaches for Restoring Ovarian Function in Premature Ovarian Insufficiency: Current Advances and Future Perspectives

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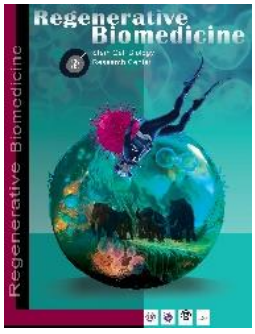
Abstract

POI is a complex disorder characterized by the loss of normal ovarian function before the age of 40, profoundly affecting fertility, hormonal regulation, and overall quality of life. Current therapeutic approaches, including hormone replacement therapy and oocyte donation, primarily manage symptoms and are unable to restore the physiological function of the ovaries. Despite notable advancements, several challenges remain, such as ensuring the long-term safety of cell transplantation, achieving precise control over stem cell differentiation, and minimizing the potential risk of malignancies. Tissue engineering, as a rapidly evolving field in regenerative medicine, offers a promising strategy to overcome these limitations. By integrating stem cells, biomaterial scaffolds, and growth factors, tissue engineering aims to reconstruct the natural architecture and function of ovarian tissue. This approach holds potential for addressing hormonal imbalances, metabolic disturbances, and infertility issues caused by POI. This review examines the latest progress in ovarian tissue engineering, highlighting the roles of different components in ovarian regeneration and discussing remaining technical and clinical challenges. By providing a comprehensive overview, this work emphasizes the potential of tissue engineering to form the basis for future regenerative therapies, ultimately improving reproductive health and enhancing the quality of life for women affected by POI.

Keywords: Biomaterial scaffolds, Growth factors, Premature ovarian insufficiency (POI), Stem cells, Tissue engineering



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Introduction

Premature ovarian insufficiency (POI), also known as premature ovarian failure (POF), is a complex and common disorder among young women characterized by the unexpected cessation of ovarian function before the age of 40 (1). This condition results in infertility, hormonal imbalances, and long-term complications such as osteoporosis, increased cardiovascular risks, and psychosocial challenges (2).

Various etiological factors, including genetic, autoimmune, chemotherapeutic, radiotherapeutic, and environmental toxins, contribute to its development (3).

Current treatments, such as hormone replacement therapy (HRT), ovarian stimulation, and assisted reproductive technologies (ART), primarily address symptoms rather than restoring natural ovarian function (4, 5). Recent advances in tissue engineering and regenerative medicine have introduced promising therapeutic strategies for ovarian regeneration. Ovarian tissue engineering integrates stem cells, biomaterial scaffolds, and growth factors to reconstruct the structural and functional components of the ovary (6).

Mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs) play pivotal roles due to their differentiation capacity and paracrine signaling. Nevertheless, challenges such as tumorigenicity, immune rejection, and precise differentiation control remain (7). Biomaterial scaffolds, derived from natural (e.g., alginate, gelatin, collagen) or synthetic (e.g., Poly (lactic-co-glycolic acid) (PLGA), Polycaprolactone (PCL), Polyethylene glycol (PEG) materials, provide a supportive niche for follicular development (8). Hybrid scaffolds offer enhanced mechanical properties, biocompatibility, and porosity. Cutting-edge technologies, including as three-dimensional (3D) bioprinting, microfluidics (Organ-on-a-Chip), and follicle encapsulation, enable the precise and personalized reconstruction of ovarian microenvironments (9, 10). The incorporation of growth factors (e.g., Growth Differentiation Factor-9 (GDF-9), Bone Morphogenetic Protein-15 (BMP-15), Vascular Endothelial Growth Factor (VEGF)), exosomes, and extracellular vesicles further supports angiogenesis and follicular maturation in a cell-free manner (11).

Preclinical and clinical studies have demonstrated the potential of stem cell-based therapies and engineered scaffolds to restore follicle numbers, reduce follicle-stimulating hormone (FSH) levels, and resume menstruation (6). However, long-term safety, biodegradability, immune compatibility, and standardization require further investigation. Future directions involve personalized therapies using iPSCs, smart scaffolds, and nano-enabled delivery systems to achieve effective, safe, and durable ovarian function restoration (12). With continued scientific advances and international collaboration, ovarian tissue engineering holds the promise to revolutionize POI treatment and significantly enhance patients' quality of life (13). This review article aims to provide a comprehensive and up-to-date overview of the latest advancements, challenges, and future perspectives in the application of tissue engineering for the treatment of premature ovarian insufficiency (14). To this end, it will first elaborate on the physiology and pathophysiology of POI, then analyze the principles and practical techniques of tissue

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engineering, and finally, through a review of preclinical studies, clinical trials, and emerging technologies, suggest future research directions (15) Fig. 1.

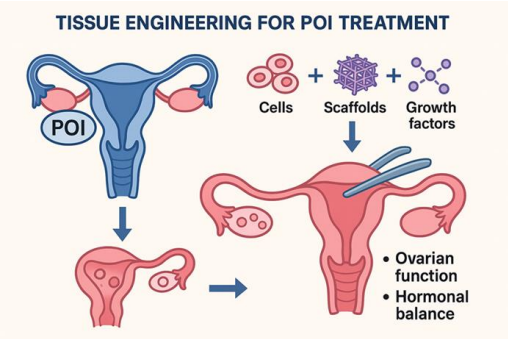

Figure 1. The role of tissue engineering in the fundamental treatment of Premature Ovarian Insufficiency (POI). This diagram illustrates how tissue engineering can be used to restore ovarian function. The process combines cells, scaffolds, and growth factors to recover hormonal balance and ovarian activity. The left side shows the anatomical representation of ovarian insufficiency, while the right side depicts the restored ovarian structure and function following tissue engineering intervention.

Definition of POI

POI is a serious and complex clinical disorder characterized by the loss of normal ovarian function before the age of 40 (16). Previously referred to as "premature menopause," POI is associated with decreased estrogen levels, the loss of menstrual cycles, and elevated levels of gonadotropins, particularly FSH (4). The estimated prevalence of POI is about 1% among women under 40 years of age and approximately 0.1% among women under 30, underscoring its significant clinical and social implications (4, 17).

POI not only leads to infertility but also has substantial psychological, metabolic, cardiovascular, and skeletal consequences (18).

The management of POI extends beyond fertility restoration. This disorder directly impacts women's quality of life, mental health, and overall longevity (4). The decline in estrogen levels can increase the risk of osteoporosis, cardiovascular disease, cognitive disorders, and depression. Therefore, effective treatment of POI requires a comprehensive and multidimensional approach aimed not only at restoring ovarian function but also at protecting other bodily systems .(19) Current conventional treatments, such as HRT, ovulation-stimulating medications, and oocyte donation, can help manage some symptoms of POI or enable pregnancy, but they do not restore the natural physiological function of the ovaries. Moreover, existing therapies are associated with risks, including an increased likelihood of cancer, cardiovascular complications, and other long-term side effects. Thus, there is a growing need for novel, biocompatible approaches (2, 20).

Tissue engineering, as a leading branch of regenerative medicine, aims to reconstruct, repair, or replace damaged or non-functional tissues and organs, offering promising new horizons for the treatment of POI (21, 22). By utilizing stem cells, biomaterial scaffolds, growth factors, and advanced technologies, tissue engineering can recreate the ovarian physiological environment, preserve or stimulate ovarian follicles, and even pave the way for the development of bioengineered artificial ovaries (23).

Pathophysiology of POI

The ovaries play a central role in reproduction and the regulation of hormonal

balance in women. These organs consist of two main parts: the cortex and the medulla (24). The ovarian cortex contains a reserve of primordial follicles that are formed during fetal development and then gradually become active or undergo atresia during the woman's life (25).

Ovarian follicles not only produce eggs but also play a crucial role in regulating the menstrual cycle and fertility by secreting hormones such as estrogen, progesterone, and androgens. Ovarian activity is controlled by the hypothalamic-pituitary-ovarian (HPO) axis (26).

Gonadotropins (FSH and Luteinizing Hormone (LH) are released from the pituitary gland, which stimulates follicles, leading to egg maturation and secretion of sex hormones. Premature ovarian insufficiency occurs when the normal function of the ovaries is disrupted prematurely (27).

This disorder can result from early depletion of the follicular reserve (follicular depletion) or dysfunction of the remaining follicles (follicular dysfunction) (27).

Several causes for POI have been identified, including:

Genetic causes: Chromosomal abnormalities such as Turner syndrome (X monosomy) and gene mutations like FMR1 mutations (28).

Autoimmune causes: Immune system attacks on ovarian tissue and follicles (29).

Medical treatments: Chemotherapy, radiation therapy, or ovarian surgeries (30).

Environmental factors: Pollution, chemical toxins, and infections (31) (Fig. 2).

Idiopathic causes: In many cases (~70%), the exact cause of POI remains unknown (32).

The ultimate result in all these cases is the loss or dysfunction of ovarian follicles and a reduction in the secretion of sex hormones, leading to widespread consequences in the body (33). The complications of POI extend beyond infertility and include several systemic effects:

Osteoporosis: Reduced estrogen leads to increased bone resorption and decreased bone density (34).

Cardiovascular diseases: Women with POI have an increased risk of coronary artery disease and stroke (35).

Psychiatric disorders: Depression, anxiety, and cognitive disturbances are more prevalent in affected women (36).

Metabolic problems: Lipid metabolism disturbances and increased insulin resistance (37) (Fig. 2).

Given the limitations of traditional treatments and the long-term risks associated with POI, there is an urgent need for therapeutic approaches that can sustainably restore ovarian function (2).

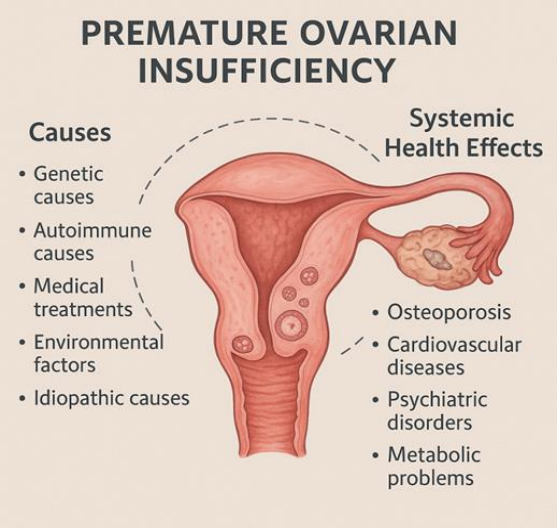

Figure 2. Schematic diagram of Premature Ovarian Insufficiency (POI), showing common causes (genetic, autoimmune, medical treatments, environmental factors, and idiopathic) on the left side, and systemic consequences (osteoporosis, cardiovascular diseases, psychiatric disorders, and metabolic problems) on the right side.

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Therapeutic Approaches for POI

Despite the high significance of this disorder, current therapeutic approaches for POI have not yet been able to provide effective solutions for restoring ovarian function (38, 39). The most common and accessible intervention in managing POI is HRT (2). This treatment is designed to compensate for the deficiency of estrogen and progesterone hormones, aiming to prevent complications associated with premature menopause, such as osteoporosis, hot flashes, and mood instability (40, 41). However, HRT has no effect on repairing ovarian tissue or restoring follicular function (42). In other words, this method is symptomatic rather than regenerative and cannot restore fertility potential. Moreover, long-term use of HRT may be associated with an increased risk of hormone-dependent cancers, thromboembolism, and liver disorders, especially in patients with a personal or family history in these areas (43).

In the field of fertility, one of the few available options for women with POI is the use of donated oocytes within the process of *in vitro* fertilization (IVF) (44). Although this method has achieved clinical success and led to live births in some countries, cultural, religious, and psychological challenges related to the use of donated gametes have caused many women to avoid this option (45). Furthermore, this approach is entirely non-personalized and does not involve any recovery of the patient's own ovaries; instead, pregnancy is achieved using another woman's egg (46). In addition, in certain countries or religious groups, this method remains ethically and legally controversial (47).

On the other hand, some emerging interventions such as pharmacological ovarian stimulation or the use of ovarian rejuvenation techniques (e.g., PRP) have also been explored. However, these methods are still in early research stages, and sufficient evidence regarding their efficacy and safety is lacking (48). For instance, injection of platelet-rich plasma (PRP) into the ovary, although showing promising results in some case studies, still lacks a clear understanding of its exact mechanism of action, appropriate dosage, frequency of injections, and long-term outcomes (49). In many cases, these interventions have merely resulted in a temporary increase in certain hormone levels without leading to oocyte maturation or successful pregnancy (50).

Efforts have also been made toward preserving ovarian reserves in patients undergoing gonadotoxic treatments, including the use of drugs that suppress the HPO axis (such as Gonadotropin-Releasing Hormone (GnRH) analogs) to temporarily silence ovarian activity during chemotherapy (51, 52). Although this strategy has been reported as beneficial in some cases, contradictory results from multiple clinical trials, limited efficacy, and potential side effects have prevented it from being recognized as a definitive solution (2).Surgical treatments, such as frozen ovarian tissue transplantation, have also been performed with the aim of preserving fertility in young women prior to chemotherapy (53). However, this method is primarily applicable in preventive settings, not in patients already diagnosed with POI. Moreover, the risk of cancer recurrence (in malignant cases) after ovarian tissue transplantation is considered a major challenge of this method (54, 55). Additionally, the success of this technique depends heavily on the patient's age, quality

of the frozen tissue, and freezing technology, all of which limit access for many patients (56). Overall, current approaches are either based on non-regenerative hormonal therapies, require the use of donated cells or external resources, or lack sufficient evidence and credible clinical experience. None of these strategies can sustainably, internally, and personally regenerate the ovarian tissue structure and natural function (3). These limitations highlight the urgent need for fully novel and biocompatible approaches—ones that can not only alleviate symptoms but also regenerate the damaged source itself (i.e., ovarian tissue).

In this context, Tissue Engineering, as one of the most advanced branches of regenerative medicine, holds immense potential to revolutionize the treatment of POI (57). This technology, combining living cells, biomaterial scaffolds, growth factors, and innovative techniques such as 3D bioprinting, aims to design living structures capable of replacing damaged or lost tissues and restoring their normal function (58). Unlike previous methods, these approaches focus on true ovarian tissue regeneration and the creation of functional follicular niches (59).

The Role of Tissue Engineering in the Treatment of POI

Innovative tissue engineering technologies, leveraging stem cells, biocompatible scaffolds, bioactive agents, and advanced systems such 3D bioprinting, nanoparticles, and organ-on-a-chip platforms, have provided multidimensional and targeted approaches for restoring ovarian structure and function (58, 60). These strategies are not only capable of reconstructing the ovarian microenvironment and stimulating folliculogenesis, but also enable targeted delivery of growth factors, modulation of immune responses, and enhancement of cell survival (61, 62).

The following provides a comprehensive overview of the most important novel technologies and approaches in tissue engineering for treating POI. These approaches are categorized into four main axes: scaffold-based cellular strategies, molecular and growth factor approaches, advanced bioengineering methods, and protective and encapsulation strategies. The goal is to outline emerging therapeutic perspectives, preclinical achievements, and the challenges ahead in translating these technologies into clinical practice. This path could lead to a fundamental transformation in the treatment of infertility among women with POI.

Scaffold-Based Cellular Approaches for Ovarian Regeneration in POI

the use of Scaffold-Based Cellular Approaches (63). These strategies aim to reconstruct the ovarian niche and stimulate the natural process of folliculogenesis by utilizing various cellular sources, including MSCs (59), iPSCs (63), ESCs (21), and immature follicles (63). Combining these cells with 3D biocompatible scaffolds provides an environment similar to natural ovarian tissue, which enhances cell survival, differentiation, and effective cellular interactions (64).

In addition to cell therapy, the use of exosomes and extracellular vesicles—as natural carriers of signaling molecules—represents a novel, non-cellular approach that can offer similar therapeutic effects with higher safety (65). Despite the valuable

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achievements of preclinical studies, clinical translation of these technologies requires further research, standardization of methods, and comprehensive evaluation of long-term safety (59).

Stem Cells, Exosomes, and Follicle Transplantation for Ovarian Regeneration in POI

The application of stem cells, exosomes, and follicle transplantation has emerged as a promising approach for ovarian regeneration in POI. Stem cells contribute to repairing ovarian structure, stimulating folliculogenesis, and restoring hormonal balance through their regenerative capacity. By releasing bioactive molecules, including growth factors and microRNAs, they inhibit granulosa cell apoptosis, reduce inflammation, enhance angiogenesis, and modulate immune responses (66). In addition, they modulate immune responses and prepare the ovarian environment for repair. Similarly, exosomes act as non-cellular mediators that support intercellular communication and create a microenvironment conducive to tissue repair. In parallel, transplantation of immature follicles provides a direct source for folliculogenesis, complementing cellular and non-cellular therapies to promote functional recovery of the ovary (67).

Use of MSCs in Ovarian Tissue Regeneration

MSCs are multipotent, non-hematopoietic stem cells capable of differentiating into various mesenchymal lineages such as osteoblasts, adipocytes, and chondrocytes (68). These cells can be extracted from multiple sources, including bone marrow (BMSCs), adipose tissue (ADSCs), umbilical cord (UC-MSCs), and endometrial layer (eMSCs). MSCs primarily act through paracrine mechanisms and have demonstrated significant therapeutic effects in tissue regeneration (21). These effects include stimulating angiogenesis via secretion of factors such as VEGF and basic Fibroblast Growth Factor (bFGF), inhibiting granulosa cell apoptosis, modulating inflammatory and immune responses in the ovarian environment, and releasing exosomes containing microRNAs and regulatory proteins (69).

Numerous preclinical studies have shown that injecting MSCs into animal models with ovarian damage caused by chemotherapy or autoimmune disorders leads to significant improvement in ovarian function, increased estradiol levels, decreased FSH levels, restoration of menstrual cycles, and even recovery of antral follicles (70, 71). These findings confirm the high efficacy of these cells in restoring endocrine function and folliculogenesis under conditions of POI (72).

Application of iPSCs in Restoring Ovarian Function

iPSCs are adult somatic cells that have been genetically reprogrammed to return to a pluripotent state (73). These cells have the ability to differentiate into all cell types of the body and functionally resemble embryonic stem cells, but unlike them, they involve fewer ethical concerns (74). In the context of treating POI, iPSCs have received considerable attention due to their potential to differentiate into granulosa-like cells and even oocyte-like cells (67).

Some studies have shown that using 3D culture systems and adding appropriate

growth and morphogenic factors, these cells can be directed toward folliculogenesis. However, their application still faces significant challenges (75, 76). The most important of these include the risk of tumorigenesis in case of incomplete or uncontrolled differentiation, difficulty in precisely standardizing cellular differentiation protocols, and the need for more extensive studies to evaluate their safety and efficacy in human clinical applications (77).

ESCs for Follicle Formation and Ovarian Reconstruction

ESCs are pluripotent cells derived from the inner cell mass of blastocysts and are capable of differentiating into all cell types of the body (78). This characteristic makes them a highly valuable resource in ovarian tissue engineering, as they can efficiently differentiate into granulosa cells, theca cells, and even primary follicles (79).

However, their use also presents notable challenges. The main limitations of this approach include extensive ethical and legal considerations present in many countries (57), a high risk of tumorigenesis due to the inherent tendency of these cells to grow uncontrollably, and the complexity involved in precisely controlling their differentiation into the desired cell lineage (79).

From a practical perspective, laboratory and preclinical studies have shown that ESCs can differentiate into follicle-like structures under appropriate culture conditions (14).

However, due to the aforementioned limitations, their clinical application in humans remains at an early research stage (79).

Transplantation of Immature Follicles for Fertility Restoration in POI

Another approach used in treating POI involves the use of immature follicles extracted from healthy or cryopreserved ovarian tissue (44). In this method, primary or early secondary follicles are isolated from ovarian tissue and cultured in 3D environments or appropriate biocompatible scaffolds to reach more advanced stages of maturation (63). These follicles are then transplanted into the patient's ovary so that they can naturally develop and eventually lead to ovulation and potentially fertility (67).

To enhance their survival and growth, these follicles are often cultured in enriched media containing specific growth factors such GDF-9 and BMP-15 before transplantation (80). These morphogenetic factors play a key role in directing differentiation and follicular maturation. Additionally, the use of natural biomaterial scaffolds such as alginate and fibrin—acting as structural support and mimicking the natural ovarian environmentis quite common in this process (63, 76). Laboratory and preclinical studies have demonstrated that transplanting immature follicles into animal models of ovarian insufficiency, using scaffolds such as collagen, Matrigel, or a collagen–Matrigel combination, can support the development of antral follicles, restore ovulation, and in some cases result in successful pregnancies (81). These findings confirm the effectiveness of this method in recovering ovarian function and restoring fertility under POI conditions (42).

Exosomes and Extracellular Vesicles as Non-Cellular Therapeutic Agents in POI

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Exosomes are nanometer-sized vesicles that are naturally secreted by cells, especially stem cells, and contain bioactive molecules such as RNA, miRNA, proteins, and lipids involved in intercellular communication (82).

These small particles have recently gained attention as important agents in repairing and regenerating ovarian tissue under POI (83).

Exosomes contribute to ovarian function recovery through various mechanisms, including: inhibiting granulosa cell apoptosis, increasing angiogenesis and improving ovarian blood flow, regulating the expression of key genes in folliculogenesis, and reducing oxidative stress in ovarian tissue (79, 84). These biological effects make them an attractive alternative compared to cellular approaches. Using exosomes offers notable advantages over direct cell transplantation (83). These particles do not require the injection of live cells, thus significantly reducing risks such as tumorigenesis and immunogenic reactions (48).

Additionally, they can be used in smart scaffolds, hydrogels, or controlled drug delivery systems, which facilitate their clinical application (83).

Types of Biomaterial Scaffolds in Ovarian Regeneration for POI

Biological scaffolds are 3D structures designed to mimic the physical, mechanical, and biochemical properties of the extracellular matrix (ECM) (85).

These structures act as frameworks on which cells can grow, differentiate, and interact with their surrounding environment (86).

In the treatment of POI, scaffolds are specifically designed with the aim of reconstructing the ovarian follicular niche, enhancing follicle survival, and releasing bioactive factors (63, 87).

Natural Biomaterial Scaffolds for Supporting Follicle Growth and Survival

Natural scaffolds are fabricated from biological materials derived from living organisms and exhibit high biocompatibility, appropriate biodegradability, and the ability to directly interact with cells (88). Due to their closer resemblance to the natural extracellular matrix, these scaffolds have found widespread application in ovarian tissue engineering (89).

Gelatin, a product of collagen hydrolysis, is one of the most commonly used components in the fabrication of biological scaffolds (90). The presence of bioactive sequences such as RGD (Arginine-Glycine-Aspartic acid) within its structure facilitates cell adhesion and induces differentiation (91). Gelatin can be used in various forms, including hydrogel, foam, or 3D matrix, to support follicular growth (88, 92). Collagen is also recognized as the main component of the extracellular matrix in ovarian tissue (63). The use of collagen-based scaffolds in the form of 3D matrices or nanofibers provides an environment similar to the (93).

physiological environment of the ovary and supports the survival of follicles and granulosa cells (48, 94).

Alginate is another naturally derived polysaccharide extracted from algae that easily forms a gel in the presence of calcium ions (95). Due to its limited support for cellular mobility, alginate is primarily used for the encapsulation of follicles and cells (96). Alginate significantly enhances the survival of transplanted cells by facilitating

nutrient exchange and protecting them from immune responses (63).

Synthetic Scaffolds with Tunable Properties for Ovarian Regeneration

Synthetic scaffolds are made from artificial biodegradable polymers whose mechanical properties, degradation rate, and biocompatibility can be precisely controlled (93). One of the most commonly used materials is PLGA, which has found extensive application in the delivery of growth factors and in supporting follicles within the ovarian environment due to its tunable degradation rate by adjusting the lactide-to-glycolide ratio (48, 69). PCL is also suitable for long-term applications because of its high mechanical strength and slow degradation rate (64), and it can be combined with other materials or biological elements (97). PEG is a hydrophilic, biocompatible, and non-immunogenic polymer (98) that is often used in copolymer form or as a hydrogel to provide a suitable environment for the growth of ovarian cells (99).

Hybrid Scaffolds Combining Natural and Synthetic Materials for Enhanced Ovarian Repair

To benefit simultaneously from the advantages of both natural and synthetic scaffolds, hybrid scaffolds have been developed (100). By combining materials such as alginate and PLGA or gelatin and PEG, these structures can provide favorable biological properties, biocompatibility, and mechanical strength at the same time (101, 102). These hybrid scaffolds play a significant role in follicle reconstruction, preservation of granulosa cell function, and oocyte development (63).

Development of Scaffold-Based Nanofibrous and Biomimetic Approaches for Reconstructing the Ovarian Niche and Treating POI

Electrospinning is one of the most advanced techniques for scaffold fabrication at the nanoscale and has gained significant attention in ovarian tissue engineering (103). In this method, natural and synthetic polymers such as PCL, gelatin, collagen, polylactic acid (PLA), and polyglycolic acid (PGA) are transformed into nanofibrous structures using a strong electric field (104). These nanofibers provide an ideal environment for adhesion, proliferation, and differentiation of ovarian cells due to their structural similarity to the ECM (105). Nanofibers possess a high surface-to-volume ratio, high porosity, and tunable mechanical and biochemical properties—making them an optimal choice for reconstructing the ovarian niche (106, 107).

In designing biologically relevant scaffolds for treating POI, the main goal is to mimic the natural ovarian microenvironment or "Ovarian Niche." This region includes granulosa cells, theca cells, endothelial cells, stromal cells, and an extracellular matrix rich in growth factors and cellular signaling molecules (79). The interactions among these components are essential for follicle survival, development, and maintenance of ovarian endocrine function (66). Therefore, designed scaffolds must be capable of recreating such a complex environment to successfully restore ovarian function (63).

Suitable biological scaffolds for application in ovarian reconstruction should possess several key characteristics: first, high biocompatibility without inducing inflammatory or immune responses; second,

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adjustable porosity, stiffness, biodegradability (64), and permeability (63); third, the ability to be loaded with growth factors (61) such as Insulin-like Growth Factor-1 (IGF-1), GDF-9, BMP-15, VEGF, and Fibroblast Growth Factor (FGF) to facilitate folliculogenesis and angiogenesis (76, 83); and fourth, the capacity to support co-culture of granulosa cells and mesenchymal stem cells or iPSCs to regenerate natural cellular interactions (87). Designing scaffolds that can simulate the physiological microenvironment of the ovary plays a critical role in the success of tissue reconstruction (64).

In preclinical studies, electrospun scaffolds made from PCL or gelatin, when used in combination with cultured immature follicles, have shown promising results (61). For example, alginate-based scaffolds used for follicle encapsulation have successfully restored ovulation in animal models (63). Additionally, gelatin-PCL scaffolds used as culture substrates for human follicles have supported oocyte growth and maturation. These studies indicate that combining appropriate scaffolds with enriched culture media containing growth factors can effectively restore ovarian physiological function (61, 108).

Moreover, the use of scaffolds containing stem cells, particularly MSCs and iPSCs, in biological matrices has enhanced cell survival, differentiation into ovarian lineages, and secretion of effective paracrine factors involved in tissue repair (109, 110). Combining these scaffolds with exosomes or extracellular vesicles derived from stem cells provides a novel strategy to improve efficacy without the need for live cell transplantation (83). This approach reduces the risk of tumorigenesis and immunological reactions while maintaining reparative effects (79).

Despite these advancements, there remain important challenges on the path toward clinical translation of these technologies (59). Precise tuning of scaffold mechanical and biochemical properties to match target tissue (59, 111), controlling scaffold retention time in vivo (112), evaluating long-term safety (113), and meeting regulatory and ethical standards (59) are among the major challenges. Furthermore, establishing standardized protocols for loading scaffolds with cells or growth factors, as well as developing controlled and targeted release systems, are essential for achieving clinical success (60, 114).

In the future, integrating emerging technologies such as 3D bioprinting, smart growth factor delivery via nanoparticles, use of stimuli-responsive smart biomaterials (115), and implantable biosensors for real-time monitoring of scaffold function may enable more effective and precise ovarian reconstruction (61). Bioprinting allows different ovarian cell types to be placed in their natural spatial arrangement, creating an environment highly similar to native ovarian tissue (59).

Overall, scaffold-based approaches leveraging interdisciplinary technologies have opened new avenues toward definitive treatment of POI (116).

The integration of engineering, biology, nanomedicine, and reproductive medicine has created a robust platform for developing effective strategies in repairing damaged tissues (117, 118).

These advances not only offer renewed hope for restoring fertility in women with POI but also represent a major step forward in

personalized and targeted regenerative medicine.

Biomolecular and Biotechnological Approaches for Ovarian Function Restoration in POI

Biomolecular and biotechnological approaches are considered one of the main pillars in the treatment POI, designed to mimic natural biochemical signals within the ovarian environment (119). These strategies focus on using growth factors, chemokines, cytokines, and bioactive molecules that can stimulate critical processes such as cell growth, differentiation, survival, and ovarian tissue regeneration (120).

Key growth factors play a fundamental role in this field. IGF-1 (Insulin-like Growth Factor 1) supports follicular development and reduces apoptosis by stimulating granulosa cell proliferation and increasing estradiol synthesis (121).

VEGF, as a central player in angiogenesis, plays a significant role in repairing damaged tissue by improving ovarian blood flow and facilitating nutrient and oxygen transport to follicles. bFGF is effective in stromal and granulosa cell proliferation and ECM repair (59, 63). BMPs (Bone Morphogenetic Proteins), particularly Bone Morphogenetic Protein-4 (BMP-4) and BMP-15, play key roles in regulating follicular development and oocyte maturation (122).

Controlled-Release and Delivery Systems

Due to the short half-life and high sensitivity of these factors to environmental conditions, the use of controlled-release systems is essential (123). Microgels and nanogels, with their high loading capacity and responsiveness to external stimuli (such as pH, temperature, and enzymes), enable gradual and localized release (124). Polymeric nanoparticles, such as PLGA and PEGylated systems, protect growth factors from premature degradation and allow direct injection into tissue or integration within scaffolds (64, 125). Multilayered systems or biological capsules also provide the possibility of releasing different factors in an appropriate sequence, enabling more accurate simulation of physiological folliculogenesis processes (76, 126).

Engineering the Ovarian Microenvironment

Engineering the ovarian microenvironment represents a pivotal strategy in tissue engineering approaches for POI (59). This microenvironment encompasses extracellular matrix (ECM) components, somatic cells such as granulosa and theca cells, paracrine signals, oxygen tension, pH, and mechanical cues, all interacting to regulate follicular development and function (64). Modulating substrate stiffness and utilizing surfaces with tunable elastic properties can influence granulosa cell behavior and follicle activation (127, 128), Oxygen regulation, including controlled hypoxic conditions (129), and incorporation of angiogenic factors such as VEGF enhance nutrient and oxygen delivery to developing follicles (130) .The addition of ECM molecules like laminin (131), fibronectin, and hyaluronic acid provides structural support and promotes cell adhesion and differentiation (132) . Furthermore, paracrine factors and exosomes derived from mesenchymal stem cells or granulosa cells supply critical signaling molecules, including growth factors and

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microRNAs, that support follicular proliferation, reduce apoptosis, and facilitate ECM remodeling (96, 133).

Together, these strategies enable the construction of a biomimetic ovarian niche capable of supporting follicle survival, maturation, and hormone production, providing a foundation for regenerative therapies in POI.

Preclinical Evidence, Outcomes, and Future Directions

Numerous preclinical studies have shown that the use of these factors and smart delivery systems can lead to improved ovarian function, increased sex hormone levels, formation of antral follicles, and even oocyte maturation (134, 135).

For example, the release of IGF-1 from nanogels has led to a significant increase in estradiol levels and recovery of hormonal function (136).

In addition, the delivery of VEGF in gelatin-based scaffolds has facilitated angiogenesis and improved follicle viability (61).

The application of BMP-15 and GDF-9 has also been reported to promote the *in vitro* development of human primary follicles to more advanced stages of maturation (137).

Despite these achievements, challenges remain, including determining optimal dosages and appropriate release timing, synchronizing with mechanical and biological signals (138), and developing multifunctional nanosystems for simultaneous delivery of factors, drugs, and exosomes (139).

The future of this field is moving toward the integration of molecular technologies with biocompatible scaffolds, 3D bioprinting, and smart delivery systems (140).

Ultimately, molecular and biotechnological approaches serve as a crucial complement to cellular and scaffold-based therapies, providing an intelligent platform for restoring ovarian function (63, 64).

These strategies, based on deeper understanding of physiological signaling mechanisms, hold great potential for restoring fertility in women with POI (64).

With continuous advancements in nanotechnology, tissue engineering, and drug delivery systems, these methods are increasingly approaching clinical trials and opening new horizons for personalized and safe treatment options for patients.

Advanced Bioengineering Approaches for Ovarian Regeneration in POI

Advanced bioengineering approaches for treating POI are based on the use of complex, multi-layered technologies designed to mimic the physiological function of the ovary—either in vitro or as implantable substitutes within the body (141). These strategies have been developed with the aim of reconstructing follicular structure and function, hormone production, oocyte development, and ultimately restoring fertility (142).

3D Bioprinting for Ovarian Tissue Engineering

One of the most promising techniques in this field is 3D bioprinting, which enables the precise fabrication of 3D structures with organized spatial arrangements (97). This technology utilizes "bioinks" composed of cells, biocompatible materials, and growth factors (143). The main steps include: digital 3D modeling of ovarian anatomy, selection of appropriate bioinks (such as gelatin, collagen,

alginate, or fibrin), cellular loading (e.g., granulosa cells, mesenchymal stem cells, or follicles), layer-by-layer printing using bioprinters, and finally culture in a controlled environment or bioreactor (61, 144). Advantages of this method include precise control over microstructural architecture, simulation of the follicular niche and hormonal activity, and compatibility with controlled release systems for growth factors (145). Experimental studies have shown that printing mouse ovarian structures using gelatin can lead to restored hormonal function and even pregnancy (64). Moreover, multi-nozzle printers allow for accurate positioning of follicles within a 3D matrix (97).

Microfluidic and Organ-on-a-Chip Systems

Microfluidic and organ-on-a-chip systems also play a crucial role in accurately modeling the ovarian microenvironment (39). These platforms use microscale channels to simulate fluid flow, nutrient exchange (146), oxygen delivery, and biochemical signaling in a highly controlled setting (147). Key components include microfluidic channels, cell culture chambers, biosensors for monitoring hormonal responses, and 3D matrices for follicle cultivation (39).

Beyond mimicking the menstrual cycle and hormonal signaling, these technologies serve as valuable tools for drug screening, toxicity testing (148), and studying inter-organ interactions—such as between the ovary and uterus or the ovary and pituitary gland on a chip (62).

Examples include the development of an ovary-on-a-chip capable of producing estrogen in response to FSH or modeling the ovarian microenvironment for long-term human follicle culture (39).

Nanotechnology in Ovarian Engineering

Nanotechnology also plays a significant role in ovarian engineering (149). Targeted nanoparticles enable the precise delivery of growth factors (such as IGF-1, VEGF, and BMP-15) to ovarian tissue, thereby reducing required dosages (83, 150). Nanostructures that mimic the

ECM, such as nanofibers and nano-gels (151), enhance cell-matrix interactions and support follicle growth and differentiation (152). Smart nano-capsules can release their contents in response to changes in pH, temperature, or enzymatic activity, making them suitable for intra-ovarian injection or integration into bio-scaffolds (153-155).

Integrated Bioengineering Platforms

To fully harness the potential of these technologies, integrated bioengineering approaches are emerging. In these multi-layered systems, bioprinted ovarian scaffolds made from biomimetic materials are combined with precisely positioned cells, microfluidic networks simulating blood flow and hormonal stimulation, and embedded nanoparticles for controlled release of bioactive factors (156). Such integrated platforms hold promise for both *in vivo* tissue regeneration and fertility preservation in clinical settings (97). Animal studies have demonstrated that artificially printed ovarian structures can secrete sex hormones and induce pregnancy (157). However, several challenges remain, including scalability, long-term safety, standardization of bioinks, and immune compatibility. Research is also

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advancing on hybrid systems incorporating iPSCs and multi-stage growth factor delivery systems (61, 116).

In summary, advanced bioengineering approaches represent a shift from supportive care to regenerative therapies for POI (118). Techniques such as 3D bioprinting, organ-on-a-chip systems, and nanotechnology not only replicate the complex physiology of the ovary but also open new horizons in personalized treatment, biological response analysis, and fertility preservation at younger ages (39, 61).

Integrating these technologies into combinational therapies could mark a turning point in achieving definitive treatments for ovarian insufficiency and restoring fertility.

Immune-Protective and Encapsulation Approaches for Ovarian Regeneration in POI

In the field of regenerative medicine and tissue engineering, one of the major challenges in cell and tissue transplantation is the host immune response (158). This issue becomes particularly critical in the treatment of POI, where transplanted ovarian follicles or stem cells are at risk of being recognized as foreign bodies and subsequently eliminated by the immune system (159). In response to this challenge, immune-protective and encapsulation strategies have been developed to enable effective therapy without the need for systemic immunosuppression (160). These technologies aim to create a supportive environment for cell survival, function, and differentiation—by physically and functionally isolating the transplanted units—while preventing immunological attack (161). This is achieved through the use of biocompatible materials and advanced design principles (160).

Hydrogel-Based Encapsulation of Follicles

One of the most successful strategies in this area involves the use of biocompatible hydrogels such as alginate for the encapsulation of immature follicles (99). Alginate, a natural polysaccharide extracted from the cell walls of brown algae, is widely used in bioencapsulation due to its unique properties, including rapid gelation in the presence of divalent ions, high biocompatibility, lack of cytotoxicity, and the ability to fine-tune physical characteristics such as porosity and stiffness (162, 163). In preclinical studies, immature animal follicles have been encapsulated in alginate-based matrices and implanted in various anatomical sites, such as the renal capsule, subcutaneous space, or peritoneal cavity. These studies have shown that such capsules can provide a three-dimensional, hydrated microenvironment that supports continued follicular growth and maturation up to the antral stage (64, 164). Moreover, these systems allow free diffusion of nutrients, oxygen, and growth factors while simultaneously blocking the infiltration of larger immune cells (160). Additionally, the mechanical and chemical properties of these hydrogels can be modified through the incorporation of nanoparticles (165), adjustment of ion concentration, or blending with other polymers such as gelatin, hyaluronic acid, or chitosan, thereby enhancing their stability in the in vivo environment (166, 167). Furthermore, coaxial systems capable of generating double-layered capsules offer improved control over release

kinetics and internal content protection (168).

Microcapsule Fabrication and Advantages

Another significant advancement in the development of immune-protective systems is the production of microcapsules — spherical structures typically under 500 micrometers in diameter (169)—that can encapsulate individual cells, follicles, or even miniature tissue constructs (170). These capsules are usually fabricated from natural or synthetic polymers that are biocompatible and non-immunogenic (171). Common materials include alginate, PEG, chitosan, collagen, or ECM-derived derivatives (172). Various technologies exist for microcapsule fabrication, including electrospraying, electrostatic droplet generation, microfluidic platforms, or multiphase systems (173, 174). Notably, microfluidic technologies have played a key role in designing customizable microcapsules due to their high precision in controlling size, shape, and composition (175). Advantages of microcapsules include prevention of antigen recognition by the immune system (176), maintenance of small molecule exchange (e.g., nutrients and gases) (177), compatibility with implantation into different tissues (174), and the potential for integration with scaffolds or in vitro bioreactors (178). Several successful studies have demonstrated the ability of these capsules to preserve human follicles in immunodeficient mice while enabling estradiol secretion (179). Moreover, in vitro maturation of encapsulated follicles in simulated environments has also become feasible, offering promising prospects for future clinical applications (76).

Anti-inflammatory and Immunomodulatory Enhancements

One of the key factors contributing to the failure of bioengineered grafts is the early inflammatory response at the implantation site (59).

Even if cells are protected from direct immune attack, the presence of inflammatory cytokines, free radicals, and macrophage activity can lead to cell death, matrix degradation, and impaired graft function (180).

In this context, several strategies have been introduced to reduce or modulate the inflammatory response (181). These include loading scaffolds with anti-inflammatory agents such as curcumin, dexamethasone, resveratrol (182), or even biologic drugs like anti-IL-6 or anti-TNF-α antibodies (183); utilizing immunomodulatory cells—particularly MSCs (83), which naturally possess anti-inflammatory properties; and modifying capsule surfaces with immune-resistant polymers such as PEGylation or incorporating molecules that prevent complement activation (184, 185).

These interventions can be incorporated independently or in combination within the design of capsules or implantable scaffolds, playing a crucial role in enhancing follicular survival and function in vivo (186).

To date, numerous animal studies have evaluated the effectiveness of these approaches. In animal models such as chemotherapy or gonadotoxic-induced POI mice (59, 64), alginate-encapsulated follicles have successfully restored estradiol levels, sex hormone secretion, and even induced estrous cycles (64).

Moreover, scaffold designs incorporating anti-inflammatory components have

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significantly increased follicle survival rates (187).

At the clinical level, companies and research groups are actively developing encapsulation systems aimed at preserving fertility in young cancer patients whose ovaries are at risk of destruction due to cytotoxic treatments (188). The integration of these capsules with 3D bioprinting technologies, controlled growth factor delivery systems, or biosensors has enabled the development of personalized artificial ovaries (61).

These approaches are currently undergoing safety and efficacy testing and may soon transition into clinical applications (38).

Remaining Challenges and Future Perspectives

Despite significant advancements, major obstacles remain on the path toward widespread use of these technologies. These include precise control over capsule size and porosity, long-term stability *in vivo*, late-onset immune responses, design personalization, and integration with smart technologies (170, 189, 190). Capsules must be small enough to avoid central necrosis but large enough to prevent immune recognition (160).

Some biomaterials degrade or lose functionality over time, highlighting the need for more durable materials with dynamic biological properties (165). In certain cases, immune responses may activate after several weeks, necessitating predictive modeling and suppression strategies (191). Depending on the patient's immune status, age, baseline hormone levels, and individual needs, capsule structures must be customized accordingly. Developing capsules equipped with internal biosensors capable of reporting follicular status will represent a major step toward personalized treatment (189, 192).

In summary, protective and encapsulation strategies play a pivotal role in advancing ovarian regeneration therapies for women with POI (48). By reducing the need for systemic immunosuppression, improving graft cell survival, and creating an optimal microenvironment for follicle maturation, these technologies hold immense potential to transform infertility treatment paradigms in the future (14).

With rapid progress in biomaterial design, bioprinting, nanotechnology, and cellular engineering, the horizon for precise, personalized therapies to preserve or restore fertility is becoming increasingly accessible (61). Undoubtedly, integrating these technologies with artificial intelligence algorithms and biological modeling will pave the way for next-generation smart and body-compatible artificial ovaries (193, 194).

Therefore, novel tissue engineering technologies for treating POI are evolving rapidly and involve the use of stem cells, biocompatible scaffolds, and growth factors to regenerate ovarian tissue (195). These approaches aim to reconstruct the ovarian niche and enhance tissue function, including improved survival and growth of ovarian follicles (7). 3D bioprinting and cell encapsulation within bioactive scaffolds enable controlled release of growth factors (196, 197). Preclinical models have demonstrated promising results; however, many challenges remain before clinical application in humans. Safety, standardization, and ethical considerations are among the most critical hurdles (198). Nevertheless, these technologies hold great promise for restoring fertility and offering a

definitive cure for POI. Further research is essential to achieve this goal (199).

Clinical Treatments Using Tissue Engineering in POI

Tissue engineering-based therapies for POI are currently receiving widespread attention. One of the most innovative tissue engineering strategies for POI treatment is the development of artificial ovaries. In this approach, primary or pre-antral follicles are placed inside biocompatible scaffolds, such as alginate or gelatin, and then transplanted (61, 88). Transplantation of scaffolds containing follicles in animal models has led to ovarian reconstruction and the production of mature eggs (76). Preliminary human studies have shown that follicle encapsulation can prevent their degradation after transplantation and restore hormonal function (14). By harvesting the ovarian ECM (extracellular matrix) and removing its cells (a process known as decellularization), a natural scaffold remains, which provides the appropriate spatial and biochemical structure for follicle reconstruction (57). This scaffold is then reseeded with immature follicles and, upon transplantation, mimics the natural function of the ovary (63). In animal models, decellularized ovarian ECM has been able to promote follicle survival and growth, and restore hormonal production (39). In targeted tissue engineering strategies using nanoparticles, follicles or reparative agents can be delivered to the damaged ovary site using nanoparticles (200). This technique can improve integration into tissue and therapeutic efficacy (149). The development of environment-sensitive smart nanoparticles for precise delivery to the damaged ovary has shown promising results in preclinical animal models (201). One of the main concerns regarding the use of biological scaffolds is the potential for immune responses or rejection (67). Even in artificial ovaries or decellularized ECMs, the presence of antigenic remnants may lead to inflammation or secondary damage (202). Many follicles undergo degradation after transplantation into the damaged ovarian environment (203). Oxidative stress, hypoxia, and lack of supportive signals can threaten the survival of these grafts (204). Improving scaffold design and techniques to enhance follicle survival (such as encapsulation or the use of growth factors) remains an active area of research (14). Ensuring that transplanted follicles properly function (such as hormone secretion) is critical (205). There is a risk of improper development or tissue degradation, which could compromise regenerative outcomes (79). In some countries, the use of human follicles in reproductive treatments faces legal and ethical restrictions. Concerns related to storage and long-term culturing are significant obstacles (57, 67).

In summary, tissue engineering approaches for POI focus on artificial ovaries, biocompatible scaffolds, ECM-based matrices, and nanoparticle-assisted delivery to reconstruct the ovarian niche, support follicle survival, and restore endocrine function. These strategies move beyond cell therapy alone, emphasizing the importance of scaffold design, controlled microenvironments, and biomaterial-follicle interactions for effective ovarian regeneration. However, only one study was found on the application of tissue engineering in the clinical treatment of POI (Table 1), indicating the need for further efforts to

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Table 1: Clinical POI Treatments Based on Tissue Engineering Constructs

Study Title	ClinicalTrials.gov ID	Study Objective	Treatment Method	Target Group	Number of Participants	Study Status	Final Results
Transplantation of Human Umbilical Cord-derived Mesenchymal Stem Cells (HUC-MSCs) With Injectable Collagen Scaffold in Women With Premature Ovarian Failure (POF)	NCT02644447	To evaluate the safety and efficacy of intra-ovarian injection of HUC-MSCs with injectable collagen scaffold in women with POF	Intra-ovarian injection of HUC-MSCs with injectable collagen scaffold	Women with POF	23 participants	Completed	Final results not yet published (206)

translate the results from animal model-based studies into clinical practice.

Future Perspectives and Research Opportunities in Tissue Engineering Applications for POI Treatment

Future scaffolds in ovarian tissue engineering must be able to meet the complex microbiological needs of ovarian follicles (57). The design of bioactive scaffolds with the ability to control the release of growth factors, protective drugs, and oxygen environment regulation is a key area of research (207). The use of nanoparticles and materials responsive to biological stimuli could revolutionize scaffold efficiency (208). 3D bioprinting technology allows for the creation of more precise ovarian structures with architecture similar to natural tissue (39). This method could enable the printing of primordial follicles along with customized scaffolds, facilitating improved follicle survival and ovarian function restoration (59). The use of iPSCs as a cellular source provides a promising outlook for POI treatment (14). These cells can be derived from the patient's own cells, reducing the risk of immune rejection. The challenges of efficiently and safely differentiating these cells into granulosa or oocyte-like cells remain a major focus of ongoing research (67). The design of targeted release systems for growth factors, cytokines, and antioxidants can help rebuild the ovarian environment and stimulate folliculogenesis

(48). pH-sensitive, temperature-sensitive, or specific ovarian enzyme-sensitive polymers are shaping the next generation of drug delivery systems (209). Humanized animal models that are reconstructed with human cells will be an important tool for testing the efficacy and safety of new tissue engineering therapies (210). These models will help ensure the reliable translation of laboratory findings to human applications (211). With advancements in genomics and proteomics, the design of personalized treatments based on the genetic, epigenetic, and metabolic characteristics of POI patients will become possible (212). This approach could significantly improve treatment success rates (213).Ovarian tissue engineering, in the near future, thanks to the integration of advanced technologies such as smart biomaterials, 3D printing, iPSCs, targeted drug delivery, and personalized treatments, has the potential to become an effective and accessible treatment for POI (14, 57). However, overcoming existing challenges will require deeper research, extensive preclinical testing, and more interdisciplinary efforts (61).

Discussion

POI remains one of the most critical challenges in women's reproductive health, characterized by the loss of normal ovarian function before the age of 40, often resulting in infertility, hormonal imbalances, and a reduced quality of life (214). Recent studies have highlighted the potential of tissue engineering strategies—particularly the use of stem cells, bioengineered scaffolds, growth factors, and emerging technologies such as 3D bioprinting and nanomedicine—as promising avenues for curative treatment of POI (118, 215).

Among current strategies, scaffold- and cell-based approaches are of particular importance. These involve embedding mesenchymal stem cells MSCs, induced pluripotent stem cells iPSCs, embryonic stem cells ESCs, or immature follicles into natural or synthetic scaffolds that mimic the native ovarian tissue microenvironment (79). Preclinical results have shown improved estradiol levels, reduced FSH, and the restoration of menstrual cycles following these interventions (42). However, potential risks such as tumorigenesis, immune reactions, and challenges in controlling cellular differentiation remain significant barriers to clinical application (59). Molecular and biotechnological approaches also play a crucial complementary role in restoring ovarian function (48). The use of growth factors such as IGF-1, VEGF, BMP-15, and GDF-9 in targeted delivery systems (e.g., nanogels, nanoparticles, hydrogels) has demonstrated the ability to stimulate folliculogenesis, angiogenesis, and extracellular matrix repair (83, 216). Nevertheless, achieving precise control over dosage, release timing, and biological synchronization continues to pose a challenge (48). Advanced bioengineering technologies—including 3D bioprinting, microfluidic systems (organ-on-a-chip), and nanomedicine—are designed to closely replicate the ovarian niche (61). Bioprinting using bioinks composed of cells and growth factors enables reconstruction of follicular structures and hormonal function. Experimental studies have even demonstrated that such printed constructs can induce pregnancy in animal models (97). Microfluidic platforms, by simulating fluid

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dynamics, oxygen exchange, and hormonal signaling, serve as powerful tools for drug screening, ovarian function analysis, and personalized therapy development (64).

Protective strategies such as cell encapsulation have also been developed to overcome host immune responses (59). Encapsulating follicles or stem cells in hydrogels like alginate provides physical protection while allowing nutrient and oxygen exchange (99). The addition of anti-inflammatory agents, immuno-inert polymer coatings, or microfluidic capsules has been shown to enhance graft survival and functionality (59, 217). However, the long-term biocompatibility, prevention of delayed immune responses, and control over capsule degradation still require further investigation (3). Clinically, tissue engineering approaches are entering early-phase trials (60). Limited human studies—particularly those using MSCs and biologically derived scaffolds—have shown restoration of menstrual function and improvement in hormonal profiles in some patients (218). Nonetheless, challenges such as tumorigenic potential, ethical concerns related to ESCs, and interpatient variability continue to slow clinical translation (219). Overall, the convergence of interdisciplinary expertise in engineering, biology, nanomedicine, and reproductive medicine has established a powerful foundation for effective ovarian regeneration therapies. Hybrid strategies that combine smart scaffolds, stem cells, growth factors, and controlled release systems offer hope for developing safe, precise, and personalized treatments for women affected by POI in the near future.

Conclusion

The application of advanced tissue engineering technologies especially the integration of stem cells, bioengineered scaffolds, growth factors, and targeted delivery systems represents a major milestone in regenerative medicine for treating premature ovarian insufficiency (POI) (219-223).

These approaches aim to reconstruct the natural follicular microenvironment and restore both hormonal function and fertility in affected women.

Preclinical studies have generated significant optimism about the potential for a curative solution to POI. Although early human trials have shown promising outcomes, several obstacles remain, including tumorigenic risks, immune responses, lack of standardized protocols, ethical concerns, and the need for long-term efficacy. Future directions include the development of smart biomaterials, precise modeling using 3D bioprinting, the application of iPSCs, and designing therapies tailored to patients' genetic and biological characteristics. Ultimately, the future of POI treatment depends on sustained interdisciplinary progress, large-scale clinical trials, and close collaboration between researchers and clinicians. With continued advancements, the realization of safe effective, and accessible treatments for POI is within reach.

Conflict of Interest

The authors declare that they have no competing interests.

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Abbreviations

POI	**Premature Ovarian Insufficiency**
POF	Premature Ovarian Failure
HRT	Hormone Replacement Therapy
ART	Assisted Reproductive Technologies
MSCs	Mesenchymal Stem Cells
iPSCs	Induced Pluripotent Stem Cells
ESCs	Embryonic Stem Cells
PLGA	Poly(lactic-co-glycolic acid)
PCL	Polycaprolactone
PEG	Polyethylene Glycol
3D	Three-Dimensional
GDF-9	Growth Differentiation Factor-9
BMP-15	Bone Morphogenetic Protein-15
VEGF	Vascular Endothelial Growth Factor
bFGF	Basic Fibroblast Growth Factor
FSH	Follicle-Stimulating Hormone
PRP	Platelet-Rich Plasma
GnRH	Gonadotropin-Releasing Hormone
HPO	Hypothalamic-Pituitary-Ovarian
LH	Luteinizing Hormone
BMSCs	Bone Marrow-Derived Mesenchymal Stem Cells
ADSCs	Adipose-Derived Stem Cells
UC-MSCs	Umbilical Cord-Derived Mesenchymal Stem Cells
eMSCs	Endometrial Mesenchymal Stem Cells
IVF	In Vitro Fertilization
microRNAs	Micro Ribonucleic Acids

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