

Ovarian Tissue Engineering on Polycystic Ovary Syndrome: Emerging Strategies for Fertility Restoration

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine illnesses affecting women of reproductive age. It is distinguished by hyperandrogenism, ovulatory failure, and polycystic ovarian morphology. The syndrome is frequently linked to metabolic abnormalities such as insulin resistance, obesity, and an elevated risk of type 2 diabetes and cardiovascular disease. Conventional therapy treatments, such as pharmaceutical treatment and assisted reproductive technologies, are largely concerned with symptom management and fertility induction, but frequently fail to address the underlying ovarian dysfunction. In recent years, developments in regenerative medicine and bioengineering have created new opportunities for restoring ovarian function. Ovarian tissue engineering is a promising strategy that uses biomaterials, cellular therapies, and advanced fabrication techniques to recreate the ovarian microenvironment and promote follicular formation. Biomimetic scaffolds, extracellular matrix-based constructions, and three-dimensional bioprinting platforms have shown promise for boosting folliculogenesis and hormone synthesis. Furthermore, technologies such as organ-on-chip systems and *in vitro* follicle maturation platforms offer new opportunities to investigate ovarian physiology and to develop targeted therapeutics. This study examines the pathogenesis of PCOS, the limitations of current treatment techniques, and new advances in ovarian tissue engineering approaches for restoring ovarian function and fertility. The combination of biomaterials, stem cell technologies, and microengineering platforms may enable individualised and regenerative therapeutic approaches in PCOS therapy.

Keywords: Biomaterials, Fertility Restoration, Folliculogenesis, Ovarian Tissue Engineering, Polycystic Ovary Syndrome, Regenerative Medicine.

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INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is one of the most common endocrine and metabolic illnesses affecting women of reproductive age worldwide (Teede *et al.*, 2010). It is distinguished by several clinical characteristics, including hyperandrogenism, chronic anovulation, and polycystic ovarian structure as shown in Figure 1. In addition to reproductive issues, women with PCOS frequently have metabolic abnormalities such as insulin resistance, obesity, dyslipidemia, and an increased risk of type 2 diabetes and cardiovascular disease. Because of its numerous clinical symptoms, PCOS is a complex condition with serious consequences for reproductive health and long-term metabolic well-being (Deswal *et al.*, 2020; Teede *et al.*, 2014).

PCOS has a multifaceted etiology that includes complex interactions between genetic susceptibility, hormonal imbalance, metabolic abnormalities, and environmental factors. A key pathological hallmark is the disruption of normal follicular development, which results in the buildup of immature follicles in the ovary and reduced ovulation (Eagleson *et al.*, 2000). Conventional management options, such as lifestyle changes, hormone therapy, and insulin-sensitizing drugs, are largely intended to reduce symptoms and improve metabolic parameters. Although assisted reproductive technologies have improved fertility results for many patients, they do not completely address the underlying ovarian malfunction (Riepl, 2019).

In recent years, developments in regenerative medicine and biomedical engineering have introduced new approaches to restoring ovarian function. Among these, ovarian tissue engineering stands out as a promising interdisciplinary strategy that combines biomaterials, cellular treatments, and biofabrication technologies to rebuild the ovarian microenvironment. Engineered ovarian structures, which enhance follicular survival, growth, and hormone production, may provide novel therapeutic



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options for reproductive problems (Diamanti-Kandarakis and Dunaif, 2012; Vågnes and Pranić, 2023). The purpose of this review is to provide an overview of the pathophysiological mechanisms of PCOS while also highlighting recent advances in ovarian tissue engineering approaches, such as biomaterial scaffolds, stem cell-based strategies, and emerging technologies like three-dimensional bioprinting and organ-on-chip systems. Understanding these improvements may help to develop regenerative and customized therapy options for enhancing ovarian function and reproductive outcomes in women with PCOS.

METHODOLOGY

A comprehensive literature search was conducted using electronic databases including PubMed, Scopus, Google Scholar, and ScienceDirect. Relevant articles published between 2000 and 2025 were retrieved using keywords such as “Polycystic Ovary Syndrome,” “Ovarian Tissue Engineering,” “Biomaterials,” “Folliculogenesis,” and “Regenerative Medicine.” Both experimental and review studies were included to provide a broad perspective. Articles were selected based on relevance, scientific quality, and contribution to the field.

REVIEW OF LITERATURE

Pathophysiology of PCOS

PCOS is a diverse endocrine condition marked by intricate interplay between hormonal, metabolic, genetic, and environmental variables. Although the specific etiology is unknown, various pathways have been recognized as contributing to the condition's development and progression. PCOS is defined by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, all of which are caused by disruptions in the Hypothalamic-Pituitary-Ovarian (HPO) axis and metabolic regulatory pathways (Cena *et al.*, 2020; Rath, 2020).

Hyperandrogenism is a key mechanism in PCOS that comes from increased androgen synthesis by ovarian theca cells and, in rare circumstances, the adrenal glands. Elevated androgen levels disrupt normal follicular maturation, halting follicle formation in its early stages (Kicińska *et al.*, 2023). As a result, many tiny follicles develop within the ovaries, resulting in the typical polycystic ovarian morphology seen in affected individuals. This disturbance in folliculogenesis leads to irregular menstrual periods and infertility (Naz *et al.*, 2020).

Insulin resistance is another important component in the pathogenesis of PCOS, and it occurs in a considerable proportion of individuals, regardless of body weight. Hyperinsulinemia increases androgen synthesis in ovarian theca cells while suppressing hepatic production of Sex Hormone-Binding Globulin (SHBG), increasing the bioavailability of circulating androgens. The consequent hormonal imbalance exacerbates

ovarian dysfunction and adds to metabolic problems that are frequent with the syndrome (Liu *et al.*, 2022; Vanky and Løvvik, 2020).

Alterations in the hypothalamic-pituitary-ovarian axis are also relevant in PCOS. Increased frequency of Gonadotropin-Releasing Hormone (GnRH) pulses results in increased secretion of Luteinizing Hormone (LH) in comparison to Follicle-Stimulating Hormone (FSH). This imbalance encourages excessive androgen production and disrupts normal follicular growth. Reduced FSH levels inhibit the development of ovarian follicles, causing to anovulation. In addition to endocrine and metabolic abnormalities, persistent low-grade inflammation and oxidative stress have been linked to PCOS. Inflammatory cytokines, such as TNF- α and interleukin-6, can lead to insulin resistance and ovarian dysfunction. These inflammatory processes can impede follicular development and worsen reproductive and metabolic issues (Di Lorenzo *et al.*, 2023; Merhi *et al.*, 2019).

Overall, the pathogenesis of PCOS is a complex interaction of hormone dysregulation, metabolic imbalance, and ovarian structural abnormalities. Figure 2 shows the Pathophysiology of PCOS, understanding these pathways is critical for creating new therapeutic techniques, such as regenerative and tissue engineering approaches to restore normal ovarian function (Dadachanji *et al.*, 2018; Koike *et al.*, 2023; Mukherjee *et al.*, 2014; Stener-Victorin *et al.*, 2020).

Limitations of Current Therapeutic Strategies

Despite the availability of several treatment options, managing Polycystic Ovarian Syndrome (PCOS) remains difficult due to the disorder's complex nature. Current therapy techniques are primarily concerned with treating clinical symptoms, controlling menstrual cycles, and improving metabolic parameters rather than addressing underlying ovarian dysfunction. As a result, long-term illness control and restoration of normal ovarian physiology are limited (Balen, 2012). Lifestyle modification, such as dietary adjustments and increased physical activity, is frequently advised as the first-line treatment, especially for individuals with obesity or metabolic abnormalities. Although these treatments can enhance insulin sensitivity and hormonal balance, their efficacy varies by individual and may necessitate long-term adherence to produce meaningful therapeutic effects (Dapas and Dunaif, 2022; Devaraji and Thanikachalam, 2025; Günelan *et al.*, 2018; Mahalakshmi *et al.*, 2025; R *et al.*, 2024).

Pharmacological therapies for hyperandrogenism, menstrual abnormalities, and metabolic changes include combined oral contraceptives, anti-androgen medicines, and insulin-sensitizing medications. While these treatments may provide symptom relief, they do not directly restore normal follicular growth or the ovarian microenvironment. Furthermore, long-term usage of certain drugs may cause side effects and may not be appropriate

for many patients (Diamanti-Kandarakis *et al.*, 2006; Goodarzi *et al.*, 2011; Marx and Mehta, 2003).

Assisted Reproductive Technologies (ART), such as ovulation induction and *In vitro* Fertilization (IVF), are widely used to treat infertility caused by PCOS. Although these methods have considerably improved pregnancy outcomes, they may raise the risk of problems, including ovarian hyperstimulation syndrome (Dapas *et al.*, 2020; T.L. and A.E., 2003). Furthermore, these procedures do not address the underlying ovarian abnormalities that cause the condition. Given these constraints, there is a growing demand for novel therapeutic approaches that can restore normal ovarian anatomy and function. Emerging techniques, including ovarian tissue engineering and regenerative medicine, aim to recreate the ovarian microenvironment and promote follicular formation, providing intriguing options for future PCOS therapy ("American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Hyperandrogenic Disorders," 2001; Laven, 2019; Oyebanji *et al.*, 2018; Wang *et al.*, 2023)

Ovarian Tissue Engineering

Ovarian tissue engineering is gaining popularity as a novel regenerative strategy for repairing ovarian shape and function. Unlike conventional PCOS treatments, which largely address symptoms, tissue engineering strategies aim to recreate the ovarian microenvironment that promotes follicular growth, hormone secretion, and reproductive function (Fekkes *et al.*, 2003; J *et al.*, 2024; Jayaprakash *et al.*, 2025; Nandhini *et al.*, 2024a). This interdisciplinary field combines biomaterials, biological components, and advanced biofabrication technologies to create functional ovarian tissue that can support folliculogenesis and endocrine activity (Azziz *et al.*, 2005; Boivin *et al.*, 1995).

The ovary has a complex architecture made up of follicles at various developmental stages, stromal cells, vascular networks,

and an extracellular matrix that governs cellular interactions. The disruption of this microenvironment contributes to the aberrant follicular growth and hormone imbalance seen in PCOS (Goldzieher and Axelrod, 1963; Oddens *et al.*, 1999). Ovarian tissue engineering aims to duplicate these morphological and biochemical characteristics by utilizing synthetic scaffolds and biological components that imitate the native ovarian niche, as shown in Figure 3 Fertility Preservation Technique.

Biomaterials and Scaffold Design

Biomaterials play an important role in ovarian tissue creation because they provide the structural foundation for cell adhesion, proliferation, and differentiation. An ideal scaffold should have the same physical and biochemical properties as the native ovarian extracellular matrix while retaining biocompatibility, mechanical stability, and controlled degradation (Dadashzadeh, Moghassemi, and Amorim, 2021; Ghahremani-Nasab *et al.*, 2020; Izadpanah *et al.*, 2023).

Natural biomaterials like collagen, fibrin, alginate, gelatin, and hyaluronic acid have been extensively studied because of their capacity to promote cellular connections and tissue regeneration (Almeida *et al.*, 2023). These materials resemble the natural extracellular matrix, allowing for efficient nutrition absorption and follicular growth. Alginate-based hydrogels, in particular, have shown promising results *in vitro* for follicle encapsulation and maturation (Dadashzadeh, Moghassemi, Shavandi, *et al.*, 2021; Devaraji *et al.*, 2024; Hutmacher, 2001; Zivari-Ghader *et al.*, 2022).

In addition to natural polymers, synthetic biomaterials like polyethylene glycol and polycaprolactone have been investigated. These materials have tunable mechanical characteristics and increased structural stability. Decellularised ovarian extracellular matrix scaffolds have emerged as a promising alternative because they preserve native biochemical signals that aid in follicular

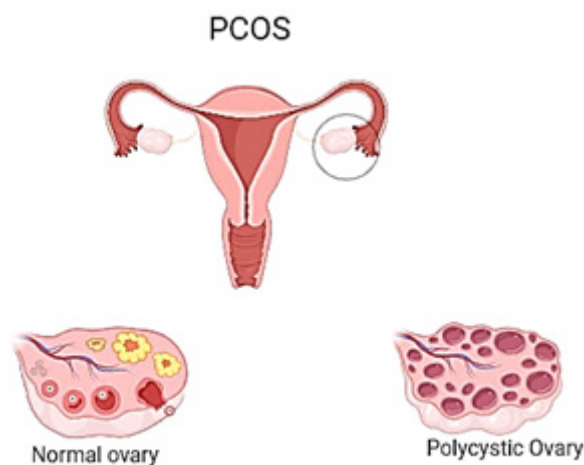


Figure 1: Normal ovary and Polycystic ovary.

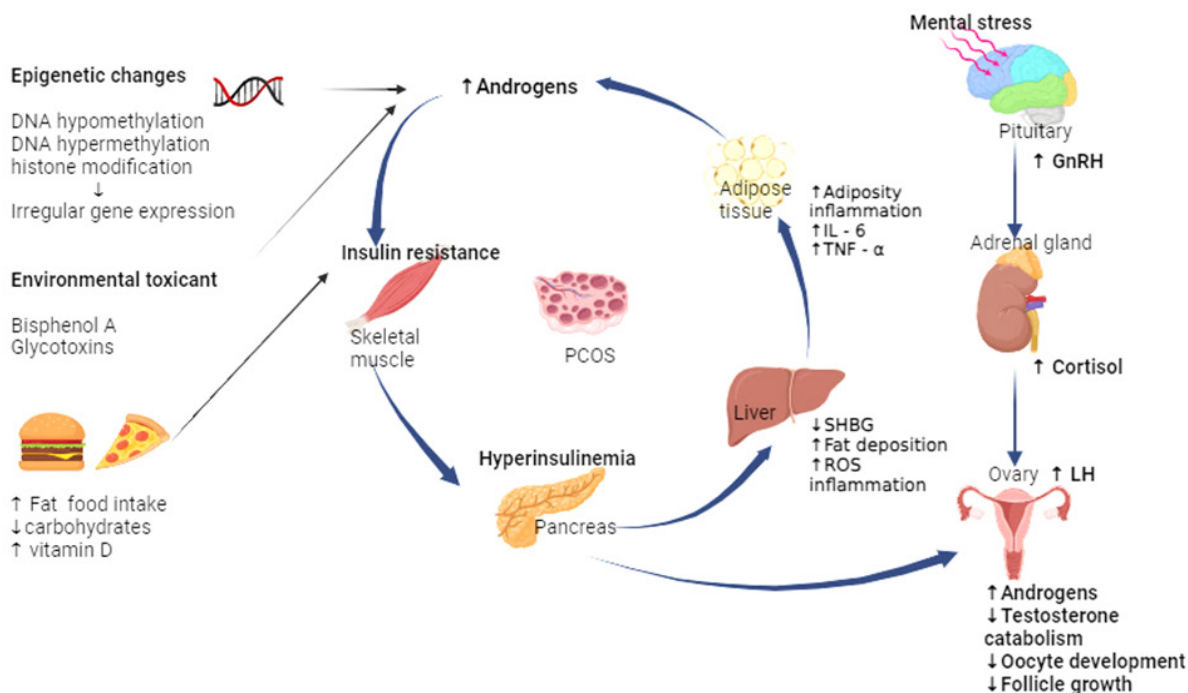


Figure 2: Pathophysiology of PCOS: GnRH (Gonadotropin-releasing hormone), DNA (Deoxyribonucleic acid), LH (Luteinizing Hormone), IL-6 (Interleukin 6), SHBG (Sex hormone binding globulin), PCOS (Polycystic ovary syndrome), TNF-α (Tumor Necrosis-alpha).

growth and cell communication. The design of biomaterial scaffolds is thus critical in providing a supportive milieu that promotes folliculogenesis and preserves ovarian function (Ding *et al.*, 2014; Glowacki and Mizuno, 2008; Kim *et al.*, 2012; Li *et al.*, 2011; Su *et al.*, 2016). Figure 4 illustrates the Biomaterial used for Ovarian Tissue Engineering.

Cell-Based Approaches

Cellular components are critical for regenerating functioning ovarian tissue. Ovarian follicles, granulosa cells, theca cells, and stromal cells all have important roles in hormone synthesis and follicular development (Ding *et al.*, 2014). Incorporating these cells into manufactured scaffolds can help recreate the natural ovarian microenvironment. Recent studies have also looked into the therapeutic potential of stem cells in ovarian regeneration. Mesenchymal stem cells generated from bone marrow, adipose tissue, or the umbilical cord have been shown to increase tissue healing and follicular survival using paracrine signalling. These cells produce growth factors and cytokines, which promote angiogenesis, reduce inflammation, and improve ovarian function (Elumalai *et al.*, 2024; Li *et al.*, 2011; Nandhini *et al.*, 2024b; Su *et al.*, 2016).

Additionally, ovarian stem cells have been studied for their ability to develop into functional ovarian cell types. When paired with biomaterial scaffolds, these cellular therapies may help restore endocrine function and improve reproductive outcomes (Bayda *et al.*, 2020; Javid-Naderi *et al.*, 2023; W. Y. Liu *et al.*, 2017; Villalona *et al.*, 2010).

Three-Dimensional Bioprinting

Three-dimensional bioprinting is a key technological leap for tissue engineering and regenerative medicine (Bishop *et al.*, 2017). This technology allows for accurate deposition of biomaterials and living cells in specified patterns, resulting in complex tissue architectures that closely mimic biological organs. In ovarian tissue engineering, 3D bioprinting can be utilized to create scaffolds that mimic the spatial arrangement of follicles and supporting cells in the ovary. Bioprinted constructions can establish a biomimetic environment for follicular survival and growth by regulating scaffold architecture, pore size, and mechanical qualities (Agarwal *et al.*, 2020; Hockaday *et al.*, 2012; Kang *et al.*, 2016; Vijayavenkataraman *et al.*, 2018; Xie *et al.*, 2020).

In animal models, bioprinted ovarian constructions have been shown to support follicular growth and hormone production. These findings emphasize the potential of bioprinting methods to create functional ovarian tissues for regenerative therapy (Tan *et al.*, 2021; Vermeulen *et al.*, 2017).

Organ-On-Chip and Microfluidic Systems

Microfluidic technologies have resulted in the creation of organ-on-chip devices that mimic the physiological conditions of human tissues *in vitro*. These devices include living cells in microchannels that simulate the dynamic environment of biological systems, such as fluid movement, nutrient exchange, and hormone signalling (Mirzaei *et al.*, 2019; Xiao *et al.*, 2017).

Organ-on-chip technologies enable researchers to examine ovarian physiology, follicular development, and endocrine interactions in a controlled environment. These methods can keep viable ovarian follicles alive for long periods of time, allowing researchers to study reproductive processes that are difficult to mimic with typical cell culture models (Che *et al.*, 2023; Rashid *et al.*, 2022).

Organ-on-chip technologies, in addition to providing insights into ovarian biology, have the potential to be used in drug testing, toxicity research and customized medicine. Such technologies may aid in the identification of targeted treatments for reproductive illnesses such as PCOS (Sfetsas *et al.*, 2021; Vach Agocsova *et al.*, 2023).

Therapeutic Potential in PCOS

Ovarian tissue engineering has great potential for treating the underlying ovarian dysfunction associated with PCOS. Engineered constructions that recreate a functioning ovarian milieu may promote normal follicular maturation and restore ovulatory cycles. This regenerative technique may also help to enhance hormonal balance by allowing the natural generation of reproductive hormones (Ansari *et al.*, 2021; Ganie *et al.*, 2019; Malhotra *et al.*, 2023).

Although most ovarian tissue engineering projects are still in the experimental stage, preliminary results indicate that integrating biomaterial scaffolds, cellular therapies, and sophisticated

fabrication processes may provide promising solutions for restoring ovarian function. Continued study in this area may lead to new therapy options for women with PCOS who are infertile or have hormonal imbalances (Indrani and Sowmya, 2020; Nikitha and Laxmi, 2021; Sah and Rath, 2016; Wu *et al.*, 2022; Zieliński *et al.*, 2023).

FUTURE PERSPECTIVES

Although ovarian tissue engineering has shown promise in experimental models, significant scientific and clinical difficulties must be overcome before these techniques may be adopted as standard therapeutics for Polycystic Ovary Syndrome (PCOS) (Piltonen, 2022). Future research should concentrate on enhancing the design and functionality of biomaterial scaffolds in order to more accurately mimic the structural and biochemical aspects of the natural ovarian microenvironment. Advanced biomaterials with customizable mechanical properties, increased biocompatibility, and controlled degradation profiles may help to promote follicular survival, growth, and endocrine activity (Jia *et al.*, 2021; Rizk and Thackray, 2021).

Another critical area of progress is the combination of stem cell technologies and regenerative medicine approaches. Mesenchymal stem cells and ovarian stem cells have demonstrated promising results in tissue healing and follicular development via paracrine signalling and differentiation. Further research is needed to discover the best cell sources, culture conditions, and delivery strategies for maximizing therapeutic effects while

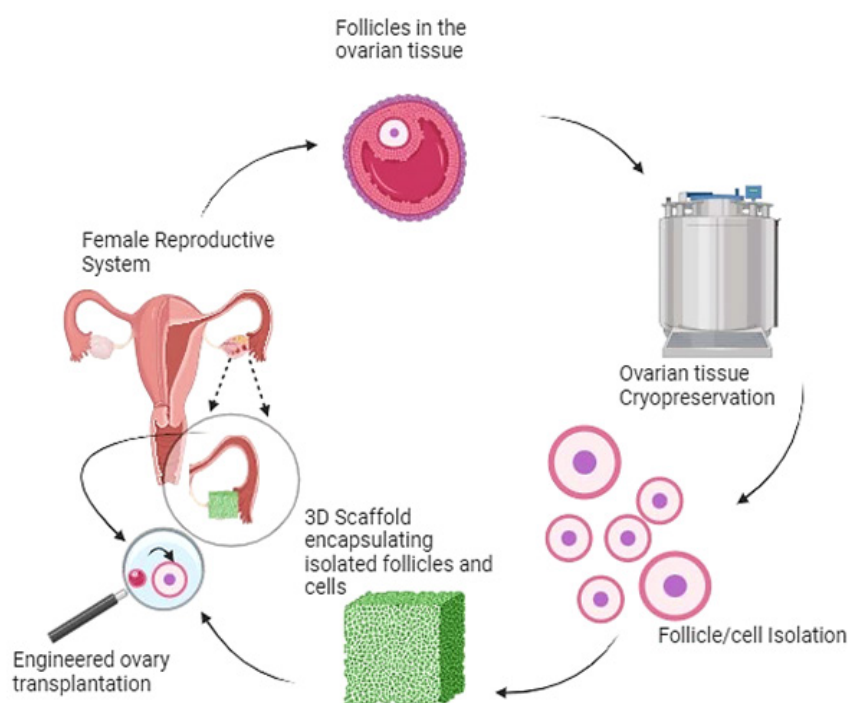


Figure 3: An illustrated diagram of the fertility preservation technique involving cryopreservation of ovarian tissue and tissue engineering of the ovaries. Prior to chemotherapy or radiotherapy, the ovarian tissue is extracted and maintained using cryopreservation. After the patient is healed, the tissue fragments are defrosted, and their follicles and cells are separated and placed in a 3D bioengineered scaffold. Ultimately, the construct is transplanted orthotopically.

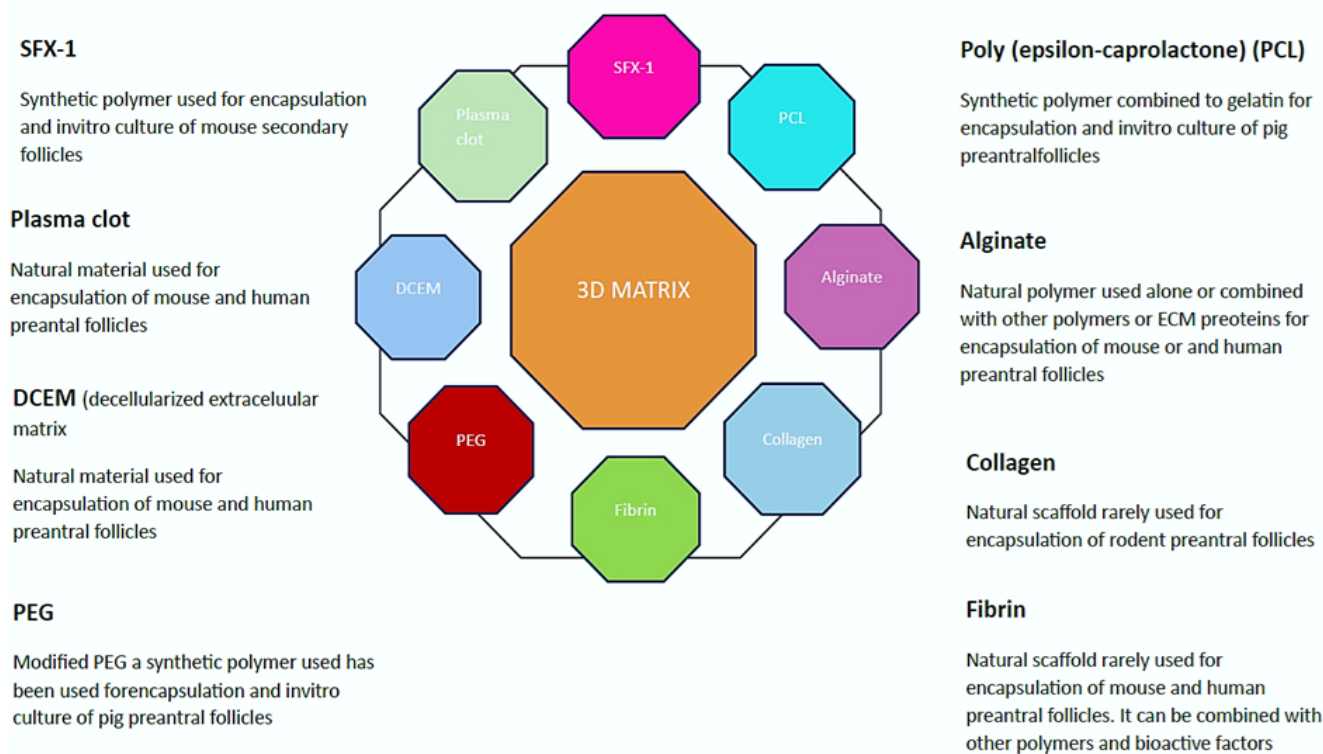


Figure 4: Biomaterials used for Ovarian Tissue Engineering.

maintaining safety and long-term stability (Abraham Gnanadass *et al.*, 2021; Liyanage *et al.*, 2021; Singh *et al.*, 2023).

Three-dimensional bioprinting and microfluidic organ-on-chip devices are likely to play an important role in the future of ovarian tissue engineering. These platforms enable the precise spatial arrangement of cells and biomaterials, allowing for the creation of biomimetic ovarian structures that closely match real tissue structure. Furthermore, ovary-on-chip devices enable dynamic *in vitro* models for studying ovarian physiology, assessing medication responses, and investigating disease processes linked with PCOS (Mikkelsen and Lindenberg, 2001; Siristatidis *et al.*, 2018; Tannus *et al.*, 2018; Walls *et al.*, 2015; Zhao *et al.*, 2009).

Future research should focus on vascularization and immunological compatibility of modified ovarian structures, as these traits are crucial for long-term functionality after transplantation. Using angiogenic agents and improved scaffold designs may improve tissue integration and clinical results. Finally, the combination of biomaterials research, stem cell biology, and bioengineering technologies could pave the way for personalised regenerative therapeutics for PCOS. Continued interdisciplinary research and clinical validation will be required to move ovarian tissue engineering from laboratory studies to realistic therapeutic options for restoring ovarian function and fertility in impacted women (Bishop *et al.*, 2017; Brown *et al.*, 2006; Grauss *et al.*, 2005; Salem *et al.*, 2019).

CONCLUSION

PCOS is still one of the most common and complex endocrine illnesses affecting women of reproductive age, with serious reproductive, metabolic, and psychological consequences. The syndrome's complex nature, which includes hormonal imbalance, insulin resistance, and altered follicular development, poses significant hurdles to effective long-term therapy. Although current therapy options, such as lifestyle changes, pharmaceutical therapies, and assisted reproductive technologies, can reduce symptoms and improve fertility outcomes, they focus on the clinical manifestations rather than the underlying ovarian malfunction. Recent advancements in regenerative medicine have introduced ovarian tissue engineering as a promising approach for restoring ovarian structure and function. By integrating biomaterial scaffolds, cellular therapies, and advanced fabrication technologies, this strategy aims to recreate the ovarian microenvironment necessary for follicular maturation and hormone production. Emerging tools such as three-dimensional bioprinting and organ-on-chip systems further enhance the ability to model ovarian physiology and develop innovative therapeutic interventions.

Despite encouraging progress, ovarian tissue engineering is still in its early stages of development, and several challenges remain, including ensuring long-term viability, vascularization, and immune compatibility of engineered tissues. Continued interdisciplinary collaboration among reproductive biologists, biomedical engineers, and clinicians will be essential to overcome

these limitations. Overall, ovarian tissue engineering represents a promising frontier in reproductive medicine. With continued research and technological advancement, these regenerative strategies may ultimately lead to personalized therapeutic solutions capable of restoring ovarian function and improving fertility outcomes in women affected by PCOS.

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ABBREVIATIONS

PCOS: Polycystic Ovary Syndrome; **HPO:** Hypothalamic-Pituitary-Ovarian; **GnRH:** Gonadotropin-Releasing Hormone; **LH:** Luteinizing Hormone; **FSH:** Follicle-Stimulating Hormone; **SHBG:** Sex Hormone-Binding Globulin; **TNF- α :** Tumor Necrosis Factor-alpha; **IL-6:** Interleukin-6; **ROS:** Reactive Oxygen Species; **DNA:** Deoxyribonucleic Acid; **ART:** Assisted Reproductive Technologies; **IVF:** *In vitro* Fertilization; **PEG:** Polyethylene Glycol; **PCL:** Polycaprolactone; **DCEM:** Decellularized Ovarian Extracellular Matrix.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

VV: Wrote the Manuscript; **TR:** Reviewed and corrected the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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