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HISTOMORPHOLOGICAL AND MOLECULAR CHANGES IN OVARIAN TISSUE IN AN EXPERIMENTAL MODEL OF POLYCYSTIC OVARY SYNDROME-LIKE DISORDERS.

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Abstract. This study investigated histomorphological and molecular alterations in ovarian tissue using a letrozole-induced rat model of polycystic ovary syndrome (PCOS). Forty immature female Wistar rats were randomized into control (n=20) and PCOS (n=20) groups. The model was induced with oral letrozole (1 mg/kg) for 21 days and validated by estrous cycle disruption, hormonal changes, and ovarian morphology. Results showed disrupted folliculogenesis with reduced preantral/antral follicles and increased atresia, stromal hyperplasia, fibrosis, and disorganized angiogenesis[1,2]. Decreased Ki-67 and increased Caspase-3 indicated impaired proliferation with enhanced apoptosis. Elevated TNF-α and IL-6 reflected chronic inflammation. Molecularly, CYP17A1 was upregulated, CYP19A1 downregulated, AMH increased, and PI3K/Akt signaling was impaired; oxidative stress (ROS, MDA) was elevated with weakened antioxidant defense.

In conclusion, PCOS-like conditions produce integrated morphological, cellular, and molecular disturbances that arrest follicular development and sustain anovulation. These findings support multi-target therapeutic strategies addressing insulin signaling, inflammation, oxidative stress, and steroidogenesis[3,4,5].

Keywords: polycystic ovary syndrome, ovary, folliculogenesis, insulin resistance, oxidative stress, inflammation, PI3K/Akt, aromatase, AMH, apoptosis

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine disorders among women of reproductive age, with an estimated prevalence of 6–15% depending on diagnostic criteria and population characteristics. It is clinically defined by the presence of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, although its manifestations vary widely across individuals[6,7,8]. Beyond its reproductive implications, PCOS is increasingly recognized as a systemic metabolic disorder, significantly increasing the risk of insulin resistance, central obesity, metabolic syndrome, and type 2 diabetes mellitus.

Current evidence indicates that PCOS is a multifactorial condition with a complex pathogenesis involving genetic susceptibility, epigenetic modifications, environmental influences, and endocrine dysregulation. A central role is played by insulin resistance, which leads to compensatory hyperinsulinemia. Elevated insulin levels enhance androgen production in ovarian theca cells, suppress hepatic synthesis of sex hormone-binding globulin (SHBG), and consequently increase circulating free androgen fractions[9,10,11]. This endocrine imbalance disrupts granulosa cell differentiation, reduces aromatase activity, and impairs the conversion of androgens to estrogens, thereby altering the physiological estrogen–androgen equilibrium.

In addition, dysregulation of the hypothalamic–pituitary–ovarian (HPO) axis contributes to increased luteinizing hormone (LH) secretion relative to follicle-stimulating hormone (FSH), resulting in an elevated LH/FSH ratio. This imbalance interferes with dominant follicle selection during early folliculogenesis and leads to the accumulation of numerous small antral follicles, a hallmark morphological feature of PCOS[12,13,14].

At the cellular and microenvironmental levels, ovarian tissue in PCOS is characterized by increased oxidative stress, mitochondrial dysfunction, and activation of pro-inflammatory signaling pathways. Elevated levels of reactive oxygen species (ROS), along with increased expression of inflammatory mediators such as TNF-α and IL-6, contribute to disruption of

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cellular homeostasis. These factors disturb the balance between proliferation and apoptosis in granulosa cells, ultimately leading to follicular arrest and increased atresia[15,16,18].

Clinically, PCOS is a heterogeneous disorder with multiple phenotypic presentations (Rotterdam phenotypes A–D), reflecting varying degrees of hyperandrogenism, ovulatory dysfunction, and ovarian morphology. This heterogeneity complicates diagnosis and treatment and underscores the importance of using standardized experimental models for mechanistic studies. Among these, letrozole-induced rodent models have proven particularly valuable, as they closely mimic key features of human PCOS, including hyperandrogenism, anovulation, and cystic ovarian changes. These models provide a reliable platform for investigating histomorphological and molecular alterations in ovarian tissue[19,20,21].

Furthermore, the long-term complications associated with PCOS—including metabolic syndrome, endometrial hyperplasia, infertility, and increased cardiovascular risk—highlight the importance of early detection and intervention. In this context, detailed investigation of ovarian tissue at the histological, cellular, and molecular levels is essential for elucidating pathogenic mechanisms and identifying novel therapeutic targets[22,23,24]. A comprehensive understanding of signaling pathways involved in steroidogenesis, inflammation, oxidative stress, and cell survival is particularly important for the development of targeted and personalized treatment strategies.

Aim of the study. To identify and analyze histomorphological and molecular changes in ovarian tissue in an experimental model of PCOS-like condition.

Materials and methods. A prospective controlled experimental study was conducted using 40 immature female Wistar rats (8–10 weeks old, 180–220 g). Animals were housed under standard vivarium conditions (22±2°C, 50–60% humidity, 12-hour light/dark cycle) with free access to food and water. All procedures complied with international bioethical standards.

Animals were randomly divided into two groups: control (n=20) and PCOS model (n=20). The PCOS model was induced by administering letrozole (1 mg/kg) orally for 21 days. Model validation included vaginal cytology, hormonal analysis (testosterone, LH/FSH), and ovarian morphology assessment.

Ovarian tissues were fixed in 10% formalin, embedded in paraffin, and sectioned (4–5 μm). Histological staining (H&E) and morphometric analysis were performed. Fibrosis was assessed using Masson's trichrome stain.

Immunohistochemical analysis included Ki-67, Caspase-3, TNF-α, IL-6, VEGF, AMH, and AR markers. Expression was evaluated using H-score.

Molecular analysis included RT-qPCR (CYP17A1, CYP19A1, StAR, INSR, PI3K, AKT, NF-κB) and Western blot (Akt signaling, apoptosis markers, antioxidant system). Oxidative stress markers (MDA, SOD, CAT) were measured.

Statistical analysis was performed using SPSS, with significance set at $p<0.05$.

Results and discussion. Significant histomorphological and molecular changes were observed in the PCOS group. Detailed morphometric evaluation demonstrated a marked disruption of normal folliculogenesis, characterized by a relative preservation of primordial follicles alongside a significant reduction in preantral and antral follicles, accompanied by a pronounced increase in follicular atresia. This pattern reflects a failure of follicular maturation and dominant follicle selection. In parallel, ovarian stromal remodeling was evident, including stromal hyperplasia, increased deposition of fibrotic extracellular matrix, and disorganized angiogenesis, indicating profound alterations in tissue microarchitecture and microcirculatory support.

Immunohistochemical analysis provided further insight into cellular dynamics. A significant decrease in Ki-67 expression indicated suppressed proliferative activity in granulosa cells, while a marked increase in Caspase-3 expression confirmed activation of apoptotic pathways. This imbalance between proliferation and apoptosis represents a critical mechanism underlying follicular arrest. Moreover, elevated expression of pro-inflammatory cytokines TNF-α and IL-6

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confirmed the presence of a chronic low-grade inflammatory state within ovarian tissue, which is known to exacerbate both insulin resistance and androgen excess.

At the molecular level, substantial dysregulation of key signaling pathways was identified. The PI3K/Akt pathway, essential for cell survival and insulin signaling, showed impaired activity, suggesting disrupted metabolic regulation in ovarian cells. Concurrently, steroidogenic imbalance was evident, with increased expression of CYP17A1 (enhanced androgen synthesis) and decreased expression of CYP19A1 (reduced aromatase activity), leading to a shift toward hyperandrogenism. Elevated AMH levels further indicated inhibition of follicular maturation and accumulation of small antral follicles. In addition, increased oxidative stress markers (ROS, MDA) combined with insufficient antioxidant defense mechanisms contributed to mitochondrial dysfunction, energy imbalance, and further cellular damage.

Collectively, these alterations demonstrate that folliculogenesis is disrupted through a complex, multi-layered interaction of endocrine, inflammatory, oxidative, and molecular mechanisms. Hormonal imbalance, chronic inflammation, oxidative stress, and signaling pathway dysregulation act synergistically, forming a self-perpetuating pathogenic cycle. This cycle leads to persistent anovulation, progressive ovarian dysfunction, and the maintenance of the PCOS phenotype, highlighting the multifactorial and interconnected nature of its pathogenesis.

Conclusion. The study demonstrates that PCOS-like conditions induce complex, multi-level alterations in ovarian tissue encompassing morphological, cellular, and molecular domains. These changes include disrupted folliculogenesis, increased follicular atresia, stromal hyperplasia, fibrosis, chronic low-grade inflammation, oxidative stress, and dysregulation of key signaling pathways such as PI3K/Akt and steroidogenic enzymes. Together, these processes culminate in impaired granulosa cell function, enhanced androgen production, and persistent anovulation.

Importantly, the findings highlight that these alterations are not isolated but interconnected, forming a self-sustaining pathogenic network driven by endocrine imbalance, inflammatory activation, and mitochondrial dysfunction. The observed increase in AMH levels, coupled with reduced aromatase activity and heightened androgen receptor signaling, further reinforces the inhibition of follicular maturation and the maintenance of the PCOS phenotype.

From a translational perspective, understanding these integrated mechanisms provides a strong scientific foundation for the development of targeted and personalized therapeutic strategies. Interventions aimed at improving insulin sensitivity, reducing oxidative stress, modulating inflammatory pathways, and restoring steroidogenic balance may offer significant clinical benefit. Thus, early identification and multi-target therapeutic approaches are essential for preventing long-term reproductive and metabolic complications associated with PCOS.

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