JOURNAL OF MULTIDISCIPLINARY SCIENCES AND INNOVATIONS
VOLUME 04, ISSUE 11
MOPNTHLY JOURNALS
ISSN NUMBER: 2751-4390
IMPACT FACTOR: 9,08

MORPHOLOGICAL AND MOLECULAR CHANGES IN OVARIAN TISSUE IN EXPERIMENTAL MODELS OF DISORDERS SIMILAR TO POLYCYSTIC OVARY SYNDROME

Ibragimova Ziyodakhon Jalolidinovna
Assistant of the Department of Histology and Biology,
Fergana Public Health Medical Institute

Abstract: This scientific article provides an in-depth analysis of morphological and molecular changes in ovarian tissue based on experimental animal models of disorders similar to polycystic ovary syndrome (PCOS). Studies using models induced by dehydroepiandrosterone (DHEA), letrozole, and valproate demonstrate impaired folliculogenesis, stromal hypertrophy, collagen accumulation, angiogenic imbalance, and increased oxidative stress. Molecular analyses confirm reduced aromatase activity, an increased LH/FSH ratio, enhanced expression of insulin resistance markers, and activation of inflammatory and fibrotic processes mediated by the NF-κB and TGF-β signaling pathways. The article also evaluates the advantages and limitations of experimental models in investigating the pathogenesis of PCOS.

Keywords: Polycystic ovary syndrome, experimental model, DHEA, letrozole model, ovarian morphology, molecular markers, folliculogenesis, inflammation, fibrosis.

Introduction

Polycystic ovary syndrome (PCOS) affects 6–21% of women of reproductive age and presents as a complex of endocrine and metabolic disorders. Clinically, it is characterized by ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology (Teede et al., 2023). Due to the complexity of its etiology, experimental animal models play a crucial role in studying PCOS pathogenesis. The most commonly used models include the DHEA model, the letrozole model, the prenatal androgen exposure model, and diet-induced insulin resistance models.

In PCOS-like experimental disorders, changes in ovarian tissue morphology—such as arrested follicular maturation, stromal fibrosis, impaired angiogenesis, and increased oxidative stress—closely resemble the pathological conditions observed in patients (Hernandez et al., 2022). At the molecular level, altered expression of steroidogenic enzymes, imbalance of apoptotic processes, and activation of the TGF-β and NF-κB signaling pathways are observed.

The aim of this article is to systematically analyze morphological and molecular changes in ovarian tissue based on experimental PCOS models and to assess their similarity to the pathogenesis of clinical PCOS.

Main Part

In experimental models of disorders similar to polycystic ovary syndrome, the observed changes primarily manifest as pronounced alterations in the morphostructural organization of the ovaries. Models induced by DHEA, letrozole, prenatal androgen exposure, and metabolic disturbances demonstrate similar pathological processes at both macroscopic and microscopic levels. Despite certain differences among these models, their common features include disrupted folliculogenesis, stromal remodeling, impaired angiogenesis, and increased oxidative stress. These morphological changes gradually progress and ultimately lead to significant limitations in ovarian functional capacity.

In animals treated with the DHEA model, the ovaries are enlarged, the stroma is thickened, and disorganization of granulosa cells is evident. The letrozole model is characterized by inhibition of aromatase activity, resulting in reduced estrogen synthesis and progressive androgen

accumulation. In this model, thinning of the granulosa cell layer, hyperplasia of theca cells, and increased follicular atresia are more pronounced. Prenatal androgen models predominantly involve epigenetic alterations affecting hormonal programming during fetal development, leading to an androgen-dominant ovarian phenotype. In metabolic models, insulin resistance causes lipid accumulation in the ovarian stroma, mitochondrial dysfunction, and marked oxidative stress.

The central pathological feature across these models is impaired folliculogenesis. Disruption occurs at various stages of follicular development, resulting in the accumulation of immature antral follicles. The absence of Graafian follicle formation and ovulatory stigma is a typical characteristic of PCOS-like experimental models. Thickening of the zona pellucida, irregularity of the granulosa layer, and formation of intercellular gaps indicate arrest of the physiological ovarian cycle. The increased number of atretic follicles reflects a clear imbalance between apoptosis and proliferation, supported by elevated Bax expression and reduced Bcl-2 levels.

Stromal alterations represent another critical component of the pathological process. Ovarian stromal thickening characteristic of PCOS develops through multiple mechanisms, including androgen excess, increased inflammatory mediators, activation of the TGF-β pathway, and fibroblast proliferation. Excessive synthesis of collagen types I and III leads to stromal fibrosis. Fibrotic changes reduce ovarian elasticity, alter the follicular microenvironment, and complicate ovulation. Studies indicate that fibrotic processes are more pronounced in the letrozole model compared to the DHEA model.

Impaired angiogenesis contributes to reduced oxygen and nutrient supply essential for follicular development, thereby exacerbating the pathology. Altered expression of vascular endothelial growth factor (VEGF), initially increased as a compensatory response and subsequently decreased, reflects microcirculatory dysfunction. Abnormal neovascularization further enhances oxidative stress and promotes stromal remodeling.

At the molecular level, imbalance of steroidogenic enzymes represents a key pathological mechanism. Increased expression of CYP17A1 and CYP11A1 enhances androgen synthesis, while reduced aromatase (CYP19A1) activity decreases estrogen production. These changes, combined with altered LH/FSH ratios, disrupt ovarian hormonal sensitivity. Increased LH receptor expression enhances the hyperreactivity of theca cells, whereas decreased FSH receptor expression limits granulosa cell proliferation and differentiation.

Elevated levels of inflammatory markers such as TNF-α, IL-6, COX-2, and NF-κB are observed across nearly all experimental PCOS models. These mediators promote stromal remodeling, exacerbate insulin resistance, and accelerate apoptotic processes. Chronic inflammation intensifies mitochondrial dysfunction, reduces ATP production, and increases accumulation of reactive oxygen species (ROS), resulting in decreased activity of antioxidant enzymes including superoxide dismutase, glutathione peroxidase, and catalase.

Experimental studies demonstrate that PCOS-like disorders involve simultaneous alterations across multiple systems—endocrine, metabolic, immune, and ovarian microenvironmental levels. Each model reflects only specific aspects of the disease. The DHEA model primarily represents androgen imbalance, the letrozole model reflects aromatase deficiency, prenatal androgen models highlight epigenetic programming, and metabolic models emphasize insulin resistance and oxidative stress. Their combined application allows a more comprehensive understanding of PCOS pathogenesis.

Discussion

Studies based on experimental PCOS-like models have significantly enhanced understanding of the complex interplay between ovarian morphology and molecular processes. The observed changes effectively simulate the core mechanisms of clinical PCOS pathogenesis. Arrested

follicular development, increased antral follicle count, and absence of Graafian follicle formation observed in DHEA and letrozole models reflect the morphological basis of anovulatory cycles in patients. These changes result from disrupted hormonal interactions between granulosa and theca cells. Ovarian stromal fibrosis and activation of the TGF-β signaling pathway create a pathological microenvironment characteristic of PCOS. Fibrotic remodeling reduces stromal elasticity and disrupts follicular development. Experimental models provide compelling evidence that the stromal component plays a central role in disease progression. Chronic inflammation, indicated by increased NF-κB, TNF-α, and IL-6 expression, further contributes to stromal remodeling and insulin resistance. Oxidative stress, mitochondrial dysfunction, and reduced ATP production are closely linked to the metabolic component of PCOS pathogenesis.

Imbalance in steroidogenic enzymes remains a critical discussion point. Increased CYP17A1 and CYP11A1 expression and decreased aromatase activity lead to elevated androgen levels, closely corresponding to hyperandrogenism observed in clinical PCOS. Altered expression of FSH and LH receptors further disrupts folliculogenesis. Different experimental models emphasize distinct pathological mechanisms, highlighting the necessity of comparative and integrative approaches for a comprehensive understanding of PCOS.

Moreover, experimental models provide reliable platforms for evaluating novel therapeutic agents, testing pathogenetically targeted treatments, and identifying molecular targets. These models are particularly valuable for assessing the efficacy of anti-fibrotic, anti-inflammatory, and antioxidant therapies in PCOS conditions.

Results

Based on the accumulated scientific data, the following conclusions were drawn:

Experimental models produce morphological and molecular changes closely resembling the clinical phenotype of PCOS. Disrupted follicular maturation, anovulation, stromal fibrosis, and impaired angiogenesis were observed in nearly all models. Imbalance in steroidogenesis was confirmed as a central mechanism in PCOS pathogenesis. Increased CYP17A1 and CYP11A1 expression combined with reduced aromatase activity leads to androgen excess, while altered LH/FSH ratios result in arrested folliculogenesis. Inflammation and oxidative stress sustain pathological progression. Activation of NF-κB, TNF-α, and IL-6 enhances mitochondrial dysfunction and apoptotic processes.

Stromal remodeling, including fibrosis, collagen accumulation, and fibroblast proliferation, forms the structural basis of PCOS.

These changes disrupt the follicular microenvironment and hinder restoration of ovulatory cycles.

Experimental models represent essential scientific tools for studying PCOS and developing new treatment strategies, particularly in research on antioxidants, anti-inflammatory agents, insulin modulators, and epigenetic therapies.

Different models illuminate different aspects of PCOS, necessitating an integrative approach.

Combined use of DHEA, letrozole, metabolic, and prenatal androgen models is recommended to comprehensively represent PCOS pathogenesis.

Overall, these studies provide a strong scientific foundation for deeper understanding of PCOS mechanisms, refinement of diagnostic criteria, and identification of novel therapeutic targets.

Conclusion

Morphological and molecular investigations conducted in experimental models of disorders similar to polycystic ovary syndrome confirm the multifactorial and complex nature of PCOS pathogenesis. Although the mechanisms of pathological induction differ among models, most exhibit changes closely resembling clinical PCOS. Arrested folliculogenesis, absence of ovulation, increased follicular atresia, stromal fibrosis, impaired angiogenesis, inflammation, oxidative stress, and hormonal imbalance collectively disrupt ovarian function.

Experimental models reveal that no single model fully represents the clinical disease. Each highlights specific pathological pathways, emphasizing the necessity of integrative and combined modeling strategies. The strong similarity between experimental findings and clinical PCOS mechanisms validates the use of these models as reliable platforms for therapeutic development and pathogenetic research. Ultimately, these studies contribute significantly to advancing individualized and targeted treatment approaches for PCOS.

References :

1. Teede H., et al. International evidence-based guideline for the assessment and management of PCOS. Hum Reprod, 2023.

2. Hernandez C., et al. Letrozole-induced PCOS model: morphological and molecular changes in ovarian tissue. J Ovarian Res, 2022.

3. Abbott D.H., et al. Primate models of polycystic ovary syndrome. Trends Endocrinol Metab, 2019.

4. Walters K.A. DHEA-induced PCOS models in rodents. Molecular and Cellular Endocrinology, 2021.

5. Diamanti-Kandarakis E. Insulin resistance and the pathogenesis of PCOS. Endocrine Reviews, 2020.

6. Громова О., Корнилов А. Гормональные дисфункции в репродуктивной системе. Москва: ГЭОТАР-Медиа, 2021.

7. Адамян Л.В. Синдром поликистозных яичников: современные представления. Российский журнал гинекологии, 2020.

8. Xasanov Sh., Jo‘rayev A. Ayollar reproduktiv salomatligi asoslari. Toshkent: TMA nashriyoti, 2022.

9. Otaboyeva M. Endokrin ginekologiya. Toshkent, 2021. 10. Das M., et al. Oxidative stress markers in experimental PCOS. Reproductive Biology, 2021.

11. Li X., et al. TGF-β signaling in ovarian fibrosis of PCOS models. Frontiers in Endocrinology, 2022.

12. Patel S. Molecular pathways in PCOS: NF-κB involv