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ПАТОЛОГИЯ ЭНДОМЕТРИЯ У ЖЕНЩИН С СИНДРОМОМ ПОЛИКИСТОЗНЫХ ЯИЧНИКОВ

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ENDOMETRIAL ABNORMALITIES IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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Резюме. Синдром поликистозных яичников (СПКЯ) –это сложное, многофакторное заболевание, наблюдаемое у женщин репродуктивного возраста и сопровождающееся многочисленными нарушениями эндокринно-метаболического характера. В статье проведен анализ исследований различных патологических изменений эндометрия с целью выявления этио-патогенетических факторов, лежащие в основе репродуктивных нарушений, которые возникают при этом заболевании. Установлено, что СПКЯ сопровождается молекулярно-биологическими, протеомными, рецепторными эндометриальными нарушениями, обусловливающими развитие бесплодия, невынашивания беременности, а также аномальных кровотечений и риска рака эндометрия.

Ключевые слова: синдром поликистозных яичников, эндометрий, резистентность к прогестерону, воспаление, бесплодие.

Resume. Polycystic Ovarian Syndrome (PCOS) is a complex, multifactorial disorder affecting reproductive-age women with changes in the endometrium of the affected women. Many studies have been done on different changes of the endometrium to try understand the underlying causes for symptoms and disorders that come with the disease. Thus in this study we look into changes of the endometrium of women of reproductive age to try understand different molecular and pathological changes that happen.

Keywords: polycystic ovarian syndrome, endometrium, progesterone resistance, inflammation, infertility.

Introduction. Polycystic Ovarian Syndrome (PCOS) is a complex, multifactorial disorder affecting 8%−13% of reproductive-age women, with variations depending on diagnostic criteria and population studied [8]. PCOS is primarily characterized by reproductive, endocrine, and metabolic dysfunctions. The 2003 Rotterdam consensus, the most widely accepted diagnostic criteria, defines PCOS as the presence of at least two of the following three features: oligoovulation and/or anovulation, biochemical or clinical hyperandrogenism, and polycystic ovarian morphology.

PCOS is traditionally recognized as a reproductive endocrinopathy, presenting with irregular menstrual cycles, anovulatory infertility, acne, hirsutism, and hormonal imbalances. However, its impact extends beyond reproductive health, as it is strongly associated with

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insulin resistance and metabolic abnormalities, including impaired glucose tolerance, hyperinsulinemia, obesity, type 2 diabetes, metabolic syndrome, non-alcoholic fatty liver disease, and an increased risk of cardiovascular disease [5]. Given its diverse clinical presentation, PCOS is best understood as a syndrome with overlapping reproductive, endocrine, and metabolic manifestations [6]. Despite advances in research and treatment, the etiology of PCOS remains incompletely understood, and standardizing management strategies remains a challenge. The 2018 international guidelines by Teede et al [9]. aim to address these challenges by providing evidence-based recommendations for the diagnosis and management of PCOS across different healthcare systems. In the following scientific review we will study into different endometrial changes in women with PCOS and its effect on lifestyle.

Purpose: to have a better understanding of the molecular changes that lead to changes in the endometrium of women with PCOS

Objectives:

1. Study of changes in the endometrium both in molecular level and morphological level.
2. Answer questions about what the pathological changes in the endometrium can lead to diseases which affect the normal lifestyle of these women.

Material and methods. This scientific review compromises of many articles found on scientific databases such as Google Scholar and Pubmed about endometrial abnormalities in women with polycystic ovarian syndrome. As the disease affects women of reproductive age we have gathered journals relating to fertility problems. We have excluded any articles that do not comply with the criteria of study.

Proteomic Alterations in the Endometrium

In the study that follows, we have identified key proteins and evaluated literature regarding the proteomic alterations in women with PCOS. which are downregulated in some cases and upregulated in others. We shall investigate its effects on the female reproductive system's endometrium based on the expression [1].

Tab. 1. Different proteomic alterations and their expressions post weight loss [1]

Protein Function	Expression in PCOS	Effect of Lifestyle Interventions	Role in Endometrial Receptivity
Legumain (LGMN)	Cysteine endopeptidase involved in extracellular matrix remodeling.	Dysregulated; altered expression in PCOS. Increased expression post-weight loss.	Supports implantation by enhancing epithelial adhesion and endometrial remodeling.
IGFBP-7	Glycoprotein involved in IGF metabolism and endometrial receptivity.	Dysregulated in PCOS. Increased abundance post-weight loss.	Enhances uterine preparation for implantation and supports decidualization.
HGF Receptor (MET)	Transmembrane tyrosine kinase receptor for hepatocyte growth factor.	Altered expression in PCOS. Increased expression post-weight loss.	Facilitates epithelial and trophoblast function essential for implantation.

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Continuation of table 1

Cytokeratin-7 (CK-7)	Epithelial marker involved in DNA synthesis and cellular transformation.	Possibly downregulated in PCOS. Upregulated after weight loss.	Suggests a role in epithelial transformation and implantation.
CD20	B cell activation and immune modulation.	Increased levels in PCOS, associated with immune dysregulation. Decreased expression post-weight loss.	Reduction may contribute to improved immune balance, reducing implantation failure.

Endometrial Hyperplasia, Cancer Risk, and Uterine Changes in PCOS

Women with PCOS have a threefold increased risk of endometrial carcinoma (EC) due to chronic anovulation, prolonged estrogen exposure, insulin resistance, and hyperinsulinemia, which promote abnormal endometrial proliferation.

Insulin resistance and hyperinsulinemia contribute to endometrial hyperplasia via the insulin-like growth factor (IGF) system. Increased IGF-1/IGF-2 expression and IGF-1R activation stimulate the pathway, promoting cell proliferation, suppressing apoptosis, and increasing tumor growth risk. Reduced IGFBP-1 further enhances IGF bioavailability, exacerbating uncontrolled endometrial proliferation [5]. It has been found that chronic low-grade inflammation in PCOS contributes to endometrial carcinogenesis. Studies indicate an overexpression of inflammatory and proto-oncogenic genes, independent of BMI, increasing the risk of endometrial intraepithelial neoplasia and EC progression [5].

Uterine Morphology and Function in PCOS

PCOS may affect uterine structure and function, impacting fertility. While no significant myometrial differences were found in PCOS patients, uterine peristalsis –critical for sperm transport –was reduced during the periovulatory phase. Animal studies show that hyperandrogenism increases uterine thickness, alters cell proliferation, and affects collagen organization and water absorption, suggesting a direct androgenic impact on uterine architecture, requiring further research.

Hyperandrogenism (HA) and Endometrial Changes in Polycystic Ovary Syndrome (PCOS)

Hyperandrogenism (HA) disrupts normal endometrial function by impairing cellular growth, differentiation, and decidualization, leading to reduced embryo implantation rates. Androgen receptors (AR) and Wilms tumor protein (WT1) play a crucial role in this process, with WT1 regulating AR expression and endometrial responsiveness to androgens[10]. In PCOS, elevated androgens disrupt AR-WT1 balance, contributing to infertility and impaired endometrial function. Additionally, dehydroepiandrosterone (DHEA), an androgen precursor, negatively affects progesterone secretion and endometrial receptivity. HA also disrupts the uterine cell cycle, increasing the risk of endometrial hyperplasia and malignancy by promoting cellular dysregulation, oxidative stress, and inflammation [10]. Hyperandrogenism (HA) disrupts the cell cycle, increasing the risk of endometrial hyperplasia and malignancy. Elevated

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reactive oxygen species (ROS) contribute to oxidative stress, enhancing endothelial permeability and inflammation. Androgens further stimulate TNF-α and IL-1, activating the ROS system and NF-κB inflammatory pathway, which promotes endometrial proliferation and affects early pregnancy outcomes.

Tab. 2. Pathological processes that contribute to chronic inflammation in the endometrium in women with PCOS [3] [5] [10]

Category	Key Findings
Endometrial Receptivity and Immune Regulation	- **Embryo implantation** involves immune cells and cytokines regulated by sex hormones. - **T cells** dominate the **follicular phase**, while **uNK cells** increase in the **secretory phase**, improving receptivity. - Balance between **Th1 (immune rejection)** and **Th2 (immune tolerance)** cytokines is crucial. - **Progesterone-induced decidualization** remodels spiral arteries for stable **maternal-fetal interface**
Endometrial Dysfunction in PCOS	- **Low-grade chronic inflammation** disrupts metabolism and reproduction. - Increased **oxidative stress** and **CRP levels** correlate with **high IL-6 and CCL2** during the **proliferative phase**. - **Secretory phase: Reduced uNK cells** disrupt immune homeostasis, lowering receptivity. - **Activated uNK cells** increase **Th1 cytokines**, decrease **Th2 cytokines**, leading to **implantation failure**. - Altered immune composition: **↑CD68+ macrophages, CD163+ M2 macrophages, CD1a+ immature dendritic cells, CD83+ mature dendritic cells, CD8+ T cells**, impairing implantation and increasing **miscarriage risk**. - **Animal models suggest mesenchymal stem cells** may **restore receptivity** by rebalancing **Th1/Th2 cytokines** and **uNK cells**.
Key Inflammatory Cytokines in PCOS Endometrium	**1. uNK Cells:** Essential for implantation; **reduced in PCOS**, impairing endometrial remodeling. **2. CRP:** Elevated in PCOS, linked to **insulin resistance** and **endometrial cancer** via the **MAPK/ERK pathway**. **3. TNF-α:** Increases **endometrial proliferation** and **estrogen levels**, disrupts the menstrual cycle, and induces **insulin resistance** by inhibiting **IRS-1**. **4. IL-6:** Overexpressed in PCOS; worsens **insulin resistance** by impairing the **PI3K/AKT pathway**, contributing to **endometrial dysfunction**.

Progesterone Resistance in PCOS

1. Impaired estrogen antagonism is describing as the main factor of endometrial proliferation. In PCOS, progesterone resistance leads to unopposed estrogen action, promoting endometrial hyperplasia and increasing endometrial cancer risk [8].

2. Altered progesterone receptor expression is contributed by:

- PR exists in two isoforms: PRA and PRB, with PRA mediating estrogen antagonism.

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• PCOS patients exhibit increased PR expression during the secretory phase, but dysregulated hormonal balance leads to impaired function.

• PCOS-like rat models show increased PR and estrogen receptor expression, indicating hormonal dysregulation.

3. Downstream signaling defects in the progesterone pathway is found as impaired mechanism of action due to:

• Mitogen inducible gene 6 (Mig-6) inhibits estrogenic effects and promotes apoptosis. Deficient Mig-6 in PCOS contributes to progesterone resistance, hyperplasia, and carcinogenesis.

• Impaired expression of homeobox A10 (HOXA10) which is critical for endometrial receptivity and implantation. Reduced HOXA10 in PCOS impairs implantation and fertility[10].

Impact of Progesterone Resistance on Endometrial Health

1. Endometrial Hyperplasia and Cancer Risk. Chronic estrogen exposure due to progesterone resistance increases the risk of atypical hyperplasia and endometrial carcinoma.

2. Endometrial Dysfunction and Infertility. Progesterone insensitivity disrupts the implantation window, leading to implantation failure and recurrent pregnancy loss (RPL) in PCOS [5].

Conclusion. As was thoroughly covered, uterine and endometrial dysfunction are major contributors to infertility associated with PCOS. Furthermore, women with PCOS exhibit a variety of endometrium-related conditions, such as proteome changes and hormone imbalances, such as progesterone downregulation, which can have a long-term impact on uterine health and result in endometrial hyperplasia, remodeling, and cancer. It is hypothesized that changes in uterine morphology and function are caused by metabolic abnormalities linked to PCOS, such as hyperandrogenism, hyperinsulinemia, and insulin resistance. Recent research suggests that metformin and anti-androgens may be able to reverse harmful endometrial alterations. Unfortunately, there is currently no specific treatment plan that can be advised to patients in order to guarantee a cure.

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