**МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ**
**НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ**
**КАФЕДРА НОРМАЛЬНОЇ ТА ПАТОЛОГІЧНОЇ ФІЗІОЛОГІЇ**

**VI науково-практична internet-конференція**
**з міжнародною участю**

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**16 листопада 2023 р.**
**ХАРКІВ – Україна**

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Механізми розвитку патологічних процесів і хвороб та їх фармакологічна корекція : матеріали VI науково-практичної internet-конференції з міжнародною участю, м. Харків, 16 листопада 2023 р. Х. : НФаУ, 2023, 520 с.

Збірник містить матеріали VI науково-практичної internet-конференції з міжнародною участю «Механізми розвитку патологічних процесів і хвороб та їх фармакологічна корекція». В матеріалах конференції розглянуто сучасні проблеми медицини і фармації: молекулярні основи патології, клітинні та гуморальні механізми розвитку захворювань; роль генетичних факторів у патогенезі захворювань; механізми розвитку патологічних процесів і хвороб; вікова патофізіологія; проблемні аспекти хвороб цивілізації; клінічна патофізіологія; питання викладання патофізіології; експериментальна терапія найбільш поширених захворювань; фармакологічна корекція патологічних процесів; проблеми та перспективи створення лікарських препаратів різної спрямованості дії; інформаційні технології і автоматизація наукових досліджень з розробки лікарських засобів; створення нутрицевтичних засобів та виробів медичного призначення; маркетингові дослідження сучасного фармацевтичного ринку; нанотехнології у фармації; таргетна терапія захворювань людини; трансляційна медицина; новітні технології діагностики та лікування; біомедичні технології; вплив сучасних технологій на здоров'я людини; актуальні питання фізичної реабілітації та сучасні технології збереження здоров'я людини; ментальне здоров'я та інновації у медико-психологічній реабілітації військовослужбовців в умовах воєнного стану; глобальні проблеми громадського здоров'я.

Для широкого кола наукових і практичних працівників медицини та фармації.

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Mechanisms of pathological processes development and diseases, their pharmacological correction: collected papers of to the VI$^{th}$ scientific and practical internet-conference for the international participation, Kharkiv, November 16, 2023. Kh.: NUPh, 2023, 520 p.

Collected papers includes the materials of VI$^{th}$ scientific and practical internet-conference for the international participation «Mechanisms of pathological processes development and diseases, their pharmacological correction». The modern problems of pathophysiology were considered the materials of the Conference: molecular basis of pathology, cellular and humoral mechanisms of disease development; role of genetic factors in the pathogenesis of diseases; mechanisms of pathological processes and diseases development; age-related pathophysiology; problematic aspects of the diseases of civilization; clinical pathophysiology; issues of pathophysiology teaching; experimental therapy of the most common diseases; pharmacological correction of pathological processes; problems and prospects for the development of medicines with different orientation of action; information technology and automation of scientific research on drug create; development of nutraceutical drugs and products for medical purpose; marketing research of the modern pharmaceutical market; nanotechnology in pharmacy; targeted therapy of human diseases; translational medicine; the latest diagnostic and treatment technologies; biomedical technologies; impact of modern technologies on human health; current issues of physical rehabilitation and modern technologies for preserving human health; mental health and innovations in medical and psychological rehabilitation of military personnel under martial law; global public health issues.

For a wide audience of scientific and practitioners of medicine and pharmacy.

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# ROLE OF RISK FACTORS IN THE DEVELOPMENT OF ENDOMETRIOSIS

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**Introduction**. Endometriosis is a hormone-dependent chronic inflammatory disease. It is characterized by the appearance of the mucosa of the uterine body, including submucosal and glandular cells, beyond the uterine cavity. The three most typical types of endometrioses are peritoneal endometriosis, ovarian cysts (chocolate cysts) and nodules of deeply infiltrating endometriosis in the gut or vaginal–rectal septum. The current scientific evidence suggests that the diet and lifestyle may influence the presence of inflammation in the body, estrogen activity, menstrual cycle, and prostaglandin metabolism. Immune, endocrine, genetic, and anatomical disorders have been mentioned as risk factors, but the etiology of the disease is not fully understood. The most significant risk factor and cellular mechanism underlying pelvic endometriosis is Sampson's retrograde menstruation hypothesis. Retrograde menstruation is the process in which endometrial cells and fragments of the tissue shed during menstrual bleeding and are transported into the peritoneal cavity due to the retroperistaltic movements of the fallopian tubes. Endometriosis is characterized by estrogen dependence and progesterone resistance. Risk factors known to be associated with endometriosis include age, family history, educational attainment, age at menarche, and exposure to endocrine-disrupting chemicals. Lifestyle factors such as alcohol/caffeine intake, smoking, and physical activity influence estrogen levels in the body and, therefore, may impact development of endometriosis. Genetic and epigenetic changes in endometrial cells are also observed in endometriosis. Imbalances in gut and reproductive tract microbiota composition, known as dysbiosis, disrupt normal immune function, leading to the elevation of proinflammatory cytokines, compromised immunosurveillance and altered immune cell profiles, all of which may contribute to the pathogenesis of endometriosis. Environmental factors such as elevated levels of phthalate esters, persistent organochlorine pollutants, perfluorochemicals, and exposure to cigarette smoke can increase risk of developing endometriosis by inducing oxidative stress, altering hormonal homeostasis, or by changing immune responses.

**Purpose**. To evaluate the literature to examine, which risk factors impact on the development of endometriosis.

**Material and methods**. Search methods: A comprehensive English language PubMed, Medline and Google Scholar search was conducted with key search terms that included endometriosis, inflammation, immune system, female hormones, pathology (histopathology).

**Results and discussion.** Molecular defects in eutopic endometrial tissues of women with endometriosis, such as activation of oncogenic pathways or biosynthetic cascades that favor increased production of estrogen, cytokines, prostaglandins, and metalloproteinases. The endometriotic stromal cell is epigenetically misprogrammed

and displays partial phenotypes of ovarian theca/granulosa cells and tissue macrophages. The endometriotic stromal cell also expresses and secretes large amounts of immune molecules such as IL-1β, IL-6, TNF, regulated upon activation normal T cell expressed and secreted, and monocyte chemoattractant protein-1. For example, endometriotic stromal cells express the full cascade of steroidogenic proteins and enzymes such as steroidogenic acute regulatory protein and aromatase and convert the precursor molecule cholesterol to substantial quantities of progesterone and estradiol. Estradiol is essential for endometrial tissue attachment to peritoneum; lesion survival; production of inflammatory substances such as metalloproteinases, cytokines, or prostaglandins and growth factors; and angiogenesis. Epigenetic abnormalities in the vascular system may affect the process of separation between the functionalis and basalis and thus affect the risk for endometriosis. Apoptosis is significantly decreased in endometriotic stromal and epithelial cells compared with eutopic endometrial tissues that may be linked to pathologic levels of local estradiol biosynthesis. Endometriotic foci have estrogen and progesterone receptors that mediate their responsiveness during the menstrual cycle. Estrogen receptor β mediates the effects of estradiol in endometriosis and triggers pathways that enhance lesion survival, remodel pelvic peritoneal tissue, and produce inflammatory substances, which stimulate nociceptors in pelvic tissues, leading to pain. With the upregulation of 17β-hydroxysteroid dehydrogenase-1 and aromatase genes, the level of estradiol in endometriotic lesions is higher than normal endometrium. The local environment that allows the growth of endometrial cells and stroma includes estrogen exposure and chronic inflammation. The production of cytokines and prostaglandins and infiltration of immune cells are some of the hallmarks of inflammation. It leads to pain, remodeling of neighboring tissues, fibrosis, adhesion formation, and infertility. Endometriosis is a unique condition whereby progesterone resistance occurs owing to a deficiency of progesterone receptor in endometriotic stromal cells. A critical observation in endometriosis is deficient differentiation (decidualization) of the stromal cell, which has been linked to progesterone resistance. The oxidative stress in the uterus during menstruation and in the peritoneal cavity following retrograde menstruation are recognized as potential causative factors to induce genetic or epigenetic changes. Excessive release of reactive oxygen species induces cellular damage and alters cellular function by regulating protein activity and gene expression, leading to harmful effects. This may be prevented by progesterone, which does not allow the implant to attach to the local matrix, but it seems that in abdominal wall endometriosis, there is resistance to progesterone action. Methylation defects of genes encoding transcription factors (gamma-aminobutyric acid 6, steroidogenic factor-1) and estrogen receptor β cause increased production of estrogens in the lesion, with secondary inhibition of progesterone receptor. In eutopic endometrial tissue, the epithelial cell proliferates under the influence of estrogen. The strikingly rapid rate of proliferation possibly contributes to the acquisition of somatic epithelial mutations in eutopic endometrial tissue. Subsequently, retinol uptake and further metabolization are decreased, causing defects in the endometriotic tissue, with a high level of inflammation and anomalies of prostaglandin production. Genome wide association studies have identified 12

single nucleotide polymorphisms at 10 independent genetic loci that are associated with endometriosis. The identified epigenetic changes comprise methylation and demethylation of deoxyribonucleic acid and modifications of the histone code. In conjunction with endocrine imbalance and oxidative stress, immune dysregulation is a major factor that contributes to disease pathogenesis. The patients show dysfunctional macrophages, depressed killing capacity of natural killer cells, increased accumulation of regulatory T suppressor cells all of which may favor chronic inflammation and promote the initiation and progression of endometriosis-associated ovarian cancer. Neutrophil depletion with the antibody RB6-8C5 not only affected endometrial breakdown, but also can remarkably delayed endometrial repair, highlighting their importance in the destruction of endometrial tissue and concomitant repair. One of the possible pathogenic factors affecting both endometriosis and dysmenorrhea is prostaglandin levels. Omega-6 fatty acids derived from the diet are the precursors of the proinflammatory prostaglandins E2 and F2α that probably increase uterine cramps and cause the painful symptoms. However, prostaglandins E3 and E3α derived from the Omega-3 fatty acids were linked to reduced inflammation and thus, lesser pain. Alcohol has been shown to increase the body's inflammatory response. Tobacco may alter aromatase as well as increase the body's inflammatory response. While physical activity has been shown to reduce many diseases in women, including gynecological disorders, high intensity physical activity has been linked to reproductive disorders including anovulation and infertility. Post-surgical subgroups of endometriosis have increased due to the higher use of caesarean sections worldwide. Food may also contain chemical compounds from contaminated environments, especially chlorinated hydrocarbons including polychlorinated biphenyls and pesticides. The consumption of the dietary fiber, ham, beef, and other kinds of red meat was connected with higher endometriosis risk. Red meat exerts an antagonistic effect on the development of endometriosis compared to vegetables and fruits. It is characterized by a high content of dioxins, hormones and fat, increasing the concentration of estrogens. The gut flora is necessary in maintaining physiologic gastrointestinal function, it has also been found to be a key regulator in many inflammatory and proliferative conditions, to affect estrogen metabolism and stem-cell homeostasis. It is worth noting that the fiber contained in vegetables interacts in the control of the intestinal bacterial flora and affects hormonal balance.

**Conclusion.** Endometriosis is characterized by increasing inflammation and oxidated stress which appear with reduce of function of the immune and endocrine systems. This can cause by the dietary factors that include consumption of trans unsaturated fatty acids, red meat and ham, alcohol, genetic and epigenetic factors, age (25-35), family history, infertile women who are active smokers and whose body mass index is normal or low.

**Key words:** endometriosis, risk factors, inflammation, estrogen, progesterone, neutrophil, lipids, dysbiosis.

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# MECHANISMS OF PATHOLOGICAL PROCESSES DEVELOPMENT AND DISEASES, THEIR PHARMACOLOGICAL CORRECTION

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