

The modern pathogenetic challenges of polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is one of the neuroendocrine syndromes in women of reproductive age. In the pathogenesis of its development a great importance is paid to the hormonal disbalance, metabolic changes, overweight and obesity, diabetes mellitus, insulin resistance, genetic factors, etc. Very often, PCOS is accompanied by infertility, cardiovascular risks, diabetes mellitus.

The article is devoted to a review of modern scientific literature about the last researches devoted to the mechanisms of metabolic disorders which are connected with insulin resistance, overweight and obesity, also, with psychological disturbance and stress. The article describes the specific of psychological conditions in PCOS patients. On the basis of the analyzed scientific publications the connection between hormonal disbalance, psychological disorders, overweight, obesity and lipidogram parameters is presented.

Also, the researches about gut and vaginal microbiota are described in this paper. The last studies demonstrate the significant changes of human microbiome in the development and course of polycystic ovary syndrome. The article presents the concepts of the difference in the composition of the gut and vagina microbiota in women with this neuroendocrine syndrome.

The pathogenetic mechanisms of the role of the microbiota in the processes of PCOS pathogenesis, namely, the regulation of the immune response and inflammation processes in this pathology, are described. It has been shown that in women with PCOS there are differences in the microflora composition of the intestines, manifested by a decreased concentration of Lactobacillus and the presence of a variety of other microorganisms compared to the healthy women.

Thus, the main pathogenetic links of PCOS development are closely connected with each other. That is why multimodal approaches for study of PCOS and for management of the patients with PCOS are extremely important.

Keywords: polycystic ovary syndrome, pathogenesis, metabolic syndrome, overweight, obesity, insulin resistance, stress, psychological disorders, vaginal microbiota, microorganisms, microbiome, gut microbiota, dysbiosis.

Сучасні патогенетичні виклики синдрому полікістозних яєчників

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Синдром полікістозних яєчників (СПКЯ) – один із нейроендокринних синдромів у жінок репродуктивного віку. У патогенезі його розвитку велике значення надається гормональному дисбалансу, метаболічним змінам, надмірній масі тіла та ожирінню, цукровому діабету, інсулінорезистентності, генетичним факторам тощо. Дуже часто СПКЯ супроводжується безпліддям, серцево-судинними ризиками, цукровим діабетом.

Стаття присвячена огляду сучасної наукової літератури про останні дослідження, які охоплюють дані стосовно механізмів метаболічних порушень, пов'язаних з інсулінорезистентністю, надмірною масою тіла та ожирінням, а також із психологічними розладами та стресом. У статті описано особливості психологічних станів у хворих із СПКЯ. На підставі проаналізованих наукових публікацій продемонстровано зв'язок між гормональним дисбалансом, психологічними розладами, надмірною масою тіла, ожирінням і показниками ліпідограми.

Також у статті представлені дослідження мікробіоти кишечника та піхви. Останні дослідження демонструють суттєві зміни мікробіому людини при розвитку СПКЯ та перебігу СПКЯ. Наведено дані про відмінність у складі мікробіоти кишечника та піхви у жінок із цим нейроендокринним синдромом.

У статті описано патогенетичні механізми ролі мікробіоти у процесах патогенезу СПКЯ, а саме – регуляції імунної відповіді та запальних процесів за цієї патології. Установлено, що у жінок із даним нейроендокринним синдромом спостерігаються відмінності у складі мікрофлори кишечника, що проявляється зниженням концентрації Lactobacillus та наявністю низки інших мікроорганізмів порівняно зі здоровими жінками.

Отже, основні патогенетичні ланки розвитку СПКЯ тісно пов'язані між собою. Тому мультимодальні підходи до вивчення СПКЯ та ведення пацієнток із цим нейроендокринним синдромом є надзвичайно важливими.

Ключові слова: синдром полікістозних яєчників, патогенез, метаболічний синдром, надмірна маса тіла, ожиріння, інсулінорезистентність, стрес, психологічні розлади, мікробіота піхви, мікроорганізми, мікробіом, мікробіота кишечника, дисбіоз.

Neuroendocrine syndromes in gynecology includes various pathologies which are actual for study till today. Among these syndromes the most spread are premenstrual syndrome, polycystic ovary syndrome (PCOS), hyperandrogenism, climacteric syndrome, hyperprolactinemia, postcastration syndrome, etc. Menstrual disorders are the typical problem for women of reproductive age. Mostly, the basic pathogenetic mechanisms of neuroendocrine syndromes development are connected with hormonal disorders [1–6]. Currently, in the last years a great attention is paid for the genetic predisposition [7–12], gut and vaginal dysbiosis [13–15], oxidative stress factors [16, 17], etc. in their occurrence.

Near 10% of women of reproductive age are diagnosed with PCOS [18]. This syndrome consists of the presence of different combinations of various problems, in particular, reproductive, metabolic, psychological, dermatological disorders, cardiovascular risks [19]. Diagnostic recommendations for PCOS include irregular cycles and ovulatory dysfunction, biochemical and clinical hyperandrogenism, ultrasound and polycystic ovary morphology [18, 20]. Among 719 patients, the rate of ultrasonography changes typical for polycystic ovaries was the most common – 94.2%, 88.6% of persons suffered from menstrual disorders, almost one third of women – insulin resistance (IR), hyperandrogenism was diagnosed in 21.1%, acne – 13.3%, hirsutism – 6.1% [21].

It was found the higher concentrations of serum testosterone, fasting insulin, longer menstrual cycle, number of ovarian follicles and the higher lutenizing hormone (LH) / follicle-stimulating hormone (FSH) ratio and the statistically lower LH level in women with PCOS and obesity compared to non-obese PCOS-patients; but the estradiol concentration and ovarian volume were determined similar in obese and non-obese PCOS-women [21]. The high concentration of androgens in PCOS women rise the type 2 diabetes mellitus (T2DM) and insulin resistance (IR) development [22], which are the common risk factors for oncological development [23].

Overweight, obesity, insulin resistance are the part of metabolic disorders which are typical for patients with PCOS [24, 25]. The prevalence of IR and metabolic syndrome in PCOS patients can differ and depends on many factors. According to the results of M. R. Garcia-Senz et al. their frequency is considered to be at the level of 37.5% and 18.8%, respectively [26]. V. Artyomenko et al. presented the similar level of metabolic syndrome rate by PCOS – 30.6% [27].

It is known that not normal concentrations of such hormones as insulin, gonadotropin-releasing hormone, growth hormones, ratio LH/FSH, androgens, estrogens are related not only to the mechanisms of PCOS, but also to their metabolic disorders as obesity, overweight, diabetes, IR, infertility [2]. It was assumed that the basic common mechanism between obesity, PCOS and other metabolic disorders is IR [28]. Hyperinsulinemia and IR are related to hormonal disorders, inflammation processes of chronic course, infertility, receptivity changes in endometrium [29].

Regarding to the other research, visceral adiposity index is more in PCOS-patients and it positively correlates

with the disease severity (there are a negative correlation with a number of menstrual cycles per years and a positive correlation with anovulatory cycles, fasting blood glucose, oral glucose tolerant test indices, systolic blood pressure) and ovarian morphology; but there was no correlation between homeostatic model assessment for insulin resistance (HOMA-IR) and androgen concentration [30].

In patients with PCOS and metabolic syndrome who have body mass index (BMI) more than 30 kg/m² a significantly greater concentration of triglycerides and lesser amount of high-density lipoprotein cholesterol were found [27]. The following proteins play role in the pathogenesis of PCOS and IR – adipocytokines (adiponectin, visfatin, vaspin and apelin), copeptin, irisin, PAI-1 and zonulin. Also, there is a discussion about the meaning of resistin, overweight leptin, RBP4, kisspetin and ghrelin in the PCOS and IR genesis [31].

Thus, on the other hand, the prevalence of PCOS among women with and obesity is 26%. It was determined higher glucose blood level and insulin level in obese PCOS patients than in obese women without this neuroendocrine syndrome, even when PCOS individuals were younger [32].

F. Alvarez-Blasco et al. found the similar rate of PCOS among women with overweight and obesity – at the level of 28.3% [33]. Furthermore, the risk for PCOS development is greater in women with overweight (odds ratio (OR) 3.80, 95% confidence interval (CI) 2.87-5.03), obesity (OR 4.99, CI 3.74-6.67), and central obesity (OR 2.93, 2.08-4.12). The probability for PCOS development is associated for every standard deviation in increased BMI (4.8 kg/m²) in 2.76 (CI 2.27-3.35) times [22]. Additionally, there are the following associations with PCOS – genetically determined body fat percentage (OR 3.05, CI 2.24-4.15), whole body fat mass (OR 6.98, CI 2.02-24.13), fasting serum insulin (OR 6.98, CI 2.02-24.13), hormone-binding globulin concentration (OR 0.74, CI 0.64-0.87) [22].

It was found that the higher prevalence for diabetes in PCOS patients compared to controls – 12.9 and 4.9 per 1,000 person-years, respectively [34]. Even younger PCOS women have increased T2DM risk [35]. PCOS women have a 2.6-fold elevated risk of gestational diabetes [36]. There is a more risk for T2DM in women with PCOS than in persons without PCOS (relative risk (RR) 3.45, 95% CI 2.95-4.05, p<0.001). The risk of T2DM development in PCOS patients also depended from the BMI. In obese PCOS women the RR was 3.24 (95% CI 2.25-4.65; p<0.001) compared to healthy obese persons, in non-obese PCOS individuals – 1.62 (95% CI 0.14-18.50; p=0.70) compared to healthy non-obese subjects [37].

Recently, the role of the central nervous system is also actual for the PCOS development. Changes in the central nervous system in patients with PCOS can be related to those that are in persons with depression, bipolar disorder, type 1 diabetes mellitus and the autism spectrum [38]. The research data demonstrated that waist-to-hip ratio is inversely associated with anxiety, psychoticism, hostility, psychological distress; also, inverse relationship was found between plasma testosterone concentration and trait-anger, and between total

cholesterol and hostility [39]. Psychological stress is a common feature for the patients with PCOS [40].

The score results of the Perceived Stress Scale (PSS-10) in women with PCOS were higher than in healthy persons; the main stimulators for the higher stress level can be increased BMI, hirsutism and a higher age; for the chronic stress the role of prolactin concentration is important [41]. Also, the patients with PCOS are more sensitive to stress [42, 43].

Very often the PCOS patients feel depression and anxiety [44]. It was determined that women with PCOS have higher levels of depression, anxiety because of the low ego-resiliency compared to the healthy persons [45]. Also, the level of sadness was established to be higher in these patients [46]. The results of D. Glintborg et al. research, in which the scientists learn the rate of depression using the data of Danish National register in which 25203 Danish women with PCOS and age-matched control subjects (n=112 414) were included, found that there is a 40% increased risk of depression in women with PCOS compared to controls (hazard ratio 1.42 (95% CI 1.38; 1.47)) [47].

The regression analyses have determined that such additional factors as diabetes, medical comorbidity, infertility, hormonal contraception, and low family income were important indicators of depression [47].

The contribution of the microbiota in the development and course of various gynecological diseases was studied by a number of scientists [14, 48–50]. Nowadays a great attention is to the meaning of vaginal and gut microbiota in PCOS course [51, 52]. Gut microbiota influences of the development and course of PCOS and other diseases that can be associated with coronary pathology, obesity, T2DM. Mostly researches about the influence of gut microbiota on PCOS are related on animal models [53]. The experiment on mice models demonstrated that lactic acid bacteria decrease the severity of PCOS symptoms [54]. When studying the role of gut microbiota on letrozole-induced PCOS mice model it was determined that gut microbiota disbalance may have a meaning in the progression of PCOS [55].

So, there is a close relations and correlations between intestinal bacteria and indicators of blood glucose, blood lipids, steroid hormones, and oxidative stress in PCOS mice models [56]. The concentrations of Gemmiger, Flexispira та Eubacterium are meaningly higher in PCOS patients and letrozole-induced PCOS mice model [57]. Also, it was established that PCOS rats have the lower Lactobacillus, Ruminococcus and Clostridium and higher amount of Prevotella compared to control rats. The treatment of them with Lactobacillus and fecal microbiota transplantation revealed the normalization the estrous cycles, androgen biosynthesis and the amount of Lactobacillus, Clostridium and Prevotella [58].

It was found the dysbiosis of gut microbiota in PCOS women are similar that in persons with high low-density lipoprotein cholesterol [59]. The study of A. Babu et al. confirmed that the influence of gut microbiota on the PCOS development and course can be associated with lipopolysaccharides, bile acids, carbohydrates, short-chain fatty acids and others [60]. It is considered that gut microbiota act through homeostasis, regulation of lipid and glucose levels on the PCOS course [53].

The researches showed that there is gut dysbiosis in PCOS patients, “which might be characterized by the reduction of short-chain fatty acid-producing and bile-acid-metabolizing bacteria, suggests a shift in balance to favor pro-inflammatory rather than anti-inflammatory bacteria” [51].

P. J. Torres et al. found that low α diversity by PCOS which was negatively correlated with hyperandrogenism, total testosterone and hirsutism [61]. The similar results were presented by M. Insenser et al. The scientists found lower α diversity in PCOS women, and low β was determined in obese PCOS women; increased abundance of Catenibacterium and Kandleria genera was also established by PCOS [62]. Another study confirmed the high diversity of Bacteroidetes in PCOS women and patients with visceral obesity, it was established that Prevotella, Magamonas and Dialister genera positively associated with metabolic parameters ($p<0.05$), while low abundance of Phascolarctobacterium and Neisseria genera – negatively correlated [63].

PCOS women have increased amount of Bacteroidaceae and decreased Prevotellaceae the changes of which were more expressed in the case of IR presence compared to the control subjects. Additionally, high amount of Bacteroidaceae was positively correlated with IR, sex hormones, inflammation, and low Prevotellaceae – negatively one [64]. The results of PICRUST found the significant deviations in 73 pathways of gut microbiota in PCOS women.

The data of other research showed that the most considerable changes in PCOS women are related to such microorganisms as Bacteroidaceae, Coprococcus, Bacteroides, Prevotella, Lactobacillus, Parabacteroides, Escherichia/Shigella, and Faecalibacterium prausnitzii [65]. The most expressed changes were connected with Actinomycetaceae, Enterobacteriaceae and Streptococcaceae [59].

It was determined that “genera Streptococcus (odds ratio (OR)=1.52, 95% confidence interval (CI):1.13-2.06, $P=0.006$) and RuminococcaceaeUCG005 (OR=1.39, 95%CI: 1.04-1.86, $P=0.028$) were associated with a high risk of PCOS, while Sellimonas (OR=0.69, 95% CI:0.58-0.83, $P=0.0001$) and RuminococcaceaeUCG011(OR=0.76, 95% CI:0.60-0.95, $P=0.017$) were linked to a low PCOS risk. The genus Coprococcus (OR=1.20, 95% CI 1.01-1.43, $P=0.039$) was correlated with an increased risk of female infertility, while Ruminococcus torques (OR=0.69, 95%CI: 0.54-0.88, $P=0.002$) were negatively associated with the risk of female infertility. The genera Olsenella (OR=1.11, 95% CI:1.01-1.22, $P=0.036$), Anaerotruncus (OR= 1.25, 95% CI:1.03-1.53, $P=0.025$), and Oscillospira (OR= 1.21, 95% CI:1.01-1.46, $P=0.035$) were linked to a high risk of endometriosis” [66].

The research of K. Chen et al. presented the reduced gut microbiota diversity and richness in PCOS patients compared to the controls, in particular reduced Basidiomycota and increased Ascomycota [67].

The results of 19 human observational studies (617 women with PCOS and 439 healthy persons) revealed that in PCOS patients there is alpha diversity of gut microbiota (relative abundance of Bacteroidaceae), though there were no statistical differences in Actinobacteria,

Bacteroidetes, Firmicutes, Proteobacteria, Alcaligenaceae, Bifidobacteriaceae, Clostridiaceae, Enterobacteriaceae, Lachnospiraceae, Prevotellaceae, Ruminococcaceae, Veillonellaceae, Bacteroides, Bifidobacterium, Blautia, Dialister, Escherichia-Shigella, Faecalibacterium, Lachnoclostridium, Lachnospira, Megamonas, Phascolarctobacterium, Prevotella, Roseburia, and Subdoligranulum [68].

The rate of bacterial vaginitis (15.7%) and vulvo-vaginal candidiasis (13.5%) was more in PCOS women compared to healthy ones ($p < 0.05$) [69]. The significant association of presence of acanthosis nigricans, intermenstrual bleeding, pregnancy history, testosterone level and anti-müllerian hormone level was found with vaginal microbiota, no association was determined with manifestations of PCOS, such as obesity and acne, with the vaginal microbiome [69].

The results of literature search in PubMed of the authors Y. Gu et al. allowed to conclude that in PCOS patients compared to healthy persons there is a reduction of Lactobacillus and increased of Chlamydia trachomatis and Prevotella in vagina and the changes of gut microbiota are connected with the α and β diversity [70]. Another study showed that in PCOS patients there is a lower relative abundance of Lactobacillus crispatus ($P=0.001$), and a higher the relative abundance of Mycoplasma and Prevotella was higher than controls ($P < 0.001$, $P=0.002$, respectively) [71].

Also, different associations of Lactobacilli were determined according to their species – the concentration of Lactobacillus crispatus was higher ($P=0.010$) while that of Lactobacillus iners was lower ($P=0.036$) among PCOS patients with increased testosterone blood amount [69].

The results of cross-sectional study of 713 PCOS women showed higher β diversity and intra-group variability, Gardnerella vaginalis, Ureaplasma (5.1% versus 3.3%, false discovery rate (FDR)=0.006; 1.2% versus 0.6%, FDR=0.002, respectively) while the proportion of Lactobacillus decreased (85.1% versus 89.3%, FDR=0.02) [72].

A positive correlation was found between L. acidophilus with serum levels of anti-müllerian hormone, and triglyceride ($P=2.01E-05$, $P=0.004$, respectively), G. vaginalis and serum levels of anti-müllerian hormone, estradiol and progesterone ($P=0.004$, $P=0.005$, $P=0.03$, respectively); a negative correlation – between P. buccalis and serum levels of anti-müllerian hormone and testosterone ($P=0.002$, $P=0.003$, respectively). According to the results of meta-analysis which included 20 studies Actinomyces (ORIVW=1.369, FDR=0.040), Streptococcus (odds ratio inverse-variance weighted (ORIVW)=1.548, FDR=0.027), and Ruminococcaceae UCG-005 (ORIVW=1.488, FDR=0.028) were identified as risk factors for PCOS. Conversely, Candidatus Soleiferrea (ORIVW=0.723, FDR=0.040), Dorea (ORIVW=0.580, FDR=0.032), and Ruminococcaceae UCG-011 (ORIVW=0.732, FDR=0.030) were found to be protective factors against PCOS [52].

Recently, the use of the supplements with gut or vaginal microbiota is one of the treatment approaches for gynecological disease which are caused by vaginal microbiota dysbalance including endometriosis and PCOS [73].

The results of 9 meta-analysis researches demonstrated that additional probiotic use leads to significant decrease of HOMA-IR ($p=0.03$, moderate certainty) and fasting glucose concentration ($p=0.03$, low certainty). Also, positive results of certainly low or very low evidence for probiotic supplements was found for glycemic control, lipid profile, hormonal levels, waist/hip circumference, fasting glucose concentration, dehydroepiandrosterone sulfate concentration, high-sensitivity C-reactive protein, and hirsutism score [74]. On the other hand, PCOS influence negatively on gut microbiota functions and in a such way can impairment the disease course [75].

Thus, PCOS is a complex problem which includes different mechanisms. The main pathogenetic links are closely connected with each other. That is why multimodal approaches for study of PCOS and for management of the patients with PCOS are extremely important.

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