New about the etiology and pathogenesis of polycystic ovary syndrome

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Abstract. The article provides modern views on the etiological and pathogenetic factors of polycystic ovary syndrome and reviews the results of the latest research in this area. Based on the study, recommendations have been developed for the timely diagnosis and successful treatment of this disease.

Purpose: present a modern point of view on the etiology and pathogenesis of polycystic ovary syndrome, generalize knowledge about this syndrome and develop a list of recommendations for timely diagnosis and successful therapy.

Materials and methods. The analysis and generalization of modern medical literature of electronic library systems Elibrary.ru, Cochrane, Medline, PubMed, HINARY are carried out.

Keywords: polycystic ovary syndrome, infertility, polycystic disease, reproductive disorder, genetic predisposition

Introduction

Relevance of the topic. Polycystic ovary syndrome (PCOS) is a widespread reproductive disorder accompanied by dysfunction of the ovaries and affecting various metabolic processes in the body [1]. The prevalence of polycystic ovary syndrome (PCOS) is high: according to various authors, in the general population it ranges from 5 to 10%, and in obese women it reaches 30% [2]. However, the fact made public by Australian researchers is even more alarming: two out of every three patients simply do not know about their diagnosis, that is, the real incidence can reach 21% and higher. Meanwhile, medical care for women with PCOS is necessary from a very young age [3].

PCOS is manifested by menstrual irregularities, hirsutism, alopecia, hyperinsulinemia, disorders of carbohydrate and lipid metabolism, obesity, insulin resistance, mental disorders,

infertility and is currently one of the leading causes of menstrual complications and infertility in women [4, 5].

The contribution of the syndrome to a decrease in reproductive function is impressive: PCOS is guilty of infertility in every third infertile woman, and on this basis, Stein-Leventhal syndrome is a serious competitor to endometriosis. [2].

Since the time of I. Stein and M. Leventhal, who in 1935 for the first time gave a clear description of polycystic ovary syndrome (PCOS), issues related to the etiology and pathogenesis of ovarian hyperandrogenic syndrome of non-tumor genesis have not lost their relevance [5].

Modern international diagnostic criteria include the following features:

1) signs of polycystic ovaries according to the ultrasound examination of the small pelvis (the presence of more than 10 follicles in each ovary);

2) oligo- or anovulation;

3) clinical (presence of hirsutism) or biochemical (increased androgen levels) manifestations of ovarian hyperandrogenism [6, 7].

These criteria were established by the Rotterdam Consensus in 2003. According to this document, the presence of 2 of the 3 above criteria allows for the diagnosis of PCOS [8].

Etiology of PCOS

Despite intensive clinical and experimental research in the field of PCOS, the mechanisms, issues of etiology and pathogenesis underlying the formation of this pathology and chronic anovulation are still insufficiently studied and debatable, which indicates a multifactorial etiology and the lack of a single view of this pathology, which is very difficult for diagnosis and treatment [8]. Many factors are involved in the pathogenesis of PCOS: genetic, endocrine, and environmental factors.

Genetic predisposition is of great importance in the etiology of PCOS [9]. The patterns of genetic transmission of this disease have not been completely studied, the nature of inheritance is assumed, but, taking into account the clinical and laboratory heterogeneity, research data show that PCOS most likely has a polygenic or multifactorial type of inheritance [5]. It has been proven that PCOS is a polygenic and multifactorial syndromic disease [10]. Many genes associated with PCOS directly or indirectly affect fertility [11]. The genetic factor is detected in 70% of PCOS cases [12].

Candidate genes can be combined into pathogenetic groups:

1) genes involved in the synthesis and action of steroid hormones;

2) genes responsible for the synthesis and regulation of pituitary hormones;

3) genes responsible for the synthesis and effects of insulin;

4) genes that regulate body weight;

5) genes encoding inflammatory mediators;
6) genes of the major histocompatibility complex [5].

Recently, in the pathogenesis of PCOS, special attention has been paid to insulin resistance, because in patients with PCOS, insulin resistance is detected 2-3 times more often than in the population [8]. Also, in the pathogenesis, an important role is played by obesity and the production of leptin [13].

According to the data of many years of research, it has been shown that the development of polycystic ovary syndrome (PCOS) can be influenced by various environmental factors, namely: a low socioeconomic level and an unhealthy lifestyle, but a genetic predisposition is of particular importance in the etiopathogenesis of PCOS [5].

Pathogenesis of PCOS

Over the long history of the study of PCOS, many different theories about its pathophysiology have been put forward, and it is still too early to put an end to the research, but even based on the data already available, the pathogenesis of PCOS seems to be extremely complex. Nevertheless, it is possible to formulate a list of the most studied and endocrinological and metabolic disorders in this disease.

Basically, there are three leading reasons for the formation of this syndrome:

1) "failure" of the feedback of neurohumoral regulation of the reproductive axis (hypothalamic-pituitary-ovarian system) [14]. Primary damage to the hypothalamic production of gonadotropin-releasing hormone (GnRH) increases the production of luteinizing hormone (LH) and reduces the formation of follicle-stimulating hormone (FSH) [1];

2) metabolic disorders that lead to insulin resistance (IR) and hyperinsulinemia (HI). It is well known that IR and HI play an important role in the development of hyperandrogenism and ovulatory dysfunction in PCOS. At the same time, an increased level of insulin increases the secretion of GnRH, which leads to disruption of the action of LH and FSH [15, 16, 17, 18];

3) enzymatic disorders of steroidogenesis, which increase the synthesis of androgens [8].

New in the pathogenesis of PCOS

The latest research from 2020-21 has identified new factors that can presumably influence the development of PCOS.

For example, in a number of works it was described that PCOS has genetically different reproductive and metabolic subtypes [10, 19].

In an attempt to find new etiological factors, scientists have found that adverse changes in the composition of the gut microbiome are present even in adolescents with PCOS, whether or not

they are obese. A relationship has been established between the gastrointestinal microbiome and metabolic disorders such as obesity, type II diabetes mellitus and PCOS [20, 21].

Based on the results of the work carried out, it was not possible to form a consensus as to which bacterial taxa are most relevant for this disease, however, for the first time, an increase in the species of bacteria producing γ-aminobutyric acid was found in these patients, which positively correlated with serum LH levels and the ratio of LH to FSH [10].

Currently, data have been obtained indicating the association of vitamin D balance with the pathogenesis, signs and symptoms of PCOS [22, 23]. Vitamin D receptors and enzymes that metabolize it are found in almost all tissues of the human body, including the organs of the reproductive system [23]. In women, vitamin D imbalance is associated with ovulatory dysfunction, insulin resistance, and hyperandrogenism [2].

In a small experiment (n=57), Austrian researchers demonstrated that vitamin D treatment can improve glucose metabolism and normalize the menstrual cycle in women with PCOS [22].

Another study showed that PCOS increases ovarian blood flow and, presumably, the blood supply to follicles in ovarian tissue. It is hypothesized that abnormal angiogenesis may disrupt the maturation of the preovulatory follicle, inhibit ovulation, and promote cyst formation. [2] Recent studies have identified several types of ovarian angiogenesis abnormalities in PCOS, in which the blood supply to the ovaries and, possibly, the supply of nutrients, oxygen and hormones to the follicles are impaired [24]. The authors suggest that these vascular disorders may be responsible for anovulation and cyst formation, considering the restoration of normal angiogenesis as a promising approach to the treatment of PCOS [25].

Research results

Summarizing the main modern ideas about this syndrome, it can be noted that PCOS is a multifactorial pathology, genetically determined, in the pathogenesis of which the central mechanisms of the gonadotropic function of the pituitary gland (from puberty), local ovarian factors, extraovarian endocrine and metabolic disorders that determine the clinical symptoms and morphological changes in the ovaries [26].

To reduce the risks and the possibility of complications, first of all, it is necessary to timely identify the signs of the disease and start therapy. It is necessary to conduct a thorough examination of girls of puberty to identify the first symptoms of the disease [13, 27]. In order to exclude the possibility of untimely diagnosis of polycystic ovary syndrome, it is recommended:

1) Conduct thorough preventive examinations of schoolgirls 16 and 17 years old;
2) Conduct regular preventive conversations with adolescent girls;
3) Conduct educational activities with parents;

4) To popularize the relevance of the topic of maintaining reproductive health, starting from puberty.

In order for PCOS therapy to be most successful, it is recommended:

1. The diagnosis is established according to the Rotterdam criteria;
2. At each visit, determine the body mass index, measure the waist circumference and blood pressure;
3. Assess metabolic and other risk factors for cardiovascular diseases (dyslipidemia, obesity, impaired glucose tolerance, type 2 diabetes mellitus, smoking, low physical activity, high blood pressure);
4. To study the socio-economic status of patients, their lifestyle and dietary habits;
5. Inform women about the importance of lifestyle modification, giving up bad habits;
6. Analyze the psychoemotional state of patients;
7. Conduct differential diagnostics.

References

1. Guriev, T.D. Polycystic ovary syndrome / T.D. Guriev // Obstetrics, gynecology and reproduction. – 2010. – V. 4. – № 2. – P. 10-15.
2. Gustovarova, T.A. Syndrome with many unknowns / T.A. Gustovarova, Y.A. Bril // StatusPraesens. Gynecology, obstetrics, sterile marriage. – 2018. – № 4(49). – P. 51-57.
3. Ellis E., Gibson-Helm M., Boyle J.A. Polycystic ovary syndrome
4. Ziganshin, AM Clinical manifestations of polycystic ovary syndrome / AM Ziganshin, Yu. I. Gaisina, GR Galyautdinova // Medical Bulletin of Bashkortostan. – 2019. – V. 14. – № 1(79). – P. 77-81.
5. Modern ideas about the pathogenesis of polycystic ovary syndrome (literature review) / OV Panarina, MA Rashidova, LV Belenkaya [et al.] // Acta Biomedica Scientifica (East Siberian Biomedical Journal). – 2017. – V. 2. – № 4(116). – P. 9-14.
6. Rotterdam ESHRE/ASRM-Sponsored Consensus Workshop Group. (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Hum. Reprod.*, 19 (1), 41-47.
7. Zawadzki J, Duniaf A, Givens JR, et al. (1992). Polycystic ovary syndrome. *Blackwell Scientific Publications,* 377-384.
8. Zhylkichieva, Ch. S. Polycystic ovary syndrome: a modern view of the problem / Ch. S. Zhylkichieva, RR Tukhvatshin, AA Askerov // Bulletin of the I.K. Akhunbaev KSMA – 2016. – № 6. – P. 47-52.

9. Polycystic ovary syndrome at reproductive age: modern views on pathogenesis and clinical manifestations / O.V. Paramonova, EG Korenskaya, A. P. Trofimenko [et al.] // Problems of women's health. – 2013. – V. 8. – № 2. – P. 74-80.
10. Artymuk, N.V. New about the pathogenesis and treatment of polycystic ovary syndrome / NV Artymuk, O.A. Tachkova // RMJ. Mother and child. – 2021. – V. 4. – № 1. – P. 17-22. – DOI 10.32364/2618-8430-2021-4-1-17-22.
11. Mykhalchenko K., Lizneva D., Trofimova T. et al. Genetics of polycystic ovary syndrome. Expert Rev Mol Diagn. 2017;17(7):723–733. DOI: 10.1080/14737159.2017.1340833.
12. Khan M.J., Ullah A., Basit S. Genetic Basis of Polycystic Ovary Syndrome (PCOS): Current Perspectives. Appl Clin Genet. 2019;12:249–260. DOI: 10.2147/TACG.S200341.
13. Ilizarova, N. A. Missed diagnosis / N. A. Ilizarova // StatusPraesens. Gynecology, obstetrics, sterile marriage. – 2016. – № 4(33). – P. 75-83.
14. In the loop of metabolic risk / M.B. Khamoshina, A.A. Epishkina-Minin, V.A. Ryabova [et al.] // StatusPraesens. Gynecology, obstetrics, sterile marriage. – 2020. – № 4(69). – P. 35-41.
15. The use of metformin in polycystic ovary syndrome / T.A. Zykova, G.A. Melnichenko, A.V. Strelkova [et al] // Problems of endocrinology. – 2004. – V. 50. – № 1. – P. 34-40. – DOI 10.14341
16. Pathophysiological aspects of the formation of insulin resistance in women with polycystic ovary syndrome / A. N. Taits, I. N. Vorobtsova, L. V. Kurdynko [et al] // Medicine: theory and practice. – 2018. – V. 3. – № 2. – P. 19-25.
17. Pathophysiological aspects of the formation of insulin resistance in women with polycystic ovary syndrome / A. N. Taits, I. N. Vorobtsova, L. V. Kurdynko [et al] // Medicine: theory and practice. – 2018. – V. 3. – № 2. – P. 19-25.
18. Rasin, M.S. Systemic inflammation and insulin resistance in the pathogenesis of polycystic ovary syndrome / M.S. Rasin, V.P. Zhitnik // Obstetrics and gynecology. – 2015. – № 8. – P. 26-32.
19. Dapas M., Lin F.T.J., Nadkarni G.N. et al. Distinct subtypes of polycystic ovary syndrome with novel genetic associations: An unsupervised, phenotypic clustering analysis. PLoS Med. 2020;17(6):e1003132. DOI: 10.1371/journal.pmed.1003132.
20. Jobira B., Frank D.N., Pyle L. et al. Obese adolescents with PCOS have altered biodiversity and relative abundance in gastrointestinal

microbiota. J Clin Endocrinol Metab. 2020;105(6):e2134–e2144. DOI: 10.1210/clinem/dgz263.

21. Guo J., Shao J., Yang Y. et al. Gut microbiota in patients with polycystic ovary syndrome: a systematic review. Reprod Sci. 2021 Jan 6. DOI: 10.1007/ s43032-020-00430-0. Online ahead of print
22. Wehr E., Pieber T.R., Obermayer-Pietsch B. Effect of vitamin D3 treatment on glucose metabolism and menstrual frequency in polycystic ovary syndrome women: A pilot study // J. Endocrinol. Invest. 2011. V. 34. №10. P. 757–763. [PMID: 21613813]]
23. Trummer C., Pilz S., Schwetz V. et al. Vitamin D, PCOS and androgens in men: A systematic review // Endocr. Connect. 2018. V. 7. №3. P. R95–R113. [PMID: 29449314]
24. Di Pietro M., Pascuali N., Parborell F. et al. Ovarian angiogenesis in polycystic ovary syndrome // Reproduction. 2018. V. 155. №5. P. R199–R209. [PMID: 29386378]
25. Alcazar J.L., Kudla M.J. Ovarian stromal vessels assessed by spatiotemporal image correlation-high definition flow in women with polycystic ovary syndrome: A case-control study // Ultrasound Obstet. Gynecol. 2012. V. 40. P. 470–475. [PMID: 28656781]
26. Ibragimova, N.S. Polycystic ovary syndrome: main points / N.S. Ibragimova, B.F. Ibragimov, M. A.K. Mamadierova // Bulletin of Science and Education. – 2021. – № 2-2(105). – P. 69-71.
27. Patent № 2592235 C1 Russian Federation, IPC G01N 33/48. Method for differential diagnosis of ovarian and adrenal hyperandrogenism in adolescent girls: № 2015126820/15: Appl. 03.07.2015: publ. 07/20/2016 / A. V. Moskovkina, V. A. Linde, O. Z. Puzikova [et al]; applicant Federal State Budgetary Institution "Rostov Research Institute of Obstetrics and Pediatrics" of the Ministry of Health of the Russian Federation.
28. Patent № 2116053 C1 Russian Federation, IPC A61B 17/42, A61K 31/56, G01N 21/76. Method for restoring reproductive function in women with polycystic ovary syndrome: № 95121708/14: Appl. 12/22/1995: publ. 07/27/1998 / V. I. Orlov, T. N. Pogorelova, L. V. Kaushanskaya [et al]; applicant Rostov Research Institute of Obstetrics and Pediatrics.
29. Patent № 2237491 C1 Russian Federation, IPC A61K 38/21, A61P 15/08. Method for the treatment of infertility due to hyperandrogenism and hyperprolactinemia: № 2003126845/14: Appl. 01.09.2003: publ. 10.10.2004 / V. B. Tskhai, M. V. Yamanova, I. I. Evdochenko; applicant Krasnoyarsk State Medical Academy.
30. Rotterdam ESHRE/ASRM-Sponsored Consensus Workshop Group. (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Hum. Reprod.*, 19 (1), 41-47.

31. Pathogenetic aspects of metabolic syndrome in women of reproductive age (literature review) / N.D. Kastueva, T.I. Tsidaeva, Z.F. Belikova, L.V. Maisuradze // Kuban Scientific Medical Bulletin. – 2019. – V. 26. – № 2. – P. 162-172. – DOI 10.25207/1608-6228-2019-26-2-162-172.