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The treatment of polycystic ovary syndrome and systematization of knowledge - literature review

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ASBTRACT

Polycystic ovary syndrome (PCOS) is a known disease among endocrinologists and gynecologists. The aforementioned disease entity affects up to six to twelve percent of women of reproductive age. ¹ In 2017, the incidence among women of childbearing age was

¹ Skiba MA, Islam RM, Bell RJ, Davis SR. Understanding Variation in Prevalence Estimates of Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. *Hum Reprod Update*

82.44 per 100,000 population. A decade ago, it was 1.45% lower.² PCOS is a disease in which we have abnormal hormone levels. The result may be a problem with regular menstruation, problems with becoming pregnant, acne or excessive body weight.³ Most often, patients are diagnosed only when complications occur. It is closely related to a significant reduction in living standards. There are problems such as hair loss, acne and infertility.

⁴ In this literature review, we present current treatments for polycystic ovary syndrome based on the latest guidelines. The area of our interest is the use of metformin in the treatment of hyperinsulinemia and after-effects, clomiphene citrate to stimulate ovulation, alleviation of symptoms PCOS with hormone replacement therapy, behavioral changes and diet treatment.

Keywords: PCOS treatment; lifestyle change, diet, metformin, clomiphene citrate, Hormone Replacement Therapy

Introduction

Polycystic ovary syndrome is an endocrine and metabolic disorder that affects women of childbearing age.⁵ This disease was first described by two gynecologists, Irving Stein and Michael Leventhal in 1935. For this reason, its original name was the Stein-Leventhal syndrome.⁶ The 2018 evidence-based guidelines for the evaluation and treatment of polycystic ovary syndrome are currently in use. The authors of this document support the ESHRE or ASRM criteria published in 2003 in Rotterdam.

- two clinical and / or biochemical markers of hyperandrogenism
- oligo - or anovulation

(2018) 24:694–709.

² Liu, J. *et al.* Measuring the global disease burden of polycystic ovary syndrome in 194 countries: Global Burden of Disease Study 2017. *Hum Reprod.* 36(4), 1108–1119 (2021).

³ Bani Mohammad, M. & Majdi, S. A. Polycystic ovary syndrome (PCOS), diagnostic criteria, and AMH. *Asian Pac. J. Cancer Prev.* 18(1), 17–21 (2017).

⁴ Azziz, R. *et al.* The prevalence and features of the polycystic ovary syndrome in an unselected population. *J. Clin. Endocrinol. Metab.* 89(6), 2745–2749 (2004).

⁵ Yuanyuan Gu 1 2, Guannan Zhou 2 3, Fangyue Zhou 4, Qiongwei Wu 1, Chengbin Ma 1, Yi Zhang 1, Jingxin Ding 2 3, Keqin Hua 2 3 ; Life Modifications and PCOS: Old Story But New Tales ; *Front Endocrinol (Lausanne)*. 2022 Apr 13;13:808898. doi: 10.3389/fendo.2022.808898. eCollection 2022.

⁶ <https://emedicine.medscape.com/article/404754-overview>

- polycystic ovaries on ultrasound ⁷

In this disease, the diagnosis is based on the exclusion of other diseases with similar symptoms, such as Cushing's syndrome, hyperprolactinaemia, hypothyroidism or hyperthyroidism, acromegaly, and androgen-secreting tumors. ⁸ Due to the presence of a wide variety of clinical symptoms and inconsistent clinical picture of patients, the current diagnostic criteria are not fully clear. There are still studies modifying these recommendations. The exact pathogenesis of PCOS has not been elucidated. ⁹ There are 3 pathophysiological models: 1. gonadotropic model in which LH secretion and FSH biological activity are disturbed 2. ovarian model in which androgen synthesis and metabolism in the ovary are disturbed 3. insulin-dependent model - disturbance of insulin secretion and activity.

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Method

review of the recent literature based on PubMed, Google scholar research based on the following key words: polycystic ovary syndrome, treatment of polycystic ovary syndrome, recommendations of PCOS

Purpose of the work

systematization of information on the treatment of polycystic ovary syndrome based on the latest research and findings

Keywords: PCOS treatment; lifestyle change, diet, metformin, clomiphene citrate, Hormone Replacement Therapy

⁷ International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018; Helena Teede, Marie Misso, Michael Costello, Anuja Dokras, Joop Laven, Lisa Moran, Terhi Piltonen and Robert Norman on behalf of the International PCOS Network in collaboration with funding, partner and collaborating organisations, 2018: 18-36

⁸ Krzysztof Katulski, Adam Czyżyk, Błażej Męczałski; Hiperandrogenizacja i zespół policystycznych jajników; Ginekologia Grzegorz H. Bręborowicz; Wydawnictwo Lekarskie, Warszawa 2020, Wydanie III - 4 dodruk Warszawa 2021 - 196-202

⁹ Agnieszka Drosdzol-Cop, Agata Sidło-Stawowy, Dominika Sajdak, Violetta Skrzypulec-Plinta; Diagnosing polycystic ovary syndrome in adolescent girl; Ginekol Pol. 2014, 85, 145-148

¹⁰ Radomski D. Orzechowska A., Barcz E. ; Współczesne koncepcje etiopatogenezy zespołu policystycznych jajników; Ginekol Pol. 2007; 78, 393-399

State of knowledge

There is no easy treatment to address the underlying cause in the treatment of PCOS. For this reason, the treatment relieves symptoms. The most commonly used drug is metformin to treat insulin resistance. Another equally common option is to change your current lifestyle to a healthier one. Choosing the treatment is quite difficult. Be careful when choosing drugs, as some may be disadvantageous. For example, the use of contraceptives may suppress ovulation and anti-androgenic drugs may have a teratogenic effect on the fetus.

Accordingly, two lines are used in the treatment. In the case of anovulation, infertility drugs are used. On the other hand, when the patient has a chronic problem with the previously mentioned symptoms or with one of them, the treatment consists in counteracting and exacerbating them.¹¹

Siew S Lim from Monash University, Monash Center for Health Research and Implementation, School of Public Health and Preventive Medicine and co-authors studied the influence of lifestyle on the development of PCOS. They argue that maintaining a healthy body weight through exercise, dietary changes, and behavioral changes should be considered as the first step in PCOS treatment.¹²

A systematic review described 20 studies involving 894 women with PCOS and 574 women without PCOS, a lower level of ghrelin in PCOS was noted (standardized mean difference -0.40; 95% confidence interval -0.73, -0.08). It is associated with the disturbance of the feeling of hunger and satiety in PCOS patients as well as inadequate functioning of the intestinal hormones.¹³ In addition, women with PCOS feel hungry and unsatisfied much faster after eating a meal. Which also speaks for the above.¹⁴ There are also studies that have

¹¹ Richard S Legro, M.D. Department of Obstetrics and Gynecology, Penn State College of Medicine, 500 University Drive, Hershey, PA, USA; Evaluation and Treatment of Polycystic Ovary Syndrome; Feingold KR, Anawalt B, Boyce A, et al., editors. South Dartmouth (MA): MDText.com, Inc.; 2000-.

¹² Tracy Williams 1, Rami Mortada 2, Samuel Porter; Diagnosis and Treatment of Polycystic Ovary Syndrome; Am Fam Physician 2016 Jul 15;94(2):106-13.

¹³ Gao T, Wu L, Chang F, Cao G. Low circulating ghrelin levels in women with polycystic ovary syndrome: a systematic review and meta-analysis. Endocr J. 2016;63(1):93–100

¹⁴ Moran LJ, Noakes M, Clifton PM, Wittert G, Tomlinson L, Galletly C, Luscombe N, Norman RJ. Ghrelin i miary sytości są zmienione w zespole policystycznych jajników, ale nie mają na nie wpływu skład diety. Asia Pac J Clin Nutr. 2003;12:S52.

examined the levels of postprandial cholecystokinin and GLP-1. In the case of GLP-1, regardless of whether it was before or after eating, its level decreased. A similar correlation occurs with cholecystokinin. Such observations allow for the suspicion of coexistence of obesity with PCOS. For this reason, patient education is important.

¹⁵ ¹⁶ The diet should be based on the appropriate caloric requirements and the selection of products with a low glycemic index.

It is also important to remember about vitamin D and inositol supplementation. The metabolism of carbohydrates is significantly improved. Patients have better insulin resistance scores. It is easier to lose unnecessary kilograms of body weight. Most importantly, they help maintain ovulation and this allows you to get pregnant. Diet is very important, but exercise should not be forgotten. The most important thing is to choose them correctly to the patient's abilities and willingness in balance with the needs. ¹⁷

The primary factor in PCOS is insulin resistance, which leads to hyperinsulinemia, so consideration has been given to using metformin for treatment. It works by lowering insulin levels. Insulin stimulates the production of androgens, which results in an increase in the concentration of free testosterone, and this is manifested by clinical symptoms. Therefore, it has been proven that the biguanide derivative, i.e. the mentioned metformin, in addition to its hypoglycaemic effect, also reduces the concentration of LH and testosterone. ¹⁸ ¹⁹In the study, Fleming et al. Studied 94 patients, 47 of whom received placebo and 45 received metformin. 2 patients were not enrolled in the study. They examined ovarian function in women with infrequent menstruation consuming metformin. Number of weeks in which ovulation has been to weeks in which it has been ovulation is an indicator of ovulation. It was significantly higher $p < 0.01$ in treated women compared to placebo treated women. The time to ovulation was shorter, $p < 0.05$ in women taking the drug.

¹⁵ Lin T, Li S, Xu H, Zhou H, Feng R, Liu W, Sun Y, Ma J. Wydzielanie hormonów żołądkowo-jelitowych u kobiet z zespołem policystycznych jajników: badanie obserwacyjne. *Reprodukcja szumu*. 2015;30(11):2639–44.

¹⁶ Aydin K, Arusoglu G, Koksall G, Cinar N, Aksoy DY, Yildiz BO. Glukagonopodobny peptyd 1 na czczo i po posiłku oraz doustna antykoncepcja w zespole policystycznych jajników. *Clin Endocrinol*. 2014;81(4):588–92.

¹⁷ Magdalena Smyka ¹, Barbara Grzechocińska ¹, Mirosław Wielgos ¹; The role of lifestyle changes in the treatment of polycystic ovary syndrome; *Neuro Endocrinol Lett*. 2018 Feb;38(8):521-527.

¹⁸ Krysiak R, Okopief B, Gdula-Dymek A, [et al.]. Update on the management of polycystic ovary syndrome. *Pharmacol Rep*. 2006, 58, 614-25

¹⁹ Ehrmann D. Polycystic ovary syndrome. *N Engl J Med*. 2005, 352, 1223-1236.

The effect of metformin on follicular maturation was rapid as circulating E2 levels increased in the first week of treatment only in the metformin group.²⁰ There are also a number of other studies examining the effects of metformin in the treatment of PCOS. One of them found that patients previously treated with clomiphene respond well to treatment with metformin, insulin levels fall and they ovulate.^{21 22} It is also possible to combine clomiphene with metformin in the treatment of PCOS. The use of metformin and clomiphene as monotherapy has been studied as well as their combined administration as first-line treatment for inducing ovulation. It turned out that the combination of both drugs gave the highest rates of ovulation and live births.²³

For women for whom it is not important to become pregnant, hormone replacement therapy is possible. They reduce hyperandrogenism by increasing SHBG production and exerting negative feedback on LH.²⁴ One of the newest OCPs, which limits the growth of new terminal hair and the formation of acne, is a formula containing a combination of non-androgenic progestin, drospirenone and ethinylestradiol; therefore it is potentially ideal for treating women with PCOS.²⁵ Combined estrogen-progestogen therapy remains the dominant treatment for hirsutism and acne in PCOS.²⁶

²⁰ Fleming R, Hopkinson Z, Wallace A, [et al.]. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. *J Clin Endocrinol Metab.* 2002, 87, 569-574.

²¹ Nestler J, Jakubowicz D, Evans W, [et al.]. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med.* 1998, 338, 1876-1880.

²² Vandermolen D, Ratts V, Evans W, [et al.]. Metformin increases the ovulatory rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone. *Fertil Steril.* 2001, 75, 310-315

²³ Sujata Kar and Smriti Sanchita; Clomiphene citrate, metformin or a combination of both as the first line ovulation induction drug for Asian Indian women with polycystic ovarian syndrome: A randomized controlled trial; *J Hum Reprod Sci.* 2015 Oct-Dec; 8(4): 197–201.

²⁴ Ahmed Badawy1 and Abubaker Elnashar2 ; Treatment options for polycystic ovary syndrome ; *Int J Womens Health.* 2011; 3: 25–35.

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²⁶ Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med.* 2005;352(12):1223–1236. [PubMed] [Google Scholar]

Conclusions

Treatment of polycystic ovary syndrome should be tailored to the patient's needs and the desire to have children. When we have a patient with difficulties in maintaining an appropriate weight, we should persuade her to change her lifestyle, lose weight and eat healthy eating habits, which is the first line of treatment. Clomiphene citrate and letrozole are first-line drugs in the treatment of infertility. Metformin should be considered in patients with insulin resistance, hyperinsulinemia or metabolic syndrome. Hormone replacement therapy should be considered in patients with irregular menstruation and dermatological symptoms.²⁷ Nevertheless, more research is needed to understand the exact pathophysiology of this syndrome and to propose a specific treatment. There is currently no single test to make a diagnosis. Moreover, once a diagnosis is made, treatment options are limited as they focus only on the symptoms and not the cause. Patients with PCOS have a much higher risk of civilization diseases, therefore prospective studies are necessary.

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- 5 Yuanyuan Gu^{1,2}, Guannan Zhou^{2,3}, Fangyue Zhou⁴, Qiongwei Wu¹, Chengbin Ma¹, Yi Zhang¹, Jingxin Ding^{2,3}, Keqin Hua^{2,3} ; Life Modifications and PCOS: Old Story But New Tales ; *Front Endocrinol (Lausanne)*. 2022 Apr 13;13:808898. doi: 10.3389/fendo.2022.808898. eCollection 2022.

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