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MODERN WAYS OF TREATMENT OF METABOLIC DISORDERS IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

Alina Urbanovych* ✉, *Krystyna Kozlovska, Myroslava Urbanovych
Department of Endocrinology, Danylo Halytsky Lviv National Medical University, Ukraine

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Abstract

Article represents complex approach to PCOS problem from the position of prophylaxis and therapy of metabolic disorders, which include overweight and obesity, insulin resistance, carbohydrate and lipid metabolism deviations. Lifestyle modification specifically including healthy diet was provided as an example. Also, were described medications, which increase insulin sensitivity and method of treatment in case of 3rd class obesity.

key words: *polycystic ovarian syndrome, metabolic deviations, metformin, thiazolidinediones*

Introduction

Polycystic ovarian syndrome (PCOS) is a common illness among women of all ages from puberty to menopause. Presence of PCOS is the main reason, which leads to development of many metabolic deviations: dyslipidemia, hyperinsulinemia, insulin resistance, obesity, glucose intolerance, type 2 diabetes mellitus and cardiovascular disease, which can possibly develop and manifest in young women of active working age. Modern therapy of this syndrome must be aimed at prevention of deviations mentioned above.

PCOS can be found in 6-19 % of women of reproductive age [1]. Its characteristic symptoms are disorders of menstrual cycle, hyperandrogenism (HA), and polycystic ovarian morphology. PCOS can usually be diagnosed in an early stage of a woman's reproductive period, although its clinical manifestations are quite variable.

Clinical types of PCOS

Diagnostic criteria of PCOS have been changing throughout time. For example, in 1935 Stein and Levental described 7 women suffering from infertility, amenorrhea or anovulatory oligomenorrhea along with obesity and ovarian enlargement of polycystic character [2]. Nowadays according to Amsterdam ESHRE/ASRM published in 2012 [3] it is recommended to distinguish 4 PCOS phenotypes:

- phenotype A (classical): hyperandrogenism + anovulation + polycystic ovaries (recognizable by medical ultrasound)

✉ Department of endocrinology, Lviv National Medical University; 79010, Lviv, Pekarska str, 69, Ukraine
Phone: +380322764673; *corresponding author e-mail*: alinaur@dr.com

- phenotype B (semi classical): hyperandrogenism + anovulation (without medical ultrasound signs)
- phenotype C (ovulatory): hyperandrogenism + polycystic ovaries (recognizable by medical ultrasound)
- phenotype D (non-androgenic): anovulation + polycystic ovaries (recognizable by medical ultrasound)

Distinguishing PCOS by phenotypes helps doctor to estimate risk levels and types of possible related health issues. Thus, hyperandrogenism is more often connected with metabolic disorders, while deviations of menstrual cycle and polycystic ovaries (recognizable by medical ultrasound) are associated with infertility [1].

The purpose of the diagnostic search is to assess the severity of clinical symptoms, metabolic, cardiovascular and cancer risks, find the source and pathogenesis of androgen hyperproduction and determine the effect of the disease on the reproductive function [4]. According to the ESE recommendations from 2014, in order to ascertain treatment tactics, it is necessary to determine the phenotype of PCOS.

The main goals and methods of PCOS treatment:

Goals:

- normalization of menstrual cycle and hormonal profile
- reduction of skin manifestations of hyperandrogenism
- increase of fertility
- normalization of metabolic disorders
- reduction of cardiovascular risks factors.

Methods:

- changing patient's lifestyle by following a proper diet and having regular physical exercise;
- prescribing oral estrogen-progestogenic anti-conception combinations in order to regulate menstrual cycle and normalize androgen level, which is the first-line therapy of PCOS. Prescription of these drugs requires assessment of risk factors and possible complications according to WHO's eligibility of contraceptive methods [5];
- prescribing antiandrogens and cosmetic procedures for reduction of skin manifestations of hyperandrogenism (laser therapy and intense pulsed light);
- prescribing insulin sensitizers for reduction of insulin resistance and compensatory hyperinsulinemia;
- using vitamin D and magnesium preparations.

It is important to take into account heterogeneity of phenotypes of this syndrome and apply individual approach throughout the whole life of each female patient with PCOS.

Metabolic disorders associated with PCOS

It should be noted that along with PCOS very often comes obesity, especially its abdominal type. Although, there are no representative data on its spreading. It has now been proved that PCOS and obesity are closely interrelated, and that the presence of obesity (especially abdominal type), has a detrimental effect on the metabolism and reproductive capacity of patients with PCOS [6]. The excess of androgens contributes to the development and progression of abdominal obesity starting from an early age, which again affects insulin resistance [7]. Obesity and insulin resistance with PCOS are undoubtedly associated with high risks of developing type 2 diabetes.

It is also proved that adipose tissue in women with PCOS has abnormal morphology and function. The cause of the abnormal

structure and the function of adipose tissue in case of PCOS remain still unknown. However, such patients have hypertrophic adipocytes and impaired activity of the sympathetic nervous system in relation to adipose tissue. There are certain studies which prove conclusively that functional connections between the indicators of the state of the hypothalamo-pituitary-adrenal system and the indicators of adipose tissue function (adipocytokines) are violated even in the absence of excess body mass, which indicates the essential role of fat tissue dysfunction in pathogenesis of PCOS. Combined with the excess of fat tissue, these disorders are more pronounced. Thus, the effect on the state of adipose tissue and its restoration may affect the restoration of hormonal homeostasis in women with PCOS. It should also be noted that one of the mechanisms of deviation of normal functioning of adipose tissue is the reduction of vascularization, which leads to the development of hypoxia. In turn, this brings on development of chronic nonspecific inflammation and hypersecretion of adipocytokines, which cause progression of obesity, type 2 diabetes, dyslipidemia and cardiovascular disease [8].

Thus, in case of patients with PCOS, a great deal of attention should be paid to prevention and treatment of metabolic disorders, especially pre-obesity and obesity, insulin resistance, carbohydrate and lipid metabolism disorders.

Changing a lifestyle with following a healthy diet

First and foremost, a proper low-calorie diet with a low glycemic index should be recommended along with regular physical activity which improves psychological, reproductive and cardiovascular parameters for women with PCOS [9]. It is also important to give up smoking which increases adverse effects of the medicine prescribed for patients with PCOS; specifically, it leads to increased risks of thrombosis and endothelial dysfunction.

There is an elevated level of circulating insulin for the majority of patients with PCOS regardless of their body mass compared to healthy women with the same complexion [10]. Thus, the risk of developing hyperinsulinemia should be taken into account while planning therapeutic tactics for patients who are not overweight. The presence of adiposity in its turn is thought to cause a higher frequency of anovulatory cycles, miscarriages and other complications during late pregnancy and gestational diabetes [11]. In addition, women with adiposity and PCOS show a worse respond to induction of ovulation by clomiphene, gonadotropins or cauterization of the ovaries. In such patients it requires higher doses of drugs, which in turn increases the possibility of side effects and adverse events. Weight loss even by 5 % improves insulin sensitivity, concentration of SHBG, lowers testosterone level and can bring about normalization of menstrual cycle disorders, spontaneous ovulations and higher percentage of ovulations. Thus, while treating women with PCOS and without obesity, all efforts should be directed at obesity prevention [12].

Medicinal treatment of metabolic disorders

The golden standard of PCOS therapy is appliance of medicine that improves insulin sensitivity. Most often it is metformin which improves insulin sensitivity in the liver and peripheral tissues, lowers hyperinsulinemia and does not cause episodes of hypoglycemia. In addition, it reduces concentration of leptin and proinflammatory cytokines [13]. It also lowers concentration of proinsulin and androstenedione, especially in women with pre-obesity and obesity [14]. Metformin has an antilipolytic effect and reduces the content of free fatty acids.

According to scientific research the effect of metformin on content of atherogenic lipids is variable [15,16].

According to the results of clinical studies, metformin regulates menstrual cycle in 23 – 90 %, but the effect that it has on the percentage of ovulations and pregnancy is ambiguous [11]. It is proved that women with PCOS who took metformin before and during pregnancy had lower frequency of miscarriages, fetal malformations and gestational diabetes is lower [17]. Metformin is relatively safe for the fetus during pregnancy (FDA Pregnancy Category B) [18].

According to recommendations of European Society of Endocrinologists in 2014, Thiazolidindiones (Pioglitazon) are insulin sensitizers that belong to the second series of drugs which can be used for women with PCOS in case of intolerance or lack of a therapeutic effect from metformin. First of all, they should be recommended for patients with severe insulin resistance caused by genetic disorders [19]. Pioglitazon lowers insulin level, reduces manifestations of insulin resistance and regulates menstrual cycle and ovulation for women with PCOS regardless of the presence overweight [20]. It also regulates the content of non-specific inflammation indicators. There are contradictory data about the effect that Pioglitazon has on the content of atherogenic lipids in case of PCOS. Meta-analysis of the research that studied the influence of metformin and Pioglitazon administered to women with PCOS on parameters of the lipidogram did not find any tangible difference in the content of total cholesterol and triglycerides [21]. However, it should be noted that Pioglitazon may enlarge the amount of peripheral and reduce visceral adipose tissues [22]. Pioglitazon may reduce ectopic fat depositions including the liver and muscles and in such way increase insulin sensitivity [23]. In some patients, thiazolidinedione may increase body mass because of fluid retention [24].

Introduction of glucagon-like peptide-1 analogues opens new prospective in treating women with PCOS. Findings of so far scarce research on adding these drugs to already prescribed metformin prove a positive effect of exenatide and liraglutide on body weight reduction at the expense of visceral adipose tissue, normalisation of testosterone concentration and parameters of the lipidogram for women with PCOS [25-27].

In case obesity of the third degree, bariatric surgery can be used to reach a palpable effect on reduction of body weight and metabolic disorders and thus restore ovulatory function and fertility.

It also should be noted that administering of combined oral contraceptives (COC) of the third generation, which have an antiandrogenic component that is often necessary for women with PCOS, does not have a strong negative effect on the metabolic profile of these patients. Furthermore, according to some information, COC also positively affect the parameters of lipid profile and adipocytokines secretion [28,29].

Conclusions

In female patients with PCOS significant attention should be directed to prevention and treatment of metabolic disorders, in the first-place pre-obesity and obesity, insulin resistance, deviations of lipids and carbs metabolism. It is essential to follow low-calorie diet containing low glycemic index food products. Regular physical activity allows to promote psychological, reproductive, cardiovascular and metabolic indications in women with PCOS. Important part is cutting up smoking, because it augments negative effects of drugs, used for PCOS therapy, by increasing risk of endothelial

dysfunction and thrombosis. Pharmacological treatment of PCOS involves prescription of medications which improve insulin sensitivity: metformin, thiazolidinedione (pioglitazone), glucagon-like peptide analogues exenatide and liraglutide, combined oral contraceptives.

REFERENCES

1. Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS consensus Workshop Group. Consensus on women's health aspects of polycystic ovary syndrome (PCOS) *Hum Reprod* 27(1): 14-24, 2012.

2. Stein IF, Leventhal ML. Amenorrhe aassociated with bilateral polycystic ovaries. *Am J Obster Gynecol* 29(2): 181-191, 1935.

3. Frauser BC, Tarlazis BC, Rebar RW et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-sponsored 3rd PCOS Consensus Workshop Group. *Fertil Steril* 97(1): 28-38, 2012.

4. Urbanovych AM. Polycystic ovary syndrome in every day practice. *Int J Endocrinol* 14(1): 40-45, 2018

5. WHO. Medical eligibility criteria for contraceptive use. 5th edition, 2015. https://www.who.int/reproductivehealth/publications/family_planning/Ex-Summ-MEC-5/en/

6. Lim SS, Norman RJ, Davies MJ, Moran LJ. The effect of obesity on polycystic ovary syndrome: asystematic review and meta-analysis. *Obesity Rev* 14: 95–109, 2013.

7. Welt CK, Carmina E. Life cycle of polycystic ovary syndrome (PCOS): from in utero to menopause. *J Clin Endocrinol Metab* 98(12): 4629–4638, 2013.

8. Urbanovych AM. Hormones of adipose tissue and their clinical significance. *Endokrynologia* 18(1): 69-72, 2013.

9. Jiskoot G, Benneheij SH, Beerthuizen A et al. A three component cognitive behavioural life style program for preconceptional weight lossin women with polycystic ovary syndrome (PCOS): a randomized controlled trial. *Reprod Health* 14(1): 34, 2017.

10. Duleba AJ. Medical management of metabolic dysfunction in PCOS. *Steroids* 77(4): 306-11, 2012.

11. Milewicz A. Endokrynologia kliniczna. Wroclaw, 1224, 2017.

12. Jędrzejuk D, Łaczmański Ł, Kuliczkowska J, Lenarcik A, Trzmiel-Bira A. Selected CNR1 polymorphism and hyperandrogenemia as well as fat mass and fat distribution in women with polycystic ovary syndrome. *Gynecological Endocrinology* 31(1): 36-39, 2015.

13. Urbanovych AM. Effect of metformin therapy on the levels of certain adipose tissue hormones and mediators of nonspecific generalized inflammation in patients with newly diagnosed type 2 diabetes. *Int J Endocrinol* 4(68): 34-38, 2015.

14. Kruszyńska A, Słowińska-Srzednicka J, Jeske W. Proinsulin, adiponectin and hsCRP in reproductive age women with polycystic ovary syndrome (PCOS) the effect of metformin treatment. *Endokrynol Pol* 65(1): 2–10, 2014.

15. Kiałka M, Gałuszka-Bednarczyk A, Wajda A et al. Metformin and changes in serum lipidprofile in lean patients with polycystic ovary syndrome. *Przegl Lek* 74(4): 144-6, 2017.

16. Wróbel MP, Marek B, Kajdaniuk D, Rokicka D, Szymborska-Kajanek A, Strojek K. Metformin - a new old drug. *Endokrynol Pol* 68(4): 482-496, 2017.

17. Glueck CJ, Goldenberg N, Pranikoff J. Effects of metformin-diet intervention before and throughout pregnancy on obstetric and neonatal outcomes in patients with polycystic ovary syndrome. *Curr Med Res Opin* 29(1): 55–62, 2013.

18. Ghazeeri GS, Nassar AH, Younes Z, Awwad JT. Pregnancy outcomes and the effect of metformin treatment in women with polycystic ovary syndrome: an overview. *Acta Obstet Gynecol Scand* 91(6): 658–678, 2012.

19. Gambineri A, Semple RK, Forlani G et al. Monogenic polycystic ovary syndrome due to a mutation in the lamin A/C gene is sensitive to thiazolidinediones but not to metformin. Eur J Endocrinol 159(3): 347–353, 2008.

20. Koo YA, Shin SY, Yoon BK, ChoiD. Pioglitazone for treating polycystic ovary syndrome in non-obese women of reproductive age with different clinical presentations. *Gynecol Endocrinol* 23(8): 461-7, 2007.

21. Yifeng X, Yanxiang W, Huang Q. Comparison of the effect between pioglitazone and metformin in treating patients with PCOS: a meta-analysis. *Arch Gynecol Obstet* 296(4): 661–677, 2017.

22. Rasouli N, Raue U, Miles LM, Lu T, Di Gregorio GB, Elbein SC. Pioglitazone improves insulin sensitivity through reduction in muscle lipid and redistrib ution of lipid into adipose tissue. *Am J Physiol Endocrinol Metab* 288(5): 930–934, 2005.

23. Bajaj M, Baig R, Suraamornkul S, Hardies LJ, Coletta DK, Cline GW. Effects of pioglitazone on intramyocellular fat metabolism in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 95(4): 1916–1923, 2010.

24. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 98(12): 4565–4592, 2013.

25. Frøssing S, Nylander M, Chabanova E et al. Effect of liraglutide on ectopic fat in polycystic ovary syndrome: A randomized clinical trial. Diabetes Obes Metab 20(1): 215-218, 2018.

26. Niafar M, Pourafkari L, Porhomayon J, Nader N. A systematic review of GLP-1 agonists on the metabolic syndrome in women with polycystic ovaries. *Arch Gynocol Obstet* 293(3): 509-515, 2016.

27. Tzotzas T, Karras SN, Katsiki N. Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists in the Treatment of Obese Women with Polycystic Ovary Syndrome. *Curr Vasc* 15(3): 218-229, 2017.

28. Legro RS, Legro RS, Arslanian SA, Ehrman DA. Diagnosis and treatment of polycustic ovary syndrome; an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 98: 4565-4592, 2013.

29. Conway G, Dewailly D, Diamanti-Kandarakis E. The polycystic ovary syndrome: position on statement from the European Society of Endocrinology. *Eur J Endocrinol* 171(4): 1–29, 2014.