REVIEW

A Modern View of the Polycystic Ovarian Syndrome

MIHAELA BRAGA[1]✉, ELENA ALINA BORDEA[1,2], ELVIRA BRATILA[1,2], BOGDAN MARINESCU[1,2], ANDREEA CARP-VELISCU[1,2]

[1] *Clinical Hospital of Obstetrics and Gynaecology, "Prof. Dr. Panait Sîrbu", Bucharest, Romania*

[2] *University of Medicine and Pharmacy "Carol Davila", Department of Obstetrics and Gynaecology*

Correspondence to: Mihaela Braga, Clinical Hospital of Obstetrics and Gynaecology, "Prof. Dr. Panait Sîrbu", Bucharest, Romania, e-mail: mihaela.cosma1403@gmail.com

Abstract

The polycystic ovarian syndrome (PCOS) is the most common endocrinopathy, which affects between 8 and 13% women of reproductive age.Its most common and disturbing features are hyperandrogenism and infertility. Due to its many implications, there is an utter need to improve the diagnosis and management of this pathology. It will help women improve their quality of life, fertility and prevent cardiovascular effects. The most important part of the management is the correct diagnosis. Specialists are trying to elaborate tighter and more specific criteria of diagnosis. Besides these disturbing features, one can not ignore the more important effects of PCOS: cardiovascular disease, diabetes mellitus, endometrial cancer and mental disorders (anxiety and depression)In order to prevent all these problems, the patients need constant guiding with a major change in lifestyle.

Key words: PCOS, hyperandrogenism, infertility, lifestyle.

Introduction

The polycystic ovarian syndrome (PCOS) is the most common endocrinopathy, which affects between 8 and 13% of the women of reproductive age [1].This complex pathology has many implications: reproductive, metabolic and psychologic [2]. Over the years, scientists have elaborated different methods of diagnosis and treatment but clinical practice is still inconsistent. Recently, articles have been published about women's disatissfaction with care and delayed diagnosis [3, 4]. The Rotterdam diagnostic criteria have been released in 2003 and since then, have been intensely used. Due to the complexity of the pathology, there is an obvious need for tighter criteria, in order to include the pacients who were previously undiagnosed. That is the reason why we started writing this paper, in order to offer a modern perpective of the polycystic ovarian syndrome to women all around the globe. This article's purpose is to facilitate

diagnosis of the polycystic ovarian syndrome and to avoid overdiagnosis in adolescents.

Rotterdam criteria include the following:

(1) ovulatory dysfunction – oligo/anovulation,

(2) clinical and/or biochemical hyperandrogenism,

(3) polycystic ovarian morphology in pelvic ultrasound.

In order to establish the diagnosis, the patient need to meet two out of three criteria. Other pathologies must be excluded, such as: congenital adrenal hyperplasia, androgen secreting tumors, Cushing syndrome, thyroid dysfunction (thyroid stimulating hormone) and hyperprolactinemia (prolactin) [1, 5]. Beside the Rotterdam diagnostic criteria, the National Institute of Health suggested in 2012 four phenotypes of the polycystic ovarian syndrome:

(Phenotype A) hyperandrogenism, ovulatory dysfunction andpolycystic ovarian morphology in pelvic ultrasound

(Phenotype B) hyperandrogenism and ovulatory dysfunction

(Phenotype C) hyperandrogenism and polycystic ovarian morphology in pelvic ultrasound

(Phenotype D) ovulatory dysfunction andpolycystic ovarian morphology in pelvic ultrasound

This new classification is very useful, especially for infertility specialists. It helps them to personalize treatment and improve outcomes [6].

Contents

Ovulatory dysfunction

Irregular cycles and ovulatory dysfunction are common in adolescence and menopause and finding the right criteria for diagnosis can be challenging. Irregular cycles are physiologic in the first year post-menarche. During the second year, almost 50% of the cycles range between 21 - 45 days. Cycles can remain irregular until the fifth year. So it may be difficult to diferentiate between physiologic ovulatory dysfunction and PCOS in adolescents. They may experience primary amenorrhea until the age 15 or > 3 years after telarche. In PCOS adolescents, in the second year after menarche, cycles tend to be very short (< 21 days) or very long (> 45 days) [7]. In the third year, menstrual cycles appear < 21 days or > 35 days or < 8 cycles/year. These fluctuations last until perimenopause. If an adolescent presents with both hyperandrogenism and irregular cycles, there is no need to perform a pelvic ultrasound. The clinicians need to take into account the impact of the psychosocial and cultural factors at this age and find the optimal timing for assessment, diagnosis and treatment (if necessary). Even if the patient has regular cycles, the ovulatory dysfunction can still exist. Serum progesterone can be tested.

Biochemical hyperandrogenism

Hyperandrogenism is a key diagnostic feature of PCOS and assessment of biochemical hyperandrogenism can be challenging, due to different methods of testing, different assays and cost of high quality tests.Testing the androgen hormones is useful in patients with unclear or absent biochemical hyperandrogenism. The formula of Vermeulen et al. is often used, which includes calculated bioavailable testosterone and calculated free testosterone. Free androgen index is also commonly used (FAI – free androgen index = 100 x (total testosterone/SHBG) [8]. Dehydroepiandrosterone sulfate (DHEAS)and androstenedione are less relevant, but can be used if testing other hormones is not available [9]. In women on hormonal contraception, treatment must be stopped for three months or more for a correct diagnosis, due to the effects on sex hormone-binding globulin (SHBG) and

gonadotropines.As clinicians, we must always keep in mind differential diagnosis until final diagnosis.

Clinical hyperandrogenism

Signs and symptoms of hyperandrogenism are: acne, hirsutism and androgen-relating alopecia. There are available different assessment scales for alopecia and hirsutism, for example the visual Ludwig score and the visual assessment tool, the Ferriman Gallwey scale [10]. Taking into consideration the ethnic variations in vellus hair density, some women can overestimate hirsutism. This is the reason why we should only consider terminal hair (>5mm). In postmenopause, patients cand still have clinical hyperandrogenism, but if it appears de novo, we should exclude androgen secreting tumors [11].

Polycystic ovarian morphology in pelvis ultrasound

The ultrasound aspect should not be used as a part of diagnosis in those with a gynaecological age < 8 years (< 8 years after menarche), because of the commonly seen multifollicular aspect of the ovary in these early years. For diagnosis, we need more than 20 follicles per ovary between 2 - 9 mm and/or ovarian volume ≥ 10 ml [12].

Cardiovascular Risk

As formerly mentioned in the first part of the article, patients with polycystic ovarian syndrome most often have metabolic changes and high risk of cardiovascular diseases. This, mostly affects postmenopausal women, although cardiovascular diseases can develop even in the early stages of adult life. Thus, the recommendations are: periodic weight evaluation and BMI, best regarding waist circumference (at least once every 6 - 12 months), all women with PCOS should investigate the risk factors for cardiovascular diseases, considering a hypolipidic diet and assessing lipid profile for overweight and obese patients and blood pressure monitoring [13, 14].

Gestational diabetes, impaired glucose tolerance and diabetes mellitus

PCOS represents an important risk factor for gestational diabetes, impaired glucose tolerance and diabetes mellitus regardless of age, a risk that is soared by obesity [15]. Glycemic status (fasting glycemia and/or glycate hemoglobin – HbA1c) must be routinely monitored, from the first consultation, for all PCOS patients and then assessed at least once every 1 - 3 years, however, this recommendation can vary depending on the glycemic status and other risk factors for diabetes [16]. If the patient belongs to a high risk ethnic population (asians), has a high BMI (≥ 25 kg/m^2 or ≥ 23 kg/m^2 for asians), has a history of high fasting glycemia, impaired glucose tolerance or gestational diabetes, heredo-collateral history of diabetes mellitus or hypertension, it is recommended to conduct an oral-intake glucose tolerance test (OGTT) with 75 g of glucose [16, 17]. Considering the hyperglycemic risk in pregnancy and its associate comorbidities, it is recommended OGTT with 75 g of glucose for all patients planning pregnancy. If the test was not assessed preconceptional, this may be offered < 20 weeks, and if not sustained in this period, it is mandatory to perform it between 24 - 28 weeks [16, 17].

Endometrial cancer

PCOS patients have a 2 to 6 -fold higher risk to develop endometrial cancer, which usually appears before menopause [18, 19]. It is recommended to perform a transvaginal echography and endometrial biopsy for patients with PCOS or with history of PCOS and thickened

endometrium, with prolonged amenorrhea, vaginal bleeding or overweight [20]. Prevention of endometrial cancer is not yet clearly understood, but an accurate approach seems to be consisting of correct administration of combined oral contraceptives or progesterone therapy for patients with > 90-day menstrual cycles.

Quality of life, body image alteration, depression and axienty, eating disorders

A recent metaanalysis showed that PCOS patients have a higher risk of mental disorders, like depression and anxiety (36.6 vs 14.2% and 41.9 vs 8.5%, respectively) [21]. As a result, the AE-PCOS Society recommends screening for depression and anxiety form the first consultation. The majority of patients with PCOS present acne, hirsutism or obesity, all of these leading to body image alteration and low quality of life. When considering medication for psyhiatric disorders, caution is needed for adminitration of antidepressants and anxiolitics for obese patients. Usually, women with PCOS and obesity tend to have eating disorders, this is a reason why it is important for the clinician to identify this issue and guide the patient properly [24, 25]. These patients need support and counseling to cope with major life changes. They need a healthy life-style, consisting of diet (1200 - 1500 kcal/day) and physical activity. A 5 - 10% weight-loss in 6 months leads to significant improvement regarding android obesity, insulin resistance, fertility and quality of life.

Treatment in PCOS

Combined oral contraceptives (COC)

COC are indicated for PCOS patients with hyperandrogenism and/or irregular cycles. The international guidelines recommend low dose ethinyloestradiol (20 - 30 microgram) and natural estrogen preparations because of the thromboembolic risk. COC can be recommended also to adolescents with hyperandrogenism and/or irregular cycles. When prescribing COC, we should not forget to take into consideration the patients history, his family history and other risk factors, such as hyperlipidemia, BMI and hypertension [26].

Metformin

Metformin is an insulin sensitiser and has been used for seven decades in diabetes and for several decades in PCOS. There is a variability in recommendations across specialists. If lifestyle changing and COC are not sufficient, metformin can be added to the treatment. It can be administered also as an only treatment for PCOS [26]. Metformin can offer great benefit in patients with diabetes risk factors, impaired glucose tolerance and high risk ethnic groups. In obese patients undergoing and IVF procedure, metformin should be considered. In this case, the treatment should start with at least 8 weeks before ovum-pick up, in order to eliminate the risk of hyperstimulation ovarian syndrome, to improve pregnancy rates and diminish abortion rates. [27, 28]. It is recommended to start with a low dose (500 mg) and increase up to 1500 mg, depending on the patient's status. The most common adverse effects are the gastrointestinal effects, which are dose dependent and self-limiting. Even though metformin seems to be safe in the long term, concerns on B12 deficiency have been raised and more research is needed [29].

Antiandrogens

Cosmetic therapy and COC should be applied correctly for at least 6 months in any patient with hirsutism. In those patients, in which treatment is not efficient and those with androgenic alopecia, an antiandrogen can be added to the COC scheme. If there is a contraindication for

COC, the antiandrogen can still be administered [30 - 32].

Inositol

Inositol works as an insulin sensitiser but its efficiency remains unclear. There is a need for larger studies [33].

Ovulation induction agents - letrozole, gonadotropines, clomiphene citrate

Letrozole is the first line treatment for ovulation induction in patients with PCOS and anovulation. In case of failure, gonadotropines can be added, but we should counsel the patient on the multiple pregnancy risk and costs [34].If there is no other option (letrozole pr gonadotropines) clomiphen citrate can be used, but with caution, regarding the possible detrimental effects on the endometrium and cervical mucus [35].

Laparoscopy

Ovarian drilling is the last option for ovulation induction. The specialist must bear in mind the following: high costs, high intraoperative and postoperative risks in obese patients, risk of decreasing the ovarian reserve or even loss of ovarian function , periadnexal adhesion [36].

IVF

If ovulation induction treatment is not effective, specialists should opt for in vitro procedure. Regarding the stimulation protocol used, it is recommended the short protocol with antagonist GnRH and final oocyte maturation with GnRH agonist. The specialist should counsel the patients in order to adopt freeze-all strategy, in order to prevent hyperstimulation ovarian syndrome [36, 37]. Urinary or recombinant follicle stimulating hormone can be used for stimulation and luteinizing hormone treatment should be avoided [38, 39].

Conclusions

There is still a need for prospective randomized studies regarding PCOS, in order to make stronger recommendations. Even so, we consider that the information available for assessment and manangement of PCOS is useful. Nowadays, it is very important that we guide our treatment according to evidence-based medicine, and not to personal experience.

References

[1]. Teede HJ, Misso ML, Costello MF, et al. International evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril. 2019; 110(3):365-379.

[2]. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Medicine. 2010; 8:41.

[3]. Gibson-Helm M, Teede H, Dunaif A, et al. Delayed diagnosis and a lack of information associated with dissatisfaction in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2017; 102(2):604-612.

[4]. Dokras A, Saini S, Gibson-Helm M, Schulkin J, Cooney L, Teede H. Gaps in knowledge among physicians regarding diagnostic criteria and management of polycystic ovary syndrome. Fertil Steril. 2017; 107(6):1380-1386.

[5]. The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Human Reproduction. 2004; 19(1):41-47.

[6]. NIH Evidence based workshop panel. NIH evidence based workshop on Polycystic Ovary Syndrome. 2012.

[7]. Lemarchand-Béraud T, et al. Maturation of the hypothalamo-pituitary-ovarian axis in adolescent girls. J Clin Endocrinol Metab. 1982; 54(2):241-246.

[8]. Vermeulen A, Verdonck L, Kaufman J. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab. 1999; 84(10):3666-3672.

[9]. Rosner W, H. Vesper. Toward excellence in testosterone testing: a consensus statement. J Clin Endocrinol Metab. 2010; 95(10):4542-4548.

[10]. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol Metab. 1961; 21:1440-1447.

[11]. DeUgarte CM, et al. Degree of facial and body terminal hair growth in unselected black and white women: toward a populational definition of hirsutism. J Clin Endocrinol Metab. 2006; 91(4):1345-1350.

[12]. Bili AE, et al. The combination of ovarian volume and outline has better diagnostic accuracy than prostate specific antigen (PSA) concentrations in women with polycystic ovarian syndrome (PCOS). Eur J Obstetrics Gynecol Reproductive Biol. 2014; 179:32-35.

[13]. Wild R, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: A consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab. 2010; 95(5):2038-2049.

[14]. National Vascular Disease Prevention Alliance, Guidelines for the assessment of absolute cardiovascular disease risk, National Heart Foundation of Australia, Editor. 2009.

[15]. Rubin KH, et al. Development and risk factors of type 2 diabetes in a nationwide population of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2017; 102(10):3848-3857.

[16]. American Diabetes Association. Standards of Medical Care in Diabetes-2017. Diabetes Care 2017, 40(Suppl 1).

[17]. Colagiuri S, et al. National Evidence Based Guideline for Case Detection and Diagnosis of Type 2 Diabetes, Diabetes Australia and the NHMRC, Editor. 2009, Canberra, Australia.

[18]. Charalampakis V, et al. Polycystic ovary syndrome and endometrial hyperplasia: an overview of the role of bariatric surgery in female fertility. Eur J Obstet Gynecol Reprod Biol. 2016; 207:220-226.

[19]. Hardiman P, Pillay OC, Atiomo W. Polycystic ovary syndrome and endometrial carcinoma. Lancet. 2003; 361(9371):1810-1812.

[20]. Dumesic DA, Lobo RA. Cancer risk and PCOS. Steroids. 2013; 78(8):782-785.

[21]. Cooney LG, Lee I, Sammel MD, Dokras A. High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod. 2017; 32:1075-1091.

[22]. National Institute for Health and Care Excellence. Antenatal and postnatal mental health: clinical management and service guidance. 2014, 10, March 2017; Available

from: https://www.nice.org.uk/guidance/cg192/resources/antenatal-and-postnatal-mental-health-clinical-management-and-service-guidance-35109869806789.

[23]. Siu AL, U.S.P.S.T.F., Screening for depression in adults. US preventive services task force recommendation statement. JAMA. 2016; 315(4):380-387.

[24]. Mansson M, et al. Women with polycystic ovary syndrome are often depressed or anxious-A case control study. Psychoneuroendocrinology. 2008; 33(8):1132-1138.

[25]. Fairburn CG, Harrison PJ. Eating disorders. The Lancet. 2003; 36:407-415.

[26]. Hoeger K, et al. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. J Clin Endocrinol Metabol. 2008; 93(11):4299-4306.

[27]. Tso LO, Costello MF, Albuquerque LET, et al. Metformin treatment before and during in vitro fertilization or intracytoplasmic sperm inhection in women with polycystic ovary syndrome: summary of a Cochrane review. Fertil Steril. 2015; 104:542.

[28]. Palomba S, Falbo A, La Sala GB. Effects of metformin in women with polycystic ovary syndrome treated with gonadotrophins for in vitro fertilisation and intracytoplasmic sperm injection cycles: a systematic review and meta-analysis of randomised controlled trials. BJOG. 2013; 120:267.

[29]. Liu Q, et al. Vitamin B12 status in metformin treated patients: systematic review. PLoS One. 2014; 9(6):e100379.

[30]. Gambineri A, et al. Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. J Clin Endocrinol Metabol. 2006; 91(10):3970-3980.

[31]. Ganie MA, et al. Comparison of efficacy of spironolactone with metformin in the management of polycystic ovary syndrome: an open-labeled study. J Clin Endocrinol Metabol. 2004; 89(6):2756-2762.

[32]. Ganie MA, et al. Improved efficacy of low-dose spironolactone and metformin combination than either drug alone in the management of women with polycystic ovary syndrome (PCOS): a six-month, open-label randomized study. J Clin Endocrinol Metabol. 2013; 98(9):3599-3607.

[33]. Pundir J, et al. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. BJOG. 2018; 125(3):299-308.

[34]. Franik S, et al. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. Cochrane Database of Systematic Reviews. 2014; 2:CD010287.

[35]. Banerjee Ray P, Ray A, Chakraborti PS. Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with polycystic ovarian syndrome. Archives Gynecol Obstet. 2012; 285(3):873-877.

[36]. American Society for Reproductive Medicine. Prevention and treatment of moderate and severe hyperstimulation syndrome: a guideline. Fertil Steril. 2016; 106(7):1634-1647.

[37]. Corbett S, Shmorgun D, Claman P, et al. The Prevention of ovarian

hyperstimulation syndrome. J Obstet Gynaecol Can. 2014; 36(11):1024-1033.

[38]. Figen Turkcapar A, et al. Human menopausal gonadotropin versus recombinant fsh in polycystic ovary syndrome patients undergoing in vitro fertilization. Int J Fertil Steril. 2013; 6(4):238-243.

[39]. van Wely M, et al. Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles. Cochrane Database Syst Rev. 2011; 16(2): CD005354.

Received: January 15, 2020

Accepted: February28, 2020