Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Praca poglądowa | Review Paper
Pediatr Endocrinol Diabetes Metab 2017;23,4:203-207
DOI: 10.18544/PEDM-23.04.0094

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Metabolic disorders in polycystic ovary syndrome

Zaburzenia metaboliczne w zespole policystycznych jajników

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Abstract

Polycystic ovary syndrome (PCOS) is a complex disease. Depending on the used criteria the prevalence of PCOS ranges from 6 to 20%. It is necessary to exclude diseases leading to androgen excess. The participation of genetic and environmental factors is considered in the etiology of PCOS development. The highest rate of incidence of PCOS is assessed in girls who were born SGA and developed premature adrenarche later in life.The free androgen index (FAI) is concerned as the most sensitive marker of hyperandrogenaemia in PCOS although insulin resistance, anti-Müllerian hormone (AMH),and deficiency of vitamin D may intensify metabolic disturbances. The ultrasound criteria used in adolescent patients prefer the estimation of the ovarian volume or the ratio of ovarian stroma to total ovary, rather than the number of ovarian follicles. PCOS is connected with different metabolic disorders. Post-binding defect in signal transduction is responsible for insulin resistance. This defect results from an impaired activity of the kinase receptor. Moreover, the adipose tissue of PCOS women differs substantially from the tissue of the others according to morphology and function. The adipocytes produce lower amounts of adiponectin, which is an insulin-sensitizing agent. Dyspidemia with high triglycerides and low high density lipoprotein cholesterol concentrations is frequently noticed. Cardio-metabolic risk factors, insulin resistance, and endothelial dysfunction accompany PCOS from the very beginning. Oxidative stress plays a role as a link among systemic inflammation and dysfunction of endothelial cells and abnormal thecal cell action. The treatment efforts in PCOS depend on the patient's main problems. Modification of diet and lifestyle is the most important recommended advice to each woman independent of age and weight.

Key words

Polycystic ovary syndrome, insulin resistance, adipose tissue

Streszczenie

Zespół policystycznych jajników (PCOS) jest złożoną chorobą. W zależności od zastosowanych kryteriów częstość występowania PCOS wynosi od 6 do 20%. Konieczne jest wykluczenie chorób prowadzących do nadmiaru androgenów. W etiologii rozwoju PCOS uwzględniany jest udział czynników genetycznych i środowiskowych. Najwyższy wskaźnik zachorowalności na PCOS jest stwierdzany u dziewcząt, które urodziły się z SGA i rozwinęły przedwczesne adrenarche w późniejszym życiu. Indeks wolnego androgenu (FAI) jest uważany za najbardziej czuły marker hiperandrogenemii w PCOS, chociaż oporność na insulinę, hormon anty-Müllerowski (AMH) i niedobór witaminy D mogą nasilać zaburzenia metaboliczne. Kryteria ultrasonograficzne stosowane u pacjentek w wieku młodzieńczym preferują ocenę objętości jajników lub stosunku zrębu jajnika do całkowitej objętości jajnika, a nie liczbę pęcherzyków jajnikowych. PCOS wiąże się z różnymi zaburzeniami metabolicznymi. Wadliwy defekt w transdukcji sygnału jest odpowiedzialny za insulinooporność. Wada ta wynika z zaburzonej aktywności receptora kinazy. Ponadto tkanka tłuszczowa kobiet z PCOS różni się zasadniczo od tkanki innych osób odnośnie do morfologii i funkcji. Adipocyty wytwarzają mniejszą ilość adiponektyny, która jest czynnikiem uwrażliwiającym na insulinę. Często obserwuje się dyslipidemię z wysokim stężeniem trójglicerydów i niskim stężeniem cholesterolu frakcji HDL. Czynniki ryzyka chorób sercowo-naczyniowych, insulinooporność i dysfunkcja śródbłonka towarzyszą PCOS od samego początku. Stres oksydacyjny odgrywa rolę jako ogniwo między ogólnoustrojowym stanem zapalnym i dysfunkcją komórek śródbłonka a nieprawidłowym działaniem komórek tekalnych jajnika. Cele terapeutyczne w PCOS zależą od głównych problemów pacjentki. Modyfikacja diety i stylu życia jest najważniejszą zalecaną wskazówką dla każdej kobiety, niezależnie od wieku i masy ciała.

Słowa kluczowe

zespół policystycznych jajników, insulinooporność, tkanka tłuszczowa

Received: 15.12.2017
Accepted: 30.01.2018
Conflict of interests: none declared.

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Introduction

Polycystic ovary syndrome (PCOS) is a complex disorder. Depending on the used criteria the prevalence of PCOS ranges from 6 to 20%. The Rotterdam European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine consensus statement termed PCOS as two out of three of the following: polycystic ovaries, oligo-ovulation and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and exclusion of other etiologies [1–6]. It is necessary to exclude diseases leading to androgen excess, such as congenital adrenal hyperplasia, virilising tumors, Cushing syndrome, or states disturbing functional integrity of the hypothalamo-pituitary-ovarian axis such as hyperprolactinemia, severe insulin resistance thyroid dysfunction.

More recently, NIH Experts Panel determined four different phenotypes of PCOS 1) clinical or biochemical hyperandrogenism (H) and chronic anovulation (CA) (H-CA); 2) hyperandrogenism and polycystic ovarian morphology on ultrasound (PCOm) but with ovulatory cycles (H-PCOm); 3) CA and polycystic ovaries without hyperandrogenism (CA-PCOm); and, 4) hyperandrogenism, CA and polycystic ovaries (H-CA-PCOm) [4].

Etiology

PCOS is a heterogeneous disease; genetic and environmental factors participation is considered in its development. The carbohydrate metabolism and the secretion of adrenal hormones during the fetal development can influence PCOS development later in life [7–10]. The girls with normal birth weight less frequently suffer from PCOS later in life than a group of girls born small for their gestational age (SGA). This observation supports the importance of intrauterine milieu [11]. The other group of patients also prone to PCOS development contains girls with precocious pubarche, a state caused by early androgen hypersecretion. The visceral adiposity and insulin resistance are found very early in this group [12,13]. The highest rate of incidence of PCOS was assessed in girls who were born SGA and developed premature adrenarchelater in life [11].

PCOS seems to be polygenic or oligogenic in origin. The investigation of the genetic background of the disease did not confirm single gene mutation in the pathogenesis so far [9]. The importance of the excessive androgen secretion during the fetal development is confirmed. This state leads to early puberty, particularly early growth of pubic hair, and the clinical features of PCOS develop later in life [14,15]. Hyperandrogenemia may also disturb programming of the activity of hypothalamo-pituitary-ovarian axis which develops in the second trimester of pregnancy. Luteinizing hormone (LH) secretion is, in turn, connected with hyperinsulinemia and insulin resistant state [9]. In such an environment, ovarian function and ovulation are disturbed [9,11,15]. Franks et al. reported on higher concentration of anti-Müllerian hormone (AMH) in daughters of women with PCOS in infancy, early childhood and prepuberty [9]. Moreover Maliqueo et al. confirmed lower activities of3β-hydroxysteroid dehydrogenase 1 and aromatase in the placentas of women with PCOS. This would augment fetal androgens exposure [16].

The other factor involved in the pathogenesis of PCOS is vitamin D. It is postulated that the deficiency of vitamin D may intensify metabolic disturbances. Women with PCOS and obesity, insulin resistance and glucose intolerance states have more frequently lower concentration of vitamin D [17]. Low concentration of vitamin D may affect fertility, and is observed in PCOS, in connection with obesity and metabolic alterations [18–21]. A relationship between vitamin D and AMH has also been confirmed [20,21].

Diagnosis

The essential in the diagnostic procedure of PCOS is estimation of serum testosterone concentration. There is no substantial fluctuation of testosterone during the menstrual cycle. The testosterone concentration in PCOS can be elevated or normal. The free androgen index (FAI) should be calculated in case of normal testosterone concentration. FAI is the ratio of total testosterone and sex hormone-binding globulin (SHBG). FAI is concerned as the most sensitive marker of hyperandrogenaemia in PCOS [6].

The marker of insulin resistance and androgen excess frequently observed in PCOSis a low SHBG concentration. Women with PCOS and low SHBG are prone to gestational diabetes metabolic syndrome [5,6]. Recently discovered polymorphism in the gene encoding SHBG may be associated with reduced SHBG levels in PCOS, regardless of the effects of insulin resistance and obesity [22,23].

The other methods used in the diagnosis of PCOS include: gas chromatography with mass spectrometry (GC–MS) or liquid chromatography with tandem mass spectrometry (LC–MS/MS); both are very sensitive and specific but expensive and time-consuming. Fanelli at al. applied LC–MS/MS method in a group of late adolescent, and young women, and noticed higher T and androstendione concentrations in anovulatory females compared to ovulatory ones [24].

The estimation of gonadotropins and calculation of LH/FSH ratio is not recommended in the diagnosis of PCOS in recent consensus. Similarly there is no recommendation for measurement of anti-Müllerian hormone (AMH) in this disease. Despite this, AMH is an important marker of the number of small antral follicles. The concentration of AMH reflects ovarian reserve. Higher concentration of AMH in PCOS is connected with a greater number of follicles in the ovaries, correlating with the antral follicle count and degree of menstrual disturbances [25,26]. Moreover, the concentration of AMH correlates with the severity of both hyperandrogenism and oligoanovulation in PCOS [27].

Ultrasound diagnostic criteria of PCOS changed within the last decade as the result of marked improvements in technical ability of newer ultrasound scanners. It is suggested that raising the diagnostic threshold from 19 to 26 or more follicles

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per ovary respectively instead of 12 or more follicles measuring 2–9 mm in diameter [28–30]. The number of follicles per ovary is difficult to count in adolescent girls when the transvaginal route is not feasible. The ovarian volume of at least 10 ml can be used as ultrasound criteria or the ratio of ovarian stroma to total ovary, with a cutoff value of 0.32 in these circumstances [31].

Metabolic disorders

Post-binding defect in signal transduction is responsible for insulin resistance. This defect results from impaired activity of the kinase receptor. PCOS is frequently connected with insulin resistance, which occurs in 50% to 80% of women. Additionally concomitant beta cell dysfunction is responsible for impaired insulin secretion in response to glucose. In PCOS obesity, particularly the accumulation of adipose tissue in the abdominal/visceral region is frequently observed and worsens the metabolic and reproductive features [32]. It is connected with insulin resistance and may be favored by androgen excess during each step of individual development. Obese women with PCOS frequently develop type 2 diabetes mellitus (T2D), the highest risk is for those with BMI over 30 [33]. Moreover, the adipocyte function is changed in PCOS [34]. They produce lower amounts of high molecular weight (HMW) adiponectin, which is an insulin-sensitizing agent. It's activity is mediated by activation of AMP kinase [35]. In patients with PCOS HMW–adiponectin concentration is low, and dependent on the concentration of androgens and their influence on adipocyte function [36].

The adipose tissue of PCOS women differs substantially from the tissue of the others according to morphology and function [37]. Adipocytes in PCOS are hypertrophic. An impaired activity of the sympathetic system in the abdominal fat, and reduced vascularization was confirmed [38]. Hypoxia of the adipose tissue leads to the development of inflammatory reactions with an increased secretion of cytokines, chemokines, adipokines (free fatty acid (FFA), leptin, resistin, and visfatin) and a decreased secretion of adiponectin [38]. In such conditions, insulin sensitivity is reduced and T2D subsequently develops [39]. The role of androgens in adipocyte hypertrophy stimulation is confirmed. They facilitate maturation of adipocytes and play a role in activation of enzymes involved in lipid and carbohydrate metabolism, and increase lipolysis [40,41].

Recently, it has been observed that the high gene expression of CD11c (ITGAX), and tumor necrosis factor α (TNFα) in subcutaneous adipose tissue were significantly higher in PCOS women. TNF α has a proinflammatory activity and therefore may contribute to the pathogenesis of insulin resistance in PCOS women [42]. About 70% of PCOS not only obese women commonly suffer from dyslipidemia with high triglycerides and low high density lipoprotein cholesterol concentrations as the result of the above mentioned mechanisms. In other states of insulin resistance this atherogenic pattern of lipids is also observed. PCOS is strongly connected with the risk of cardiovascular disease (CVD), especially in adulthood. Cardiometabolic risk factors, and endothelial dysfunction and insulin resistance accompany the disease from the very beginning. Especially hyperandrogenemia negatively influence CVD [43].

Insulin resistance in the endothelial cells of arteries results in adiminished synthesis and release of nitric oxide (NO). NO released from endothelial cells is quickly inactivated. On the other hand, increased synthesis of vasoconstricting factors results in the increased vascular stiffness and impaired vasodilatory action of insulin [44]. Insulin is a potent growth factor and exerts a hypertrophic effect on the vascular endothelium and the vascular smooth muscle cells. Insulin resistance stimulates endothelin-1 (ET1) synthesis, harmful for endothelial function [45]. Moreover, in PCOS, decreased total antioxidant concentration in serum and increased secretion of free radicals, even in non-obese women, was described [46]. Oxidative stress plays a role as a link among dysfunction of endothelial cells, systemic inflammation and abnormal thecal cell activity [47]. Children born from mothers with PCOS, display increased oxidative stress markers comparable to offspring from gestational diabetes [48].

The other player active in glyco-oxidative stress, are advanced glycosylation end products (AGEs). AGEs are the products of glycation or glycooxidation of proteins and lipids and play an important role as proinflammatory mediators. The concentration of AGEs is elevated in women with PCOS [49]. Christakou et al. established in women with PCOS a close and positive correlation between serum AGEs and serum ET1 concentration, and postulated its role in endothelial dysfunction [50]. Thus, increased serum AGEs in young PCOS women may play a role as a predictive marker of CV morbidity. The positive correlation of serum testosterone with serum AGEs levels in PCOS points towards a linkage of metabolic and reproductive status [49].

Therapy

The treatment efforts in PCOS depend on the patient's main problems. The modification of diet and lifestyle is the most important recommendation to each woman independent of age and weight. It is of great importance to reduce intake of carbohydrates with a high glycemic index. Moreover, overweight and obese women should be advised to maintain a low calorie diet to lose weight. The reduction of BMI improves the metabolic and hormonal profile and helps in the normalization of menstrual cycle regularity. An increase in physical activity is helpful in reducing insulin resistance. As young girls are not attempting to be pregnant and their complaints focus on the symptoms related to hyperandrogenemia, such as: acne, oily skin and hirsutism, therapy should be tailored to their needs. Oral contraceptive pills (OCP), antiandrogens and insulin sensitizers are the most frequently used. The most widely used insulin sensitizer drug is metformin. The benefits of metformin treatment are connected with ameliorating cardiometabolic disorders, and the reproductive abnormalities in PCOS. It improves insulin sensitivity

in the liver and peripheral tissue, and ovarian steroidogenesis diminishes the concentration of inflammatory and atherogenic molecules [51]. It is suggested that AGE dietary interventions or inhibitors might represent an emerging therapeutic approach with significant applications in the metabolic and reproductive consequences of PCOS [51,52].

Summary

PCOS is a complex and heterogeneous disease. Further investigations are necessary to clear the etiological aspects of PCOS. Genetic, epigenetic and environmental factors should be considered. The results of further studies could help to develop preventive strategies. The implementation of these strategies early in life, before or during adolescence could probably alleviate clinical picture of the disease and prevent dysmetabolic consequences.

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