

## Polycystic ovary syndrome (PCOS) and the accompanying disorders of glucose homeostasis among girls at the time of puberty

Zespół policystycznych jajników (PCOS) i towarzyszące mu zaburzenia homeostazy glukozy u dziewczynek w okresie pokwitania

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### Abstract

Polycystic ovary syndrome (PCOS) usually arises during puberty and is marked by insulin resistance, hyperinsulinemia, and hyperandrogenism. The principle is that the diagnosis of PCOS must be based on the presence of at least two of the following three criteria: chronic anovulation, hyperandrogenism (clinical or biological), and polycystic ovaries. The diagnosis of PCOS in adolescents is particularly difficult due to developmental problems in this group. Many symptoms of PCOS, including acne, menstrual irregularities, and hyperinsulinemia, are common in normal puberty. Adolescents with PCOS are at an increased risk of developing health problems later on in life, such as diabetes, cardiovascular disease, and infertility. One should reckon with the frequent occurrence of the PCOS in type 1 diabetes, when the ovaries and the adrenals are exposed to excessive insulin concentrations. Ovarian hyperandrogenism is common in adolescent girls with type 1 diabetes. Methods of treatment for an adolescent with PCOS include diet and exercise. Metformin is commonly used in young girls and adolescents with PCOS as first-line monotherapy or in combination with anti-androgen medications.

### Key words

hyperandrogenism, polycystic ovary syndrome, insulin resistance, diabetes

### Streszczenie

Zespół policystycznych jajników (PCOS) zwykle pojawia się w okresie dojrzewania i charakteryzuje się występowaniem insulinooporności, hiperinsulinemii i hiperandrogenizmu. Przyjęta jest zasada, że diagnoza PCOS musi opierać się na obecności co najmniej dwóch z trzech następujących kryteriów: przewlekłego braku owulacji, hiperandrogenizmu (klinicznego lub biologicznego) i policystycznych jajników. Rozpoznanie PCOS u nastolatek jest szczególnie trudne. Wiele objawów PCOS, w tym trądzik, zaburzenia miesiączkowania i hiperinsulinemia, są częste w okresie dojrzewania. U nastolatek z PCOS istnieje zwiększone ryzyko wystąpienia problemów zdrowotnych w późniejszym życiu, takich jak cukrzyca, choroby sercowo-naczyniowe i niepłodność. Należy liczyć się z częstym występowaniem PCOS w cukrzycy typu 1, gdy jajniki i nadnercza są narażone na nadmierne stężenia insuliny. Hiperandrogenizm pochodzenia jajnikowego występuje często u nastolatek z cukrzycą typu 1. Leczenie młodzieży z PCOS obejmuje dietę i ćwiczenia fizyczne. Metformina jest powszechnie stosowana u młodych dziewcząt z PCOS w monoterapii pierwszego rzutu lub w połączeniu z lekami przeciwandrogenowymi.

### Słowa kluczowe

hiperandrogenizm, zespół policystycznych jajników, insulinooporność, cukrzyca

## Introduction

The so-called “hormonal storm” [1–5] occurs during puberty. Thus, in this period there may occur a number of abnormalities due to underlying genetic disorders or exogenous factors [6].

Polycystic ovary syndrome (PCOS) usually arises during puberty. The diagnosis of PCOS in girls in the early period of its manifestation is very important because it makes it possible to implement appropriate preventive and curative treatment, and thus preventing many serious metabolic and gynecological abnormalities associated with this syndrome.

## Polycystic ovary syndrome

In the deliberations on the pathogenesis of PCOS, either genetic or environmental factors are taken into account. In the adolescent population, polycystic ovary syndrome (PCOS) typically manifests itself with a combination of menstrual dysfunction and symptoms of hyperandrogenism. So far, a single reason for this syndrome has not been established, but many researchers suggest a complex interplay between genetic and environmental components [7].

Franks suggested that PCOS in adolescents is caused by a genetically determined disorder of ovarian function which results in the hypersecretion of androgens, possibly during fetal life and also during physiological activation of the hypothalamic-pituitary-ovarian axis in infancy and at the onset of puberty [8]. The author believes that the identification of the major susceptibility loci is likely to provide key insight into the etiology of the syndrome and to improve diagnosis and management.

The genetic precondition of PCOS is indicated, among others, in researches that show significantly an elevated, compared with control group, level of androgens and insulin resistance, with a high risk of glucose intolerance and diabetes in first-degree relatives of women with this syndrome [9,10].

Recently, studies in genetic bases of PCO syndrome have been submitted by Su et al [11]. The authors stated that unsupervised clustering of expressed genes could readily differentiate PCOS from the control group. According to the mentioned authors, inflammatory response pathway including 14 deregulated genes was highly enriched in PCOS.

An extensive review of PCOS backgrounds within adolescent patients was presented by Connor [12].

Excess weight is one of the factors conducive to the occurrence of hormonal disturbances and PCO syndrome [13]. The authors examined sources of overnight testosterone (T) and progesterone (P4), and potential sources of obesity-associated hyperandrogenemia during puberty. They stated that peripubertal hyperandrogenemia – a precursor of polycystic ovary syndrome – is prominent in girls with obesity. Similar studies have been carried out by McCartney et al. [14,15], who claimed that peripubertal obesity is associated with marked hyperandrogenemia, which is especially pronounced

in early puberty. It was indicated that obese PCOS vs. non-PCOS girls had a decreased lipid mobilization, diminished fat oxidation, and metabolic inflexibility [16].

PCOS is frequently associated with obesity, insulin resistance (IR), diabetes, hypertension, and dyslipidemia – conditions conducive to an increased risk of cardiovascular disease (CVD) risk.

Insulin resistance occurs physiologically during puberty, but it predisposes children to develop abnormal glucose tolerance, diabetes, hypertension, and polycystic ovary syndrome in girls [17].

Insulin resistance is a recognized pathogenetic factor in the development of PCOS and it is associated with overweight. The results of research on the decreased peripheral insulin sensitivity and  $\beta$ -cell function in children with the metabolic syndrome have recently been presented by Frithioff-Bøjsøe et al. [18].

Although PCOS is commonly associated with excessive body weight and obesity, a lean phenotype also exists. Most of the research concerns adult subjects. There is little information regarding the clinical presentation of PCOS in adolescents.

The purpose of this study was thus to characterize PCOS in adolescents, and to determine whether a distinct clinical presentation differentiates normal-weight (NW) and overweight (OW) PCOS patients [19].

Research by Silfen et al. indicates a more pronounced alteration in the hypothalamo-pituitary-adrenal axis in non-obese adolescents with PCOS and a dysregulation of insulin levels as well as the impairment of insulin sensitivity in obese patients [20]. This data also suggest differences in the IGF system between non-obese and obese adolescents with PCOS.

Based on the research conducted the Chinese authors, concluded that increased serum adipokine chemerin may be involved in the development of the pathogenesis of PCOS [21].

Discussions on defining the criteria of PCOS diagnosis in adolescent patients are still ongoing. The possibility of making the diagnosis of PCOS is controversial if a patient is adolescent. In fact, the same criteria (anovulation, hyperandrogenism, and polycystic ovaries) that are used for the diagnosis in adults, in adolescents may be transitory or within evolution [22].

The recognition of PCOS in adolescents is particularly challenging given significant age and developmental issues in this group. Menstrual irregularities with anovulatory cycles and varied cycle length are common due to the immaturity of the hypothalamic-pituitary-ovarian axis in the 2- to 3-year period post-menarche. In adolescent girls, large and multicystic ovaries are a common finding, so ultrasound is not a first-line investigation in women <17 years old. Ovarian dysfunction in adolescents should be diagnosed on the basis of biochemical evidence including free testosterone, serum 17-hydroxyprogesterone, and anti-Müllerian hormone [23,24].

Recently, authors from Turkey have reported the study conducted on 52 patients aged between 13-18 years. Patients were categorized according to 6 different criteria for PCOS. The study shows that the choice of particular guidelines has a great impact on whether an adolescent receives the PCOS diagnosis or not [25].

Recently reviewed diagnostic criteria for PC presented Merino et al [26].

## Insulin resistance in PCOS

Insulin resistance is believed to play an intrinsic role in the pathogenesis of PCOS. The mechanism by which insulin resistance or insulin itself gives rise to oligomenorrhea and hyperandrogenemia is, however, unclear [27].

It was found that both- obese and lean women with PCOS, have some rate of insulin resistance. Resistance to insulin is implicated in the ovulatory dysfunction in PCOS by disrupting the hypothalamic-pituitary-ovarian axis. Numerous researches have confirmed that insulin resistance and hyperinsulinemia are disruptions with early onset – possible to detect during childhood, which indicate the risk of PCO syndrome development [28–30].

The insulin resistance leads to compensatory hyperinsulinemia, which plays an essential role in the pathogenesis in the course of hyperandrogenism noted in PCOS [31].

Girls with PCOS have a decreased peripheral IS (insulin sensitivity), muscle mitochondrial dysfunction, abnormal glucose disposal, relative postprandial hyperinsulinemia, and an increased hepatic fat content in comparison with normal-weight controls [32].

It was shown with PCOS that impaired glucose tolerance is associated with a decrease in the first phase of insulin secretion, lowered glucose consumption rate and also with increased glucose production in the liver in obese girls with PCOS. These metabolic irregularities are already present in the early phase of PCO syndrome [33–35].

Early diagnosis of insulin resistance in PCOS is crucial due to the fact that PCOS constitutes not only a risk factor of glucose intolerance but also a very serious risk of developing cardiovascular diseases, presenting as, for instance, the progress of hypertension.

The results of a study recently submitted by American authors indicate that adolescent girls with PCOS have greater cIMT (carotid intima-media thickness) and stiffer arteries than girls without PCOS, which may perhaps be related to altered lipid metabolism. Therefore, the management of adolescent PCOS should include the assessment of CVD risk factors [36].

Studies on the risk occurrence of cardiovascular diseases in the population of patients with PCOS have also been conducted by Hughan et al [37]. The authors stated that, in adolescent girls, obesity and PCO syndrome appear to be associated with elevated CVD risk. The mentioned authors are of the opinion that further, long-term longitudinal studies are needed.

According to the relevant possibility of diabetes in patients with PCOS, the insulin sensitivity evaluation is recommended [38].

It is advisable to assess • fasting glucose and insulin levels (FGIR – fasting glucose-to-insulin ratio) • values of HOMA-IR (HOMA of insulin resistance) and HOMA- $\beta$ % (HOMA of percent  $\beta$ -cell function) • values of QUICKI (quantitative insulin-sensitivity check index) and insulin sensitivity ( $S_i$ ) measured in time of intravenous glucose tolerance test (FSIVGTT – frequently sampled intravenous glucose tolerance test).

For many years, the occurrence of PCO syndrome has been considered to be related to insulin resistance, associated with hyperinsulinemia and type 2 diabetes. Currently, there is an increasing number of reports emphasizing the presence of this syndrome amongst girls and women suffering from type 1 diabetes [30,39,40].

Recently, the French authors have presented results of the study conducted on 53 adolescent girls [41]. These authors found a high incidence of PCOS in adolescent girls with type 1 diabetes mellitus. It is not elucidated what is the mechanism leading to the concomitance of the mentioned disorders. Insulin resistance in type 1 diabetes may be the favorable factor for such correlation with PCOS. Resistance to insulin in patients with type 1 diabetes might be caused by impairments in the range of insulin receptors – that is their insufficient amount or improper functions. Abnormalities may also be connected with post-receptor processes within the destined cell.

## Therapeutic management

As the resistance to insulin and the accompanying hyperinsulinemia are among the basic disturbances of PCOS, coping with these phenomena is a crucial aim in PCOS treatment.

Studies, in which either insulinaemia lowering or enhancing insulin-sensitivity-enhancing medications were used, showed that, secondarily to reducing insulin concentration, a the decrease of androgen level occurs. In the treatment of insulin-resistance an essential role is played by changing one's lifestyle, which means increasing physical activity, revising nutritional habits, and reducing excess body weight. In case of insufficient efficacy of such behaviour, the implementation of pharmacological therapy might be necessary. Metformin, which enables the reduction of hyperandrogenism, is the drug of the first choice for the patients, including adolescents. [42–44].

The treatment method PCOS in juvenile patients is under discussion [45,46].

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