THE IMPACT OF POLYCYSTIC OVARY SYNDROME IN ADOLESCENT GIRLS

Brad Giorgiana[1,2], Marcovici Tamara [1,2], Craciun Adrian[1,2], Belei Oana[1,2], Popoiu Calin[1,2] , David Vlad[1,2], Vlad Mihaela[1,3], Marginean Otilia[1,2]

Abstract

Introduction: Polycystic ovary syndrome (PCOS) is a common endocrinology disorder in adolescence.

Objectives: To assess the phenotypes and biochemical parameters among adolescent girls diagnosed with PCOS and to estimate the metabolic syndrome among these cases.

Methods: Adolescent girls hospitalized in the Endocrinology Department of Children Emergency Hospital, Timisoara were evaluated clinically, anthropometric (height, weight, BMI), hormonal (estrogen, progesterone, testosterone, LH, FSH, SHBG, FAI), metabolic (glucose, oral glucose tolerance test, insulin, HOMA and lipid profile) and ultrasound (polycystic ovaries) for 3 years.

Results: According to Rotterdam criteria, 37 girl adolescents (mean age 16.7 ± 1.9 years) were diagnosed with PCOS. 88.23% of them had a body mass index higher than 75% percentiles for age. All were associated with irregular cycle, 72.97% of them with hirsutism and acne and 51.35% with polycystic ovaries. High levels of LH, testosterone and FAI and low level of FSH and SHBG were encountered. Oral glucose tolerance test was altered in 24.32% patients, hyperinsulinemia was found in 16.21% of them. Dyslipemia was identified in 10.81% patients, while the metabolic syndrome in 8.10% cases. Metformin was prescribed at adolescents diagnosed with insulin resistance (29.41%).

Conclusions: The presence of PCOS imposed extensive metabolic and hormonal tests. The lifestyle changes and metformin are the first-line intervention in obese adolescents

Key words: polycystic ovaries, obesity, insulin resistance, metabolic syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is the most common female endocrine disorder, affecting approximately 5-10% of all females and 4-6% of adolescent girls and young women[1]. It can be diagnosed in all phases of life - in young girls as 8-9 years of age till post-menopausal females. According to a common view PCOS is a multifactorial and polygenic in nature, but studies failed to identify genes responsible for PCOS[2].

PCOS is a hormonal disorder that involves multiple organ systems within the body, fact that explain the great variety of clinical presentations. Overproduction of ovarian androgens, increased luteinizing hormone secretion, incomplete maturation of ovarian follicle development and insulin resistance with compensatory hyperinsulinemia are some serious reproductive and metabolic. Common clinical findings include irregular menstrual cycles with anovulation, hirsutism and acne secondary to hyperandronism and polycystic ovaries. These symptoms can be accompanied by acanthosis nigricans, important sign of insulin resistance, obesity or infertility. Patients diagnosed with PCOS are predisposed to develop diabetes mellitus, endometrial carcinoma and cardiovascular disease[3,4].

Metabolic syndrome is associated with development of hyperandrogenism and PCOS, but the question is what was at the beginning: the metabolic syndrome or hyperandrogenism.

The symptoms of PCOS usually emerge at or soon after puberty, which may, in some cases, lead to a failure of diagnosis and potentially to a delay in the initiation of treatment.

Objective

The aims of this study were to assess the phenotypes and biochemical parameters among adolescent girls diagnosed with PCOS and to estimate the metabolic syndrome among these cases.

Material and methods

We performed a cross-sectional study of 37 adolescents (13-18 years old) with PCOS admitted in the Endocrinology Department of Children Emergency Hospital Timisoara from June 2011 to June 2014. These patients attained menarche more than 2 years before the study and were diagnosed with PCOS according to the Rotterdam 2003[5] criteria.

To put this diagnosis should present at least two of the following criteria:

[1]"Louis Turcanu" Children Emergency Hospital, Timisoara
[2]"Victor Babes" University of Medicine and Pharmacy, Timisoara
[3]General County Hospital, Timisoara
E-mail: giorgiana.brad@gmail.com, tmarcovici@yahoo.com, ad_craciun@yahoo.co.uk, belei.oana@gmail.com, mcpopoiu@yahoo.com, david.vlad@yahoo.com, mmvlad@excite.com, omarginean@ymail.com

1. oligo- and/or anovulation (< 6-9 menses per year or menstrual cycles more than 35 days in length);
2. clinical hyperandrogenism (acne or modified Ferriman-Gallwey scores ≥ 8 over 9 body parts) and/or biochemical hyperandrogenism (serum total testosterone ≥ 2.6 nmol/l, free testosterone ≥ 6.0 pg/ml)
3. polycystic ovaries (the presence of ≥ 12 antral follicles in one ovary measuring 2-9 mm in diameter and/or ovarian volume ≥10 cm^3)

Patients with abnormal cycle secondary to the congenital adrenal hyperplasia, androgen secreting tumors, Cushing's syndrome and hypothyroidism were excluded from the study.

All patients enrolled in the study were clinical examined and were noted down aspects suggestive for the androgen status (hirsutism, temporal recession of hair, acne) and insulin resistance (acanthosis nigricans). Ferriman-Gallwey score and acne scores were assessed and calculated by at least two observers.

Weight, height, body mass index (BMI), waist and hip circumferences and blood pressure were measured after the same standard protocols in all patients. Waist circumference was measured midway between the lowest rib and the iliac crest with the subject standing at the end of gentle expiration and hip circumference at the greater trochanters. Blood pressure was measured twice with oscillometric sphygmomanometer, with subjects seated quietly for at least 5 minutes and the readings were averaged as the final value.

They were asked to fill out a questionnaire on their menstrual cycle (age at menarche, cycle pattern, sexual activity, hormone treatment prescribed), family history and diabetic history.

After overnight fasting, blood samples were taken from adolescents in order to measure PRL, LH, FSH, estradiol, total testosterone, sex hormone-binding globulin (SHBG), DHEAS, 17-OHP, TSH and lipid profile. An oral glucose-tolerance test using 75 g of glucose was then performed and blood samples were taken at 0 and 120 min for glucose and insulin measurement. Manufacturer's instructions were followed for preparation, set-up, dilutions, adjustments, assay, and quality control procedures.

HOMA-IR was calculated using this formula: fasting plasma glucose (mmol/l) × insulin (mU/ml)/22.5 and insulin resistance was defined as the HOMA-IR value ≥ 95^{th} percentile. For the calculation of the Free Androgen Index (FAI), the next formula was used: total testosterone/SHBG × 100.

For the diagnosis of metabolic syndrome is requires the presence of three of the following criteria: waist circumference ≥80 cm, serum triglyceride ≥1.7 mmol/L, serum high-density lipoprotein cholesterol <1.3 mmol/L, blood pressure ≥130/85 mm Hg and fasting blood sugar of >100 g/dL[6].

The pelvic transabdominal ultrasound examination was performed by the gynecolog in order to evaluate the ovaries aspects using a mechanical 6-MHz probe.

Statistical tests were performed using SPPP version 19.00.This study was approved by the institutional review board of the Hospital and the informed consent was signed by the parents of the patients.

Results

A total of 37 patients fulfilled the inclusion study and were invited to participate to the study (Table no.1). The mean age of the patients was 16.7 (± 1.9) years, majority of them (81.08%) were from the urban are. Their mean age at menarche was 13.5 (±1.4) years and these girls were diagnosed with PCOS at 3.5 (±1.7) years after the menarche. Regarding the family history, almost a quarter of adolescent girls had their mother or sibyls diagnosed with hirsutism or PCOS.

Table no.1 The prevalence of the aspects characteristic for PCOS.

Aspects	Number of patients	Percent of patients
Irregular cycle	37	100%
Hirsutism, acne	27	72.97%
Biochemical hyperandrogenemia	23	62.16%
Ultrasound aspects of polycystic ovaries	19	51.35%

The duration of the cycle ranges between 35 and 43 days with a mean of 37.2±1.8 days. Acne was found in the majority of cases (64.86%) and the mean Ferriman-Gallwey scores was 13.5 (Table no.2). Among those who underwent clinical and ultrasound assessment, the characteristic aspects of polycystic ovary was detected in 51.35% patients suspected to have PCOS using Rotterdam criteria. All four signs/symptoms specific for PCOS were present in only 13.51% of the cases, 48.65% had three and majority (37.83%) had two symptoms/signs.

Table no.2 Clinical parameters of patients diagnosed with PCOS.

Variable	Mean ± SD
BMI (kg/m^2)	31.7 ±2.6
Waist circumference (cm)	79.1±1.3
Ferriman-Gallwey score	13.5±8
Global acne scores	5.3±4.2
Systolic pressure (mmHg)	110±14
Diastolic pressure (mmHg)	71±3

Among patients diagnosed with PCOS, 18.91% were non obese, 29.72% cases were overweight (BMI between 75th - 97th percentiles) and 51.37% were obese (BMI $\geq$ 97th percentiles). 16.21% of adolescents had acanthosis nigricans, while 56.75% of girls presented abdominal adiposity/central adiposity. The blood pressure was higher than the 95th percentiles for age and sex in 10.81% of cases.

In table no.3 the increased serum level of LH and testosterone and high FAI can be observed, while level of FSH and SHBG were decreased. The mean plasma glucose levels were normal in all PCOS cases except 9 patients (24.32%), where 2 h post 75 g plasma glucose value was above 140 g/dL. Hyperinsulinemia was present among 16.21% cases and 10.81% had serum triglycerides above normal. Insulin resistance was encountered in 18.91% of adolescent girls and 8.10 % of them were diagnosed with metabolic syndrome.

Table no. 3 Hormonal and biochemical aspects of patients diagnosed with PCOS.

Parameters	Mean ± SD	Parameters	Mean ± SD
FSH mIU/mL	3.9±1.2	Fasting blood sugar g/dL	74.2±7.5
LH mIU/mL	9.1±3.8	2-h post 75 g glucose g/dL	121.8±8.9
FSH/LH ratio	>2.7	Insulin µU/mL	14.1±10.2
Testosterone ng/mL	0.56±0.21	HDL mg/dL	47.7±6.7
SHBG nmol/L	52.6±24.3	Triglyceride mg/dL	68.4±14.6
Free androgen index	4.3±2.9		

Statistically, significant differences were observed between overweight and obese patients and non-obese PCOS girls regarding symptoms and biochemical and hormonal parameters. Obese and overweight girls were more hirsute (40.5%) and hypertensive (8.10%) and had higher mean values of post 75 g glucose and insulin and lower levels of SHBG compared with non-obese and the differences were statistically significant ($p<0.05$). No differences were found in the lipid profile of these two groups.

A hypocaloric diet with low carbohydrates and lipids intake was recommended for all overweight and obese girls, metformin were prescribed for all the patients with insulin resistance and oral contraceptives for the patients with polycystic ovaries.

Discussion:

The first report about seven women with amenorrhea hirsutism and bilateral polycystic ovaries was published by Stein and Leventhal in 1935[7]. Since then, the definition of PCOS has undergone several changes. According to the National Institutes of Health consensus conference held in 1990, the definition of PCOS consisted in the association of the chronic anovulation with clinical and/or biochemical hyperandrogenism[8]. In the year 2003, the Rotterdam European Society for Human Reproduction/ American Society of Reproductive Medicine proposed that the diagnosis of PCOS should include two of the following three criteria: oligo- and/or anovulation, clinical and/or biochemical hyperandrogenism and polycystic ovaries on ultrasound[9]. More recently, in 2009, the Androgen Excess and PCOS Society defined PCOS as a hyperandrogenic disturbance which included hyperandrogenism and ovarian dysfunction[10].

We used in this study the Rotterdam criteria to define PCOS because it extended the diagnosis to women polycystic ovaries with oligo-ovulation (non hyperandrogenic), as well as to women with hyperandrogenism, fact that allows us to study a great number of patients.

Because a history of menstrual irregularity is considered normal in the first 1-2 years after menarche secondary to anovulation, we decided to analyze only adolescent girls with oligomenorrhea more than 2 years postmenarche, this period of time being considered a good screening indicator to diagnose PCOS. Acne, the first sign of hyperandrogenism manifested in the adolescent and hirsutism observed in our patients examined were suggestive for the clinical hyperandrogenism, while the biological form suggested by the increased serum level of total and free testosterones were presented in the majority of the adolescents. 51.35% of girls were diagnosed at ultrasound with polycystic ovaries, but at 21.62% of patients, the ovarian morphology did not corresponded to the criteria of Rotterdam regarding the size or the number of the follicles.

The disease was confirmed if all three signs/ symptoms specific to PCOS were presented, fact observed in 48.65% of cases and the diagnosis was considered when only two signs/symptoms were observed[11].

According to the medical literature, prenatal exposure to androgens demonstrated in animal studies and in daughters of PCOS mothers and peripubertal obesity are important predisposing factors, which was observed in almost 25% of girls whose mother or sibyls had a history of PCOS and 88.23% of them had the BMI higher than 75% percentiles for age and sex[12,13].

Almost 80% of our adolescent girls with PCOS were obese, although this is not a criteria required for the diagnosis. It is well known that obesity plays an important role in PCOS contributing to hyperandrogenism, anovulatory cycles and infertility. Studies demonstrated that centrally deposited fat is metabolically active, releasing inflammatory cytokines being responsible for the adverse metabolic effects[14]. It worsens the underlying insulin resistance and insulin resistance-associated reproductive and metabolic features[15]. The pathophysiologic mechanism is

related to hyperinsulinemia induced by insulin resistance independent of the presence of the obesity[16]. In our study, the central obesity was highly associated with increased value of insulin, insulin resistance and metabolic syndrome.

PCOS can develop many complications such as insulin resistance and compensatory hyperinsulinemia, impaired glucose tolerance, dyslipidemia and metabolic syndrome. In order to prevent these serious disturbances, it is necessary to identify them as soon as possible and to take measures. Regarding the metabolic complications, we identified in this study a high prevalence of impaired glucose tolerance (24.32%), insulin resistance (18.91%), hyperinsulinemia (16.21%), dyslipidemia (10.81%) and metabolic syndrome (8.10 %). No patient was diagnosed with type 2 diabetes.

Similar prevalence of impaired glucose tolerance in obese adolescents with PCOS such as 29.6% and 27.3%, respectively[17,18] have been identified in two American studies. In a study enterprise in Turkey, in which obese and non-obese adolescents with PCOS were compared, increased values of blood pressure and blood serum levels of fasting insulin, lipids and testosterone were encountered in the obese group, much alike with our study results[19].

As PCOS is associated with a 10-fold risk to develop type 2 diabetes and a 2-fold increased rate of metabolic syndrome in adulthood, it is important to treat these adolescents[20,21].

It is important to keep in mind that insulin resistance and impaired glucose tolerance are important precursors to type 2 diabetes mellitus so quick measures should be taken. Lifestyle changes are a first-line intervention in adolescents with PCOS and consisted in diet, exercise, and appropriate weight control. The medication used in PCOS consisted in Metformin and oral contraceptives. Metformin prescribe in doses varying from 1.5 to 2.5 mg/day and divided into 2or 3 doses improve insulin resistance, hyperandrogenemia, and in some cases, anovulation, while decreasing hyperinsulinemia. Contraceptives (estrogen-progestin combination pills) are used for management of oligomenorrhea or amenorrhea and good results were obtained in patients with hirsutism and acne.

Conclusions:

1. PCOS is the most frequent endocrinology disorder diagnosed in adolescent girls and should be considered when irregular menses, excess weight, acanthosis nigricans or hirsutism are presented.

2. PCOS in adolescents imposed the testing for glucose intolerance and dyslipidemia particularly in the presence of obesity.

3. Lifestyle changes are the first-line intervention in young women with PCOS, who are overweight.

4. Management of the PCOS adolescent with metformin is beneficial and well tolerated.

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Correspondence to:
Brad Giorgiana Flavia
Iosif Nemoianu Street, No. 1-3, Timisoara, Romania
Tel: 0744649232
E-mail: giorgiana.brad@gmail.com