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Prevalence of the different phenotypes of polycystic ovarian syndrome in adolescents and its association to metabolic and cardiovascular risk

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Abstract:

BACKGROUND: Polycystic ovarian syndrome (PCOS) is a prevalent heterogeneous disorder in females. Timely diagnosis and management are important, especially in adolescents; despite this, there is a paucity of data focusing on this group.

OBJECTIVE: The aim of this study was to determine the prevalence of the different phenotypes of PCOS in adolescents and identify their association with metabolic and cardiovascular risk.

METHODOLOGY: All medical records of patients seen at the OPD of a tertiary institution from January 2015 to December 2019 that had a diagnosis of PCOS were reviewed. The data that were extracted included the patient's age, blood pressure at the time of consult, weight, height, signs and symptoms (anovulation and hirsutism), and laboratory results (transvaginal ultrasound, 75 g oral glucose tolerance test [OGTT], and lipid profile). Purposive sampling was done for this study.

RESULTS: The prevalence of phenotypes A is 31.9%, B at 31.9%, C around 5.8%, and D at 49.6%, respectively. Those Phenotype D adolescents had significantly higher body mass index (BMI) (P = 0.021), while those having phenotype B had significantly higher total cholesterol levels (P = 0.038). No significant differences were noted in the blood pressure, 75 g OGTT, low-density lipoprotein (LDL), very LDL, high-density lipoprotein, and triglycerides among the different PCOS phenotypes.

CONCLUSION: Adolescents with PCOS have an increased risk for metabolic and cardiovascular outcomes; however, there is no significant difference when compared across all phenotypes. It was among those having phenotype D that were found to have a BMI classified as overweight, and phenotype B have elevated total cholesterol levels.

Keywords:

Adolescents, phenotype, polycystic ovarian syndrome

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Introduction

Polycystic ovarian syndrome (PCOS) is a common reproductive disorder that affects more than 10% of the female population and affects 5%–10% of adolescent girls, irrespective of ethnic background (National Institution of Health, 2008). According to World Health Organization, Adolescence (age 10-19 years) is the period that includes significant and critical chanees in growth, development and puberty. In adolescents, PCOS is associated with a higher incidence of obesity and in first-degree relatives and patients with a history of premature adrenarche and diabetes.[1]

The causes of PCOS are still unknown, although it is characterized by chronic anovulation with oligo/amenorrhea and infertility, as well as clinical and biochemical hyperandrogenism.[2]

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The diagnosis in adults is well established with multiple guidelines; it is also established that this heterogeneous syndrome could present with four phenotypes in adults. Each phenotypic division presents with different cardiometabolic risk; hence identification helps in prognosticating the severity of the disease, which leads to earlier prevention of possible metabolic conditions such as diabetes and cardiovascular diseases. In adolescents, diagnosis of PCOS is challenging and controversial because the diagnostic criteria used in adults may be present in the normal pubertal physiological changes; there have also been limited international studies and no local studies regarding the phenotypes in adolescents.

Because of this difficulty, the risk of underdiagnosis and delayed diagnosis in PCOS adolescent patients increases.

Given the significant health implications related to PCOS, it is important to explore further the different phenotypes of PCOS to help advance our current knowledge with this heterogenous syndrome. Furthermore, this can aid in establishing its diagnosis with further characterization of the clinical metabolic profile of these patients and promote early and timely management of PCOS.

Review of related literature

PCOS in adults is diagnosed using the Rotterdam criteria, which emerged following a European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) conference in 2004.[3] Menstrual irregularity, symptoms or findings of hyperandrogenism, and polycystic ovaries on ultrasound are the three criteria used in the definition. However, in order to establish a diagnosis of PCOS only two of these three criteria are required.

It is important to remember that adolescence is a period of hormonal and reproductive transition, such that some girls will present with clear features of mature PCOS, whereas some with less clear and subtle signs suggestive only of the disorder.[4] Hence, the ESHRE/ASRM working group suggests formulating adolescent PCOS criteria. When PCOS is not clearly evident by adult standards (Rotterdam criteria), the diagnosis could be considered on the basis of the presence of increased serum androgen levels and/or progressive hirsutism, in association with persistent oligo/amenorrhea for at least 2 years after menarche and/or primary amenorrhea by age 16 years, and/or an ovarian volume >10 cm^3. This is done after the exclusion of secondary causes.[4]

PCOS is primarily characterized by ovulatory dysfunction (OD) and hyperandrogenism, which may manifest as hirsutism or acne. In adolescents with PCOS, hirsutism commonly occurs even before puberty.[5] It is also associated with insulin resistance and obesity, which appears to further amplify the severity of the presentation.[6]

The challenges in the diagnosis of PCOS in adolescents include the risk of underdiagnosis and delayed and poor diagnostic experiences. In addition, overdiagnosis as well as an additional risk of the use of inconsistent nonevidence-based approaches in the diagnosis and management of PCOS among specialists, general practitioners, and allied health professionals.

A computer-based literature search was done to find relevant articles for the study. The search terms PCOS, adolescents, and phenotypes, metabolic syndrome, cardiovascular diseases, impaired glucose tolerance test, and lipid profile, according to rank, were used. Union and intersection of the free text and MeSH terms were done, which yielded three articles that were relevant to the study.

In a prospective study done by Altintas *et al*. in 2017, a total of 144 Turkish adolescents were categorized into four phenotypes according to the presence of oligo/anovulation (O), hyperandrogenism (H), and polycystic ovarian morphology (P) as follows: Phenotype A (O + H + P), Phenotype B (H + O), Phenotype C (H + P), and Phenotype D (O + P). The incidence and the presence of parameters of metabolic syndrome were assessed among the four groups. About 54.9% of the adolescents with PCOS were overweight and 25.7% had metabolic syndrome. The incidence of metabolic syndrome in Phenotypes A is 39.5%, for Phenotype B is 20.5%, Phenotype C is 26.5%, and 15.2% for Phenotype D. Dyslipidemia was common in all phenotypes, the most common was low high-density lipoprotein-cholesterol (HDL-C), and this was present in more than half of the adolescents with PCOS. Insulin resistance was the same for all phenotype groups, while the body mass index was significantly higher in the Phenotype A group. Both body mass index and total testosterone levels were significantly higher in adolescents with metabolic syndrome in comparison to those without metabolic syndrome. They concluded that low HDL-C levels and insulin resistance are common PCOS findings in adolescents, and the metabolic profile seems to be worse in Phenotype A than the other phenotypes.[7]

In a study by Lakshmanan *et al*., a low HDL-C is associated with a higher risk of death from cardiovascular causes; furthermore, their study also showed that there is also a higher risk of death from cancer and other causes for those with low HDL-C compared with those having average levels of HDL cholesterol. On the other hand, insulin resistance can result in hyperglycemia, hypertension, dyslipidemia, visceral adiposity, hyperuricemia,

elevated inflammatory markers, endothelial dysfunction, and a prothrombic state.[8] Therefore, screening programs should evaluate patients based on the known risk factors and phenotypes in adolescents with PCOS.

In another study done by Fruzzetti *et al*., they studied 109 girls retrospectively and compared the phenotypes present among these patients. There were 63 patients in the adolescent age group (3–5 years beyond menarche), while 46 patients were young adults (6–9 years beyond menarche). Diagnosis of the different PCOS phenotypes was made according to the Rotterdam criteria. Menstrual cycles, body mass index (BMI), hirsutism, androgen circulating levels, and ovarian morphology by ultrasound were collected. Phenotype A was by far the most common phenotype (73.4%), followed by phenotype B (21.1%). Only a few patients had phenotype C (4.6%) or phenotype D (0.9%). When patients were divided into two groups (adolescent and young adult patients), no significant difference in prevalence and features of the different phenotypes was observed. In this study, they concluded that the prevalence and features of PCOS do not change with the progression of age.[9]

In one study done by Zore *et al*., they studied about the risks for obesity and acne. They enrolled 204 adolescents aged 13–18.9 years old and young adults aged 19–24 years old. They were categorized into four phenotypes (HIR + HA + OA, HA + OA, and HIR + OA). They found that there was minimal difference in the prevalence of the PCOS phenotypes, or component features, between adolescent and young adult patients. This study concluded that the PCOS phenotype is established in early adolescence and remains constant into adulthood.[10]

Hand search was done, which yielded one article relevant to this study. In a study done by Principe *et al*., at the same institution, they determined the prevalence of phenotypes of PCOS among adults; out of 169 records, 43.7% belonged to phenotype A. Phenotype A was significantly associated with hypertension (52.1%), abdominal obesity (54.7%), and type 2 diabetes mellitus (77.1%). Phenotype A was also associated with a decreased level of HDL. In this study, they also concluded that phenotype A was significantly associated with infertility when compared with other studies. However, this study only included patients >19 years old and did not include adolescents (Principe, 2005, unpublished data).[11]

Based on computer and hand search, there are no local publications that reviewed the phenotypes present among Filipino adolescent girls. According to the evidence available, it is important to establish the phenotype prevalent in one's region so as to be able to create better screening programs for metabolic illnesses, such as diabetes mellitus, and cardiovascular diseases.

Significance of the study

Worldwide, PCOS causes a burden not only in reproductive women but to adolescents as well. Women with PCOS were believed to have the same overall morbidity in terms of type 2 diabetes mellitus, coronary heart disease, dyslipidemia, cerebrovascular morbidity, and anxiety and depression later in life. However, recent studies show that PCOS has different phenotypes and may have differences in the previously mentioned risks; therefore, it may be treated differently.

There were limited literature locally to describe the demographic and anthropometric characteristics and hormonal profile of Filipino adolescent patients. Hence, the characterization of PCOS based on the Rotterdam criteria among Filipino adolescents would help clinicians develop a cost-effective and directed patient workup. This will facilitate the implementation of effective management, which includes preventive measures such as proper counseling on the metabolic and cardiovascular risks of patients. When effective management is carried out early, the complications of PCOS later in their life may be prevented. Hence, the lifelong consequences that cardiovascular risk brings can be reversed. Offering better health outcomes in their adulthood era and, subsequently, better quality of life.

Objective

General objective

To determine the prevalence of the different phenotypes of PCOS in adolescents in a tertiary hospital and its association with metabolic and cardiovascular risk.

Specific objectives

1. To determine the proportion of the different phenotypes among adolescents with PCOS
2. To compare the following clinico-metabolic parameters across the different PCOS phenotypes.
   a. Blood pressure
   b. Weight/body mass index
   c. 75 g oral glucose tolerance test (OGTT)
   d. Lipid profile (very low-density lipoprotein (VLDL), low-density lipoprotein [LDL], HDL, triacylglycerol [TAG], cholesterol).

Definition of variables and operational terms

a. Independent variable refers to the different phenotypes of PCOS and will be categorized, entered, and encoded as:
   1. Phenotype A: Presence of hyperandrogenism (HA) (clinical or biochemical), OD, and polycystic ovaries (PCO) in ultrasound

2. Phenotype B: Presence of hyperandrogenism (HA) (clinical or biochemical) and OD
3. Phenotype C: Presence of hyperandrogenism (HA) (clinical or biochemical) and polycystic ovaries (PCO) in ultrasound
4. Phenotype D: Presence of OD and polycystic ovaries (PCO) in ultrasound

b. Dependent variables refers to the clinicometabolic profile of the adolescents with PCOS
   a. Blood Pressure – This was based on American Association of Pediatrics blood pressure definitions and was measured in mmHg. It will be categorized, entered, and encoded as:
      1. Normal: systolic of <120 and diastolic of ≤80 mmHg
      2. Elevated: systolic of ≥120–129 and diastolic of ≤80 mmHg
      3. Hypertension: systolic of ≥130 and diastolic of >80
   b. Weight/body mass index – This will be derived based on the 2000 WHO Classification in adult Asians and measured in kg/m^2. This will be later categorized, entered, and encoded as:
      1. Underweight: <−3SD- to >−2SD
      2. Normal: <+1SD to >−2SD
      3. Overweight/Obese: >+1SD
   c. 75 g OGTT – This will be based on This was based on American Association of pediatrics guidelines on diabetes screening, and was measured in mg/dL. This was categorized, entered and encoded as: This will be measured in mg/dL and later categorized, entered, and encoded as:
      1. Normal
      2. Impaired glucose tolerance (2 h postprandial of >140–199 mg/dL) and impaired fasting glucose (fasting blood sugar [FBS] of >100–125)
      3. Diabetes (FBS ≥126 mg/dL and/or 2 h postprandial of ≥200 mg/dL
   d. Lipid profile – This will be based on the American Association of Pediatrics Guidelines "Lipid Screening in Children and Adolescents." This will be measured in mg/dL and later categorized, entered, and encoded as:
      1. Normal
         a. Total cholesterol: <170 mg/dL
         b. LDL <110 mg/dL
         c. VLDL <120 mg/dL
         d. HDL >45 mg/dL
         e. Triglycerides <90 mg/dL.
      2. Borderline
         a. Total cholesterol: 170–199 mg/dL
         b. LDL 110–129 mg/dL
         c. VLDL 120–144 mg/dL
         d. HDL 40–45 mg/dL
         e. Triglycerides 90–129 mg/dL.
      3. Abnormal
         a. Total cholesterol: >200 mg/dL
         b. LDL >130 mg/dL
         c. VLDL >150 mg/dL
         d. HDL <40 mg/dL
         e. Triglycerides >130 mg/dL.

Methodology

Research design

This is a retrospective cross-sectional study.

Setting and population

This study included the medical records of female adolescents aged 14–19 years old seen at the obstetrics and gynecology outpatient department of a tertiary private medical center with ultrasound from January 2015 to January 2019 diagnosed with PCOS. The diagnosis of PCOS had any two of the following:

1. Irregular or absent menstruation/ovulation
   - In adolescents, >1 year to <3 years postmenarche, menses occurring <21 days >45 days
   - >3 years post menarche to perimenopause: <21 or >35 days or <8 cycles per year.
2. Clinical signs of hyperandrogenism, such as hirsutism
   i. Modified Ferriman Gallwey score with a level >3
3. Polycystic ovaries on ultrasound
   a. Ovary containing 12 or more follicles measuring 2–9 mm in diameter
   b. Or an ovary that has a volume of >10 mL on ultrasonography. (A single ovary meeting either or both of these definitions is sufficient for the diagnosis of polycystic ovaries).

Inclusion criteria

Charts of female patients aged 14–19 years old who satisfied the diagnosis of PCOS with the following physical examination and laboratory tests were included:

- Blood pressure and weight
- 75 g OGTT
- Lipid profile.

Exclusion criteria

- Those female adolescents who were diagnosed to have PCOS but have an intake of hormones/drugs known to affect insulin sensitivity
- Patients who have been pregnant before.

Methodology proper

This was a retrospective study involving medical records of female adolescents aged 14–19 years old who consulted at the OBGYN outpatient department diagnosed to have PCOS. This study utilized purposive sampling. The principal investigator screened the charts for eligibility for inclusion in this study. The data that were gathered from the charts included age,

weight, height, body mass index, presenting signs and symptoms, history of medication use, menstrual bleeding pattern, and ultrasound result, and laboratory test results such as 75 g OGTT and lipid profile. A standard data collection tool was used to gather the necessary data.

Sample size calculation

Samples size was calculated based on the test of hypothesis for the difference of prevalence of triglyceridemia across different phenotypes of PCOS adolescent patients. Assuming that those with phenotype A prevalence of 40.7% and in among phenotype C, 23.5%, (Atintas, *et al*., 2017), with an alpha error of 5% power of 80%–90% and one-tailed alternative hypothesis sample size required is 61–84 per group or 244–336 for four groups. The study was able to meet the required sample size.

Data management and analysis

Data entry and encoding were done using Microsoft Excel. Data were analyzed using Stata version 9.0. Univariate analysis, such as mean and range, was used to describe the continuous variables such as age, weight, height, and body mass index, lipid profile levels, and 75 g OGTT value results. The categorized variables, which include PCOS phenotypes, BP range, BMI GROUP, OGTT, level, and lipid profile levels, were described using frequency distribution and percentage. The 95% confidence interval of the percentage was also calculated. The Chi-square test was used to analyze the dependent variables. For the analysis of the clinico-metabolic parameters measured quantitatively according to the PCOS phenotypes, ANOVA was used. Bonferroni ANOVA was used for multiple comparisons across the phenotypes. The level of significance was set at 0.05.

Ethical consideration

The study proposal, before its implementation, underwent review was approved by the technical and ethics review board of the Research Development office. Permission to retrieve and review the records was obtained from the office of the chief medical officer, the data privacy officer, and the medical records section.

This study complied with the Data Privacy Act of 2012. The anonymity and confidentiality of the records were ensured by assigning number codes on their data collection sheet. None of the identifiers or marks pertaining to the patient appeared on this paper.

This study is retrospective in nature, wherein no interaction nor direct risk was acquired by the patient hence informed consent was waived. All information regarding the outcome of the study remained confidential. Only the principal investigator had access to the medical records of the participants. The data collected was stored in a password protected file.

The data collected will be erased 5 years after the final paper has been submitted and approved for publication. The results of the study shall be available to the participants and to the department for their perusal.

Results

All OPD charts that had a diagnosis of PCOS were reviewed if eligible for the study. A total of 260 chart records of adolescents were retrieved from the medical record section. The age range of the case records was 14–19 years old, with a mean of 15.8 years old. Among women adolescents, 129 (49.6%) belonged to Phenotype D, about 83 (31.9%) to Phenotype A, while 33 (12.7%) to Phenotype B, and the least common is Phenotype C which only comprised 5.8% (n = 15) of the total population.

The mean systolic BP of all the records retrieved was 105 for systolic blood pressure with a range of 90–130 and 69 for diastolic blood pressure that ranged from 60 to 90 mmHg. When BP was categorized, there were four case records having BP considered elevated for age, two each from phenotype A and D. For those with BP elevation, the recorded BP was 130 mmHg SBP and 80–90 mmHg DBP. When the BP levels were compared across all phenotypes, there was no statistically significant difference [Table 1].

Across all the phenotypes, the mean BMI was 22.9, which fell under the overweight/obese category for age. When compared across the four phenotypes, those with phenotype D had the highest mean BMI at 22.63, followed by phenotype A (22.43), then phenotype C (22.13) and D (22.11), which was statistically significant. However when the BMI was categorized as underweight,

Table 1: Comparison of blood pressure across polycystic ovarian syndrome phenotypes

BP parameter	A	B	C	D	*P*
SBP, mean (±SD)	105.42 (±1.0)	104.54 (±1.63)	106 (±1.63)	105.19 (±0.86)	0.253
DBP, mean (±SD)	68.31 (±0.83)	69.69 (±1.40)	72 (±1.44)	68.91 (±0.68)	0.470
BP category					
Normal	81 (97.6)	33 (100)	15 (100)	127 (98.4)	0.761
Elevated	2 (2.4)	0	0	2 (1.5)	

SD: Standard deviation, BP: Blood pressure, SBP: Systolic BP, DBP: Diastolic BP

normal, and overweight/obese, the differences across phenotypes were not statistically significant [Table 2].

Majority of the charts reviewed had normal 75 g OGTT. The mean FBS was 76.25, ranging from 54 to 112. However, Impaired glucose tolerance test levels were noted at 7.8% (N=10/129) for those with phenotype A and 7.2% (N=6/83) for those with phenotype D. There was no significance found when the 75 g OGTT parameters of all case reports were compared, whether categorized or not, as seen in Table 3.

As for the lipid profile, in the total population, the mean total cholesterol level was 162.48 mg/dL (+14.7). Out the 260 case reports, 61 (23.46%) has significantly elevated total cholesterol ($P < 0.05$), but when categorized and was compared across phenotypes, no statistically significance was found. With regard to LDL, VLDL and TAG levels for all phenotypes were mostly normal. The mean LDL was 85.6 mg/dL ranging from 62 to 137 mg/dL, while all case reports had normal VLDL. For the TAG, the mean value was 72.12 (+16.75) mg/dL. Meanwhile, the mean HDL level was 45.17, ranging from 38 to 53 mg/dL. It is noteworthy that 37.69% of case records had borderline low levels (40–45 mg/dL), and 21.15% had low HDL levels (<45 mg/dL), but this was found statistically insignificant [Table 4]. As mentioned above, all parameters were not significantly different across the four phenotypes.

Discussion

PCOS is a complex, heterogeneous disorder that frequently manifests during puberty. It affects more than 10 percent of the female population and affects 5%–10% of adolescent girls.[1] Despite the burden of the disease in adolescents, only few studies have been made to identify their phenotypic prevalence and whether the identification of such is beneficial.

Identification of phenotypes of PCOS in adults has been shown to be important in multiple studies. In a local study done by Principe *et al*., in Filipino adults, it was noted that phenotype A poses the greatest risk for cardiometabolic diseases. This was also seen in a study done by Sachdeva *et al*., wherein they have noted that among Caucasians full-blown PCOS (phenotype A) is the most prevalent (67.7%) and at the same time they are at a higher risk of adverse metabolic and cardiovascular outcomes as compared with the others.[12] In studies done by Fruzzetti *et al*. among Mediterranean adolescents and young adults, and by Altintas *et al*. among Turkish adolescents, the prevalence of Phenotype A was by far the most common phenotype, followed by phenotype B, C with phenotype D being the least.[9,7] In the same studies, they also both concluded that adolescents with PCOS had a greater risk for metabolic syndrome when compared to healthy adolescents.[10]

In this study, we reviewed and categorized 260 charts and were categorized into four phenotypes according to the presence of oligo/anovulation (O), hyperandrogenism (H), and polycystic ovarian morphology (P) as follows: Phenotype A (O + H + P), Phenotype B (H + O), Phenotype C (H + P), and Phenotype D (O + P). In contrast with the studies cited above, our results showed that phenotype D (OD and polycystic ovaries) was the most common which was 49.6%, followed by phenotype A (31.9%), B (12.7%), and the least is phenotype C (5.8%). The difference in the distribution of phenotypes may be attributed to the ethnicity of the population. Asians are much less likely to present with hirsutism resulting from an androgen excess state compared with their Mediterranean counterparts (26). In our study, most cases reported had ODs (Phenotypes A, B, and D), phenotype C, the ovulatory type of PCOS was the least common group. These cases with hyperandrogenic symptoms such as acne and hirsutism are more likely to consult dermatologists than gynecologists. Hence, there is a chance that these women were not accurately accounted for.

Overweight and obesity in childhood are known to have a significant impact on both physical and psychological health. Overweight and obese children are likely to stay obese into adulthood and more likely to develop diabetes and cardiovascular diseases at a younger age. In our study, 36.18% of the total population was overweight/obese majority belonging to Phenotype D, followed ($P < 0.05$).

Increased total cholesterol levels are associated with high cardiovascular disease risk in adolescents in the future. In this study, a significant portion of the population (23%) had elevated total cholesterol

Table 2: Comparison of body mass index across polycystic ovarian syndrome phenotypes

BMI parameter	A	B	C	D	*P*
Mean (±SD)	22.43 (±0.52)	22.11 (±0.71)	22.13 (±1.21)	22.63 (±0.53)	0.021*
BMI					
Underweight	6 (7.2)	0	2 (1.3)	8 (6.2)	0.171
Normal	52 (62.7)	27 (81.81)	8 (53.33)	74 (57.3)	
Overweight/obese	25 (30.1)	6 (18.18)	5 (33.33)	47 (36.4)	

*Statistically significant *P*<0.05. SD: Standard deviation, BMI: Body mass index

Table 3: Comparison of 75 g oral glucose tolerance test across polycystic ovarian syndrome phenotypes

75 g OGTT parameter	A	B	C	D	*P*
FBS, mean (±SD)	76.39 (±1.23)	78.33 (±1.50)	77.26 (±2.75)	75.51 (±1.03)	0.239
1 h, mean (±SD)	123.99 (±3.2)	119.87 (±3.84)	115.20 (±5.16)	119.80 (±2.07)	0.051
2 h, mean (±SD)	88.78 (±3.01)	83.12 (±3.62)	85.2 (±5.95)	84.35 (±2.01)	0.174
75 g OGTT					
Normal	76 (91.56)	32 (96.9)	14 (93.3)	119 (92.2)	0.799
Impaired fasting glucose tolerance	6 (7.22)	1 (3.0)	1 (6.6)	10 (7.8)	
Diabetic	1 (1.2)	0	0	0	

*Statistically significant *P*<0.05. SD: Standard deviation, OGTT: Oral glucose tolerance test, FBS: Fasting blood sugar

Table 4: Comparison of lipid profile across polycystic ovarian syndrome phenotypes

Lipid profile parameter	A	B	C	D	*P*
Lipid profile levels (±SD)					
Cholesterol	161.89 (±1.61)	163.96 (±2.04)	157.26 (±2.47)	163.10 (±1.40)	0.038*
LDL	85.54 (±1.59)	86.51 (±2.34)	79.60 (±2.08)	86.10 (±1.2)	0.090
VLDL	32.27 (±0.79)	32.36 (±1.11)	31.06 (±1.06)	33.41 (±0.72)	0.205
HDL	45.10 (±0.73)	45.33 (±1.17)	46.73 (±2.03)	44.99 (±0.71)	0.245
TAG	71.02 (±1.74)	71.24 (±2.4)	68.33 (±3.66)	73.5 (±1.60)	0.211
Lipid profile levels					
Cholesterol					
Normal	61 (73.49)	22 (66.66)	14 (93.33)	97 (75.19)	0.614
Borderline	21 (25.30)	10 (30.30)	1 (6.66)	29 (22.48)	
Elevated	1 (1.2)	1 (3.03)	0	2 (2.32)	
LDL					
Normal	74 (89.15)	32 (96.96)	15 (100)	123 (95.34)	0.124
Borderline	8 (9.63)	0	0	3 (2.32)	
Elevated	1 (1.2)	1 (3.03)	0	3 (2.32)	
VLDL					
Normal	83 (100)	33 (100)	15 (100)	129 (100)	
Borderline	0	0	0	0	
Elevated	0	0	0	0	
HDL					
Normal	35 (42.16)	12 (36.36)	7 (46.66)	53 (41.08)	0.409
Borderline	29 (34.93)	17 (51.51)	7 (46.66)	45 (34.88)	
Elevated	19 (22.89)	4 (12.12)	1 (6.66)	31 (24.03)	
TAG					
Normal	74 (89.15)	31 (93.93)	14 (93.33)	108 (83.72)	0.661
Borderline	9 (10.8)	2 (6.06)	1 (6.66)	20 (83.72)	
Elevated	0	0	0	1 (0.77)	

*Statistically significant *P*<0.05. LDL: Low-density lipoprotein, VLDL: Very LDL, HDL: High-density lipoprotein, TAG: Triacylglycerol

levels, those with Phenotype B had the most elevated results, followed by Phenotype D and A. However, significant differences were noted in blood pressure, 75 g OGTT (fasting, 1-h postprandial, 2-h postprandial), and other lipid profile parameters (LDL, VLDL, TAG, HDL) [Tables 3 and 4]. One striking result, which is also congruent with the results of Fruzetti *et al*., is the the low HDL levels observed in adolescents with PCOS. Borderline levels are at 53.17% and 23.46% had low HDL levels, which is low.

Once the diagnosis of PCOS has been established in an adolescent girl, she should be screened for metabolic abnormalities. Knowing the results of this study, these adolescents have increased cardiometabolic risks, and it can manifest at an early age. The increased prevalence of high BMI and elevated total cholesterol at such a young age underscores the importance of regular screening of this population to decrease the future risk of diabetes and cardiovascular diseases.

Although the recommendation by our local society in diagnosing PCOS in adolescents is mainly through signs and symptoms such as hyperandrogenism and anovulation (irregular menstruation) and not through ultrasound, the finding of polycystic ovarian morphology in ultrasound is still helpful in the categorization of adolescents according to phenotypes. Furthermore, according to the study by Fruzzetti *et al*., the progression of age does not change the prevalence and the features of main PCOS phenotypes, hence performing pelvic ultrasound among adolescents who do

not have the classic anovulation, is not harmful and may be used to complete the diagnosis of this adolescents. Limiting ultrasound to only those who have ovulation might have caused the decrease in the prevalence of phenotype C (HA + P) in multiple studies. They also have suggested that the Rotterdam criteria might be used also in adolescents, at least in those with 2 or more years of gynecological age, for the diagnosis of PCOS.

Conclusion

In this study, phenotype D is the most prevalent phenotype of PCOS in adolescents; this same phenotype D has the highest BMI, which may suggest a higher risk of metabolic and cardiovascular outcomes in the future. Phenotype B has the highest total cholesterol levels. Knowing the phenotype of adolescents would help clinicians properly screen, guide and counsel patients regarding health risks. In addition to that, efficacious lifestyle management with specific phenotypes can be facilitated to improve the therapeutic approach and prevent long-term complications.

However, the results of this study are not robust enough to suggest that phenotypic division in adolescents helps in predicting adverse metabolic and cardiovascular outcomes in the future.

Recommendation

The main limitation of our study is its retrospective nature. Because of this, the cases that we gathered per arm were unequal. For a more accurate comparison between PCOS phenotypes a prospective study with equal participants per arm is therefore recommended. Future studies may also include comparison of metabolic profile between adolescents with and without PCOS. A biochemical test could also be done in order to accurately assess the hyperandrogenism such as free testosterone since Ferriman-gallwey scoring is highly subjective. It is also worthwhile to determine the phenotypes of the same patients when they become adults and whether PCOS will persist in those who do not seek treatment which entails longer follow up.

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Conflicts of interest

There are no conflicts of interest.

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