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ORIGINAL ARTICLE

Comparison of Levels of Androgenic Hormones in various Phenotypes of Polycystic Ovarian Syndrome in High School Girls aging 14 to 18 Years

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ABSTRACT

Introduction: Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women. Polycystic ovarian syndrome is mainly diagnosed based on oligomenorrhea or amenorrhea accompanied by clinical or laboratory evidence of hyperandrogenemia. This study aimed to compare the levels of androgenic hormones in various phenotypes of PCOS in high school girls aged 14 to 18 years in 2009.

Materials and methods: This cross-sectional study was conducted on 3200 girl students aged 14 to 18 years. The research community included high school girls in different educational districts of Shiraz. After obtaining written informed consents, demographic questionnaire was completed and clinical signs of increased androgens (acne, hirsutism and alopecia) were recorded. In addition, ultrasound for cyst was performed for the students with menstrual disorders.

Results: The mean age of the study population was 16.17 ± 1.25 years. Hyperandrogenism and polycystic ovaries phenotype compared to other phenotypes were more prevalent (45 patients, 30.8%) in the study population. In addition, the mean testosterone, free testosterone (FT), and dehydroepiandrosterone sulfate (DHEAS) levels were higher in the patients with polycystic ovaries and hyperandrogenism. However, the results of independent t-test revealed no significant difference between the patients with polycystic ovaries and hyperandrogenism and noninfected participants regarding the mean hormone levels ($p > 0.05$). Yet, the correlation was significant in the other three phenotypes ($p < 0.05$). Moreover, 144 cases (4.6%) suffered from oligomenorrhea, 29.5% of whom presented PCOS symptoms in the ultrasound.

Conclusion: Androgenic hormone levels were higher in the PCOS phenotypes with menstrual disorders, particularly oligomenorrhea. Therefore, compared to other symptoms of hyperandrogenism and ultrasound, menstrual disorders were more important in PCOS.

Keywords: Androgen, Girls, Hormones, Phenotype, Polycystic ovarian syndrome.

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the common complex endocrine disorders of the reproductive ages with variable prevalence rates and clinical presentations.[1,2] The prevalence of PCOS has been reported to vary from 6 to 10% in different studies infertile women[3-5] in another study. The prevalence of PCOS among adolescents was 22.5% by Rotterdam and 10.7% by Androgen Excess Society criteria.[6] In Iran, the prevalence of this disorder was estimated to be 7% based on National Institute of Health (NIH) criteria and 15.2% based on Rotterdam criteria.[7] Polycystic ovarian syndrome has a complex pathophysiology and its etiology is not known yet. Adult and adolescent women with hyperandrogenemia have a change in endocrine function with rapid and stable luteinizing hormone (LH) pulse frequency which results in gonadotropin releasing hormone (GnRh) stimulation and increase in serum LH concentration, eventually leading to hyperandrogenism and ovulation disorders.[8] Recent studies have also indicated that a similar abnormality is

detected in a number of adolescents with hyperandrogenism.[9]

Fruzzetti et al (2008) investigated female adolescents with PCOS and concluded that different phenotypes (oligomenorrhea, hirsutism, hyperandrogenemia, and PCOS) were associated with different metabolic disorders related to increase in androgen levels, and that hyperandrogenemia was a risk factor for dyslipidemia. Thus, they recommended that the adolescents suffering from this syndrome had to receive consultation to prevent the long-term complications of the disease.[10]

Polycystic ovarian syndrome has prepubertal origin in a large number of women because its clinical symptoms begin before puberty. This has been supported by detection of morphology of polycystic ovaries and clinical presentations of androgen increase in prepubertal girls.[11]

According to European Society of Human Reproduction and Embryology and American Fertility Association in 2003, having two out of the three of the following criteria was diagnosed as PCOS: (1) oligomenorrhea or amenorrhea, (2) clinical hyperandrogenism or hyperandrogenemia, and (3) polycystic ovaries in ultrasound (more than eight follicles in each ovary) and rejection of other etiologies.[12] The patients with two or more of the above-mentioned criteria are diagnosed with PCOS. Accordingly, four phenotypes of PCOS can be taken into account: (1) PCOS and clinical hyperandrogenism, (2) PCOS and oligomenorrhea, (3) oligomenorrhea and clinical hyperandrogenism, and (4) PCOS, oligomenorrhea, and clinical hyperandrogenism.[13] Characteristics of different phenotypes of polycystic ovary syndrome, according to the Rotterdam criteria, 2003, is described in Table 1.[14]

Up to now, a limited number of studies have been conducted on PCOS in adolescents. On the other hand, the complications of this disorder can be prevented by early diagnosis and conservative treatment. Due to the unknown etiology and lack of any specific treatment for PCOS, this disorder is considered as one of the main priorities of preventive medicine in developed countries. Therefore, this study due to the following reasons is the separation of phenotypes of PCOS:

Table 1: Characteristics of different phenotypes of PCOS

Polycystic ovarian syndrome phenotype	*Anovulation (oligomenorrhea)*	*Hyperandrogenemia*	*Polycystic ovaries in transvaginal ultrasonography*
Severe PCOS	+	+	+
Anovulation and hyperandrogenemia	+	+	–
Ovulatory PCOS	–	+	+
Mild PCOS	+	–	+

- In a study of adolescent girls with polycystic ovary syndrome, it was concluded that having different phenotypes associated with various metabolic disorders is associated with increased androgen.[10]
- Most studies have examined the overall syndrome[13,15-17] and few studies have been conducted on the phenotype of the syndrome in Iran.
- In a study, it has been shown that among the four phenotypes PCOS, in the hyperandrogenism and PCOS phenotype, patients had low cholesterol, low-density lipoprotein-cholesterol (LDL-C), total cholesterol and BMI. Then, it was concluded that the lowest risk of cardiovascular disease compared with other phenotypes.[18] Thus, the present study aimed to compare the levels of androgenic hormones in different phenotypes of PCOS in 14 to 18 years old high school girls in 2009.

MATERIALS AND METHODS

The present study was approved by the Ethics Committee of Shiraz University of Medical Sciences. This descriptive, cross-sectional study was conducted on 3200 girl students, about 14 and 18 years old, studying in high schools of Shiraz. The research was conducted in the high schools located in different educational districts of Shiraz. This environment was selected because of the availability of 14 to 18 year old girls and having easy access to the research groups. The research community included all the high school students studying in the four educational districts of Shiraz based on the previous studies[19] and considering confidence interval (CI) of 95%, p = 3.5%, d = 0.7%, z = 1.96, $\alpha = 0.05$. Using the following formula, we determined a 2648 subject sample size for the study. Yet, considering the loss rate of 20%, the sample size was increased to 3200 subjects, $n = \frac{z^2 p(1-p)}{d^2}$.

Sampling in the first stage was based on cluster sampling. Between 41 and 16 public high schools were selected as a cluster. In the second stage in each cluster, the girls were selected through simple purposive sampling.

The inclusion criteria of the study were being 14 to 18 years old, being willing to participate in the study and signing written informed consents, not suffering from adrenal and thyroid problems, and not having hyperprolactinemia. On the other hand, the exclusion criteria of the study were not being willing to participate in the study and suffering from diseases, such as thyroid problems, hyperprolactinemia, and adrenal problems, leading to withdrawal from participation in the study.

At first, the researcher explained PCOS and its long- and short-term complications to the participants and obtained written informed consents. Then, the participants completed the demographic information questionnaire.

Afterward, the modified Ferriman-Gallwey scale was used in it, scores >6 were considered as hirsutism.[20] Besides, alopecia was recorded in Ludwig's form based on the androgenic alopecia standards.[21,22] Finally, acne was classified into weak, average and severe categories. These symptoms were evaluated through examination and interview. Thereafter, the participants suffering from menstrual disorders underwent abdominal ultrasound to determine the existence of cysts. In doing so, the ovaries were scanned in both longitudinal and transverse planes and their volumes were computed using oval's volume formula. The criteria for diagnosis of PCOS in the sonography were similar to those employed by Adams et al,[23] the most important of which being existence of 10 small peripheral follicles. It should be noted that the sonography specialist was unaware of the patients' clinical examinations and the results of their biochemical tests. Therefore, in case the patients had 10 or more 2 to 8 mm cysts in the peripheral view or several 2 to 4 mm cysts in diffuse view, they were diagnosed with PCOS.[24,25] Also, in case the patients had the clinical or biochemical symptoms of hyperandrogenism or suffered from menstrual disorders together with PCOS and no reasons for androgen increase were detected, PCOS was diagnosed.[26,27]

STATISTICAL ANALYSIS

The data were analyzed through SPSS statistical software (version 18). For measuring demographic variables, Chi-square and independent sample t-test were used. In addition, the mean levels of hormones were compared through independent sample t-test and Fisher's test. Besides, $p < 0.05$ was considered as statistically significant.

RESULTS

The mean age of the study population was 16.17 ± 1.25; they were mostly aged 17 years (964 patients, 30.2%) respectively.

Out of 3240 patients, 34 had hypothyroidism, five had elevated prolactin, one had hypothalamic amenorrhea, and 10 had a loss; all of these people were excluded from the study and the results were compared with 3190 students. One hundred and thirty-eight individuals from the population-based on Rotterdam criteria, 2003, PCOS was diagnosed by an endocrinologist (the overall prevalence of the syndrome was 4.32%).

In the present study, among of 138 girls with PCOS, 21 presented phenotype 1 (14.4%), 29 phenotype 2 (19.9%), 45 presented phenotype 3 (30.8%), and 43 presented phenotype 4 (29.5%) respectively. The mean levels of testosterone, free testosterone, and dehydroepiandrosterone sulfate (DHEAS) were higher in participants with hyperandrogenism and PCOS compared to others, but the difference was not statistically significant ($p > 0.05$) (Table 2). In addition, the mean levels of testosterone, free testosterone, and DHEAS were significantly higher in participants with hyperandrogenism and oligomenorrhea compared to those without hyperandrogenism and oligomenorrhea ($p < 0.05$) (Tables 3 to 5). According to the

Table 2: Mean of hormonal tests in hyperandrogenism and PCOS phenotype

Phenotype hormone	*Without HA* + PCOS** (n = 100) mean ± SD*	*With HA + PCOS (n = 45) phenotype*	*p-value*
TSH	3.62 ± 1.90	3.36 ± 1.58	0.38
FSH	5.96 ± 2.34	6.43 ± 2.34	0.26
LH	12.63 ± 15.18	14.84 ± 10.66	0.37
PL	13.27 ± 4.85	13.12 ± 4.84	0.86
Testosterone	0.607 ± 0.35	0.655 ± 0.26	0.42
Free testosterone	1.47 ± 0.81	1.63 ± 0.57	0.22
DHEAS	2.15 ± 1.35	2.26 ± 1.24	0.62

Independent sample t-test—HA*: Hyperandrogenism; PCOS**: Polycystic ovarian syndrome; TSH: Thyroid stimulation hormone; FSH: Follicle stimulation hormone; LH: Luteinizing hormone; DHEAS: Dehydroepiandrosterone sulfate

Table 3: Mean of hormonal tests in hyperandrogenism and oligomenorrhea phenotype

Phenotype hormone	*Without HA* + oligo** (n = 116) mean ± SD*	*With HA + oligo (n = 29) phenotype*	*p-value*
TSH	3.56 ± 1.8	3.51 ± 1.84	0.90
FSH	6.27 ± 2.45	5.43 ± 1.69	0.08
LH	13.50 ± 15.12	12.51 ± 7.73	0.73
PL	13.33 ± 4.99	12.77 ± 4.174	0.57
Testosterone	0.596 ± 0.32	0.726 ± 0.31	0.05
Free testosterone	1.45 ± 0.78	0.726 ± 0.56	0.03
DHEAS	2.09 ± 1.24	2.80 ± 1.44	0.004

Independent sample t-test—HA*: Hyperandrogenism; Oligo**: Oligomenorrhea; TSH: Thyroid stimulation hormone; FSH: Follicle stimulation hormone; LH: Luteinizing hormone; DHEAS: Dehydroepiandrosterone sulfate

Table 4: Mean of hormonal tests in oligomenorrhea and PCOS phenotype

Phenotype hormone	*Without oligo*+ PCOS** (n = 102) mean ± SD*	*With oligo + PCOS (n = 43) phenotype*	*p-value*
TSH	3.46 ± 1.79	3.75 ± 1.84	0.38
FSH	6.05 ± 2.61	6.23 ± 1.51	0.61
LH	13.14 ± 15.86	13.70 ± 7.80	0.82
PL	13.50 ± 5.07	12.55 ± 4.18	0.28
Testosterone	0.575 ± 0.30	0.732 ± 0.37	0.01
Free testosterone	1.38 ± 0.73	1.82 ± 0.72	0.001
DHEAS	2.09 ± 1.35	2.40 ± 1.21	0.18

Independent sample t-test—Oligo*: Oligomenorrhea; PCOS**: Polycystic ovarian syndrome; TSH: Thyroid stimulation hormone; FSH: Follicle stimulation hormone; LH: Luteinizing hormone; DHEAS: Dehydroepiandrosterone sulfate

Table 5: Mean of hormonal tests in oligomenorrhea, hyperandrogenism and PCOS phenotype

Phenotype hormone	Without oligo* + HA** PCOS*** (n = 124) mean ± SD	Without oligo* + HA** PCOS*** (n = 21) phenotype	p-value
TSH	3.56 ± 1.83	3.50 ± 1.69	0.89
FSH	6.17 ± 2.43	5.71 ± 1.70	0.41
LH	13.23 ± 4.77	13.77 ± 7.62	0.86
PL	13.27 ± 4.89	12.92 ± 4.56	0.76
Testosterone	0.59 ± 0.33	0.75 ± 0.26	0.03
Free testosterone	1.44 ± 0.76	1.92 ± 0.51	0.007
DHEAS	2.08 ± 1.29	2.76 ± 1.36	0.02

Independent sample t-test—Oligo*: Oligomenorrhea; HA*: Hyperandrogenism; PCOS***: Polycystic ovarian syndrome; TSH: Thyroid stimulation hormone; FSH: Follicle stimulation hormone; LH: Luteinizing hormone; DHEAS: Dehydroepiandrosterone sulfate

results, 670 subjects (12%) had menstrual disorders, while 2615 subjects (83.4%) had normal menstruation. Besides, 144 subjects (4.6%) suffered from oligomenorrhea. Polycystic ovarian syndrome was detected in 60.6% of the adolescents with abnormal menstrual cycles and 16.9% of those with normal cycles. The symptoms of PCOS were also observed in 29.5% of the participants with oligomenorrhea.

DISCUSSION

Ovarian hyperandrogenism is one of the main symptoms of PCOS. In general, ovaries produce great amounts of androstenedione and dehydroepiandrostenedione, but increase in serum testosterone is more common. The chemical symptoms of this syndrome include increase of LH level, increase of LH/FSH ratio to above 2.5, increase of androgen levels (testosterone and androstenedione), and insulin resistance.[28]

The results of the current study showed higher androgenic hormone levels in the three phenotypes with oligomenorrhea. Other research has also indicated that PCOS and increase in serum androgens were more prevalent among the adolescents with menstrual disorders.[29-31] Nonetheless, some studies have reported normal menstruations accompanied by PCOS.[31,32] Gil Junior et al conducted a study on the level of androgens secreted by the women with PCOS and revealed that 81.1% had biochemical hyperandrogenism and 62.2% had adrenal hyperandrogenism.[33]

The main cause of oligomenorrhea is hormonal disorders, such as an ovulation. The diseases leading to increase in androgen levels, including adrenal hyperplasia, PCOS, hyperprolactinemia, and thyroid disorder can also result in oligomenorrhea and signs, such as hirsutism and acne.[8] Nonetheless, even mild androgen disorders require treatment interventions. Since these disorders can be risk factors for diabetes, endometrial and breast cancer, cardiovascular disorders, and cerebrovascular diseases,[34] identification of these patients and determination of their prevalence rates are of great importance. Moreover, considering the fact that PCOS is one of the major causes of oligomenorrhea, accurate examination of the patients with oligomenorrhea regarding PCOS can contribute to timely diagnosis and treatment. Jonathan et al (2002) performed a study on 100 women below 35 years old who suffered from oligomenorrhea and reported PCOS in 51% of the participants.[35] In the study by Panidis et al (2012), phenotype 1 among other phenotypes of PCOS was the most common (48.2%) phenotype.[14] The studies by Dewailly et al (2006) and Guastella et al (2010) reading, but in our study phenotype 3 was more common.[36,37]

In the present study, PCOS was detected in 60.6% of the adolescents with abnormal menstrual cycles compared to 16.9% of those with normal cycles. Farquhar et al (1994) carried out a research on 255 healthy women and reported the prevalence of PCOS to be 21% through ultrasound. This puts using sonography for diagnosis of PCOS in doubt.[38]

In the study by Aali et al (2002), the specific view of PCOS was detected in 106 patients (81.5%).[39] Besides, Khoury et al reported polycystic ovaries in 69% of the patients.[40] Additionally, Van Hooff conducted a study in 2000 and showed PCOS in 28% of the girl adolescents with abnormal menstrual cycles compared to 9% of those with normal cycles. Also, PCOS was observed in 45% of the patients with oligomenorrhea.[41] The difference in the above-mentioned measures can be attributed to the difference in length and features of the disease.

The findings of the present study demonstrated higher blood levels of total testosterone, free testosterone, and dehydroepiandrostenedione in patients with oligomenorrhea compared to those with normal menstrual cycles.

In the study by Huang et al also, free testosterone (57.6%), total testosterone (33%), and dehydroepiandro stenedione (32.7%) increased in the women suffering from PCOS compared to the noninfected individuals.[42]

Van Hooff et al (1999) conducted a research on 2248 girl students about 14 to 17 years old with a mean age of 15.6 + 0.6 years to investigate the relationship between endocrine symptoms of PCOS and menstrual disorders. The study results indicated higher blood levels of LH, androstenedione, testosterone, DHEAS, and estradiol in the girls who suffered from oligomenorrhea compared to those with normal menstrual cycles. However, no significant hormonal difference was observed between the patients with other menstrual disorders, such as polymenorrhea and metrorrhagia, and those with normal menstrual cycles.[30]

In the study by Głuszak et al, the most prevalent phenotype of PCOS (60.2%) was type I phenotype (oligomenorrhea, hyperandrogenism and PCOS), and menstrual disorders were observed in 3 out of 4 phenotypes of this syndrome.[3] Also, in the study by Panidis et al, testosterone levels in the circulation were more than in the phenotype. One but a number of other studies have not confirmed the issue(s) and there have been no differences in testosterone levels in 4 phenotypes. In our study, testosterone levels were higher in the phenotype 1,2,4 compared to phenotype 3.[17,36,37,43,44]

Although insulin resistance was not discussed in our paper, the increase in polycystic ovary syndrome and some phenotypes of PCOS is important. Now insulin resistance (IR) is known as one of the major risk factors for type 2 diabetes mellitus.[45]

Even in nonobese women with PCOS, IR amounts to a slight increase. Approximately, 50 to 70% of women with PCOS have shown some degrees of insulin resistance.[46-49] The resistance can lead to obesity or it is independent of and associated with hyperandrogenism. Increased blood insulin directly effects the vascular endothelial cells and individuals with insulin resistance and metabolic syndrome are predisposed to vascular thrombosis.[50,51]

A previous study assessed the relationship between menstrual disorders and body mass index (BMI) and existence of polycystic ovaries in sonography in 15 years old adolescents with stable oligomenorrhea cycles up to the age of 18 years. The study findings revealed that the best predictor of oligomenorrhea cycles at the ages of 18 and above was menstrual disorders 1 year after menarche. They also stated that diagnostic value of menstrual disorders at the beginning of menarche was higher than that of high androgen and LH levels or existence of polycystic ovaries in ultrasound.[52] Therefore, it can be concluded that the diseases associated with androgen increase, such as PCOS, can lead to oligomenorrhea and other accompanying symptoms, such as hirsutism and acne.

In this study, androgenic hormone levels were higher in the phenotypes of PCOS with menstrual disorders, particularly oligomenorrhea. In a study which was conducted on 1002 women aged 18 and 45 years in Tehran, the prevalence of PCOS was 8.5%, and 13% of the women had menstrual disorders. They concluded that LH disorders and PCOS were the most common endocrine disorders in women at reproductive ages.[53]

Oligomenorrhea after menarche can be the beginning of ovulation problems, infertility, and abnormal increase in estrogen and androgens in the years to come. In one study, 21% of the women with hyperandrogenism and regular menstrual cycles showed anovulation.[36]

CONCLUSION

The mean levels of testosterone, free testosterone and DHEAS were higher in various phenotypes of PCOS compared to the control group. However, a significant relationship was observed in hyperandrogenism and oligomenorrhea phenotype. Furthermore, in comparison to other symptoms of hyperandrogenism and ultrasound, menstrual disorder was more important in PCOS. Thus, serum androgenic levels are recommended to be measured in young girls with menstrual disorders, so that the necessary measures can be taken for early diagnosis of this syndrome and the necessary preventive measures.

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