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## Survey of Cutaneous Manifestations in Adolescents Suffering from Poly Cystic Ovarian Syndrome

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### ABSTRACT

The adolescents suffering from Poly Cystic Ovarian Syndrome (PCOS) are concerned about weight gain, menstrual irregularities and cutaneous manifestation (hirsutism, acne and alopecia). The present study aimed to investigate the prevalence of cutaneous manifestations in 14-18 year old female high school students based on PCOS. This descriptive-analytical study was conducted on 3200 female students between 14 and 18 years old in 2009. The intensity of hirsutism was determined using modified Ferriman-Gallwey scale. In addition, the intensity of acne was classified based on the classification consensus conference on acne. Finally, alopecia was assessed using Ludwig's scale based on scalp and forehead line hair density. Experiments (prolactin, TSH, DHEAS, total testosterone and free testosterone), hyperandrogenism clinical features and sonography were performed. Then, the data were analyzed using Chi-square test. The prevalence of hirsutism, acne and alopecia were 3.2, 5 and 4.2%, respectively. The results revealed no significant relationship between the mean of androgens as well as suffering from PCOS and hirsutism and alopecia ( $p > 0.05$ ). However, a significant relationship was found between menstrual irregularities and hirsutism ( $p < 0.001$ ). Also, a significant relationship was observed between the testosterone level and PCOS ( $p < 0.001$ ). Among the cutaneous manifestations, severe acne and androgen level were significantly related to PCOS. Considering the consequences of acne in the girls' lives, hormonal screening and sonography are recommended to be performed in the girls with average acne and normal menstrual cycles, as well.

**Key words:** Alopecia, androgenic alopecia, acne, poly cystic ovarian syndrome, hirsutism

### INTRODUCTION

Poly Cystic Ovarian Syndrome (PCOS) affects 5-10% of the women in the reproductive age. This disorder which is one of the most prevalent endocrine disorders in women is identified by high

androgen and insulin levels (Lee and Zane, 2007). This complex, multispecialty disorder is more prevalent in the individuals with menstrual irregularities, obesity, insulin resistance, acanthosis nigricans, type II diabetes, dyslipidemias, hypertension, non-alcoholic liver diseases and obstructive sleep apnea (Lowenstein, 2006). Moreover, PCOS is the most common cause of hyperandrogenism. Evidence has shown that PCOS begins at puberty. Yet, disorders in ovarian androgens production may occur at puberty, childhood and even at the time of fetal growth (Franks, 2002; Vuguin, 2010).

In general, acne, hirsutism, alopecia, obesity and acanthosis are the cutaneous manifestations of PCOS. The clinical hyperandrogenism symptoms, such as hirsutism, acne and male features, occur in almost 66% of the adolescents suffering from PCOS. Hirsutism is the most prevalent clinical signs of hyperandrogenism in PCOS (Warren-Ulanch and Arslanian, 2006). Thus, the incidence of hirsutism in an adolescent directs the diagnosis towards PCOS (Plouffe, 2000). The prevalence of hirsutism has been reported to vary from 5-5% in various societies (Azziz, 2003; Azziz *et al.*, 2000). Some studies have also estimated the prevalence of hirsutism to be 5-25% among the premenopausal women (Azziz *et al.*, 2000). The incidence of hirsutism depends on the concentration of blood androgens as well as the genetic sensitivity of the hair follicles to androgens. Thus, anovulation and androgens increase can leave no sign of hirsutism (Speroff and Fritz, 2005). The study by Ferriman and Gallwey showed that only 5% of the society members had obtained scores of 6 or above (Ferriman and Gallway, 1961).

Acne vulgaris is one other common cutaneous manifestation of hyperandrogenism (Addor and Schalka, 2010). One of the most important features of such patients is development of several closed comedones changed into tenders, lumpy nodules in the lower half of face and jaw-line (V distribution). The incidence of acne usually lasts for 5-7 days and it is also possible to occur before the menstrual cycle. In addition to face, acne can also present on the chest, shoulder and back. Moreover, the individuals with acne may also have evidence of hirsutism and alopecia as well as a family history of PCOS (Archer and Chang, 2004). In one study, the incidence rate of acne was reported as 83 and 19% in the women with PCOS and control women, respectively. Besides, almost 80% of the women with severe acne, 50% of those with average acne and 30% of the women with mild acne showed increase in the blood androgen level (Bunker *et al.*, 1989). In the study increase in the androgen level was detected in all the patients with acne; however, only 19% of them suffered from PCOS (Borgia *et al.*, 2004).

Nonetheless, Female Pattern Hair Loss (FPHL) may not have androgenic origin in all the cases (Olsen, 2001). Thus, diagnosis of hair loss is quite difficult in the patients suffering from PCOS and those with other causes of hyperandrogenism.

Various clinical manifestations of alopecia have been described by Ludwig (diffuse), Hamilton (male pattern) and Olsen (frontal accentuation) (Olsen, 2001). Increase in androgen is usually detected in the women with FPHL. Hormonal effects lead to conversion of terminal hair to vellus hair eventually leading to baldness.

Alopecia is another cutaneous manifestation of PCOS. In female androgenic alopecia, diffuse thinning of hair is detected all over the scalp at first. In addition, nearly 40% of the women with androgenic alopecia suffer from a type of hyperandrogenism (Olsen, 2001). The results of one study showed the prevalence of hyperandrogenism to be 38.5% in 109 women who suffered from average to severe alopecia. Besides, 43% of these patients had the criteria of PCOS (Futterweit *et al.*, 1988). Acanthosis nigricans which is defined as dark velvety hyperpigmentation of skin is the first sign

of insulin resistance particularly in obese individuals. Acanthosis nigricans is mainly detected on the neck, armpit and groin (Madnani *et al.*, 2013).

The present study aims to determine the prevalence of cutaneous manifestations in 14-18 year old girls as well as their relationship with the amount of androgenic hormones and polycystic ovaries.

## **MATERIALS AND METHODS**

This descriptive, cross-sectional study was conducted on 3200 female high school students between 14 and 18 years old. According to the study in Isfahan and considering CI = 95% and loss rate of 30%, a 3200-subject sample size was determined for this study ( $p = 3.5\%$ ,  $d = 0.7$ ).

In this study, 800 students in 3-4 high schools were randomly selected from each educational district. The inclusion criteria of the study were being 14-18 years old, being willing to take part in the study, signing the written informed consents and not suffering from adrenal and thyroid problems as well as hyperprolactinemia.

At first, the researcher completed the study questionnaire including the demographic information and assessment of hirsutism, acne and alopecia. Then, by observing the ethical principles, the students were examined on face, back and chest in a room with sufficient light.

The intensity of hirsutism was determined at 9 anatomic areas based on the modified Ferriman-Gallwey scale. Accordingly, the scores of 0-6, 6-9, 10-14 and 15 and above were considered as no, mild, average and severe hirsutism, respectively (Ferriman and Gallwey, 1961).

In addition, acne was categorized based on the classification consensus conference on acne. According to this classification, acne is categorized into mild, average and severe groups. It should be mentioned that comedones, a large number of papules and pustules, nodules, cysts and scars exist in the severe form of acne. In this study, the severe form was considered as acne (Pochi *et al.*, 1991).

Regarding alopecia, in addition to the above-mentioned criteria, the following were taken into account, as well: Not having referred to treatment centers due to hair loss, pregnancy, childbirth and lactation during the last year, scalp disorders, kidney failure, cardiovascular diseases, uncontrolled insulin-dependent diabetes, history of using finasteride or 5-alpha reductase inhibitors during the past 12 months, recent consumption of pencillamine, isotretinoin, zydovirax, interferon and dutasteride, treatment by specific plants from the past 2 months, consumption of minoxidil, topical estrogen and progesterone, tamoxifen, anabolic steroids, lithium and phenothiazine, consumption of hypertrichosis causing drugs, such as cyclosporine, diazoxide, phenytoin and psoralen and consumption of anti-androgenic drugs, such as cyproterone acetate, spironolactone, ketoconazole, flutamide and beclotamide, in the past 6 months.

In this study, alopecia was defined by average and severe scalp as well as forehead line hair density according to Ludwig's classification (Ludwig, 1977).

Pelvic ultrasound was performed for the patients suffering from hirsutism, acne and alopecia. In this way, the ovaries were scanned in longitudinal and transverse planes and their volume was measured using the formula for computing an oval's volume. Afterwards, PCOS was determined based on the criteria of Adams *et al.* (1986) and Berker *et al.* (2004) the most important of which being the existence of 10 small peripheral follicles. It should be mentioned that the sonography specialist was not aware of the results of the patients' clinical examinations and biochemical tests.

Thus, in case the patients showed 10 or more 2-8 mm cysts in the peripheral view or several 2-4 mm cysts in the diffuse view, they were diagnosed with PCOS (Adams *et al.*, 1986; Swanton *et al.*, 2010). Also, in case the subjects had the clinical or biochemical symptoms of hyperandrogenism or PCOS-related menstrual irregularities while presenting no other causes of androgen increase, they were considered with PCOS (Takahashi *et al.*, 1994).

After providing the subjects with sufficient information about the hormonal and biochemical experiments, the experiments were performed at the Endocrine and Metabolism Research Center, Namazi hospital, Shiraz, Iran. The patients' hormonal evaluation was performed using morning blood including prolactin (for rejection of hyperprolactinemia), dehydroepiandrosterone sulphate (for rejection of adrenal disorders), total and free testosterone and TSH (for rejection of hypothyroidism). In case the amount of testosterone was twice as much the normal level, the necessary measures were taken towards rejection of neoplasm (Franks, 2002).

After all, the collected data were analyzed using descriptive statistics, Fisher's test, chi-square test and frequency distribution tables. All the statistical tests were performed considering CI = 95% and  $\alpha = 0.05$ .

## RESULTS

In this study, most of the participants (30.2%) were 17 years old. The prevalence of hirsutism was 3.2%. In addition, the mean of total (0.685±0.354) and free testosterone (1.647±0.835) was higher in the patients suffering from hirsutism compared to the normal subjects; however, the difference was not statistically significant ( $p > 0.05$ ) (Table 1 and 2).

The results of the present study showed menstrual irregularities in 12.1% of the subjects 88.2% of whom had mild to severe hirsutism. In addition, a significant relationship was observed between menstrual irregularities and hirsutism ( $p < 0.001$ ) (Table 3).

Table 1: Distribution of cutaneous manifestations in population

|                            | None |      | Mild |      | Moderate |      | Sever |        | Total |     |
|----------------------------|------|------|------|------|----------|------|-------|--------|-------|-----|
|                            | N    | %    | N    | %    | N        | %    | N     | %      | N     | %   |
| CM                         |      |      |      |      |          |      |       |        |       |     |
| Hirsute                    | 3090 | 96.8 | 79   | 2.4  | 17       | 0.6  | 4     | 0.2    | 3190  | 100 |
| Body acne                  | 730  | 22.9 | 1648 | 51.7 | 668      | 20.9 | 143   | 0.5    | 3189  | 100 |
| Face acne                  | 1395 | 43.7 | 1121 | 35.1 | 570      | 17.9 | 103   | 3.2    | 3189  | 100 |
| Alopecia moderate to sever | 3055 |      | 95.8 |      | 161      |      | 4.2   | 3190.0 | 100   |     |

CM: Cutaneous manifestations

Table 2: Mean testosterone and free testosterone levels in patients with hirsute, acne and alopecia in the study population

| CM                  | Total testosterone |             | Free testosterone |             | PV       |
|---------------------|--------------------|-------------|-------------------|-------------|----------|
|                     | N                  | M±SD        | N                 | M±SD        |          |
| Hirsute             | 56                 | 0.685±0.354 | 55                | 1.647±0.835 | p = 0.06 |
| Without hirsute     | 91                 | 0.582±0.305 | 89                | 1.444±0.687 | Df = 143 |
| Severe acne         | 33                 | 0.775±0.250 | 33                | 1.469±0.544 | p = 0.39 |
| Without severe acne | 114                | 0.634±0.346 | 111               | 1.537±0.803 | Df = 143 |
| Alopecia            | 17                 | 0.588±0.160 | 16                | 1.493±0.523 | p = 0.69 |
| Without alopecia    | 130                | 0.626±0.343 | 128               | 1.525±0.776 | Df = 143 |

CM: Cutaneous manifestations

Table 3: Correlation of hirsute, menstrual patterns in the study population

| Pattern of menstruation | Without hirsute |      |          |      |        |      |
|-------------------------|-----------------|------|----------|------|--------|------|
|                         | Mild            |      | Moderate |      | Server |      |
|                         | N               | %    | N        | %    | N      | %    |
| Normal                  | 2553            | 84.1 | 49       | 62   | 9      | 56.3 |
| Irregular               | 357             | 11.8 | 19       | 24.1 | 2      | 12.5 |
| Oligomenorrhea          | 4.2             | 127  | 11       | 13.9 | 5      | 31.3 |
| Total                   | 100             | 3037 | 79       | 100  | 16     | 100  |

X<sup>2</sup> = 60.65, Df: 6, p = 0.001

Table 4: Distribution of alopecia, hirsute and polycystic ovarian syndrome

| CM             | Without PCOS |      | PCOS |      | PV    |
|----------------|--------------|------|------|------|-------|
|                | N            | %    | N    | %    |       |
| Hirsute        | 24           | 16.4 | 122  | 83.6 | 0.001 |
| Alopecia       | 8            | 5.5  | 138  | 94.5 | 0.202 |
| Oligomenorrhea | 43           | 29.3 | 103  | 70.5 | 0.001 |

Table 5: Distribution of facial and body acne and polycystic ovarian syndrome

| Acne             | N  | %     | N   | %     | PV   |
|------------------|----|-------|-----|-------|--|
| <b>Face acne</b> |    |       |     |       |  |
| None             | 13 | 18.1  | 43  | 42.2  | X <sup>2</sup> = 11.800<br>p = 0.008<br>Df = 3 |
| Mild             | 29 | 40.3  | 33  | 32.4  |  |
| Moderate         | 17 | 23.6  | 15  | 14.7  |  |
| Sever            | 13 | 18.1  | 10  | 10.8  |  |
| Total            | 72 | 100.0 | 102 | 100.0 |  |
| <b>Body acne</b> |    |       |     |       |  |
| None             | 18 | 25.0  | 55  | 53.9  | X <sup>2</sup> = 17.836<br>p = 0.001<br>Df = 3 |
| Mild             | 22 | 30.6  | 15  | 14.7  |  |
| Moderate         | 17 | 23.6  | 23  | 22.5  |  |
| Sever            | 15 | 20.8  | 9   | 8.8   |  |
| Total            | 72 | 100.0 | 102 | 100.0 |  |

According to the results of Fisher's test, a significant difference was found between the subjects with hirsutism and PCOS and those suffering from hirsutism but not PCOS (p<0.001) (Table 4).

In this study, the frequency of severe acne on face and body was 0.5% (143 subjects) and 3.2% (103 subjects), respectively (Table 1). Besides, the mean of total testosterone (0.775±0.250) was higher in the participants with acne compared to those without acne. On the other hand, the mean of free testosterone (1.469±0.544) was lower in the subjects with severe acne compared to those without acne. However, the results of independent T-test revealed no significant difference between the two groups (Table 2).

Furthermore, 59 subjects with acne on their faces (82%) showed PCOS in ultrasound, which was significantly different from the subjects with acne who did not have PCOS (p<0.05) (Table 5).

Also, 75 participants (75%) with acne on their bodies showed PCOS in ultrasound. According to Fisher's test, a significant difference was found between the participants with body acne and PCOS and those suffering from acne but not PCOS (p<0.05) (Table 5).

Based on Ludwig's classification, 135 study participants (4.2%) had average to severe alopecia. Considering the features investigated for alopecia, 612 subjects (3.7%) had average to severe scalp hair loss, 38 ones (1.2%) had average and severe hair loss at temples and 45 participants (1.4%) had average and severe hair loss at forehead line (Table 1). However, no significant relationship was observed between total and free testosterone levels and alopecia hair loss pattern ( $p > 0.05$ ) (Table 2).

In this study, none of the study participants had prolactin and adrenal disorders. In addition, 34 subjects presented hypothyroidism and were referred to an endocrinologist for treatment. The results of Fisher's test revealed no significant difference between the subjects with alopecia and PCOS and those suffering from alopecia but not PCOS ( $p = 0.2$ ) (Table 4).

## DISCUSSION

In this study, the prevalence of hirsutism was 3.2% (almost 100 subjects). Some studies have reported the frequency of hirsutism as 2-8% (Ehrmann, 2005; Arslanian and Witchel, 2002). In addition, the review study conducted by Escobar-Morreale *et al.* (2012) in several countries showed the prevalence of hirsutism to be 4.3-10.8%. They also stated that the prevalence of hirsutism was lower in Asian countries (Knochenhauer *et al.*, 1998).

In females, ovarian and adrenal secretions and metabolism of prohormones secreted in peripheral tissues, such as fat, are androgenic sources. Overall, 70-80% of the patients with increase in androgens present hirsutism. Yet, genetic and racial differences can change the effects of androgens on the skin (Speroff and Fritz, 2005; Ludwig, 1977). One other reason for increase in hirsutism can be the sensitivity of the final organ to 5-alpha reductase activity (increase in conversion of testosterone to dihydrotestosterone). This enzyme is affected by genetic and racial factors and plays a role in the incidence of hirsutism (Escobar-Morreale *et al.*, 2012).

The findings of the current study showed no significant relationship between PCOS and hirsutism. In other studies, however, PCOS was shown to be the most common reason for increase in hirsutism (Greep *et al.*, 1986). In that study, 91 and 92% of the patients had PCOS. Among the girls with hirsutism in the present study, on the other hand, 33.3% had cystic ovaries and 26.5% lacked ovarian cysts. This lower prevalence might be due to the difference in sonography method. These results are on the contrary to those obtained in the study performed in United Arab Emirates (90%) as well as the one conducted by Adams *et al.* (1986) in England (Ibanes and de Zegher, 2004; Gatee *et al.*, 1996).

In general, vaginal sonography provides a better image of the ovaries, particularly in obese girls; however, it is not possible to be used in adolescents (Moran *et al.*, 1994). Moreover, 20-30% of the normal women show PCOS in sonography during the reproductive ages (Azziz, 2006).

In case hirsutism does not result from PCOS, it may be due to the type of testosterone measurement. In fact, free testosterone plays the key role in hirsutism and other hyperandrogenism symptoms. On the other hand, total testosterone can be within the normal range in the women with hirsutism because the active part of testosterone increases in these women and the free part increases from 1-2% (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

In the present study, 12.1% of the subjects with hirsutism had menstrual irregularities. This rate was lower compared to that reported in other studies which might be due to the lower prevalence of hirsutism in the study population. Menstrual cycles without ovulation during adolescence can lead to irregular menstrual cycles, as well. It should also be noted that regular

menstrual cycles cannot reject PCOS and adrenal hyperplasia (Rasgon *et al.*, 2003; Carmina and Lobo, 2001). For instance, Gatti's study showed that 25.2% of the PCOS patients had regular menstrual cycles (Michelmore *et al.*, 1999).

In this study, the prevalence of severe face and body acne was 5%. In the study by Kilkenny *et al.* (1998), mild acne was detected in 83% of the subjects, while average and severe acne was observed in 17% (Gatee *et al.*, 1996). In Oktan's study (Aktan *et al.*, 2000) also, 8.8% of the girls had average to severe acne (Kilkenny *et al.*, 1998). Moreover, Karciauskiene *et al.* estimated the prevalence of acne as 73% in female adolescents and considered weight gain and obesity as the most important risk factor (Aktan *et al.*, 2000). In general, the prevalence of acne varies from 0-90% in various countries and communities (Karciauskiene *et al.*, 2013; Lehmann *et al.*, 2002; Cordain *et al.*, 2002; Poli *et al.*, 2001).

The results of the current study indicated a significant relationship between acne and PCOS in sonography. The study by Timpatanapong and Rojanasakul (1997) showed that 19 out of the 51 study women with acne (37.3%) had PCOS (Smithard *et al.*, 2001). In another study, the incidence rate of PCOS was 29.9% in the subjects with acne compared to 8.5% in the control group (Timpatanapong and Rojanasakul, 1997). Other studies have also reported acne to be accompanied by PCOS (Timpatanapong and Rojanasakul, 1997; Kelekci *et al.*, 2010).

In this study, high androgenic hormones levels were significantly related to the incidence and severity of acne. In the same line, the results of the study by Chen *et al.* showed high dihydrotestosterone levels in the PCOS patients with acne ( $6.01 \pm 3.45$  vs.  $4.87 \pm 4.29$   $\mu\text{mol L}^{-1}$ ;  $p = 0.002$ ) (Maluki, 2010). However, the results obtained by Bunker *et al.* (1991) and Puzigaic *et al.* (1991) were on the contrary to those of the present research (Chen *et al.*, 2011; Bunker *et al.*, 1991). Basically androgens increase acne and provide proper conditions for colonization of microorganisms, such as propionibacterium, through stimulation of sebum production (Puzigaic *et al.*, 1991). Of course, since a positive family history increases the probability of acne, genetic backgrounds should also be taken into account in investigation of the incidence of acne (Burkhart and Gottwald, 2003). Furthermore, some researchers have stated that the prevalence of acne is not certainly higher in PCOS patients compared to the normal population (Cunliffe and Simpson, 1998) because some forms of acne present in adolescents as well as 50% of the above 25 year old females (Azziz *et al.*, 2006).

The findings of the present research indicated the prevalence of androgenic alopecia among the 14-18 year old girls to be 4.2%. Some studies have mentioned that alopecia is a weak predictor of hyperandrogenism since alopecia and hair loss depend on various factors (Cunliffe and Simpson, 1998; Azziz *et al.*, 2006; Goulden *et al.*, 1999). These factors include age androgens increase during menopause, food diet concerning iron and other mineral and protein compounds (Barth *et al.*, 2007), stress, stressful life experiences, negative body image, adjustment disorder (Sinclair, 1998) and genetic factors. The studies conducted on twins have also shown that potential, age, pattern and speed of hair loss all depend on genetic factors (Bolduc and Shapiro, 2000; Stough *et al.*, 2002).

Furthermore, several studies have revealed a relationship between hair loss and iron deficiency (Nyholt *et al.*, 2003). In this study, however, the subjects' hemoglobin level was not assessed. Thus, hair loss in some study subjects might have resulted from iron deficiency anemia.

The results of this study showed no significant relationship between total and free testosterone levels and PCOS as well as alopecia hair loss pattern ( $p > 0.05$ ). One study reported the prevalence of hyperandrogenism to be 38.5% in 109 females with average to severe alopecia. In addition, 43% of the patients with hyperandrogenism had the criteria of PCOS (Cook, 2005). One other study also



showed that the prevalence of PCOS was 67% among the women with androgenic alopecia compared to 27% in the control group. Besides, the prevalence of hirsutism was higher in the women with alopecia in comparison to the control group (Essah *et al.*, 2006).

Based on what was mentioned above, testosterone level and PCOS increase in the patients suffering from androgenic alopecia. Yet, the difference between the results of the present study and those of other studies might be due to the age of the research population (14-18 years old), hemoglobin level (which was not assessed in this study) and other problems which might present in females in higher reproductive ages.

## CONCLUSION

In this study androgenic hormones levels were higher in the patients with acne and were significantly related to the incidence of PCOS. However, no significant relationship was observed between hirsutism as well as alopecia and androgenic hormones levels and PCOS. This might be due to the differences in genetic factors, race, nutrition, type of sonography, sonography equipment and age of the research community. Thus, further studies are recommended to be conducted on 20-25 year old subjects and on the females with regular menstrual cycles.

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