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Study of Cutaneous Manifestations of Polycystic Ovarian Syndrome

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Abstract
Polycystic Ovary Syndrome (PCOS) is common in women of reproductive age group. The usual presentation is with irregular menstrual cycles, acne, hirsutism, alopecia and acanthosis nigricans. The aim was to study the various cutaneous manifestations in PCOS and to correlate these with selected hormonal levels. This study was conducted in 18 months, wherein 87 patients diagnosed as PCOS were included.
A detailed history and clinical examination was done for each patient, along with hormonal investigations like Thyroid Stimulating Hormone (TSH), Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Prolactin, Dehydroepiandrosterone sulphate (DHEAS), Sex Hormone Binding Globulin (SHBG) and total testosterone. Acne was the commonest finding (64.3%), followed by acanthosis nigricans (47.1%), hirsutism (41.4%) and alopecia (13.8%).
TSH and LH were raised in 6.8%. LH:FSH ratio was >2 in 8.5% patients. SHBG was decreased in 5.1%. Total testosterone was elevated in 18.6%. There was a significant correlation between LH and acne (p=0.036), the LH:FSH ratio and acne (p=0.047), and between LH and hair loss (p=0.027). Acanthosis nigricans was seen in 35.6% obese women (p=0.001).
Keywords: *Polycystic ovary, cutaneous , hyperandrogenism.*

Introduction

Women with Polycystic Ovary Syndrome (PCOS) present with either a history of irregular menstrual cycles, clinical signs or biochemical parameters suggestive of elevated androgen levels. Polycystic ovary syndrome (PCOS), originally described in the 1930s by Stein and Leventhal, is one of the most common endocrinopathies in women of reproductive age. It is often characterized by hyperandrogenism, which may often be manifested as: hirsutism, acne, seborrhea, alopecia, menstrual irregularity, obesity and ovarian cysts. PCOS shows reproductive and metabolic complications that must be diagnosed and treated early due to the risk of infertility, endometrial cancer and plurimetabolic syndrome. Besides these complications, PCOS is associated with high morbidity due to aesthetic aspects that negatively affect women's self-esteem. Knowledge about the pathophysiologic mechanisms of this syndrome is very important for an appropriate therapeutic approach.

The key findings for the diagnosis of PCOS are: hyperandrogenism, chronic anovulation and

polycystic ovaries on ultrasound. However, other conditions may present with these manifestations, making differential diagnosis necessary. Only a third of the patients have the classical form of the syndrome described by Stein and Leventhal, defined by the presence of amenorrhea, hirsutism and bilateral enlargement of the ovaries. Therefore, in 1990, the conference of the National Institutes of Health (NIH) suggested new diagnostic criteria represented by clinical and/or biochemical evidence of hyperandrogenism associated with oligoamenorrhea, with the exclusion of other causes of hyperandrogenism.

Materials and Methods

This was a cross sectional study which was carried out from March 2015 to June 2016. A total of 87 patients diagnosed with PCOS, from 15 to 35 years of age were included in the study.

Inclusion criteria:

1) Non-pregnant women between 15 to 35 years of age,
2) Patients between 15 to 18 years, whose parents gave informed consent,
3) Patients with any 2 of the following criteria:

a) menstrual irregularity,
b) clinical and/or biochemical hyperandrog-enemia,
c) Polycystic Ovarian Morphology (PCOM) on Ultrasonography (USG).

Exclusion criteria:

(1) pregnancy
(2) symptomatic disease (liver, kidney, heart or other major systemic diseases),
(3) age >35 years,
(4) women not willing to give consent.

All patients were counseled about the study and informed written consent was obtained. Medical history was taken in a structured proforma and women were asked for intake of hormonal drugs, including oral contraceptive pills as well as medication for any other systemic diseases.

Family history was obtained regarding diabetes mellitus in the first and second-degree relatives, menstrual disorders, hirsutism and early baldness in family. Detailed clinical evaluation was done. Thyroid Stimulating Hormone (TSH), Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Prolactin, Dehydroepiandrosterone sulphate (DHEAS), Sex Hormone Binding Globulin (SHBG), Total Testosterone and random blood sugar were tested for each patient. Hormone assays were done on the second day of the menstrual cycle. The current definition of PCOS is based on Rotterdam consensus meeting (2003).

It defines the syndrome as presence of any two of the following three criteria:

(1) Menstrual irregularity: Oligomenorrhoea and/or anovulation,
(2) Clinical (Acne or Hirsutism) and/or biochemical Hyperandrogenemia, and
(3) PCOM on USG. Hirsutism was quantified by the Modified Ferriman-Gallwey score (Yildiz, Bolour, Woods, Moore, and Azziz, 2010).

The following 9 body areas are assessed: upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, upper arms and thighs. Hair growth is rated from 0 (no growth of terminal hair) to 4 (extensive hair growth) in each of the nine locations. So, a patient's score will range from a minimum score of 0 to a maximum score of 36. A score of 8 or higher is regarded as significant hirsutism. The Standard Consensus Statement for Indian Population (Ramanand, Ghongane, Ramanand, Patwardhan, Ghanghas and Jain, 2013) was used to grade body mass index (BMI): Normal BMI: 18.0 – 22.9 Kg/m^2, overweight: 23.0 – 24.9 Kg/m^2 , and obese: ≥25 Kg/m^2 .

Based on the number of inflammatory lesions on one half of the face, acne was classified by Hayashi, Akamatsu and Kawashima (2008), into the following four groups: Mild: 0-5, Moderate: 6-20, Severe: 21-50, and Very Severe: >50. Female pattern hair loss (FPHL) was graded based on

Ludwig's Classification (Singal, Sonthalia and Verma, 2013). In women who present with Male pattern hair loss (MPHL), the Modified Norwood-Hamilton classification (Kaliyadan, Nambiar and Vijayaraghavan, 2013) was used.

Results obtained were tabulated and statistical analysis was done using Chi-Square test and Fischer's Exact Test. A p value <0.05 was taken as a significant association.

Results

A total of 87 women were included, of which the youngest patient was 15 years and the oldest patient was 35 years with a mean age of 26.2 years. The maximum number of patients (n=33) was in the age group of 26 to 30 years. Clinical presentation 34 women (39.1%) presented primarily with dermatological complaints, of which hirsutism was the commonest presenting complaint in 15 patients (17.3%), followed by acne in 14 patients (16.1%), and acanthosis nigricans in 5 patients (5.7%). 53 women (60.9%) presented to the gynaecological out patient department, the commonest complaint was irregular menstrual cycles in 29 women (33.3%) followed by infertility in 24 women (27.6%). A family history of PCOS was seen in 5 patients (5.7%), infertility in 3 patients (3.4%), diabetes mellitus in 6 patients (6.9%), and thyroid disease in 5 patients (5.7%). 47 patients (54%) were obese and 16 (18.4%) were overweight.

Cutaneous manifestations

Acne was observed in a total of 56 patients (64.3%), of which 47 had mild acne and 9 had moderate acne. Acanthosis nigricans was present in 41 (47.1%) patients, of which 31 (35.6%) were obese women. This relationship was found to be significant (p=0.001). Hirsutism was present in 36 women (41.4%). Hair loss was present in 12 patients (13.8%), of which the commonest pattern was Telogen Effluvium (n=5), followed by FPHL (n=4), MPHL (n=2) and alopecia areata (n=1).

Investigations

80 women (92%) had a USG finding suggestive of PCOM. Of the 87 patients, 28 were lost to follow up. The hormone profile was done on the second day of the menstrual cycle. Among the remaining 59 patients, total testosterone was elevated in 18.6% patients. DHEAS was raised in 10.2% patients, and was low in 3.4% patients. The LH:FSH ratio was observed to be more than 2, in 8.5% patients.

TSH and LH were raised in 6.8% patients each. SHBG was low in 5.1%, but was raised in 1 patient. FSH was raised in only 1 patient. Prolactin levels were raised and low in 1 patient each.

Hormonal correlation

The clinical findings were compared with the hormone levels, using Chi-square Test and Fischer's Exact Test. There was a significant correlation between LH and acne (p=0.036). A normal LH:FSH ratio was seen in 32 women with mild acne. This was also found to be significant (p=0.047).

The relationship between LH and hair loss was also significant (p=0.027). TSH, prolactin, SHBG, DHEAS and total testosterone were not significantly correlated with the clinical findings.

Table 1: Cutaneous Manifestations

Clinical Feature	Number of Cases	Percentage
ACNE	56	64.3
Mild	47	54.0
Moderate	9	10.3
ACANTHOSIS NIGRICANS	41	47.1
HIRSUTISM	36	41.4
HAIR LOSS	12	13.8
Telogen Effluvium	5	5.7
FPHL	4	4.6
MPHL	2	2.3
Alopecia areata	1	1.1
SEBORRHOEA	1	1.1
ACROCHORDONS	1	1.1

Table 2: HORMONE PROFILE			
HORMONE	NORMAL	RAISED	LOW
TSH	55 (93.2%)	4 (6.8%)	-
LH	55 (93.2%)	4 (6.8%)	-
FSH	58 (98.3%)	1 (1.7%)	-
LH:FSH RATIO	54 (91.5%)	5 (8.5%)	-
SHBG	55 (93.2%)	1 (1.7%)	3 (5.1%)
PROLACTIN	57 (96.6%)	1 (1.7%)	1 (1.7%)
DHEAS	51 (86.4%)	6 (10.2%)	2 (3.4%)
TOTAL TES-TOSTERONE	46 (78%)	11 (18.6%)	2 (3.4%)

Table 3: Cross Frequencies								
Clinical Feature	LH	FSH	LH: FSH Ratio	Prol-actin	SHBG	DHE-AS	Total Testo-ster-one	BMI
BMI	1.000	1.000	0.815	1.000	0.192	0.192	0.229	-
ACNE	0.036	1.000	0.047	0.691	0.501	0.501	0.502	0.295
AN	0.681	0.492	0.516	1.000	0.172	0.172	0.292	0.001
HAIR LOSS	0.027	0.864	0.531	0.259	0.446	0.446	0.290	0.256
HIR-SUTISM	0.431	0.576	0.354	0.674	0.750	0.750	0.231	0.137

Discussion

Out of 87 patients included in the study, the mean age of the patients was 26.2 years, with the largest number of patients (37.9%) in the age group of 26 to 30 years.

In a study by Ramanand et al. (2013), 30.8% were in the age group of 19 to 22 years, and 27.5% were in the age group 23 to 26 years. The reason for a higher number of patients in this age group was probably because patients attending the infertility clinic were included in the study.

Ramanand et al. (2013) reported irregular cycles in 100% of their study subjects, while infertility was present in 21%. 54% of the patients were obese and 16% were overweight. A similar study reported that 62.5% were obese and 12.5% women were overweight (Ramanand et al., 2013). Other studies have shown a wider variation from 39% to 73% women with PCOS being obese (Legro, Kunselman, Dodson and Dunaif, 1999, Liou, Yang, Hsieh, Lee, Hsu and Hsu, 2009). Acne was seen in 64.3% of patients. 54% had mild acne and 10.3% had moderate acne. Liou et al. (2009) observed acne in 48%, while Gowri, Chandravathi, Sindhu and Naidu (2015) reported it in 67.5% of patients. Acanthosis nigricans was present in 47.1% patients. Other studies found it in 22.5% to 44.16% of their patients (Ramanand et al., 2013, Gowri et al., 2015).

In our study, acanthosis nigricans was seen in 35.6% of the obese women, which was statistically significant (p=0.001). Ramanand et al. (2013) noted that among the obese women, 56% had acanthosis nigricans while 20% women with normal BMI had acanthosis nigricans.

Hair loss was seen in 13.8% of patients. The commonest pattern was telogen effluvium (n=5), followed by FPHL (n=4), MPHL (n= 2) and alopecia areata (n=1). These findings were different from the findings of Gowri et al. (2015), where androgenetic alopecia was seen in 30% of patients. Olsen, Callender, McMichael, Sperling, Anstrom, Shapiro, et al. (2011) reported no statistically significant relationship between hyperandrogenism and central hair loss pattern.

Hirsutism was present in 41.4% of patients. Variable results have been reported from various studies with 28% to 62.5% of the women with PCOS having hirsutism (Liou et al., 2009, Gowri et al., 2015) Majority (92%) of patients had a USG finding suggestive of PCOM whereas only 8 patients had a normal USG. This was consistent with the study by Liou et al. (2009), where 93% of the patients with PCOS had PCOM on USG. TSH was raised in 6.8% patients.

Ramanand et al. (2013) reported 13.3% women had hypothyroidism. A review on the emerging relationship between thyroid disorders and PCOS by Singla, Gupta, Khemani and Aggarwal (2015) states that the prevalence of subclinical hypothyroidism or thyroid autoimmunity is increased in women with PCOS. LH was raised in 6.8% patients.

Fakhoury, Tamim, Ferwana, Siddiqui, Adham and Tamimi (2012) found increased LH levels in 35% of patients, however, no significant increase in LH levels was seen in women with PCOS women and

healthy control group. FSH was raised in one patient. Gowri et al. (2015) reported elevated FSH levels in 12.5% patients, while Fakhoury et al. (2012) found that the FSH levels were significantly lower in the women with PCOS. The LH:FSH ratio was observed to be more than 2, in 8.5% patients. This was a lesser percentage as compared to a similar study, where 27.5% of women had an elevated LH:FSH ratio (Gowri et al., 2015).

Fakhoury et al. (2012) reported a significantly higher LH:FSH ratio in PCOS women as compared to a control group. Prolactin levels were raised and low in 1 patient each. Similarly, Gowri et al. (2015) observed elevated prolactin levels in only 4 out of 40 patients. A case control study comparing PCOS women with a control group, found no significant difference in the prolactin levels (Fakhoury et al., 2012). SHBG was low in 5.1% patients. Serum SHBG levels have been reported to be significantly lower in women with PCOS (Fakhoury et al., 2012).

DHEAS was low in 2 (3.4%) patients and raised in 6 (10.2%) patients. On the contrary, Gowri et al. (2015) observed that DHEAS levels were raised in 45% of patients, while Fakhoury et al. (2012) reported no significant difference in the DHEAS levels in women with PCOS. Total testosterone was elevated in 11 (18.6%) patients. A significantly higher testosterone levels as compared to controls has been noted (Fakhoury et al., 2012).

Liou et al. (2009) reported that 46% of women with PCOS had elevated total testosterone levels, while Ramanand et al. (2013) found testosterone levels to be normal or low in all of their patients. The clinical findings were compared with the hormone levels, using Chi-square Test and Fischer's Exact Test. There were no significant correlations between TSH and the clinical findings. Similarly, in the study by Ramanand et al. (2013), even though 15% had thyroid dysfunction, there was no association between thyroid disease and PCOS. There was a significant correlation between LH and acne (p=0.036).

Contrary to this study, Borgia, Cannavo, Guarneri, Cannavo, Vaccaro, and Guarneri (2004) observed that LH levels were not significantly elevated in patients with varying severities of acne. A normal LH:FSH ratio was seen in 32 women with mild acne. This was also found to be significant (p=0.047). In the study by Borgia et al. (2004), although it was not significant, LH:FSH ratio was increased (>1) in 29.46%. The relationship between LH and hair loss was also significant (p=0.027).

In a similar study, androgenetic alopecia was associated with an elevated LH level in 15% of patients (Gowri et al., 2015). Prolactin, SHBG, DHEAS and Total Testosterone were not significantly correlated with the clinical findings. On the other hand, Walton, Cunliffe, Keczkes, Early, McGarrigle, Katz, et al. (1995), had found a significant positive correlation with DHEAS and a significant negative correlation be- Some of our findings, like obesity, acne, hirsutism, were comparable with recent studies.

Other findings, like hair loss and individual hormone levels were contradictory to other studies. Since our study had a small number of patients, this may be the reason for the inconsistent findings observed. After an extensive search of current literature, there were very few studies comparing hormone levels with skin findings. Further studies are required to establish statistically significant correlations between hormone levels and cutaneous manifestations.

Conclusion

A significant correlation was noted between acne and LH, and acne and the LH:FSH ratio. LH and hair loss were as well as acanthosis nigricans and obesity were also significantly related. There was no significant correlation between the clinical findings and the levels of TSH, prolactin, SHBG, DHEAS and total testosterone. Dermatologist plays a significant role in the early detection of PCOS in young women with a few hormones showing significant correlation with clinical findings.

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