Comparison of Clinical, Biochemical, and Sonological Parameters in Adolescents with and without Polycystic Ovarian Syndrome

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Abstract

Objectives The Pediatric Endocrine Society consensus criteria was developed in 2015 to diagnose adolescent PCOS. There are no Indian studies that use these criteria for diagnosis and then compare the clinical characteristics with those of normal controls. The objective of this study was to compare the clinical and biochemical profile in adolescents with and without PCOS and to study the ovarian morphology in adolescents with and without PCOS.

Materials and Methods We conducted a prospective case–control study on 60 adolescents who attended the outpatient department/adolescent immunization clinic. Group A included 30 adolescent girls with PCOS diagnosed as per the consensus criteria and Group B included 30 adolescents without PCOS. All participants were clinically evaluated and called empty stomach in the follicular phase for metabolic (Serum TSH, prolactin, FSH, LH, and testosterone) and endocrinal workup (2-hour OGTT, lipid profile) followed by ultrasonic examination.

Results In group A, 40% were overweight and 36.7% were obese and in group B, 20% were overweight and 20% were obese. There were no significant differences noted in gonadotropin levels in two groups. Mean testosterone levels were higher in PCO adolescents. The mean ovarian volume and ovarian follicle number were significantly higher in adolescents with PCOS. We found that if ultrasound criteria were added to the diagnosis, there would be about 7% lesser PCOS diagnosis.

Conclusion PCOS alters the fat distribution and lipid distribution in the body. These are features that lead to long-term metabolic alterations and life-threatening diseases. All PCOS adolescents thus be screened for these abnormalities and advised lifestyle modifications to keep these parameters under control.

Keywords
- adolescent
- dyslipidemia
- hyperandrogenemia
- polycystic ovarian syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common endocrinological disorders in the reproductive age group and probably starts at pubertal transition. The endocrinological pathways are developing around puberty and thus the PCOS may also evolve at that time. The normal pubertal development presents to us with certain clinical

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features (anovulatory cycles, hirsutism, and acne vulgaris) resembling that of adult PCOS. These may subside, become subdued, may continue or become further advanced to be diagnosed as PCOS.[1] Hence, the diagnosis at this stage is not easy but important to properly manage and counsel these young girls.

The diagnostic criteria for PCOS have experienced controversies and then evolution over past many years. National Institutes of Health (NIH) criteria (1992),[2] Rotterdam criteria (2003)[3], the Androgen Excess Society (AES) criteria (2006)[4] have been developed for adults based on various combinations of otherwise unexplained hyperandrogenism, anovulation, and a polycystic ovary. However, there has been an ongoing argument on the application of these criteria to adolescents. In adolescents, anovulatory cycles are frequent. The common signs of adult hyperandrogenism are less reliable in adolescents than in adults, hirsutism is often seen in a developmental phase, and acne vulgaris is common although it may be more common in PCOS.[5] Ultrasound morphology of the ovary in the early post-menarche years may also be different from that seen in adult women. It is not very clearly known as to what features on ultrasound will be useful to differentiate a normal multifollicular ovary from that of polycystic ovary morphology (PCOM). The use of transabdominal ultrasound for the assessment of ovary when girls are not sexually active may pose another limitation. Hence, clinicians are increasingly faced with adolescents showing potential features of PCOS.

Sultan et al suggested requiring four out of five of the following: oligomenorrhea or amenorrhea at least 2 years post menarche, clinical hyperandrogenism, biologic hyperandrogenism, insulin resistance, and polycystic ovary morphology.[6] Carmina et al proposed defining PCOS in adolescents by the presence hyperandrogenism, chronic anovulation, and polycystic ovaries.[7] It was also suggested by the Pediatric Endocrine Society that adolescent PCOS be diagnosed using the NIH-based criteria of otherwise unexplained hyperandrogenism and persistent anovulatory menstrual abnormality.[8] Although PCOS accounts for around 85% of androgen excess in adolescent girls, there are a number of conditions other than PCOS that present with hyperandrogenism.[9] The evaluation for a patient with hyperandrogenism utilizes pelvic ultrasonography and specific endocrine tests to exclude these disorders and establish the diagnosis of PCOS.

In 2015, the representatives of international pediatric, adult, and reproductive endocrinology, adolescent medicine, and adolescent gynecology subspecialty societies defined consensus criteria for the diagnosis of PCOS in adolescence.[10,11] Their consensus supported the criteria of persistent hyperandrogenic oligo-anovulatory menstrual abnormality based on age- and stage-appropriate standards. This consensus definition agrees with 2013 Endocrine Society clinical guidelines.[8]

We compared metabolic and endocrinal and sonological parameters of adolescents with polycystic ovarian syndrome diagnosed with the Pediatric Endocrine Society criteria with those of normal controls. There are no studies using criteria to diagnose this disorder in the Indian subcontinent. We also studied the role of ovarian morphology in PCOS. The usefulness of pelvic ultrasound in supporting the suspected diagnosis of PCOS has been controversial. The finding of polycystic ovaries on ultrasonogram has been reported to be nonspecific, overlapping with image findings seen in up to 40% of the normal population.

Objectives

To compare the clinical and biochemical profile in adolescents with and without PCOS. and study and compare the ovarian morphology in adolescents with and without PCOS.

Materials and Methods

We conducted a prospective case–control study in adolescents who attended outpatient department of tertiary hospital over a period of 12 months.

On the basis of studies conducted by Youngster et al[12] and Brown et al,[13] a sample size of minimum 30 in each group was calculated using the formula

$$n \geq \frac{P_C(1-P_C)+P_E(1-P_E)}{\delta_0^2}(Z_\alpha + Z_\beta)^2$$

where Pc = proportion of patients having follicles > 10 mm in PCOS, P_E = proportion of patients having follicles > 10 mm in normal. $\delta 0 = P_E - P_C$, where Z_α is the value of Z at two-sided alpha error of 5% and Z_β is the value of Z at power of 80%.

Group A included 30 adolescent girls with PCOS diagnosed as per consensus criteria and Group B included 30 adolescents without PCOS. All participants and their guardians were counseled, and an informed consent was taken for inclusion in the study. Inclusion criteria were 1 year post menarche up to 18 years of age. Exclusion criteria were refusal to consent for the study or follow-up.

The study was started after getting ethical clearance from the ethics committee of the hospital with Reg. number 225-20110-171-215201. All adolescent girls presenting with features suggestive of PCOS were screened and those fulfilling the consensus criteria of PCOS were included in group A. Adolescent girls without any features of PCOS were included in group B. These controls were selected from the adolescent clinic who came for some counseling or vaccination against cervical cancer and had no clinical complaints.

Demographic profile including age, socioeconomic status, and education was noted. Detailed history was recorded including age at menarche, time since menarche, and the duration of symptoms family history of PCOS. Complete general physical and systemic examination was done. Height, weight, and body mass index (BMI) and waist hip ratio (WHR) were recorded. Modified Ferriman–Gallwey (mFG) scoring was done and acne numbers were recorded.

All participants were called empty stomach on day 2 or 3 of follicular phase for metabolic and endocrinal and sonologic workup. This included serum TSH, serum prolactin, 2-hour OGTT after 75 g glucose load, lipid profile including

Table 1 Demographic characteristics in two groups

		Group A (mean ± SD)	Group B (mean ± SD)	*p*-Value	Range of group A	Range of group B
Age (y)		16.7 ± 1.18	16.93 ± 1.05	0.468	14–18	14–18
Age at menarche (y)		13 ± 1.36	13.2 ± 1.49	0.618	10–15	11–15
Time since menarche (y)		3.8 ± 1.4	3.73 ± 1.68	0.898	2–6	1–6
Duration of symptoms (mo)		18 ± 3.206	–	–	12–23	–
Family history		4/30	1/30	0.165		
Socio-economic status	High	1 (3.33%)	2 (6.67%)			
	Mid	14 (46.67%)	13 (43.33%)			
	Low	15 (50%)	15 (50%)			

serum triglycerides, cholesterol, and HDL and serum FSH, LH, and LH/FSH ratio.

Transabdominal ultrasound was done using Samsung Medison USS-H60NF3L/IN and sector curvilinear transducer (Samsung Medison PVG-366 m, 3.75 MHz). For the purpose of this study, ovarian volume (OV) was calculated using the traditional method of a simplified formula for a prolate ellipse ($0.5 \times \text{length} \times \text{width} \times \text{thickness}$).[9] The US images were evaluated for the number of antral follicles (2–9 mm) in) for each ovary. All ultrasounds were done by two ultrasonologists who were similarly trained.

Results

The study was conducted on 60 adolescents, 30 each with and without PCOS as identified by the consensus criteria. The demographic profile of two groups was similar as shown in ►**Table 1**. The age range in both the groups was 14 to 18 years. The mean age in groups A and B was 16.7 years and 16.93 years, respectively. The mean age of menarche was also comparable being 13 years and 13.2 years in groups A and B, respectively. The mean duration since menarche was 3.8 years in group A and 3.7 years in group B. The average duration of symptoms at presentation was 18 months in group A. A positive family history of PCOS was present in 13% of girls in group A as compared to 3.3% in group B.

Most patients presenting to our clinics were from middle and low socioeconomic strata. Of the 60 patients, 50% were from lower socioeconomic status and about 40% were mid-income in both groups.

In group A, all adolescents had hirsutism and menstrual irregularities but only 7 (23.3%) had acne. In group B, four (13.3%) girls had hirsutism, none had menstrual irregularity, and only two (6.7%) had acne. Mean modified Ferriman–Gallwey score in group A was 8.93 ± 0.83 (median = 9) and in group B was 4.03 ± 2.19 (median = 4).

In group A, all 30 adolescents reported oligomenorrhoea as the menstrual abnormality. Six of these girls were in second year post-menarche, 19 were in 3 to 5 years post menarche, and only 5 girls were 6 or more years post-menarche. Seven complained of acne on their first visit, out of which three had already taken treatment but acne had persisted.

Four girls presented with amenorrhea but were not included in the study as one had imperforate hymen and three had no evidence of hyperandrogenism (acne/hirsutism/weight gain).

In Group B, 7 girls were 2 years post menarche, 16 girls were 3 to 5 years post menarche, and 7 were ≥ 6 years post menarche. In group B, four (13.3%) had hirsutism and two (6.66%) had acne.

When the clinical body profile was compared, there was a statistically significant difference between the BMI, waist circumference, and waist hip ratio in two groups (►**Table 2**). The range of BMI in group A was 19.8 to 28.3 and in group B was 16.5 to 27.2. The mean BMI in groups A and B was 23.93 and 22.06, respectively. The mean weight was approximately 3 kg higher in girls with PCOS. The BMI of 36.7% fell into the overweight category in girls with PCOS as compared with 20% in nonPCOS group using the WHO global criteria.

Table 2 Clinical body parameters in two groups

	Group A (mean ± SD)	Group B (mean ± SD)	*p*-Value
Weight (kgs)	54.43 ± 5.99	51.23 ± 7.89	0.082
Height (cm)	150.7 ± 5.48	152.17 ± 4.17	0.248
BMI (kg/m^2)	23.93 ± 2.27	22.06 ± 2.92	0.008
Waist circumference (cm)	81.1 ± 8.77	75.13 ± 6.29	0.005
Waist/hip circumference ratio	0.84 ± 0.06	0.8 ± 0.04	0.01

Table 3 Endocrinological parameters in two groups

	Group A (mean ± SD)	Group B (mean ± SD)	Reference range	*p*-Value
TSH (mIU/dL)	1.48 ± 0.61	1.49 ± 0.61	0.4-5.5	0.980
Prolactin (ng/dL)	24.79 ± 11.77	16.45 ± 7.64	1.2-25.5	0.007
FSH (mIU/mL)	6.7 ± 4.72	6.85 ± 2.74	3-12	0.128
LH (mIU/mL)	10.76 ± 9.29	6.49 ± 3.68	0.5-10.5	0.13
LH to FSH ratio	1.86 ± 1.51	1.26 ± 0.74	< 2	0.109
Serum total testosterone (ng/dL)	58.27 ± 22.93	29.87 ± 19.34	14-75	< 0.001

When the Asian criteria for BMI were used, 40% were overweight and 36.7% were obese in group A and 20% were overweight and 20% were obese in group B.

The range of waist circumference in group A was 68 to 102 cm and in group B was 65 to 90 cm. The mean waist circumference was about 6 cm higher in group A. Waist hip ratio was ≥ 0.85 in 11 (36.7%) girls in group A compared to 4 (13.3%) in group B.

On comparing the hormonal profiles (►**Table 3**), the mean serum total testosterone (TT) and serum prolactin was found to the significantly higher in group A. In group A, seven (23.3%) adolescents had raised serum TT and eight (26.7%) had borderline testosterone. In group B, only five (16.7%) had borderline testosterone. Serum TT levels were significantly higher in group A (58.27 ± 22.93) as compared to group B (29.87 ± 19.34). The group B adolescents with higher TT levels were also associated with hirsutism in four out of five cases.

Serum LH more than the reference range was found in 10 (33.3%) adolescents in group A and 3 (10%) adolescents in group B. Serum FSH was high in 5 (16.7%) adolescents in group A and only 1 (3.3%) in group B. There was no statistically significant difference in the LH to FSH ratio between two groups.

On comparing biochemical parameters (►**Table 4**), it was found that the mean serum triglyceride, total cholesterol was significantly higher in group A but none of these were beyond the upper limit of normal. The mean serum HDL level was significantly lower in Group A. No adolescent in group A or B had abnormal OGTT.

On comparison of ultrasonic findings, statistically significant difference was found in the mean ovarian volume, mean follicular count, and stromal echogenicity (►**Table 5**). The ovarian volume more than 10 mL was seen in 28 adolescents in group A and none in group B. The ovarian volume of more than 12 mL was seen in 20 adolescents in group A and none in group B. The ovarian volume of more than 15 mL was seen in 13 adolescents in group A and none in group B. Ovarian follicle counts more than 10 were found in 15 adolescents in group A and none in group B. In group A, 73% of adolescents had hyperechoic stroma while none in Group B had it.

Discussion

Reproductive phases of life bring physiological, anatomical, and psychological changes in the life of women. Due to familial, cultural, and social restrictions, most women are not able to share and get right advice regarding normal or aberrant developmental changes. PCOS is one such illness, which may start developing at puberty and generate uncertainties about the changes experienced.[14]

The prevalence of PCOS depends on the recruitment process of the study population, criteria used for its definition, and the screening methods used.[15] Ethnic and racial differences have also been reported and Asian adolescents are said to have about twice higher risk of developing PCOS.[16]

We enrolled girls 1 year post menarche when hypothalamo-pituitary-ovarian axis settles down to normal. We have observed that most adolescents presented to the hospital with the complain of oligomenorrhoea, on an average 3.5 years since menarche with the duration of symptoms of about 1.5 years. Thus, there is a dilemma about when to consult reflecting a lack of public knowledge on the issue. Part of it is also due to hesitancy regarding the issue. Socioeconomic status seems to have little bearing on the disease. Because we mostly observed lower- and middle-class population in our clinics it seems to be distributed uniformly amongst the strata.

Table 4 Metabolic parameters

	Group A (mean ± SD)	Group B (mean ± SD)	Reference range	*p*-Value
Fasting blood sugar (mg/dL)	85.2 ± 7.8	82.03 ± 7.21	< 100	0.108
BS after 2 h of 75 g glucose load (mg/dL)	117.37 ± 11.24	113.23 ± 6.88	<140	0.219
Serum triglycerides (mg/dL)	149.43 ± 32.16	124.77 ± 27.41	100 - 200	0.001
Total cholesterol (mg/dL)	186.7 ± 45.17	162.63 ± 16.54	150 - 250	0.009
HDL (mg/dL)	49.23 ± 12.29	56.47 ± 9.52	30–70	0.006

Table 5 Ultrasonographic parameters

	Group A (mean ± SD)	Group B (mean ± SD)	*p*-Value
Mean ovarian volume (mL)	12.53 ± 5.32	5.07 ± 0.74	< 0.0001
Mean ovarian follicular count	8.93 ± 2.92	3.2 ± 1.13	< 0.0001
Ovarian hyperechogenic stroma	22	0	< 0.0001

Other Indian studies also reported the mean age of menarche about 13 years and mean age at presentation of about 18 years though these studies used different criteria for diagnosis of adolescent PCOS.[17–21]

The second most common problem faced by adolescents was hirsutism. We did not find a very good correlation between the perceived hirsutism and mFG scores and we feel that mFG definitely gives a better idea regarding the presence of hirsutism

The mean modified Ferriman–Gallwey score of the group A was 8.93 ± 0.83 compared to 4.03 ± 2.19 of the group B, giving us the *p*-value of < 0.001, which was significant. It is correctly said that hirsutism is a good marker for hyperandrogenism even when considering ethnic differences and systemic factors such as obesity. The literature says that hirsutism is present in approximately 70% of women with PCOS. Adolescent PCOS guidelines consider only moderate-to-severe hirsutism as clinical evidence of hyperandrogenism, and also contemplate that persistent testosterone elevation as determined in a reliable reference laboratory is more appropriate.[8]

Acne was faced by seven adolescents but most would use over-the-counter treatments or consult a dermatologist and would reach a gynecologist once referred by skin specialists. While acne is common in adolescent girls, less than 5% of girls have comedonal acne that is moderate or more (> 10 facial lesions) in early puberty, or have moderate or more inflammatory acne through the premenarchial years.[22]

The prevalence of obesity was higher in adolescents with PCOS in our study as evidenced by increased BMI, waist circumference, and waist/hip ratio. The prevalence of dyslipidemia was also higher in the PCO group than their normal counterparts. This was reflected by significantly increased serum triglycerides and cholesterol and decreased HDL. The fat distribution in PCOS is central type and this visceral fat is said to enhance the hormonal and metabolic disturbances in PCOS by altering lipolysis, lipogenesis, and insulin resistance. Joshi et al had reported a mean BMI of 21.1 ± 4.8 in PCO adolescents, while western studies reported much higher mean BMI.[23,24]

A recent study from Bangladesh reported that 88% of adolescents presented with oligomenorrhoea, 94.9% of participants had hirsutism, and 33.7% had biochemical hyperandrogenism. Most adolescents (69.1%) were overweight/obese and 65.7% had abdominal obesity. The median Ferriman–Gallwey score was 12. Metabolic evaluation testified that 24% had abnormal glucose tolerance and 90.9% had dyslipidaemia.[25] Alteration in lipid profile was noted by many authors. Silfen et al reported higher levels of low-density lipoprotein, and lower high-density lipoprotein in both obese and non-obese PCOS, compared with the non PCOS group in their study of 48 adolescents with PCOS and obesity.[26] A recent metanalysis has suggested that PCOS could increase metabolic syndrome by altering blood pressure and lipid metabolism irrespective of BMI.[27]

Fruzzetti et al studied 120 PCOS adolescents wherein triglyceride levels were significantly ($P < 0.01$) higher and HDL-cholesterol levels significantly ($P < 0.001$) lower in adolescents with PCOS than in the controls.[28] Metabolic parameters were significantly higher in adolescents with PCOS compared to controls irrespective of BMI and are worse in those who are overweight or obese.[29]

Researchers have suggested that PCOS could also lead to metabolic syndrome by influencing blood pressure and lipid metabolism independent of obesity even during the adolescent period.[27]

In this study, the mean concentration of FSH, LH, and LH/FSH ratio was not statistically significant. However, the mean LH in the study group A was higher than group B and it may be the reason behind observed hyperandrogenism. Contrary to this, a few authors have reported higher levels of LH and raised LH/FSH ratio.[23,26,30] Gülekli et al evaluated prospectively the performance of serum LH, FSH, testosterone, free testosterone, SHBG, and insulin concentration in a group of 32 patients with PCOS and 25 healthy controls. These investigators had observed that the LH/FSH, total testosterone, and insulin levels best predicted the PCOS status.[23]

Most researchers have found higher testosterone in adolescents with PCOS.[24,26,28,30] We found the mean testosterone levels to be higher in the PCOS group; however, in most adolescents, these remained within the normal range. Fruzzetti et al had reported higher mean TT levels in PCO adolescents versus non-PCO adolescents (55 ± 24 vs. 33 ± 15).[28]

The prevalence of polycystic ovarian morphology by trans-abdominal ultrasonography in girls diagnosed with PCOS according to the International Pediatric Society consensus criteria, in our study, was markedly higher than that in adolescents who served as a comparison group. It was seen that 93% of adolescents with PCOS had an ovarian volume more than 10 mL. Based on our results, trans-abdominal ultrasonography may provide useful information in the evaluation of PCOM, even in obese girls. Another author has also suggested that ultrasound criteria may still be used for PCOS diagnosis in adolescents who are 2 years or more post menarche.[31] The question remains if the new criteria underscore the utility of total abdominal ultrasound

or that the addition of ultrasound criteria would result in underdiagnosis. In our study, if ultrasound criteria were used as in Rotterdam's criteria for diagnosis, there would be about 7% lesser PCOS diagnosis.

The antral follicle count per ovary and ovarian volume are two most common features used for diagnosing polycystic ovaries. Youngster et al reported a significant difference between the ovarian volume and ovarian follicular counts amongst PCOS and non-PCOS adolescents. Similarly, other authors have also found a higher ovarian volume in PCO adolescents.[26,31] These studies did not consider ovarian follicular counts. Battaglia et al included both ovarian volume and follicular counts and reported significantly higher ovarian volumes and higher total number of ovarian follicles.[32] A recent review said that ultrasound estimation of ovarian follicle count may be more specific in adolescents with PCOS, rather than ovarian volume.[33]

Ours was a small study. There is a need of multicentric large study of mix ethnicity. Also, the use of advanced 3D or 4D ultrasound technology may enhance the ultrasonic findings to confirm the diagnosis. A combined metric of follicular number per ovary (using a cut-off of 10 follicles) and ovarian volume may provide significant predictive power in detecting PCOS.

Conclusion

There is no doubt that PCOS alters the fat distribution and lipid distribution in the body. These are the features that lead to long-term metabolic alterations and life-threatening diseases. Adolescence may be the most appropriate time to intervene in PCOS patients, as many cardiovascular risk factors are present in early adulthood. All PCOS adolescents thus be screened for these abnormalities and advised lifestyle modifications to keep these parameters under control. Efforts to define diagnostic criteria in adolescents that potentially include trans-abdominal ultrasonography so that patient-specific early interventions can be initiated as trans-abdominal ultrasonography is an easily available and accessible investigation.

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Conflict of Interest
None declared.

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