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Revisiting Hormonal profile in PCOS in Adolescents and Young Women

Ananya Bera [1], Bishista Bagchi [2], Siddhartha Chatterjee [3]

[1] Research associate, formerly at Calcutta Fertility Mission, Presently at Institute of Postgraduate Medical Education & Research & SSKM Hospital
[2] Fertility Consultant, Calcutta Fertility Mission & Reshmika IVF Center
[3] Director, Calcutta Fertility Mission, 21 Bondel Road Kolkata 700019, India

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ABSTRACT

Background: Polycystic ovarian Syndrome (PCOS) is a prevalent endocrine condition affecting women of reproductive age. The fundamental reason for the daily rise in the incidence of PCOS in adolescence is inappropriate lifestyle choices. Diagnosing PCOS in adolescent (aged 13-19 years, post 2 years of menarche) and young women (aged 20- 25years) might be difficult due to the rapid physiological and anatomical changes accompanying puberty. It's critical to be aware of the physiological quirks of puberty, which frequently resemble PCOS symptoms. There is a clustering of cardiovascular risk factors in women with PCOS, including hypertension, dyslipidaemia, obesity, and impaired glucose tolerance (IGT). The objective of the present study was to identify the most prevalent hormone in patients with single or multiple hormone disorders related to PCOS in adolescent and young women; after diagnosing them using the Rotterdam criteria This may help to evaluate the associated risks and to plan the treatment protocol.

Methods: In the last few years from October 2022 to October 2024, a total of 6,006 gynecological patients attended Calcutta Fertility Mission, 21 Bondel Road, Kolkata, West Bengal, India. Of these, 2492 were adolescent and young women; 250 of them were diagnosed with PCOS using Rotterdam Criteria. Standardized methods were used to collect anthropometric measures, including weight and height. Serum insulin, Testosterone, Dehydroepiandrosterone (DHEA), Thyroid Stimulating Hormone (TSH), Prolactin (PRL) and Homocysteine (HCY) were measured. Participants with menstrual disorders or any biochemical abnormalities were invited for ultrasonography (USG) examination. The ovarian volume and follicular size were evaluated transabdominally. Follicle stimulating Hormone (FSH), Leutinising Hormone (LH) and Anti Mullerian Hormone (AMH) were not estimated as their dysfunction is well understood. The hormones investigated influences the planning of treatment.

Results: Hyperhomocysteinemia was detected in 52.8% of cases of 250 PCOS patients whereas hyperadrenalism (4.8% in 250 PCOS patients) and hyperprolactinemia with hypothyroidism (4.8% in 250 PCOS patients) were detected in less number of patients.

Conclusion: Complications can be avoided with early detection of adolescent PCO. Early diagnosis and treatment facilitate the easy and successful stabilization of the condition for a longer duration.

Keywords: Adolescent, Polycystic Ovarian Syndrome (PCOS), Diagnosis, Prevalence, Body Mass Index (BMI)

Introduction:

Polycystic ovarian Syndrome (PCOS) is becoming more common in adolescence, with improper lifestyle being the leading cause.[1] The World Health Organisation (WHO) defines adolescence as the stage of life between 10 and 19 years old that is marked by major and crucial changes in puberty, growth, and development.[2] There are four axes to the pubertal endocrine alterations linked to adolescents PCOS- a) Gonadotropic axis, b) Adrenocorticotropic axis, c) Somatotropic axis and d) Intrinsic axis.[3-8] Polycystic ovarian syndrome (PCOS), which has been found to afflict 6–18% of adolescent girls, may have an impact on the hypothalamo-pituitary-ovarian (HPO) axis.[9] It is a functional endocrine issue, hence the appearance of the ovary is not of concern. In reality, parents are more concerned about their adolescent daughters' appearance, weight gain, somewhat masculine features like excessive hair growth and irregular menstruation. In addition, opinions made by acquaintances and neighbours as well as incorrect medical advice given by few professionals exacerbate the situation.[10] The prevalence of PCOS in adolescents has now reached a peak. About 30% of women show polycystic changes in the ovaries, of these, 10-15% may progress to develop polycystic ovary syndrome (PCOS), mainly due to three factors such as stress, obesity, and unhealthy lifestyle. This conversion of PCOS to PCO is influenced by controlling these factors, and if we can reverse 10% of them.[11,12] In adolescents, hyperandrogenism and menstruation disruption are the most common manifestations of PCOS. It is associated with abnormalities in ovulatory function, relative gonadotropin ratio, insulin secretion and function, androgen synthesis and function, genetic factors as well as the balance of pro- and antioxidant systems.[13] It is thought that homocysteine hinders implantation of embryo by disrupting the vascular integrity and blood flow of the endometrium, which may lead to an early miscarriage as well.[14, 15] Developing precise diagnostic criteria for adolescent PCOS has been difficult due to its prevalence and hence diagnosis in this group is challenging due to the rapid physiological and anatomical changes that occur throughout puberty.[16] The lack of strong evidence exacerbates over-diagnosis, General practitioners and allied health professionals use inconsistent, non-evidence-based methods for PCOS diagnosis and management.[17, 18, 19, 20] In adolescents, the number of years since menarche, which is vital to understand the progression of typical physiological changes associated with puberty, which can stay up to 2 years following menarche, after which they subside.[21] There is a need for high-quality, evidence-based guidelines because pertinent consensus statements are frequently not tailored to adolescents and/or are not supported by strong, high-level evidence and/or rigorous procedures. [22, 23, 24] This paper specifically focuses the prevalence of PCOS in adolescents (aged 13–19 years with post 2 years of menarche) and young women (aged 20–25years) using the Rotterdam criteria, as well as the risk factors that are linked to the condition. The hormonal profile examination may be helpful to chalk out treatment planning and particularly to plan treatment in preventing immediate and remote complications.

Materials and Methods:

SUBJECTS

In the last few years from October 2022 to October 2024, a total of 6006 gynecological patients attended the Calcutta Fertility Mission, 21 Bondel Road, Kolkata, West Bengal, India. Of these, 2492 were adolescent (13-19 years; post 2 years of menarche) and young patients (13-25 years); 250 of them were diagnosed with PCOS using Rotterdam Criteria. Among those 250 patients, 112 were adolescents and 138 were young women.

INCLUSION CRITERIA

All voluntarily consenting participants who are adolescents past 2 years of menarche and young adults. Informed consent was obtained from the patient as well as their guardians.

EXCLUSION CRITERIA

Lack of consent to undergo longitudinal monitoring, presence of any chronic infection, type I diabetes, addiction to tobacco and alcohol were excluded from the study. Participants undergoing treatment for other clinically diagnosed conditions or using any prescribed medications for PCOS within the past 12 months will be excluded for participation in the study.

ANTHROPOMETRY AND BIOCHEMICAL PARAMETERS

Standardized methods were used to collect anthropometric measures, including weight and height. The formula for calculating BMI is weight (kg) divided by height (m^2). Participants were grouped as based on BMI range: Mild thinness BMI (17-18.5 kg/ m^2), Normal BMI (18.5-25 kg/ m^2), Overweight BMI (25-30 kg/ m^2), Obese Class I (BMI - 30-35 kg/ m^2), Obese Class II (BMI -35-40 kg/ m^2) and Obese Class III (BMI >40 kg/ m^2). Serum insulin, Testosterone, Dehydroepiandrosterone, Thyroid Stimulating Hormone, Prolactin and Homocysteine were measured using an autoanalyzer (Cobas Integra 400 plus, Roche). 5ml of venous blood was collected from each individual in the morning preferably in empty stomach from antecubital vein of left arm. Serum was separated in room temperature and stored at 4 degrees centigrade.

USG EXAMINATION OF THE ABDOMEN

For a USG examination, participants with any biochemical abnormalities or menstrual problems were recruited. A 3.5-5 MHz curvilinear probe (Siemens Healthineers Acuson Juniper) was used transabdominally to measure ovarian volume and follicular size. In our study, participants were categorized as having PCOS or not based on USG findings according to the Rotterdam criteria.[23]

DIAGNOSIS OF PCOS

According to the 1990 National Institutes of Health (NIH) criteria, PCOS is indicated by the presence of oligo-ovulation symptoms and androgen excess (clinical or biochemical) with modification in 2003, the European Society of Human Reproduction and Embryology and American Society of Reproductive Medicine (ESHRE/ASRM) jointly suggested the diagnosis of PCOS as satisfying ***any two*** of the following: hyperandrogenism,

oligo/anovulation, and PCOM, known as the Rotterdam criteria.[23, 25] The 2006 publication of the Androgen Excess and PCOS Society (AE–PCOS) Position Statement stated that hyperandrogenism must coexist with indications of ovarian dysfunction, such as ovulatory dysfunction and/or PCOM.[26] With significant restrictions, the Rotterdam criteria were recommended for use in the 2018 International Evidence-Based Guideline for PCOS.[27] Adolescents with hyperandrogenism and irregular menstrual periods do not need an ultrasound to be diagnosed. They should be monitored for irregular cycles for at least two years following menarche. After ruling out secondary causes, the requirements for adults need the presence of two of the following three characteristics: androgen excess, ovulatory dysfunction, or polycystic ovarian morphology ***(Table 1)***. Participants in our research were categorised as having PCOS or not based on USG findings according to the Rotterdam criteria.[23]

STATISTICAL ANALYSIS

Categorical variables are expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes. The statistical software SPSS version 25 has been used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

ETHICAL CONSIDERATION

The Ethical Committee of Calcutta Fertility Mission has given clearance for the retrospective study. Every individual who took part in the study gave written informed consent.

Results:

In the present study, 45.2% cases had family history of PCOS, 52.4% cases had family history of menstrual abnormality, 9.6% cases had family history of hypertension on both side (maternal & paternal), 24% cases had family history of hypertension on paternal side, 33.2% cases had family history of hypertension on maternal side, 9.6% cases had family history of diabetes on paternal side and 4.8% cases had family history of maternal side ***(Figure- 1)***.

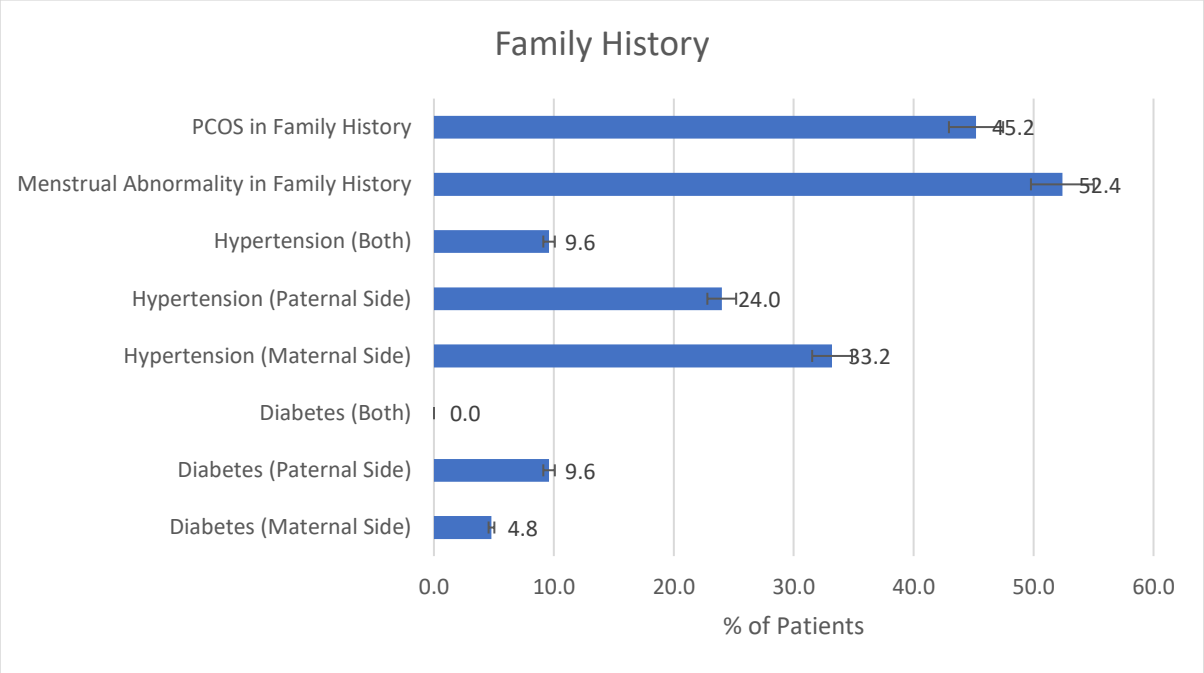

Figure 1: Distribution of cases according to family history

Figure 2 represents the greatest frequency of hyperhomocysteinemia, which was detected in 52.8% of 250 PCOS patients. We found the highest prevalence of hyperprolactinemia (44.64% in 112 patients) and hyperhomocysteinemia (44.64% in 112 patients) in adolescents (13-19 years, post 2 years menarche). Additionally, the highest prevalence of hyperhomocysteinemia (62.31% in 138 patients) was observed in young women (20-25 years).

Insulin resistance is exacerbated in PCOS-afflicted women who are often obese, with a noticeable central or abdominal obesity. These women have a higher chance of developing metabolic syndrome, cardiovascular disease, hypertension, dyslipidemia, impaired glucose tolerance (IGT), and type 2 diabetes later in life.[28-33] Our study detected only a minimal number of cases, specifically 1 or 2cases of detectable hyperinsulinemia, which can be considered negligible.

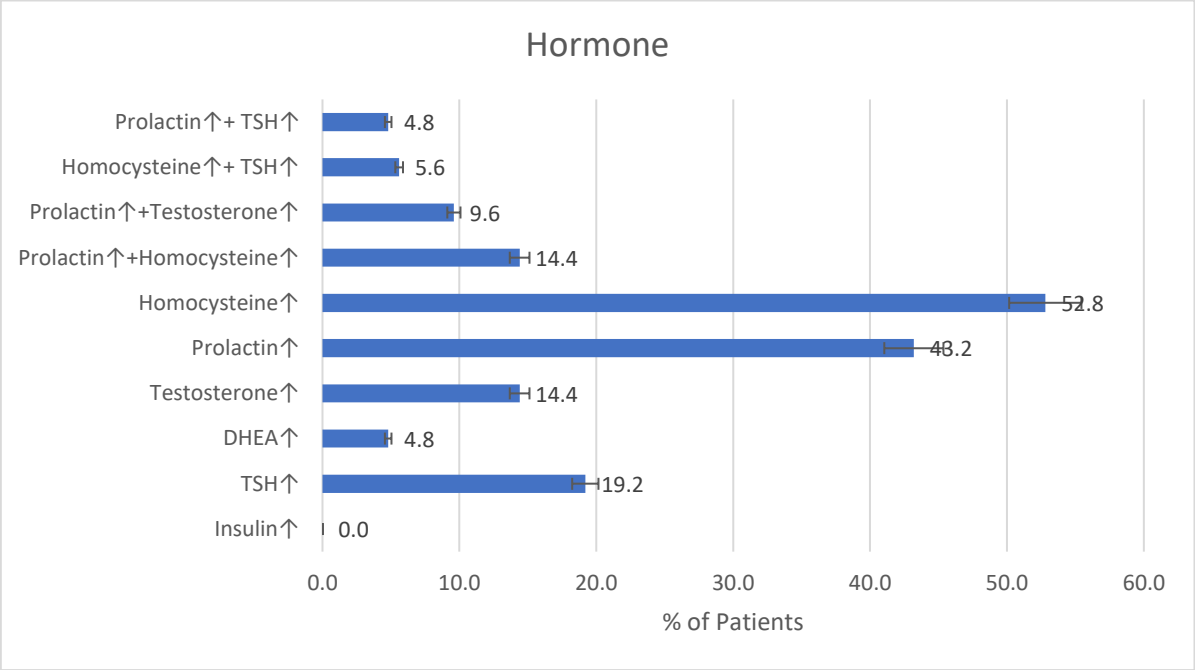

Figure 2: Prevalence of single or multiple hormone disorders among total PCOS patients.

Figure 3 illustrates the graphical representation of distribution of cases according to weight class.

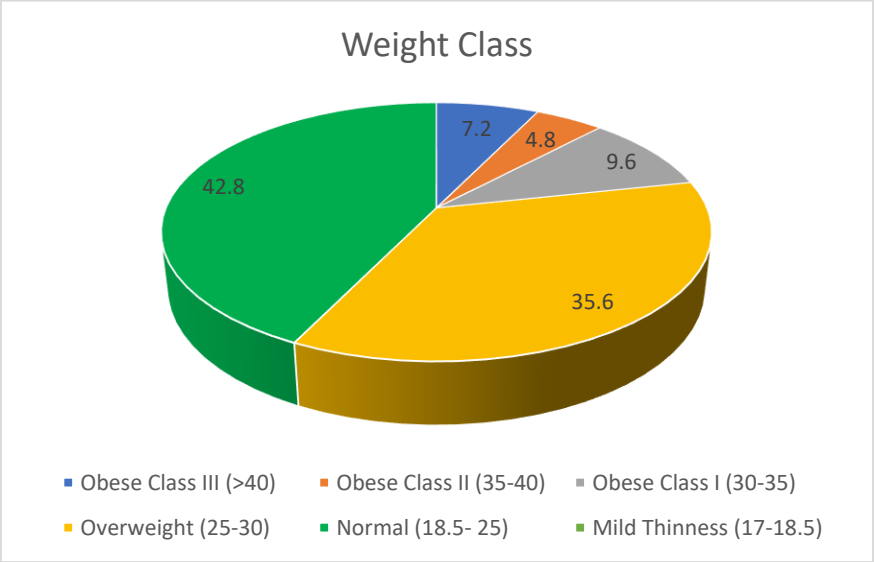

Figure 3: Graphical representation of Distribution of cases according to weight class

Table 2 represents the distribution of cases according to body-weight. Among the 250 subjects diagnosed with PCOS using the Rotterdam Criteria, 18 (7.2%) were classified as Obese Class III, 12 (4.8%) as Obese Class II, 24 (9.6%) as Obese Class I, 89 (35.6%) as Overweight, and 107 (42.8%) had Normal BMI.

We are comparing the increase in hormone levels across different weight classes (***Table- 3***). **Hypothyroidism** was observed in 100% of cases among 12 patients with PCOS in the Obese Class II, in 26.97% of cases among 89 patients with PCOS in the Overweight category, and in 11.21% of cases among 107 patients with PCOS with normal BMI. **Hyperandrogenism** was observed in 11.21% of cases among 107 patients with PCOS in the normal BMI category, in 50% of cases among 24 patients with PCOS in the Obese Class I and in 13.48% of cases among 89 overweight patients. **Hyperprolactinemia** was observed in 66.67% of cases among 18 patients with PCOS in the Obese Class III, in 50% of cases among 24 Obese Class I patients, in 26.97% of cases among 89 patients who were overweight and in 56.07% of cases among 107 patients with PCOS with normal BMI. **Hyperhomocysteinemia** was observed in 66.67% of cases among 18 patients with PCOS in the Obese Class III category, in 50% of cases among 24 patients with PCOS in the Obese Class I category, in 67.42% of cases among 89 patients with PCOS in the Overweight category, and in 44.86% of cases among 107 patients with PCOS in the Normal BMI.

Table 3 shows the prevalence of single or multiple hormone disorders across different weight classes. Hyperhomocysteinemia was predominantly detected in overweight patients, with an incidence of 67.42% among 89 patients. Hyperprolactinemia was most prevalent in obese class III patients, occurring in 66.67% of 18 patients. Both hyperprolactinemia and hyperhomocyste-

inemia were predominantly detected in obese class III patients, with an incidence of 66.67% among 18 patients.

Figure 4 shows the graphical representation of prevalence of single or multiple hormone disorders across different weight classes.

Figure 4: Prevalence of single or multiple hormone disorders across different weight classes

Discussion:

PCOS is a multifactorial disease and is found to have association with those who have family history of PCOS, menstrual abnormality, hypertension and type 2 diabetes mellitus. Women with PCO, are at increased risk for gestational diabetes mellitus (GDM) as well. It has been demonstrated that certain gene-gene interactions, and gene-environment interactions influence the development of PCOS, a X-linked polygenic condition, in around 30% of women.[34-39]

In this study, 45.2% of cases reported a family history of PCOS, while 52.4% had a family history of menstrual abnormalities. 9.6% of these women had a family history of hypertension and paternal history of diabetes, 4.8% reported a maternal family history of diabetes ***(Figure-1)*** . [34, 35] The unopposed action of estrogen leads to endometrial hyperplasia, resulting in a normal menstrual cycle, regular cycles with menorrhagia, oligomenorrhea, or amenorrhea followed by menorrhagia, spotting episodes depending on estrogen levels in the body.[34] In our present study, menstrual abnormalities were most common not only in PCOS patients but also in 52.4% of cases with a family history of menstrual abnormalities ***(Figure- 1).*** Other investigations have reported that PCOS patients frequently exhibit signs of obesity, hyperandrogenism, and hyperinsulinemia. [36, 37]

In our previous study,[11] hypothyroidism, hyperinsulinemia, and hyperandrogenism were found in the maximum number of cases (35%), while hyperinsulinemia alone was present in 25% of cases. Hyperprolactinemia with hyperadrenalism was observed in the minimum number of cases (5%). In our current investigation ***(Figure 2),*** hyperhomocysteinemia was detected in the greatest number of cases (52.8%), whereas hyperadrenalism (4.8%) and hyperprolactinemia with hypothyroidism (4.8%) were detected in the smaller number of women ***(Figure- 2)***. The highest prevalence of hyperprolactinemia (44.64% among 112 patients) and hyperhomocysteinemia (44.64% among 112 patients) was observed in adolescents.

Young women showed the highest prevalence of hyperhomocysteinemia (62.31% among 138 patients). We found only 1 or 2cases of hyperinsulinemia, which can be considered negligible. This is a noteworthy finding, indicating a changing trend in the presentation of PCOS among adolescent and young women. In women with PCOS, elevated homocysteine levels and reduced antioxidant capacity may be associated with a higher risk of cardiovascular disease, recurrent coronary events and myocardial infarction also.[38, 39, 40] The activation of apoptosis, production of oxidative stress, increased expression of inflammatory cytokines, and aberrant methylation are among the molecular pathways of homocysteine-induced cellular dysfunction.[41] Atherogenic and prothrombotic characteristics of Homocysteine like increased fibrinopeptide A and prothrombin fragments 1 and 2, decreased endothelial antithrombotic activity because of thrombomodulin function changes, and activation of factor VIIa and V, contribute to cardiovascular morbidity and mortality.[42] Hyperhomocysteinemia in PCOS women has been linked to increased pregnancy loss and diminished ovulation.[43] In PCOS women undergoing assisted reproduction, elevated follicular homocysteine levels are a strong predictor of the oocyte, embryo quality, and fertilization rate.[44] Women with hyperhomocysteinemia had greater risks of miscarriage and combining aspirin and LMWH therapy may help prevent RPL in hyperhomocysteinemia.[45, 46]

Figure 3 represents the graphical illustration of the distribution of cases by weight class.

Table 2 represents the distribution of cases according to body weight. In our current study in ***Table 3*** shows elevated hormone levels such as TSH, DHEA, testosterone, prolactin, homocysteine, were compared based on BMI. Specifically, in PCOS patients, higher TSH levels were most prevalent among those classified as obese class II, higher DHEA levels were most prevalent among those with a normal BMI, and higher testosterone levels were most prevalent among those classified as obese class I. Additionally, hyperprolactinemia showed the greatest prevalence in obese class III patients, while higher homocysteine levels were seen in the overweight group. Both prolactin and homocysteine levels were high in obese class III, combined elevation of homocysteine and TSH were most prevalent in the overweight group, and hyperprolactinemia and hypothyroidism were mostly seen among those with normal BMI. These findings suggest a potential link between elevated hormone levels and body weight in this cohort.

Figure 4 illustrates the prevalence of single and multiple hormone disorders across various weight classes.

The intricate relationship between obesity and mental and emotional functioning, hirsutism, irregular menstruation and subfertility, are frequently observed in obese women with PCOS.[47-53] Weight gain and obesity may potentially contribute to the clinical and biochemical manifestation of PCOS by affecting adipokine secretion.[54, 55, 56]

Managing PCOS in adolescent patients is challenging. The continuous debate about whether or not to diagnose PCOS in adolescents and young women, its unclear pathophysiology, or even the relatively small number of research that prioritise on PCOS in adolescents and young women make the task much more challenging.[57] This complicated disorder can be managed by addressing the patients' hormonal and metabolic conditions, preventing further concurrent issues, and improving the overall quality of life of adolescents and young women with PCOS.

National Institutes of Health (NIH) Criteria (1990) [25]	European Society of Human Reproduction and Embryology and American Society of Reproductive Medicine (ESHRE/ASRM)/ Rotterdam Criteria (2003) [23]	Androgen Excess and PCOS Society (AE–PCOS) Criteria (2006) [26]	International PCOS Guidelines (2018) [27]
Oligomenorrhea (<10 menses a year) or oligo-ovulation	Ovarian dysfunction: oligomenorrhea (<10 menses a year) or oligo-ovulation and/or	Clinical hyperandrogenism and/or	Oligomenorrhea or amenorrhea for 2 years after menarche
Clinical hyperandrogenism or Biochemical hyperandrogenism (elevated total/free testosterone	Clinical hyperandrogenism or Biochemical hyperandrogenism (elevated total/free testosterone and/or DHEAS)	Biochemical hyperandrogenism (elevated total/free testosterone and/or DHEAS), as well as one of the following: Oligomenorrhea (<10 menses a year) or oligo-ovulation and/or	Clinical hyperandrogenism and Biochemical hyperandrogenism (elevated total/ free testosterone and/or DHEAS)
	Polycystic ovaries on ultrasound (≥12 antral follicles in one ovary or ovarian volume ≥10 cm3 in one ovary)	Polycystic ovaries on ultrasound (≥12 antral follicles in one ovary or ovarian volume ≥10 cm3 in one ovary)	Ovarian volume ≥10 cm3 in one ovary
Requires 2 of 2	Requires 2 of 3	Requires hyperandrogenism	Requires 2 of 3 after exclusion for other etiologies

Table 1: In the literature, several criteria are used to diagnose PCOS

Weight Class	Number	Percent
Obese Class III (>40)	18	7.2
Obese Class II (35-40)	12	4.8
Obese Class I (30-35)	24	9.6
Overweight (25-30)	89	35.6
Normal (18.5- 25)	107	42.8
Mild Thinness (17-18.5)	0	0.0
Total	250	100.0

Table 2: Distribution of cases according to weight class

	Weight Class											
	Obese Class III (>40)		Obese Class II (35-40)		Obese Class I (30-35)		Overweight (25-30)		Normal (18.5- 25)			
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	p Value	Significance
Insulin↑	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	NA	NA
TSH↑	0	0.00	12	100.00	0	0.00	24	26.97	12	11.21	<0.001	Significant
DHEA↑	0	0.00	0	0.00	0	0.00	0	0.00	12	11.21	0.002	Significant
Testosterone↑	0	0.00	0	0.00	12	50.00	12	13.48	12	11.21	<0.001	Significant
Prolactin↑	12	66.67	0	0.00	12	50.00	24	26.97	60	56.07	<0.001	Significant
Homocysteine↑	12	66.67	0	0.00	12	50.00	60	67.42	48	44.86	<0.001	Significant
Prolactin↑+Homocysteine↑	12	66.67	0	0.00	0	0.00	12	13.48	12	11.21	<0.001	Significant
Prolactin↑+Testosterone↑	0	0.00	0	0.00	0	0.00	12	13.48	12	11.21	0.107	Not Significant
Homocysteine↑+ TSH↑	0	0.00	0	0.00	0	0.00	14	15.73	0	0.00	<0.001	Significant
Prolactin↑+ TSH↑	0	0.00	0	0.00	0	0.00	0	0.00	12	11.21	0.002	Significant

Table 3: Comparison of hormone levels across different weight class

Conclusion:

Numerous current or future complications can be avoided with early identification of PCOS in adolescence and young women. Early treatment initiation facilitates the easy and successful stability of the condition for a longer duration. In our recent investigation, increased homocysteine levels were detected in majority of women with PCOS. Since PCOS is linked to several factors such as insulin resistance, impaired glucose tolerance, hyperandrogenemia, obesity, oxidative stress and dyslipidemia, associated hyperhomocysteinemia, may add to the risk of vasculopathy and thromboembolism. Simple folic acid Vitamin B6 and Vitamin B12 replacement can control homocystein level in serum. Further research is needed to understand the function of homocysteine in human reproductive physiology, as well as it' role among different hormones involved in development of PCOS. This may develop more effective PCOS treatments that can avoid the short and long-term complications.

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