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Research Article

Association of Menstrual Disorders of PCOS Women with their Clinical and Hormonal Profile: A Prospective Observational Study

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Abstract

The aim of our study is to examine a possible association between menstrual disorders of PCOS women with their anthropometric parameters and hormonal profile. This is a prospective observational study of women diagnosed with PCOS. Phenotypic and anthropometric data were recorded for all participants. In total, 309 women with PCOS participated in the study with an average age of 24.9 years. BMI was higher in women with a cycle of more than 35 days as well as in those with amenorrhea. The findings for the waist circumference were similar, while hip circumference values were higher in those with a cycle of fewer than 26 days and the waist/hip circumference ratio was lower in those with a cycle of fewer than 26 days. Moreover, women with a cycle of fewer than 26 days and those with amenorrhea had significantly lower PRL values and higher LH. In addition, free testosterone levels were higher in participants with amenorrhea. We provide data on the kind of menstrual disorders and the different clinical and hormonal profiles of patients. Women with a lower waist/hip ratio revealed shorter cycles, while women with higher BMI had either cycles longer than 35 days or amenorrhea. Sex hormones were also affected in women with menstrual disorders, especially in those with amenorrhea or a cycle duration of fewer than 26 days. This research contributes to the research of the correlation between anthropometric parameters and hormonal profiles in women with Polycystic Ovary Syndrome (PCOS) and their impact on menstrual disorders.

Keywords: Polycystic ovarian syndrome; PCOS; Menstrual disorders; Hormonal profile; Clinical profile; Anthropometric characteristics

Introduction

Polycystic ovarian syndrome (PCOs) is the most common endocrine disorder in women of reproductive age, affecting 6-10% of women [1]. This condition is characterized by hyperandrogenism, polycystic ovaries, and oligo-anovulation, according to the Rotterdam European Society of Human Reproduction and Embryology/ American Society for Reproductive Medicine (ESHRE/ASRM) criteria [2].

A significant percentage of PCOs women reveal menstrual disorders [3,4] and it seems that there is a significant association between menstrual, metabolic, and endocrine disorders [5,6]. In another study, we have shown that PCOS women with menstrual disorders exhibit hormonal alterations and elevated fasting glucose [7]. Increased Body Mass Index (BMI) has been found to affect menstrual function, while weight loss resulted in the improvement of menstrual disorders [8,9].

However, the term "menstrual disorders" or "abnormalities" that is mentioned in many studies includes a wide range of cycle duration, constituting a potentially confusing factor. We have decided to proceed with a more detailed analysis of our data, creating subcategories of women with menstrual abnormalities based on the cycle's duration.

Moreover, in PCOs women without menstrual disorders metabolic and hormonal profiles were significantly better, compared to women with menstrual disorders [10]. Our study group has also found that correction of either menstrual or hormonal abnormalities was not corrected after treatment of mild hypercholesterolemia [11].

Until now though it remains unclear what is the exact percentage of PCOs women that have menstrual disorders, mainly due to lack of consensus in this field. Vaguer remains the impact of the patient's characteristics that can lead to any kind of menstrual disorder. The aim of this study is to examine a possible association between menstrual disorders of PCOS women with their anthropometric parameters and hormonal profile.

Materials and Methods

This is a prospective observational study of women diagnosed with PCOS, which attended the department of Gynecological Endocrinology at Attikon University hospital for the period from January 2007 until December 2015. The study population consists of 309 women, aged 17-35 years old, that fulfilled the Rotterdam ESHRE / ASRM sponsored PCOS criteria [12]. The study's protocol is in agreement with the 1964 Declaration of Helsinki and its later amendments and was approved by the Institutions Ethics Committee [13].

Phenotypic and anthropometric data were recorded for all participants. Hirsutism's degree was assessed based on the Ferriman-Gallwey- Lorenzo (FGL) index [14]. According to the FGL index, we evaluated the hair growth in nine different locations and a score ranging from 0 to 4 (extensive hair growth) was given for each location. As a result, a score ranging from 0 to 36 was produced for all women and when that score was 6 or higher this was categorized as an indication of androgen excess.

Weight measurement in kilograms was obtained with all women being dressed in light clothes, while for the height measurement in centimeters they were placed in the Frankfurt plane. A soft tape was used for the circumference in centimeters around the 12^{th} rib (waist circumference), and the iliac crest (hip circumference). We then calculated the waist-to-hip ratio by dividing the two measurements. The Body Mass Index (BMI) was also calculated from the initial measurements in kg/m^2, by dividing weight by height 2. Based on the World Health Organization criteria [15] we defined normal BMI ranging between 18.50 and 24.99, underweight BMI as lower than 18.50, and obese BMI as greater than 25.

A transvaginal ultrasound was also performed in all women on days 6-8 of the menstrual cycle to assess the uterus and ovaries appearance, in order to clarify whether they met the PCOS criteria.

The ADVIA Centaur system was used for T3, T4, TSH, and PRL measurements, with Coefficients of Variance (CV) of 3.44%, 5.55%, 5.87%, and 4.8% respectively. For the Δ4-A, 17-OHP, and FT measurements we used the RIA kits provided by the Diagnostic Setters International Inc., Corpotage Headquarters and Medical Center Blvd, Webster Texas 77598, 4217 USA, with CV of 6.3%, 9.7%, and 9.75, respectively. Finally, for Testosterone, DHEAS, and cortisol measurements we performed the analysis with Elecsys 1010/2020 and Modstar analytics E 170 by Roche with CV of 5.6%, 6%, and 7%, respectively.

Statistical analysis

Mean values, standard deviations (SD), and median and interquartile ranges were used to describe the quantitative variables. Absolute (N) and relative (%) frequencies were used to describe the qualitative variables. Pearson's x^2 test or Fisher's exact test was used to comparing ratios where necessary. The parametric dispersion analysis (ANOVA) or the non-parametric Kruskal-Wallis criterion was used to compare quantitative variables between more than two groups. The significance levels are bilateral and the statistical significance was set at 0.05. The statistical program SPSS 22.0 was used for the analysis.

Results

In total, 309 women with PCOS participated in the study, with an

average age of 24.9 years (SD=5.6 years). Tables 1 and 2 summarize the anthropometric data of the study's population. The average BMI of the participants was 25.5 kgr/m^2 and 56.2% had 20-27 kgr/ m^2. The average waist circumference was 90.4 cm (SD=15.9cm), the average thigh circumference was 79.4 cm (SD=28.8cm) and their mean ratio was 1.03 (SD=0.38). The average value of the Lorenzo index was 9.7 points (SD=4.0 points), 52.1% of the participants had mild acne, and 4.3% had severe. Androgenic alopecia revealed 36.0% of participants and 1.4% had *Acanthosis nigricans*.

		Average (SD)
BMI		25.5 (6.7)
Categories BMI, N (%)	<20	41 (17.6)
	20-27	131 (56.2)
	>27	61 (26.2)
Waist circumference (cm)		90.4 (15.9)
Hip circumference (cm)		79.4 (28.8)
Waist / Hip ratio		1.03 (0.38)

Table 1: PCOS women's BMI categories.

		N	%
HIRSUTISM INDEX (LORENZO), average (SD) median (median range)		9.7 (4.0)	10 (6-12)
Acne	No	133	43.6
	Mild	159	52.1
	Intense	13	4.3
Androgenic alopecia	No	187	64.0
	Yes	105	36.0
Acanthosis nigricans	No	292	98.6
	Yes	4	1.4

Table 2: PCOS women's Hirsutism Index and clinical features.

In table 3 we present the hormonal profile of the 309 PCOS women and in table 4 the menstrual disorders they suffered. The average FSH value of the participants was 5.9 points (SD=2.2 points) and the average PRL value was 18.2 points (SD=16.9 points). Also, the average total testosterone was 58.3 units (SD=24.4 units) and the average free testosterone was 2.2 units (SD=1.4 units). The average value of D4 androstenedione was 2.6 units (SD=1.3 units), T3 was 1.5 units (SD=0.5) and TSH was 2.3 units (SD=1.6 units). Concerning menstruation 27.8% of the participants did not have any disorder, while 58.3% had a cycle of more than 35 days, 5.2% had a cycle of fewer than 26 days and 8.7% had amenorrhea.

	Average (SD)	Median (Median range)
FSH (m/U/ml)	5.9 (2.2)	5.6 (4.4-6.8)
LH (m/U/ml)	6.4 (3.9)	5.5 (3.8-7.8)
PRL	18.2 (16.9)	15 (10.5-21.1)
E2 (pg/ml)	52 (61.2)	39 (31-53)
Testosterone (total) (ng/dl)	58.3 (24.4)	60 (40-72)
Testosterone (free) (pg/ml)	2.2 (1.4)	1.9 (1.3-2.7)
OHP17 (ng/ml)	1.3 (0.8)	1.1 (0.8-1.6)
DHEAS (μg/dl)	238.4 (203.4)	210 (139-313)
Δ4- Androstenedione (ng/mg)	2.6 (1.3)	2.4 (1.8-3.2)
SHBG (nmol/L)	49.2 (34.5)	41.8 (28.8-61)
Cortisol (serum) (mg/dl)	24.8 (35.3)	18.5 (12.6-23.2)
T3 (nmol/L)	1.5 (0.5)	1.4 (1.1-2)
T4 (μg/dl)	7.7 (1.8)	7.7 (6.8-8.7)
TSH (mU/L)	2.3 (1.6)	2 (1.3-2.7)

Table 3: PCOS women's Hormonal profile.

		N	%
Menstrual disorders	26-35 days	86	27.8
	>35 days	180	58.3
	<26 days	16	5.2
	Amenorrhea	27	8.7

Table 4: PCOS women's menstrual disorders.

Table 5 shows the association of menstrual disorders with the anthropometric data of the participants. In table 5 menstrual disorders of the participants are significantly related to anthropometric data. Specifically, BMI was higher in those with a cycle of more than 35 days as well as in those with amenorrhea. The findings for the waist circumference were similar. In contrast, hip circumference values were higher in those with a cycle of fewer than 26 days, while the waist/hip circumference ratio was lower in those with a cycle of less than 26 days.

		Menstrual disorders				**P+**
		26-35 days	**>35 days**	**<26 days**	**Amenorrhea**	
		Average (SD)	**Average (SD)**	**Average (SD)**	**Average (SD)**	
BMI, average (SD)		23.8 (4.8)	26.2 (7.3)	24.5 (5.6)	26.8 (7.9)	**0.031**
BMI categories	< 20	11 (26.8)	27 (65.9)	0 (0.0)	3 (7.3)	**0.021++**
	20-27	45 (34.4)	67 (51.1)	12 (9.2)	7 (5.3)	
	>27	10 (16.4)	44 (72.1)	2 (3.3)	5 (8.2)	
Waist circumference, average (SD)		86 (12.4)	92 (16.7)	89.1 (12.6)	93.5 (19.2)	**0.044**
Hip circumference, average (SD)		72.4 (22.6)	82.7 (31.1)	101.3 (26.5)	66.3 (19.4)	**<0.001**
Waist / Hip circumference ratio, average (SD)		1.08 (0.4)	1.01 (0.36)	0.82 (0.25)	1.34 (0.45)	**0.013**

Table 5: Association of menstrual disorders with the anthropometric data of the participants ($^{+}$ANOVA, $^{++}$Fisher's exact test).

In table 6 we present our data on menstrual disorders and their association with Hirsutism Index and clinical features and in table 7 the hormonal profile. The data in table 6 were not significantly associated with menstrual disorders. In table 7 participants' LH, PRL, and free testosterone levels differed significantly depending on their menstrual disorders. Specifically, participants with a cycle of fewer than 26 days and those with amenorrhea had significantly lower PRL values and higher LH. In addition, free testosterone levels were higher in participants with amenorrhea.

		Menstrual disorders								**P**
		26-35 days		**>35 days**		**<26 days**		**Amenorrhea**		
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
HIRSUTISM INDEX (LORENZO), average (SD) median (median range)		10.1 (4.1)	10 (6 — 12)	9.6 (3.8)	10 (6 — 12)	9.2 (4.1)	8 (6 — 13)	9.3 (5.3)	9 (5 — 12)	0.613‡
Acne	No	36	27.1	78	58.6	6	4.5	13	9.8	0.877+
	Mild/ Severe	47	27.3	102	59.3	10	5.8	13	7.6	
Androgenic alopecia	No	56	70.9	102	59.3	13	81.3	16	64.0	0.148+
	Yes	23	29.1	70	40.7	3	18.8	9	36.0	

Acanthosis nigricans	No	84	100.0	167	97.7	15	100.0	26	100.0	0.619++
	Yes	0	0.0	4	2.3	0	0.0	0	0.0	

Table 6: Association of menstrual disorders with Hirsutism Index and clinical features. (‡Kruskal-Wallis test, +Pearson's x^2 test, ++Fisher's exact test).

	Menstrual disorders								**P Kruskal-Wallis test**
	26-35 days		**>35 days**		**<26 days**		**Amenorrhea**		
	Average (SD)	**Median (Median range)**	**Average (SD)**	**Median (Median range)**	**Average (SD)**	**Median (Median range)**	**Average (SD)**	**Median (Median range)**	
FSH (m/U/ml)	6 (2.2)	5.6 (4.5-7.4)	5.8 (2.1)	5.7 (4.3-6.7)	6 (1.9)	5.6 (4.7-6.6)	6.3 (3.1)	5.6 (4.6-6.6)	0.911
LH (m/U/ml)	5.1 (2.3)	4.9 (3.5-6.8)	6.6 (4.2)	5.6 (3.9-7.8)	8.4 (4.6)	7.4 (4.6-10.6)	8 (4.7)	6.5 (4.5-10.4)	**0.002**
PRL	22.7 (27.5)	18.8 (13-26)	17.5 (10.6)	14.7 (10.5-21)	12.2 (5.5)	10.9 (8.5-15.9)	13.3 (5.3)	13 (8.5-17.6)	**0.001**
E2 (pg/ml)	57.4 (81.3)	40 (32.7-53)	46.5 (33.8)	38 (29-53.1)	37.7 (23.3)	34 (31-42.3)	81 (117.2)	37 (34.1-47.1)	0.440
Testosterone (total) (ng/dl)	61.4 (25.1)	62.6 (45-73)	56.6 (24.5)	55.5 (36-72)	48.2 (16.6)	43.6 (36.3-63.7)	65.5 (23.5)	67 (52-71)	0.061
Testosterone (free) (pg/ml)	2.1 (1.3)	1.8 (1.5-2.4)	2.1 (1.4)	1.9 (1-2.7)	2 (0.9)	2.4 (1.1-2.6)	3 (1.7)	2.7 (2.2-3.6)	**0.040**
OHP17 (ng/ml)	1.5 (1)	1.2 (0.8-1.9)	1.2 (0.8)	1.1 (0.8-1.5)	1.2 (0.6)	1.2 (0.8-1.4)	1.3 (0.8)	1 (0.7-1.8)	0.536
DHEAS (μg/dl)	226 (119.6)	194 (127-340.3)	246.7 (247.7)	206.3 (135-313)	256.1 (158.5)	211.5 (169.2-330)	209.2 (76.8)	225.9 (163-245)	0.929
Δ4 Androstendione (ng/mg)	2.6 (1.3)	2.4 (1.7-3.3)	2.6 (1.2)	2.5 (1.9-3)	2.9 (1.9)	2.4 (2-3.4)	2.6 (1.1)	2.4 (1.8-3.7)	0.946
SHBG (nmol/L)	51 (28.1)	47 (32.6-63.2)	49.8 (39.3)	41 (28-61)	38.5 (25.3)	31.2 (28-39.6)	46.6 (24.3)	46.6 (29-55)	0.205
Cortisol serum (mg/dl)	25.2 (37.4)	19.1 (10-23.2)	25 (36.5)	18.2 (12.5-22.5)	17.8 (4.6)	17 (14-21.9)	27.7 (33.4)	18.3 (14.9-26)	0.677
T3 (nmol/L)	1.47 (0.51)	1.3 (1.1-1.72)	1.55 (0.47)	1.42 (1.15-1.97)	1.55 (0.56)	1.62 (1-1.73)	1.45 (0.45)	1.3 (1.1-1.78)	0.722
T4 (μg/dl)	7.41 (1.81)	7.8 (6.7-8.29)	7.76 (1.74)	7.71 (7-8.9)	8.21 (1.75)	7.6 (7.1-9.4)	7.38 (1.72)	6.6 (6-8.71)	0.325
TSH (mU/L)	2 (1.4)	1.7 (1.2-2.4)	2.4 (1.7)	2.1 (1.4-2.9)	2 (0.7)	1.9 (1.6-2.3)	2.3 (1.5)	2.1 (1.3-2.9)	0.246

Table 7: Association of menstrual disorders with hormonal profile.

Discussion

In our previously published study [7] we have found that menstrual disorders in women with PCOs are associated with hormonal alterations and elevated fasting glucose. In this study, we have divided our study group into PCOS women with normal or abnormal menstruation and there was no mention of the duration of the menstrual cycle in the two groups.

Moreover, we have performed an analysis of our data dividing the menstrual disorders into categories, based on the duration of the menstrual cycle. This is the main strength of our study, as we have specified the kind of menstrual disorders for each subgroup. This way, we can investigate the different biological behavior of our PCOS based on menstrual duration.

Concerning anthropometric characteristics, our study showed that women with cycles less than 26 days had higher circumference values and lower waist/hip circumference ratios. Therefore, these women with lower waist/hip are more likely to have a cycle shorter than 26 days. On the contrary, patients with cycles longer than 35 days of amenorrhea had significantly higher BMI. It seems though that an increased BMI can lead to cycles of longer duration or even amenorrhea. A population-based study from Finland has also highlighted the association of increased BMI with a menstrual cycle longer than 35 days [16]. Another study on childhood and adolescent obesity showed that women with increased BMI are more prone to irregular menstrual cycles and have higher ovarian volumes than girls with lower BMI and/or lower percentage body fat. This suggests a possible link to PCOS development and that their menstrual cycles will be 21 to 45 days in length [17]. In a recently published study, Meyer et al. report that PCOS women with menstrual cycles >35 days or amenorrhea tend to have higher waist circumference and higher BMI [18]. The same findings were also documented in adolescents and in fact, West et al. claim that menstrual irregularity at 16 years is associated with increased menstrual irregularity and PCOS at 26 years [19]. On the contrary Panidis, et al. state that obesity does not appear to have an important effect on menstrual cycle patterns in PCOS [8].

Our statistical analysis revealed no statistically significant difference in Hirsutism and clinical features based on menstrual disorders for any category. This finding is opposed to the study of Willis, et al. who reported that menstrual irregularity, increased cycle and bleeds lengths, and heavier menstrual bleeds were associated with self-reported hirsutism [20]. It is necessary to point out that in our study we used objective measurement and not self–reported findings.

We have also found differences in the hormonal profile depending on the kind of menstrual disorder. Women with amenorrhea had the more affected profile, presenting with higher levels of testosterone, LH, and lower PRL serum values. These findings align with and reinforce the conclusions drawn by Pinola, et al., as reported in their previously published data [16]. The collective evidence indicates that menstrual disorders serve as robust indicators of underlying hyperandrogenemia. Elevated testosterone levels, a hallmark of hyperandrogenemia, are known to contribute to disruptions in the normal menstrual cycle, potentially leading to conditions such as amenorrhea [16].

The examination of hormonal profiles in women with cycles shorter than 26 days revealed distinct alterations, with higher Luteinizing Hormone (LH) and lower Prolactin (PRL) levels, despite the absence of increased free testosterone. This specific hormonal pattern suggests a unique endocrine landscape in this subgroup, challenging conventional expectations regarding androgen excess in Polycystic Ovary Syndrome (PCOS) women.

The absence of elevated free testosterone in women with shorter menstrual cycles raises intriguing questions about the underlying mechanisms contributing to their hormonal dynamics. The elevation in LH, a key regulator of ovulation, and the concurrent decrease in PRL, known for its role in maintaining reproductive function, present a nuanced hormonal profile that warrants further investigation. These findings diverge from the expected association between shorter menstrual cycles and heightened androgen levels, challenging existing paradigms in PCOS research.

Our results align with previous studies that have identified alterations in sex hormones among PCOS women with menstrual irregularities, supporting the notion that variations in menstrual cycle length are indicative of distinct endocrine profiles [5,9]. This reinforces the importance of recognizing the heterogeneity within the PCOS population and tailoring assessments to capture the specific hormonal patterns associated with different menstrual disorders.

The study by Chan et al. further complements our findings, demonstrating that menstrual dysfunction in PCOS women can serve as a predictive marker for androgen excess. However, it is noteworthy that our study specifically delves into the nuances between women with menstrual cycles shorter than 26 days and those with longer cycles exceeding 35 days. This granularity in analysis adds depth to our understanding of the relationship between menstrual irregularities and hormonal imbalances in PCOS.

Our study provides data on the kind of menstrual disorders and the different clinical and hormonal patient profiles. Women with lower waist/hip ratio revealed shorter cycles, while women with higher BMI had either cycle longer than 35 days of amenorrhea. Sex hormones were also affected in women with menstrual disorders, especially in those with amenorrhea or cycle duration of less than 26 days.

Moreover, the association between menstrual disorders and increased metabolic risks adds another layer of significance to these findings. The intricate interplay between hormonal imbalances and metabolic dysfunction is well-documented, and the current study contributes to this growing body of knowledge by highlighting the specific hormonal alterations linked to different menstrual disorders.

Understanding these nuances in hormonal profiles among women with distinct menstrual disorders is pivotal for both diagnostic and therapeutic considerations. Tailoring interventions to address the specific endocrine imbalances associated with amenorrhea can potentially improve the effectiveness of treatment strategies. Additionally, these findings emphasize the importance of comprehensive hormonal assessments in the clinical evaluation of women with PCOS and menstrual disorders, allowing for a more targeted and personalized approach to managing their reproductive and metabolic health.

Statements and Declarations

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Authors' Contributions

All authors contributed to the study conception and design. Conceptualization, Gerasimos Perros and Adamantia Kontogeorgi; methodology, Christos Koratzanis software, Adamantia Kontogeorgi, Eftihios Trakakis and Melpomeni Peppa; validation, Charalampos Chrelias, Gerasimos Perros and Dimitrios Zygouris; formal analysis, Nikolaos Papantoniou; investigation, Adamantia Kontogeorgi and Periklis Panagopoulos; resources, Nikolaos Papantoniou; data curation, Christos Koratzanis ,Melpomeni Peppa, Anastasia Zanettoullis ; writing—original draft preparation, Gerasimos Perros and Anastasia Zanettoullis; writing—review and editing, Peter Drakakis and Sofoklis Stavros; visualization, Peter Drakakis and Sofoklis Stavros; supervision, Peter Drakakis and Periklis Panagopoulos; project administration, Gerasimos Perros. All authors have read and agreed to the published version of the manuscript.

Ethical Approval and Consent to Participate

The protocol of this study was conducted according to the "Helsinki" declaration and approved by the Ethics Committee of Attikon, Athens, University hospital.

Patients Consent for Publication: Written informed consent were obtained from all participants included in the study.

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