

Comparison of the Clinical and Laboratory Features of Polycystic Ovary Syndrome of Women with Normal weight with Overweight and Obese Women

S.H. Sharami (MD)¹, F. Fakor (MD)^{*1}, F. Mohammadi (MD)², R. Molaee (MD)³, M. Shakiba (PhD)⁴,
S.F. Dalil Heirati (BSc)¹, M. Archang (MD)⁴, S. Archang (MD)⁴

1. Reproductive Health Research Center, Guilan University of Medical Sciences, Guilan, I.R.Iran

2. Glands Research Center, Guilan University of Medical Sciences, Guilan, I.R.Iran

3. Department of Radilogy, Guilan University of Medical Sciences, Guilan, I.R.Iran

4. Guilan University of Medical Sciences, Guilan, I.R.Iran

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ABSTRACT

BACKGROUND AND OBJECTIVE: Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder among women of the reproductive age. The complications of this syndrome such as Hyperandrogenism, infertility, Hirsutism and pregnancy complications increase in obese women with PCOS. This study aimed to compare the clinical and laboratory features of overweight and obese women suffering PCOS with women of normal weight.

METHODS: In this cross-sectional study, 368 PCOS patients were studied. According to the Rotterdam Criteria, they were divided into two groups of equal body mass index (BMI) ≥ 25 and < 25 . They were compared in terms of age, parity, infertility history, menstrual disorders, family history of diabetes, weight, BMI, waist to hip ratio (WHR), systolic and diastolic blood pressure and clinical and laboratory symptoms of PCOS.

FINDINGS: In both groups, the common phenotype was IM/ HA/PCO and the frequent menstrual pattern was Oligomenorrhea (81.2%). In group the overweight and obese group and the normal-weight group, respectively, the mean age was 26.84 ± 5.28 and 25.59 ± 4.66 ($p=0.0001$), the mean systolic blood pressure was 114.4 ± 11.61 and 106.66 ± 10.02 ($p=0.01$), the mean diastolic blood pressure was 73.24 ± 8.97 and 67.29 ± 8.36 ($p=0.01$), infertility was 45.5% and 22.61% ($p=0.0001$) and the android obesity incidence was higher in the patients than normal individuals ($p=0.0001$).

CONCLUSION: Infertility, android obesity and increased systolic and diastolic blood pressure was higher in the overweight and obese group than the normal weight group. Therefore, a follow-up for these patients in order to prevent the complications seems necessary.

KEY WORDS: Overweight, Polycystic Ovary Syndrome, Body Mass Index, Obesity.

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Introduction

Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder with the incidence of 9-18% among women of the reproductive age (1). PCOS

is associated with different clinical complications including reproductive problems (infertility, Hyperandrogenism, Hirsutism), metabolic problems

* Corresponding Author; F. Fakor (MD)

Address: Reproductive Health Research Center, Al Zahra Hospital, Namjoo Avenue, Rasht, I.R.Iran .

Tel: +98 131 3225624

E-mail: fereshtehfakor@yahoo.com

(insulin resistance, impaired Glucose tolerance, Diabetes Mellitus and cardiovascular diseases) and mental problems (anxiety, depression and poor quality of life) (2). PCOS covers a wide spectrum of phenotypes (3, 4) depending on the individual's stage of life, genotype, race and environmental factors such as lifestyle and weight. The precise physiopathology of PCOS is complex and remains unclear (2). Several studies are indicative of the prevalence of obesity in PCOS (5, 6). In the United States, more than half the PCOS patients are overweight or obese. This is not surprising because obesity is the major cause of insulin resistance and secondary Hyperinsulinemia contributing to PCOS and Hyperandrogenism (7). Obesity largely affects the phenotype of PCOS patients and it may play a pivotal role in the physiopathology of Hyperandrogenism, chronic anovulation and the metabolic system. Obesity is also clearly associated with increasing infertility, metabolic syndrome and the risk of cardiovascular diseases (8, 9). Furthermore, it affects the metabolism of sex hormones and is also correlated with the increased production of Androgen and the inhibition of Sex hormone-binding Globulin (10). In a study, it was observed that obese women with PCOS are exposed to a higher risk of Hyperandrogenism, insulin resistance, Hypercholesterolemia, Hypertriglyceridemia and higher C-reactive protein (CRP) compared to the women with normal weight (11). On the same subject, a meta-analysis revealed that the metabolic and reproductive outcomes have been worse in obese women with PCOS than the normal weight women (12). Studies have demonstrated that weight loss and adequate physical exercise could enhance Hyperandrogenism, insulin resistance and ovary function in PCOS patients. Research has it that the prevention of obesity is a vital component of PCOS treatment (12, 13). Since PCOS pathogenesis may vary in obese and normal weight women of this syndrome, the comparison of the clinical and laboratory features of the two groups seems necessary (14). Given the increasing prevalence of obesity and its associated complications in the world, this study aimed to determine the clinical and laboratory features of PCOS in overweight, obese and normal weight women in order to clarify the role and complications of obesity in PCOS patients as well as to emphasize the importance

of weight loss. For another thing, since limited research has been conducted on the association of different PCOS phenotypes and weight, the findings of the current study could lay the grounds for further studies for a better understanding of the mechanisms of the disease.

Methods

This cross-sectional study was performed on 368 married women with PCOS aging from 15 to 39 years who referred to the Endocrinology and Infertility Clinic of Razi Hospital and two other infertility clinics in Rasht, Iran in 2011 and 2012. Informed consent was obtained from the patients and the diagnosis of PCOS was based on the Rotterdam Criteria (4). At least two standard diagnostic criteria were included:

Oligoovulation (cycle duration of over 35 days), clinical or laboratory Hyperandrogenism (along with clinical signs of Hirsutism, acne and male pattern hair loss (Alopecia areata), increased Testosterone levels or Dehydroepiandrosterone (DHEA) and Androstenedione) and the appearance of morphological features of PCOS in the Sonography of the ovaries. Four phenotype groups of the patients were formed in accordance with the Rotterdam Criteria: The first group with menstrual disorders + morphological view of polycystic ovary + Hyperandrogenism, (IM/PCO/HA); The second group with menstrual disorders+morphological view of PCO (IM/PCO); The third group with menstrual disorders+Hyperandrogenism (IM/HA); and the fourth group with the morphological view of PCO+Hyperandrogenism (PCO/HA). All the patients were surveyed on the age, reproductive features (number of labours, infertility history, no pregnancy for at least 1 year without using contraception), menstrual dysfunction (Oligomenorrhea [cycles longer than 35 days or less than 9 menstrual cycles per year], Amenorrhea [no menstruation for more than 3 months] and Menorrhagia and family history of diabetes). Anthropometric measurements (weight in k.g, height, waist and hip circumference in c.m) were made and the diastolic and systolic blood pressure was measured once using the HS-50B Zyklus Zyklusmed system, made in China. Following that, all the patients were referred to the same laboratory while fasting between

the third to fifth day of their menstrual cycle. At this point, the level of Thyroid-stimulating hormone was evaluated through obtaining 10 ml of venous blood by Chemiluminescence Immunometric assay (Immulite 2000 Analyzer; CPC, Los Angeles, CA, USA). Also, prolactin, free testosterone, Androstenedione and DHEA 17-hydroxyprogesterone were measured through RIA access [Simens, Los Angeles, CA, USA] while fasting blood sugar (FBS) was determined by Hitachi 760. Moreover, Transvaginal ultrasound was performed by a radiologist (using model ACUSON X150 SIEMENS, Germany) within the first 5 days of the spontaneous menstrual cycle or the cycle induced by a week of oral or injectable progesterone. Based on the Rotterdam Criteria, if there were 12 follicles or more in each ovary with a diameter of 2 to 9 mm or the ovary was larger than 10 mm in the ultrasound image, it was a case of polycystic ovary. In this study, women with a BMI of 25 kg/m² or more were considered as overweight/obese and the women with a BMI of under 25 kg/m² were considered to be of normal weight. In each group, the sample size was calculated as 184 cases based on the study of Vasheghani and colleagues (15) with a power of 80% and an accuracy of 95%. The exclusion criteria were as follows: 1) patients with Hypothyroidism (TSH > 5), Hyperprolactinemia (prolactin ≥ 40%) and diabetes (FBS ≥ 126); 2) patients consuming medications affecting the Gonadotropins within the past 6 months (including OCP, hormonal medications and Progesterones); 3) patients with Congenital adrenal hyperplasia, Androgen making tumors and Cushing's syndrome. The collected data entered the SPSS software version 14 and the Kolmogorov-Smirnov test was used to check the normality of the quantitative data. In case of abnormality, the Mann-Whitney test was used in order

to compare the quantitative groups while the Independent T-test was used for the normal distribution of the data. To assess the qualitative data between the two groups, Fisher's exact Test and Chi-square were used and a significance level of $p < 0.05$ was considered.

Results

In the present study, 368 women with PCOS were studied. Of all the patients, 168 (45.65%) were in the normal weight group ($25 < \text{BMI}$) and 200 (54.35%) were in the overweight/obese group ($25 \geq \text{BMI}$). In the normal weight group, 11 patients were only evaluated in terms of demographic and clinical findings due to their lack of follow-up and their incomplete ultrasound test results. The mean age in the normal and overweight/obese groups was 25.59 ± 4.66 and 26.84 ± 5.28 , respectively (table 1). Moreover, the prevalence of infertility in the overweight/obese group was higher than the normal group ($p = 0.0001$). There were no significant differences between the two groups regarding their other clinical features (Hirsutism, acne, Galactorrhea, Acanthosis nigricans, Alopecia Areata, diabetes and the view of the polycystic ovary. (table 2). In both groups, Oligomenorrhea was the most prevalent menstrual disorder while the most frequent phenotype was IM/PCO/HA. Regarding the menstrual disorder patterns and the PCOS phenotypes, no differences were observed between the two groups (table 3). In addition, no statistically significant differences were found between the two groups in the mean of the laboratory features including the maximum size of the ovary, free Testosterone, DHEA androstenedione and 17-Hydroxyprogesterone (table 4).

Table 1. Mean of Demographic and Clinical Features in Overweight/obese PCOS Women and Women with Normal Weight

Group	Index	Normal Weight (N=157) Mean±SD	Overweight and Obese (N=200) Mean±SD	p-value
	Age	25.59±4.66	26.84±5.28	0.0001
	BMI	22.56±1.69	30.91±5.18	0.0001
	WHR	0.79±0.07	0.84±0.08	0.0001
	Systolic blood pressure	106.66±10.02	114.4±11.61	0.0001
	Diastolic blood pressure	67.29±8.36	73.24±8.97	0.0001

Table 2. Distribution of Clinical Findings in Overweight/obese Women and Women with Normal Weight

Group	Index	Normal Weight N(%)	Overweight and Obese N(%)	p-value
Hirsutism		66.07(11)	65.5(131)	0.824
Infertility		22.61(38)	45.5(91)	0.0001
Galactorrhea		7.4(12)	11.5(23)	0.282
Acne		34.52(58)	38.5(77)	0.318
Acanthosis		8.33(14)	7.5(15)	0.844
Alopecia		27.38(64)	27(46)	0.355
Diabetes history		35.11(59)	43(86)	0.1
Polycystic ovary		77.08(121)	78(156)	0.898

Table 3. Distribution of Clinical Findings in Women with Normal Weight and Overweight/obese Women

Group	Index	Normal Weight N(%)	Overweight and Obese N(%)	p-value
phenotype				
IM/PCO/HA		56.68(89)	56.5(113)	0.99
IM/PCO		18(29)	18.47(36)	
IM/HA		22.9(35)	22.5(45)	
PCO/HA		2.54(4)	2(6)	
pattern of menstrual disorders				
Oligomenorrhea		76.78(121)	85(170)	0.35
Amenorrhea		11.30(17)	8.5(19)	
Polymenorrhea		7.73(13)	2.5(5)	
Normal		4.16(6)	4(8)	

Table 4. Comparison of the Mean of Laboratory Findings in Overweight/obese Women with Normal Weight Women

Index	Group	Normal Weight (N=157) Mean±SD	Overweight and Obese (N=200) Mean±SD	p-value
size of ovar(mm ³)		12.34±5.33	13.1±9.24	0.82
free testosterone		1.85±1.73	2.44±7.61	0.32
17-Hydroxy progesterone		0.9±0.65	0.89±0.62	0.91
DHEA Androstenedione		236.98±135.07	216.79±129.83	0.09

Discussion

In the current study, there were no differences in the PCOS phenotypes between the two groups. However, the overweight/obese group significantly surpassed the normal weight group in the mean of the demographic data (age, weight, height and BMI), the mean of the clinical features (waist and hip circumference and WHR) and systolic and diastolic blood pressure. In the study of Yu et al(2008)., the mean age of obese women was 32 while it was 30 in the women with normal weight. However, no

statistically significant differences were found between the two groups regarding the age (16). Statistically, the mean age of the overweight and obese women in our study was higher than the normal weight women. It seems that this slight age difference (about one year) between the two groups is not clinically important but rather, only statistically significant. The mean of the BMI in the overweight/obese patients and the normal weight patients was respectively 30.91 and 22.56 in our study. A statistically significant difference was

observed between the two groups in this regard. The mean of the BMI in the study of Kumarapeli (2008) was 24.2, it was 32.1 in Wright's study(2004), 32.1 in Wijeyaratne's study(2002) on Caucasian patients and it was 30.59 in the South Asian patients (17-19).

On the other hand, Chae and colleagues(2008) concluded that the BMI of the Korean women was less than that of the Caucasian women with PCOS and it was similar to that of the Asian patients (20). In the study of Yu et al., the mean of the BMI in obese and normal patients was 29.2 and 21, respectively (16). The results of the current study are more similar to the Yu's and the slight difference between them could be justified due to racial differences. In our study, the mean WHR in all the cases was 0.82 while in the overweight and normal patients it was 0.84 and 0.81, respectively. Thus, there was a significant difference between the two groups in this regard. The mean of WHR in the study of Kumarapeli was reported to be 0.86, it was 0.83 in the study of Wright et al., in the study of Wijeyaratne on Caucasian patients it was 0.92 and it was 1.04 in South Asian patients (17-19, 21). The mean of WHR in the current study was consistent with that of Wright's et al.

It is noteworthy that in Wright's study, the sample size was smaller and the mean age was higher than the current study. In the present study, the mean of systolic and diastolic blood pressure was higher in the overweight/obese women than those with normal weight. Thus, there was a significant difference between the two groups in this regard. Meanwhile, in the study of Vasheghani et al, the blood pressure was reported to be within the normal range in all the patients (15).

On the other hand, the mean of systolic and diastolic blood pressure in Kumarapeli's study was reported to be 120 and 77, respectively. Wijeyaratne et al. reported these factors to be 114 and 72 in South Asian patients and among the Caucasian patients, they were reported to be 120 and 76, respectively (17, 18). Therefore, it seems that the mean of systolic and diastolic blood pressure in our study is more compatible with that of Wijeyaratne's study. However, since the patients were not divided into the two groups of overweight and normal weight in the aforementioned studies, it is not possible to compare the systolic and diastolic hypertension in those terms.

In the present study, the prevalence of Hirsutism in the total population was 65.67 which is similar to the prevalence of Hirsutism in the study of Vasheghani(2002) conducted in Sari, Iran (62%) (15). The prevalence of Hirsutism was reported to be 59.2% in Aali's study(2002), it was 6.8% in Azziz's study(2004) conducted in the USA and in Kumarapeli's study it was 53.1% (13, 17, 22).

In our study, the prevalence of Galactorrhea was 9.5% and there were no significant differences between the two groups of overweight/obese and normal weight. On the other hand, in the study of Aali et al. conducted in Kerman, Iran, the prevalence of Galactorrhea was 10% (22) which is compatible with the findings of the current study.

In the present study, the overall incidence of Acanthosis nigricans was 3.13% and there were no significant differences between the two groups while the overall prevalence of Acanthosis nigricans in the study of Wijeyaratne and colleagues was 64.6%. The prevalence was reported to be 7.5% and 55.31% in Caucasian patients and South Asian patients, respectively (17,18,21). Therefore, compared to the results above, the prevalence of Acanthosis nigricans in our study was far lower. To explain this difference, it should be noted that the study of Wijeyaratne was conducted on the patients with PCOS and metabolic syndrome and Acanthosis nigricans is one of the symptoms of metabolic syndrome. Thus, the high prevalence of Acanthosis nigricans in their study is justified. In general, the prevalence of acne was found to be 36.68% in our study and there were no statistically significant differences between the two groups of overweight/obese and normal weight. The overall prevalence of acne was 25.2% and 35% in the study of Aali and Vasheghani, respectively (15, 22). As a result, it is safe to say that the prevalence of acne in our study was compatible with that of Vasheghani's study. For another thing, the overall prevalence of infertility in the current study was 35.0% and it was significantly higher in the overweight/obese group than the normal group. In the study of Vasheghani, the infertility rate was reported to be 8.2% due to 6 married cases which is rather low considering the low mean of age in this study. In the study of Aali et al., the prevalence of infertility was 27%. However, it should be noted that 65 out of 130 patients were

married (22). Due to the absence of a control group for PCOS in our study, it is unclear whether the increased infertility incidence was a result of the increased weight, age and how much of that might have been caused by PCOS. This was one of the limitations of the present study. Infertility increases with age (23) and as already mentioned, the mean age of our overweight and obese patients was significantly higher than that of the normal weight group. Therefore, given the fact that both age and infertility were measured in patients with a BMI equal to or larger than 25, the increased prevalence of infertility might be a result of aging in these patients. Due to slight clinical differences with regards to the patients' age (one year), the statistical difference was not considered as clinically significant in the present study and matching on age was not performed to eliminate the possible confounding effects of age. In our study, all the patients were married. This is a major difference which might result in an inconsistency with other studies.

Furthermore, the mean of free testosterone in all our patients was 2.18 and 55.18% of the total surveyed cases showed free testosterone levels of above the normal rate. In the present study as well as the studies of Yu and Aali, no differences were found in the hormone levels in patients with normal weight and the overweight/obese women with PCOS (16, 22). Thus, the mean free testosterone in our study is similar to that of Wijeyaratne and colleagues' study (18). In our study, the mean of DHEAS androstenedione in the total number of patients was 225.67 and in 16.24% of the cases, it was above the normal rate. Similar to the studies of Aali and Yu, no significant correlations were found between obesity and increased DHEAS androstenedione. (16,22). In Aali's study, 20.4% of the patients showed a DHEAS androstenedione of above the normal rate (22).

In the present study, the mean of 17-Hydroxyprogesterone was 1.48 and all the patients were in the normal range. Consequently, there were no significant differences recorded between the two groups in this regard. In the study of Aali et al., the mean of 17-Hydroxyprogesterone was reported to be 1.9 and the level was above the normal range in 18.6% of the cases. There were no significant differences between obese patients and normal patients in this regard (22). However, their study is not comparable to

ours since we regarded normal 17-Hydroxyprogesterone as an inclusion criteria and all of our patients had normal levels of 17-Hydroxyprogesterone. The mean of ovarian volume in our study was 12.85 similar to that of Yu et al's while no statistically significant differences were recorded between the overweight and the normal patients in this regard (16). However, it should be taken into account that the ovarian volume was evaluated in only 36.41% of the patients in this study. The mean of the ovarian volume in different phenotypic subgroups of Chae's study (2004) varied from 4.2 cm³ to 11 cm³ and in Welt's study(2006), it varied from 7.3 cm³ to 14.8 cm³ (20,24).

The frequency of polycystic ovary view in overweight and obese women was slightly higher than those of the normal weight in our study and the difference between the two groups was not proven to be significant. In the study of Mardani(2009), the prevalence of polycystic ovary view was higher in obese women which was compatible with our findings. However, this difference was recorded as significant between the two groups in their study which is inconsistent with our findings (25). On the other hand, the polycystic ovary was observed in 96.7% of the patients in the study of Kumarapeli et al. as well as 81.5% of the patients in Aali's study (17,22). Therefore, the prevalence of polycystic ovary in our study is similar to that of Aali's study. The only difference is of the definition of polycystic ovary between the study of Aali and our study. Moreover, the obese patients in Aali's study had vaginal ultrasound in order to detect polycystic ovary and other patients had abdominal ultrasound whereas in our study, all the patients had vaginal ultrasound.

In our study, there were no significant differences in the menstrual disorders between the two groups of overweight/obese and normal weight. In this regard, the prevalence of Oligomenorrhea, Amenorrhea and Polymenorrhea was 79.07%, 9.23% and 4.89%, respectively while 4.34% of the patients had normal menstruation. In the study of Vasheghani and colleagues, 100% of the patients demonstrated menstrual dysfunction (15). In Aali's study, the most common form of irregular menstruation pattern was Oligomenorrhea with a frequency of 78% (22). In our study, the predominant phenotype in both groups of

patients was IM/PCO/HA and other prevalent phenotypes were IM/HA, IM/PCO and PCO/HA. There were no significant differences between the two groups in this regard. Similar to our study, the dominant phenotype was IM/PCO/HA in all the aforementioned studies with a slight difference in the prevalence of other phenotypes. For instance, in the studies of Belosi (2006) and Chae et al. in Korea, other most prevalent phenotypes were IM/PCO, IM/HA and HA/PCO, respectively (20, 26). In the study of Diamanti-Kandarakis and colleagues(2007), other most prevalent phenotypes were IM/HA, HA/PCO and IM/PCO, respectively (3). In the study of Shroff(2007) conducted in the USA, IM/PCO and IM/HA phenotypes shared the same prevalence and HA/PCO was the lowest (27). Finally, in the study of Welt and colleagues, other most prevalent phenotypes were HA/PCO, IM/PCO and IM/HA, respectively (24). In PCOS patients, there is considerable heterogeneity in terms of signs and symptoms. It seems that the racial background of women with PCOS could influence their clinical, endocrine and metabolic features. Basically, factors like infertility, android obesity, mean age and mean systolic and diastolic blood pressure are proven to be higher in overweight and obese patients than patients of normal weight. Consequently, examining these patients in order to prevent the aforementioned complications seems crucial.

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