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RESEARCH ARTICLE

Insulin Sensitivity Indices in Patients with Polycystic Ovary Syndrome with Different Body Mass Index Categories

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Abstract: ***Objective*:** This study aimed to determine the prevalence of insulin resistance among women with polycystic ovary syndrome (PCOS), describe the clinical and biochemical characteristics of women with PCOS, and determine the association between Antimullerian Hormone (AMH) and PCOS.

***Patients and Methods*:** In a clinical case series, 544 women with PCOS were included in this study. Body mass index (BMI), Homeostasis Model Assessment (HOMA), Quantitative Insulin Sensitivity Check Index (QUICKI), and Matsuda index were calculated. Sixty-three women with PCOS and 50 age- and BMI-matched control patients underwent blood sampling for AMH level.

***Results*:** The most common clinical presentation of PCOS in this study was menstrual irregularity followed by hirsutism and infertility. There was no statistically significant difference in the clinical presentation or hormonal profile in women with PCOS according to different BMI categories. The prevalence of insulin resistance among women with PCOS was 37.7%, 69.3%, and 75.8% using HOMA, QUICKI, and Matsuda index, respectively. Furthermore, the Matsuda index had the highest detection rate of insulin resistance, especially in underweight women with PCOS (94.1%). AMH levels in women with PCOS were significantly higher than that in the control group (P-value = 0.015).

***Conclusion*:** Insulin resistance is prevalent among women with PCOS. The detection rate of insulin resistance varies according to the insulin sensitivity index used. Menstrual irregularity was the most common presentation of PCOS. Women with PCOS have significantly higher levels of AMH levels compared to women in the control group.

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1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age [1, 2]. The etiology of PCOS is unknown and includes variable clinical features such as menstrual irregularities, signs of hyperandrogenism, polycystic ovaries, obesity, and insulin resistance [3].

Different criteria have been proposed to define PCOS [4-6]. The estimated prevalence rates of PCOS are highly variable according to the diagnostic criteria used, ranging from 9% using the National Institutes of Health consensus to 18% using Rotterdam consensus [1, 2, 7].

PCOS has multiple long-term health implications. Women with PCOS have three to seven times increased risk of the development of type 2 diabetes [3, 8, 9] and they are at increased risk of endometrial carcinoma as a result of chronic anovulation with unopposed estrogen exposure of the endometrium [9, 10]. There is clear evidence that women with PCOS are also at increased risk of cardiovascular disease as a result of multiple metabolic derangements associated with PCOS, such as insulin resistance, dyslipidemia, and abnormal vascular function [11-13].

Antimullerian hormone (AMH) is mainly produced by granulosa cells of preantral and small antral follicles to regulate early follicular development [14]. It is a suitable hormonal marker of ovarian follicular count and is considered as an indirect reflection of ovarian reserve [15]. Some researchers have suggested that increased AMH levels in women with PCOS result from the stimulatory effect of androgens in early follicular growth [16]. A positive correlation between serum androgens and AMH levels in women with PCOS has been reported, which might be due to intrinsic defects in theca cells [17-19]. It was suggested that AMH can be used as a diagnostic marker of ovarian hyperandrogenism [20].

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Additionally, serum AMH levels have been observed to be higher in women with PCOS with insulin resistance than those with normal insulin sensitivity [21]. However, the absence of a worldwide standard for serum AMH assay and the inability to define the threshold for high serum AMH level make the application of serum AMH level more difficult [15, 22].

This study aimed to determine the prevalence of insulin resistance among women with polycystic ovary syndrome (PCOS), describe the clinical and biochemical characteristics of women with PCOS, and determine the association between Antimullerian Hormone (AMH) and PCOS.

2. METHODS

2.1. Study Population and Data Collection

This study is a clinical case series, conducted at the National Center for Diabetes, Endocrinology and Genetics (NCDEG) in Amman, Jordan between January 2016 and May 2018. A total of 544 women aged 15 to 45 years with PCOS who attended the NCDEG were included.

PCOS was diagnosed according to the following criteria that are consistent with Rotterdam criteria [6]: presence of menstrual irregularity, clinical/biochemical signs of hyperandrogenism and polycystic ovaries seen on ultrasonography. Having two of these criteria was considered enough for the diagnosis of PCOS. Patients with the following conditions were excluded from this study: congenital adrenal hyperplasia, Cushing syndrome, malabsorptive disorder, eating disorder, postmenopause, a history of bariatric surgery, and missing data in patient charts.

Data were abstracted from Medical records. Data collected included age, weight, height, body mass index (BMI), presence or absence of any menstrual disturbance (oligomenorrhea/amenorrhea, primary or secondary amenorrhea), hirsutism, acne, male alopecia, or infertility (primary or secondary).

According to the NCDEG´s protocol, anthropometric measurements, including weight, height, and waist circumference were measured while the subjects were wearing light clothing and no shoes.

BMI was expressed as the quotient between weight (kg) and height in meters squared (m^2). Patients were classified according to BMI following the recommendation of the World Health Organization as adopted by the American Diabetes Association [23].

2.2. Hormonal Level Measurement

Hormonal profile was done at 8:00 to 8:30 am on the second to fourth day of the menstrual cycle and included luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (total and free), dehydroepiandrostendione sulphate (DHEA-S), 17-hydroxyprogesteron, prolactin, and sex hormone-binding globulin. DHEA-S, LH, FSH, prolactin, and total testosterone were assayed using ADVIA Centaur XPT Immunoassay System (Siemens Healthcare GmbH, Erlangen Germany). 17-OH-progesterone and free testosterone were assayed using enzyme-linked immunosorbent assay (Bio-Rad, Hercules, California, USA), SHBG was measured by electrochemiluminescence immunoassay (ECLIA) using Cobas e601 (Roche-Mannheim, Germany). All measurements were performed according to the manufacturer's instruction.

Seventy-five g OGTT with insulin level was done in 257 patients with PCOS at baseline, 30 min, 60 min, and 120 min after ≥ 8 h fasting. The serum concentration of glucose was measured using Cobas E-6000 (Roche Diagnostics, Manheim, Germany), serum insulin was assayed using ADVIA Centaur XPT Immunoassay System (Siemens Healthcare GmbH, Erlangen Germany).

Homeostasis Model Assessment (HOMA) index was calculated as ((fasting insulin (μU/mL) x fasting glucose (mg/dL))/405). Quantitative Insulin Sensitivity Check Index (QUICKI) was calculated as 1/log (fasting insulin μU/mL +fasting blood sugar mg/dL)). Matsuda index was also calculated as

ISI $_{(matsuda)}$ =10,000/ $\sqrt{G_o\ I_o\ G_{mean}\ I_{mean}}$ [24, 25], where:

I_o – Fasting plasma insulin concentration (mIU/L),

G_0 – Fasting plasma glucose concentration (mg/dL),

G_{mean} – Mean plasma glucose concentration during OGTT (mg/dL),

I_{mean} – Mean plasma insulin concentration during OGTT (μU/L),

10,000– Simplifying constant to get numbers from 0 to 12.

√– Correction of the nonlinear values distribution.

AMH level was assessed at 8:00 am in 63 patients with PCOS who were randomly chosen from each BMI subgroup and was compared to that in 50 patients in the control group (matched in age and BMI).

AMH was measured in serum by electrochemiluminescence using the Roche Cobas immunoassay system. The AMH assay has a limit of detection of 0.07 pmol\ L (0.01 ng /mL).

2.3. Ethical Considerations

The study was approved by the ethics committee at the NCDEG. Recognized information was kept strictly confidential and the data were used only for scientific purposes by the researcher.

2.4. Statistical Analysis

The analysis was carried out using the Statistical Package for Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). Sociodemographic, clinical, and laboratory characteristics in women with PCOS were obtained overall, and by BMI categories. Statistical significance was assessed by the chi-square method for categorical variables and by one-way ANOVA for continuous variables. A P-value ≤ 0.05 was considered statistically significant.

Table 1. Women's demographic and clinical characteristics according to body mass index categories.

p-value	Body mass index				Total N=544	Variables
	Obesity (N=161)	Over Weight (N=154)	Normal Weight (N=183)	Under Weight (N=46)		
<0.001*	25.9±7.2	26.1 ± 6.9	22.7 ±6.3	21.7 ± 5.7	24.6± 6.9	Age (mean ± SD)
0.203	158 (88.8%)	127 (82.5%)	149 (81.4%)	37 (80.4%)	471 (86.6%)	Menstrual irregularities, n (%)
0.046	17 (9.6%)	24 (15.6%)	21 (11.5%)	11 (23.9%)	73 (13.4%)	Acne, n (%)
0.138	88 (49.4%)	77 (50.0%)	99 (54.1%)	16 (34.8%)	280 (51.5%)	Hirsutism, n (%)
0.107	6 (3.4%)	12 (7.8%)	18 (9.8%)	4 (8.7%)	40 (7.4%)	Alopecia, n (%)

* Overweight and obese women were significantly older than normal and underweight women.

Table 2. Association between body mass Index and hormonal profile of PCOS patient (n= 544).

Variables*	Under Weight (mean ± SD)	Normal Weight (mean ± SD)	Over Weight (mean ± SD)	Obese (mean ± SD)	P-value
LH	7.7 ± 5.3	6.8 ± 5.3	6.3 ± 4.9	6.4 ± 4.7	0.354
FSH	4.9 ± 1.7	4.7 ± 1.8	4.8 ± 1.7	5.1± 2.6	0.421
Testosterone (Total)	0.56 ± 0.3	0.58 ± 0.4	0.53 ± 0.3	0.64 ± 0.5	0.243
Testosterone (Free)	0.81 ± 0.5	1.05 ± 0.8	1.12 ± 0.9	1.31 ± 1.0	0.142
SHBG	78.2 ± 35.3	92.9 ± 63.9	52.7 ± 17.3	70.6 ± 62.0	0.244
DHEA-S	240.4 ± 108.2	284.9 ± 129.7	263.1 ± 132.6	256.0 ± 111.1	0.223
Prolactin	18.0 ± 12.1	15.3 ± 8.7	16.7 ± 10.8	15.7 ± 11.1	0.440
17-OH progesterone	3.1 ± 1.3	3.7 ± 3.1	3.6 ± 4.1	3.1 ± 2.5	0.392

*BMI, body mass index; DHEA, dehydroepiandrostendione sulphate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; SD, standard deviation; SHBG, sex hormone-binding globulin.

3. RESULTS

3.1. Women's Characteristic

The mean BMI was 27.6 kg/m^2. Of all women, 29.6% had obesity, 28.3% were overweight, 33.6% had normal weight, and 8.5% were underweight. Table **1** shows women's demographic and clinical characteristics according to BMI categories. Overweight and obese women were significantly older than normal and underweight women. The majority of women (86.6%) presented with irregular menstrual cycles, 51.5% presented with hirsutism, 13.4% with acne, and 7.4% with alopecia. There was no statistically significant difference in the menstrual irregularities and features of hyperandrogenism (hirsutism, acne, alopecia) between women who were underweight, normal weight, overweight, and obese. (Table **2**).

3.2. Insulin Resistance Among PCOS Women

The prevalence of insulin resistance among women with PCOS was 37.7% using the HOMA index, 69.3% using the QUIKI index, and 75.8% using the Matsuda index (Table **3**).

Table 3. Insulin resistance detection rate by a different method, HOMA (n=257), QUICKI (n= 257), Matsuda index (n=252) among women with PCOS

Variables *	N (%)
HOMA	97 (37.7)
QUICKI	178 (69.3)
Matsuda index	191 (75.8)

*HOMA, Homeostasis Model Assessment; PCOS, polycystic ovary syndrome; QUICKI, Quantitative Insulin Sensitivity Check Index.

Table 4. Detection rate of insulin resistance in each BMI category by HOMA, QUICKI, Matsuda index.

Variable*	Under Weight	Normal Weight	Overweight	Obese	P-value
HOMA	2 (11.8%)	17 (21.2%)	16 (22.2 %)	62(70.5%)	<0.001
QUICKI	15 (88.2%)	66 (82.5%)	62 (86.1%)	35 (39.8%)	<0.001
Matsuda index	16 (94.1%)	69 (87.3%)	58 (84.1%)	48 (55.2)	<0.001

*BMI, body mass index, HOMA, Homeostasis Model Assessment, QUICKI, Quantitative Insulin Sensitivity Check Index.

Table 5. Characteristics of patients with PCOS and patients in the control group for AMH result.

Variable*	Cases (PCOS) (63)	Control (50)	P- value
Age	23.12± 5.8	24.50 ± 5.8	0.217
BMI	25.53 ± 6.5	25.32 ±5.4	0.855
AMH	4.64 ± 3.2	3.22 ± 2.65	0.015

*AMH, antimullerian hormone; BMI, body mass index; PCOS, polycystic ovary syndrome.

Table 6. AMH level in different BMI categories.

Variables	Under Weight mean ± SD	Normal Weight mean ± SD	Over Weight mean ± SD	Obese mean ± SD	P-value
Cases (polycystic ovary syndrome), n=63	5.86 ± 3.1	5.62 ± 3.8	4.22 ± 3.1	2.93 ±1.5	0.039
Control, n=50	4.46±2.9	2.91 ± 3.07	3.62 ± 1.84	3.11±2.19	0.703

Insulin resistance was detected in 11.8% of underweight women, 21.2% of women with normal weight, 22.2 % of women with overweight, and 70.5% of women with obesity (p-value< 0.001); using the HOMA index. The prevalence rates of insulin resistance using other indices according to body mass index are shown in Table **4**.

3.2. PCOS and AMH

Clinical characteristics of women with PCOS and the control group are presented in Table **5**; both groups were comparable in age and BMI. Women with PCOS showed a higher level of AMH compared to the control group (P-value = 0.015). A negative correlation between AMH level and BMI was found in women with PCOS. Obese women had a statistically significant lower level of AMH compared to women with underweight, normal weight, and overweight (P-value = 0.039). However, no statistically significant difference was found in the AMH level of women in the control group according to BMI subcategories (P- value= 0.703) (Table **6**).

4. DISCUSSION

The mean BMI of women with PCOS included in our study was 27.6 kg/m^2, and this finding is also consistent with data indicating that the mean BMI of women of different countries in whom PCOS was diagnosed varies widely. Women with PCOS from countries other than the United States were found to be leaner, with mean BMI of 25 kg/m^2 in England, 28 kg/m^2 in Finland, 31 kg/m^2 in Germany, and 29 kg/m^2 in Italy [26]. In contrast, in a multicenter trial at 22 sites in the United States, the mean BMI of women with PCOS ranged from 35 to 38 kg/m^2. Data from the US multicenter pregnancy in PCOS trial noted that the mean BMI among 626 patients included was 35.2 kg/m^2 [26].

It is also worth mentioning that there is a difference in the prevalence rate of PCOS in women with different BMI categories and this difference could be due to the increase in the prevalence of obesity over time, resulting in a subtle increase in the prevalence of PCOS, the use of more expansive diagnostic criteria for PCOS, or selection bias.

Women with PCOS in this study presented with the following complaints: menstrual irregularity being the most common in 84% of the women, followed by hirsutism in 50%, infertility in 40%, acne in 13%, and alopecia in 7%. Akshaya *et al*. 2016 reported that menstrual irregularity was the most common presentation (94%) among women with PCOS included in his study, followed by hirsutism, infertility, and acne in 84%, 42%, and 18%, respectively [27].

Azziz *et al*. 2004 reported a lower overall prevalence of menstrual dysfunction and hirsutism (22.8% and 6.8 %, respectively) among 400 women with PCOS [1]. The higher rate observed in our study may reflect ethnic differences or may be due to selection bias.

There was no statistically significant difference in the features of hyperandrogenism (hirsutism, acne, alopecia), menstrual irregularities, or hormonal profile (DHEAS-17-

OH progesterone- FSH LH- -total testosterone) among women who were underweight, normal weight, overweight or those with obesity and with PCOS. There was a statistically significant age difference between the groups (P-value = 0.000); women who were overweight or with obesity usually comprise the older age group. Consistent with our finding, Akshaya *et al*. 2016 also found that the clinical presentations such as acanthosis nigricans, menstrual disturbance, acne, hirsutism were of same prevalence in women with PCOS who were lean and obese [27]. However, Kiddy *et al*. 1990 also noticed that total testosterone and androstenedione serum concentrations were similar in both obese and non-obese women with PCOS, but sex hormone-binding globulin concentrations were significantly lower and free testosterone level higher in women with obesity compared with women who were lean with PCOS [28].

Insulin resistance was detected in approximately 37.7% of women with PCOS using the HOMA index, 69.3% using QUICKI, and 75.8% using Matsuda index in our study. In agreement with our finding, Hrebicek *et al*. 2002 and Katz *et al*. 2000 [29, 30] also found that in comparison with the HOMA index, QUICKI showed a higher discrimination power. These differences are due to different mathematical analysis. In the case of QUICKI, the logarithm and reciprocal of the glucose-insulin product are used, skewing the distribution of fasting insulin. The current study confirms the advantages of the QUICKI as a simple and effective quantitative method for the assessment of insulin sensitivity, especially for epidemiological and clinical practice where prevention and therapy of the consequence of insulin resistance are of paramount importance.

Our study showed that insulin resistance is a common finding in patients with PCOS and the detection rate of insulin resistance varies according to the insulin sensitivity index used. The Matsuda index has the highest positive predictive value whereas HOMA has the lowest positive predictive value of insulin resistance, and the study suggests that the Matsuda index has the highest detection rate especially in women with PCOS who are underweight.

In comparison with our study, Carmina *et al*. 2004 examined insulin resistance in 257 women with PCOS by using different methods, including HOMA and QUCIKI indices. They reported that the detection rate was 77% and 95% in lean and obese women, respectively [24]. In agreement with our findings, the HOMA index detects insulin resistance primarily in the obese women with PCOS. Also, they noticed that QUCIKI index has a higher detection rate among PCOS women with obesity (95%), while we found in our study that QUCKI had a higher detection rate among PCOS women who were normal weight or underweight. This discrepancy could be related to the difference in the ethnic group or difference in the BMI categories, as Carmina *et al*. defined lean women as having BMI less than 27 Kg/m^2, and obese women as having BMI more than 28 Kg/m^2.

Consistent with our finding, La Marca *et al*. 2009 and Caglar *et al*. 2013 also found that AMH serum levels in women with PCOS were significantly higher than in the control group [31, 32].

Finally, in agreement with our result, that AMH level was significantly lower among women with obesity and with PCOS compared to women with PCOS in other BMI categories; Moy *et al*. 2015 also reported that elevated BMI had a negative correlation with AMH level in Caucasian women [33].

CONCLUSION

Insulin resistance is prevalent among women with PCOS. The detection rate of insulin resistance varies according to the insulin sensitivity index used. Menstrual irregularity was the most common presentation of PCOS. Women with PCOS have significantly higher levels of AMH levels compared to women in the control group.

LIST OF ABBREVIATIONS

BMI	=	Body Mass Index
PCOS	=	Polycystic Ovary Syndrome
HOMA	=	Homeostasis Model Assessment
QUICKI	=	Quantitative Insulin Sensitivity Check Index
AMH	=	Antimullerian hormone
OGTT	=	Oral Glucose Tolerance Test

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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