The Relation between Diverse Phenotypes of PCOS with Clinical Manifestations, Anthropometric Indices and Metabolic Characteristics

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Abstract- Critical issue regarding to variation of findings based on different phenotypes led investigators to define whether they are distinct features or overlapping ones. Therefore, we aimed to investigate the association between diverse phenotypes of PCOS (Poly Cystic Ovary Syndrome) with clinical manifestations, anthropometric indices, and metabolic characteristics. This was a descriptive cross-sectional study conducted in 15-39 years old women with PCOS referred to infertility clinics in the north part of Iran, Rasht during 2010-2011. Data were gathered through an interview by a form consisted of demographic characteristics, laboratory findings, ovarian volume and anthropometric indices. A total of 214 patients consisted of 161 PCOS (cases) and 53 normal women (controls) participated in this study. The most prevalent phenotype in PCOS population was IM/PCO/HA (54%), followed by IM/HA (28%) and IM/PCO (13%). PCO/HA was present only in 6 PCOS patients (5%). PCOS patients were significantly younger than controls (P=0.07). Results showed that increased ovarian volume were higher in PCOS group in comparison with controls and IM/PCO/HA, and IM/PCO had respectively the largest ovarian volumes. Also, a significant relation was observed based on Cholesterol, 17OHP, LH, TG, 2hpp, and LH/FSH between patients with PCOS and control groups. There were significant differences in demographic, anthropometric, hormonal and ultrasound findings between PCOS and controls. Therefore, it seems that classification of the characteristics of each phenotype could offer an appropriate guide for screening risks of PCOS and may facilitate performing most favorable treatment for these complications.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in females, with a high prevalence. Recently, the etiology of this heterogeneous condition remained obscure, and its phenotype expression varied (1). It is commonly assumed that insulin resistance, hyperandrogenism, and obesity significantly influence the pathophysiologic process of PCOS (2).

Diagnosis of PCOS could be determined on a mixture of clinical, biological and ultrasound findings and could be defined based on the existence of 2 from 3 features of Rotterdam Criteria (2003). The mentioned criteria consisted of 1) irregular menses (IM); 2) hyperandrogenism (HA), either clinical or biochemical with the clinical manifestations of hirsutism, acne, hair loss and elevated testosterone or DHEAS; and/or 3) PCO morphology (PCOM) on pelvic ultrasound; all in the absence of another disorder that can cause the same symptoms and indicated the four following phenotypes: IM/HA/PCOM, IM/HA, HA/PCOM, and IM/PCOM (3).

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Hyperandrogenism and menstrual irregularities could signify the major complaints in young PCOS women with the symptoms related to androgen burden, oligorrhoea or amenorrhoea. Investigators showed a high prevalence of pregnancy complications in PCOS women and infertility could be indicated as the main complaint of adult PCOS women during the reproductive age (4,5). Also, Obesity has an important impact on the severity of its manifestation (4).

The elevated risk for adverse obstetric complications that was observed in women presenting PCOS varied widely depending on the different phenotypes and features of PCOS (6).

Up to now, controversial results in the body mass index (BMI) and insulin levels in women due to the comparison between phenotypes had been observed. A critical issue regarding the variation of findings based on different phenotypes led investigators to define whether they are distinct features or overlapping ones (7,8). Therefore, we aimed to investigate the relation between diverse phenotypes of PCOS with clinical manifestations, anthropometric indices, and metabolic characteristics.

Materials and Methods

This was a descriptive cross-sectional study conducted on 15-39 years old PCOS women referred to endocrinology and infertility clinics in the north part of Iran, Rasht during 2010-2011. Normal women with no complaint had been indicated in a control group, and patients with a complaint of menstrual disorders or hyperandrogenism symptoms were indicated as PCOS group, and written consents were obtained. The diagnosis of PCOS was defined based on Rotterdam Criteria (2003) and other androgen increasing factors such as hyperprolactinemia, congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome and thyroid disorders had been ruled out.

Exclusion criteria were indicated as the presence of impaired thyroid tests or hyperprolactinemia, diabetes mellitus, 17OHP>3ng/ml, OCP and progesterone consumption in preceding 6 months and breastfeeding mothers.

According to the Rotterdam criteria, an ovary would be defined polycystic when 12 or more follicles measuring 2–9 mm in diameter were presented, and/or there is an increased ovarian volume of more than 10 ml in sonography, and ovarian volume could be assessed by definite formula (0.523 x length x width x height). Furthermore, in the presence of larger than 12 mm cyst or cystic follicles, the ovarian volume would not be assessed.

Data were gathered through interview of a trained researcher by a form which consisted of demographic characteristics (age, educational level, occupation, socioeconomic status), parity, history of infertility (lack of pregnancy for a year without contraceptive drugs consumption), types of menstrual disorders (oligomenorrhea, amenorrhea, menometroragy), and familial history of diabetes.

Blood tests had been performed in the early follicular phase (Days 3–5) of the menstrual cycle, and venous blood samples were collected in the morning after an overnight fast of 12 hours. Serum FSH and LH, free testosterone, 17OHP, DHEAS, FBS, 2-hour post glucose-insulin level, total cholesterol, LDL, HDL, Triglyceride, AST and ALT had been assessed. Patients were referred to the same laboratory and results were assessed by the same kit. Also, vaginal and abdominal sonography had been performed by a trained expert during the early follicular phase of menstrual cycle (day 5) for married and single patients, respectively.

Anthropometric indices were evaluated, and weight were measured in light indoor clothing and barefoot or with stockings. Height was measured with the shoulders and bottom touching the by a tape meter in a vertical erect position. The height and weight were used to calculate the body mass index (BMI; kg/m2) using the formula: Weight (kg) divided by height (m) squared and divided into 2 groups (less than 24.99 as normal patients and more than 24.99 as obese ones).

Waist circumference was obtained immediately above the iliac crest and exactly under navel by a tape meter and for hip circumference, investigators positioned horizontally the tape meter around the maximum circumference of the buttocks and finally evaluated waist to hip ratio (WHR).

Furthermore, Galactorrhea as a common cause of hyperprolactinemia and Acanthosis nigricans (a brown to black, poorly defined, velvety hyperpigmentation of the skin) as a common cause of insulin resistance had been assessed.

In addition, the final diagnosis of PCOS had been made based on four phenotypes of Rotterdam Criteria, which consisted of IM/HA/PCOM, IM/HA, HA/PCOM, and IM/PCOM.

Statistical Analysis

Normalized distribution of quantitative variables was indicated, and data were analyzed by Kruskal-Wallis, *chi*-square and ANOVA. *P*-value less than 0.05 was indicated statistically significant, and data were analyzed

using SPSS v16.

Results

A total of 214 patients were enrolled consisted of 161 PCOs (cases) and 53 normal women (controls). Based on Rotterdam criteria, the most prevalent phenotype in PCOs population was IM/PCO/HA (54%), followed by IM/HA (28%) and IM/PCO (13%). PCO/HA was present only in 6 PCOS patients (5%). Also, PCOS patients were significantly younger than controls (*P*=0.07). Gravid differ significantly among groups (*P*=0.003), in which results showed that nulliparity had been significantly prevalent in IM/HA, IM/HA/PCOM, and HA/PCOM women compared with controls (*P*=0.001). The most prevalent menstrual disorder was oligomenorrhea I, 157 patients (73.4%), and Fisher Exact Test showed a significant difference between the groups (*P*=0.0001).

The highest prevalence of infertility had been observed in IM/HA/PCOM type and showed a significant difference between groups (*P*=0.001). Furthermore, the comparison between control and PCOS groups was performed, and chi-square test showed that IM/HA/PCOM showed 5 fold increased risk of infertility (*P*=0.0001). Also, results revealed that each remained subtypes (IM/HA, HA/PCOM, and IM/PCOM) indicated four-fold increased the risk of infertility compared with controls (*P*=0.0001). Although, there was significant difference between control and PCOS patients based on the history of infertility (*P*=0.001). However, no significant difference between PCOS groups according to the duration of infertility had been observed (0.73).

Moreover, results showed significant galactorrhea in IM/HA/PCOM and HA/PCOM women compared with control group (*P*=0.01 and *P*=0.003, respectively).

Furthermore, there were significant difference between control group with IM/HA/PCOM (OR = 6.19, 95% CI = 1.37- 28) and HA/PCOM women (OR = 10.35, 95% CI = 2.19- 48.95) regarding to the presence of acanthosis.

According to results, there was a significant relation between control group with IM/HA/PCOM (OR=2.72, 95% CI=1.29-5.71) and HA/PCOM women (OR=3.18, 95% CI=1.36-7.42) regarding to the presence of acne.

Moreover, there was significant relation between control group with IM/HA/PCOM (OR=59.64, 95% CI=16.73-212.66) and HA/PCOM women (OR=66.66, 95% CI=16.85-263.69) regarding to the presence of hirsutism (Table 1).

Table 1. Demographic characteristics, clinical manifestations and sonographic finding of participants

Variables		Control group	IM/PCO/HA	IM/PCO	IM/HA	PCO/HA	*P*-value
Age (Mean±SD)		5.82±27.23	4.81±26.16	4.79±25.00	4.73±26.00	2.10±22.12	0.07
Marital status	**single**	(24.5%) 13	19(21.8%)	4(19%)	6(13.3%)	2(25%)	0.68
	married	40(75.5%)	68(78.2%)	17(81%)	39(86.7%)	6(75%)	
Educational level	**Less than diploma**	8(15.7%)	22(26.8%)	5(27.8%)	13(29.5%)	1(12.5%)	
	diploma	22(43.1%)	36(43.9%)	6(33.3%)	9(20.5%)	5(62.5%)	
	associate degree	3(5.9%)	4(4.9%)	2(11.1%)	6(13.6%)	0	0.16
	BA	15(29.4%)	14(17.1%)	4(22.2%)	16(36.4%)	2(25%)	
	MA and more	3(5.9%)	6(7.3%)	1(5.6%)	0	0	
Job	**unemployed**	34(65.4%)	64(75.3%)	15(75%)	31(68.9%)	5(62.5%)	0.71
	employee	18(34.6%)	21(24.7%)	5(25%)	14(31.1%)	3(37.5%)	--
Place of inhabitants	**rural**	1(2%)	19(22.4%)	2(10.5%)	5(11.4%)	3(37.5%)	0.002
	urban	50(98%)	66(77.6%)	17(89.5%)	39(88.6%)	5(62.5%)	--
	History of diabetes	16(31.4%)	33(38.4%)	9(47.4%)	24(54.5%)	3(37.5%)	0.20
Gravida	**Nuliparity**	17(50%)	56(83.6%)	14(87.5%)	23(67.6%)	3(50%)	0.003
	Multiparty	17(50%)	11(16.4%)	2(12.5%)	11(32.4%)	3(50%)	--
Menstural disorders N(%)	**oligomennorhea**	10(18.9%)	78(89.7%)	20(95.2%)	43(95.6%)	0	0.0001
	amennorhea	0	9(10.3%)	1(4.8%)	2(4.4%)	0	--
	polymenorrhea	3(5.7%)	0	0	0	0	--
	Normal menstruation	40(75.5%)	0	0	0	6(100%)	--
History of abortion		2(5.9%)	6(9%)	1(6%.3)	4(11%.8)	2(33.3%)	0.31
Duration of infertility(months)(M±SD).		5.87±16.83	46.73±39.81	47.70±35.81	25.72±31.45	48.32±35.75	0.73
History of infertility		6(12%)	54(66.7%)	10(52.6%)	22(50%)	4(50%)	0.0001
Galactorrhea		0(0)	9(10.3%)	1(4.8%)	7(15.6%)	1(12.5%)	0.02
Acanthosis nigricans		2(3.8%)	17(19.5%)	6(28.6%)	13(28.9%)	0	0.003
Acnea		14(26.4%)	43(49.4%)	7(33.3%)	24(53.3%)	2(25%)	0.02
Hirsotism		3(5.7%)	68(87.2%)	0	36(80%)	2(25%)	0.0001
Alopecia		4(7.5%)	40(46%)	3(14.3%)	19(42.2%)	3(37.5%)	0.0001
PCO morphology		0	74(88.1%)	20(100%)	0	7(87.5%)	0.0001
Ovarian volume (Mean±SD)		6.64±2.00	12.35±3.18	11.53±3.51	7.17±1.28	9.56±3.45	0.0001

According to results, there was no significant relation between PCOS and control groups in terms of weight, height, BMI, waist circumference, hip circumference, WHR, CHR, systolic and diastolic pressure. As there was no significant difference between groups based on BMI, investigators defined two cutoff points. Results indicated no significant difference between groups based on first cutoff (BMI <25 and ≥ 25). However, Results showed significant difference between control group with IM/HA (OR=4.1, 95% CI=1.34- 12.52) and HA/PCOM (OR=2.4, 95% CI=0.99-6.22) based on <30 and ≥ 30 cutoff point.(*P*=0.01 *vs.* *P*=0.04, respectively) (Table 2).

Table 2. Anthropometric indices in PCOS and control groups

Variables		PCO/HA	IM/HA	IM/PCO	IM/PCO/HA	Control group	*P*-value
Weight (Mean±SD)		66.62±17.78	72.98±13.40	74.40±15.93	71.68±15.16	67.20±12.71	0.17
Height (Mean±SD)		159.62±5.96	161.15±6.22	161.15±6.22	159.54±6.02	159.39±5.99	0.72
BMI(kg/m^2)		26.59±6.35	28.68±5.14	28.39±6.04	27.86±6.43	26.49±5.09	0.45
Waist circumference (Mean±SD)		81.50±8.91	86.74±10.96	84.23±13.41	87.98±12.24	82.52±9.77	0.64
Hip circumference (Mean±SD)		105.42±11.68	107.40±10.49	99.76±25.48	104.95±15.31	102.17±7.65	0.26
WHR		0.77±0.02	0.80±0.08	1.28±2.05	0.93±1.01	0.80±0.05	0.33
CHR	**≤0.85**	7(5%)	29(20.9%)	13(9.4%)	52(37.4%)	38(27.3%)	0.12
	>0.85	0	10(22.2%)	3(6.7%)	25(55.6%)	7(15.6%)	
Systolic pressure (mm/Hg)		106.25±9.16	108.83±13.66	108.42±12.58	110.12±12.55	105.49±13.75	0.65
Diastolic pressure (mm/Hg)		63.75±9.16	67.44±10.71	68.42±10.14	68.86±9.47	66.03±11.86	0.48

Although, results showed no significant relation between PCOS and control group based on Testosterone, DHEAS, TSH, prolactin, FBS, LDL, AST, ALT, HDL, and FSH. However, a significant relation between PCOS and controls had been observed in term of FSH, Cholesterol, 17OHP, LH, TG, 2hpp, and LH/FSH.

Based on Triglyceride level, there was a significant difference between groups (*P*=0.002). Also, results indicated a significant difference between IM/HA/PCOM and HA/PCOM women compared with control group (*P*=0.001 and *P*=0.026, respectively).

The highest and lowest level of 17OHP had been observed in IM/HA/PCOM and IM/HA, respectively compared with control group and showed a significant difference between groups (*P*=0.001).

Also, there was a significant difference between controls with IM/HA/PCOM and IM/PCOM according to the level of 17OHP (*P*=0.017 and *P*=0.021, respectively).

Results showed that there was a significant difference between IM/HA/PCOM and IM/PCOM women compared with control group due to LH/FSH ratio (*P*=0.009 *vs.* *P*=0.006, respectively) (Table 3).

Table 3. The Laboratory findings in PCOS and control women

Variables		PCO/HA (M±SD)	IM/HA (M±SD)	IM/PCO (M±SD)	IM/PCO/HA (M±SD)	Control group (M±SD)	*P*-value
Testosterone		1.34±0.52	1.47±0.78	1.34±0.90	1.90±2.14	1.16±0.58	0.61
DHEAS		190.08±56.74	258.09±157.96	193.56±79.21	224.91±118.36	188.28±97.19	0.45
TSH		3.61±1.82	3.06±3.08	2.12±1.05	3.28±3.63	3.01±2.22	0.51
Prolactin		18.98±9.00	17.71±11.41	15.29±5.50	19.00±10.12	18.28±10.01	0.64
FBS		90.75±10.64	93.25±22.37	90.80±10.49	94.13±20.52	90.73±7.93	0.65
LDL		102.84±29.48	112.33±30.35	114.99±26.14	111.01±30.64	101±74±24.67	0.22
AST		17.62±4.30	22.62±14.49	24.00±9.22	21.75±9.23	19.84±11.12	0.43
ALT		14.87±5.64	20.06±14.98	22.00±12.42	18.83±10.09	16.32±16.00	0.37
HDL		42.30±5.56	41.82±9.20	41.30±9.46	41.15±8.06	43.61±8.32	0.56
FSH		6.25±1.20	6.27±1.63	6.44±1.17	6.04±2.03	6.52±2.29	0.68
Cholesterol		166.75±34.98	175.27±36.30	183.71±28.81	178.88±35.17	163.54±27.01	0.05
17OHP		1.00±0.25	0.97±0.58	0.68±0.38	1.17±0.68	0.83±0.46	0.001
LH		10.63±4.89	6.80±2.64	7.37±3.06	8.36±4.81	6.32±2.05	0.002
TG		132.12±73.74	147.76±98.90	145.76±61.40	155.40±79.69	100.07±58.39	0.002
2hpp		108.00±28.30	110.77±33.67	95.47±19.37	118.07±43.27	95.79±21.49	0.003
LH/FSH	**under2**	5(62.5%)	42(95.5%)	20(95.2%)	73(83.9%)	51(98.1)	0.003
	upper2	3(37.5%)	2(4.5%)	1(4.8%)	14(16.1%)	1(1.9%)	--

Discussion

Results showed that IM/PCO/HA and IM/HA patients were the oldest among PCOS patients and PCO/HA were the youngest which was inconsistent with the results observed by Chang *et al*., which showed that IM/PCO/HA patients were the youngest among PCOS patients, and IM/HA were the oldest (9).

The phenotypes in PCOs population were IM/PCO/HA, followed by IM/HA, IM/PCO and PCO/HA, respectively which was relatively consistent with the results mentioned by Chang *et al.,* which classified PCOS patients in three phenotypes and mentioned Oligo+HA+Hirsutism phenotype in 48%, Oligo+HA in 29%, and Oligo+Hirsutism in 23% of whole patients (9). However, Welt *et al*. reported that 298 (71%) IM/HA/PCOM, 7 (2%) IM/HA, 77 (18%) HA/PCOM, and 36 (9%) IM/PCOM had been indicated (10). The percentages of phenotypes A, B, C, and D in a Bulgarian population were 58.6%, 11.4%, 10.0% and 20.0%, respectively (11).

Yilmaz *et al*. noted that 56/127 (44.09%) of the patients were IM/HA/PCOM, 29/127 (22.84%) were IM/HA, 24/127 (18.90%) were IM/PCO, and 18/127 (14.17%) were HA/PCO. Moreover, 42/127 (33.07%) patients represented the new phenotypes (IM/PCO and HA/PCO) (12).

Results showed that increased ovarian volume were higher in PCOS group, and IM/PCO/HA and IM/PCO had the largest ovarian volumes, and all groups had a greater volume than controls which was consistent with previous investigations (13). However, Welt et al. mentioned that IM/HA and IM/PCOM had the largest ovarian volumes and all groups had a greater volume than controls (10).

Results showed no significant difference between PCOS and control groups in terms of Testosterone, DHEAS, TSH, prolactin, FBS, LDL, AST, ALT, HDL, and FSH. Also, significant relation had been obtained based on Cholesterol, 17OHP, LH, TG, 2hpp and LH/FSH. Also, Hassa *et al*., indicated no significant relation between PCOS and control group based on serum FSH and LH ($P > 0.05$). However, they noted that blood levels of DHEAS 17-HP were higher in PCOS patients. They indicated that no significant difference regarding hormonal and clinical characteristics in PCOS patients and total testosterone remained high in PCOS group (13).

Also, Katsikis *et al*., Indicated that PCOS women presented significantly higher LH and LH/FSH ratios, and lower glucose levels in comparison with controls (14). In addition, Maddani *et al.,* noted that there was no significant difference in lipid profiles between diverse phenotypes of PCOS and they obtained that the pre-diabetes status and cardiovascular risk factors such as low HDL were more prevalent in IM/HA phenotype of PCOS (15) which was inconsistent with the results mentioned in this study. However, Sung *et al.,* indicated that IM/PCO and HA/PCO patients did not seem to have metabolic derangements (16).

Waist-to-hip ratio, luteinizing hormone-to-follicle stimulating hormone ratio and testosterone were lower in PCO/HA and controls. Which was inconsistent with the results mentioned by Yilmaz *et al*., suggested PCO/IM phenotype was closer to control group than the other PCOS phenotypes in terms of WHR, LH/FSH and testosterone (12). However, Hassa *et al*., indicated no statistically significant difference between PCOS and control groups, in terms of BMI, waist-to-hip ratio (13). In addition, Chang *et al.* mentioned that phenotypes did not differ in mean BMI, waist-to-hip ratio, the prevalence of acne, or family history of hyperandrogenic symptomatology (9).

According to Pehlivanov, the IM/PCO/HA and IM /HA women were more obese compared with the women of phenotypes IM/PCO and PCO/HA 11 which was inconsistent with the results mentioned in this study. Results showed higher MBI in IM/HA and IM/PCO groups and lower in PCO/HA and IM/PCO/HA groups.

According to results, there were significant differences in demographic, anthropometric, hormonal and ultrasound findings between PCOS and controls. Therefore, it seems that classification of the characteristics of each phenotype could offer an appropriate guide for screening risks of PCOS and may facilitate performing most favorable treatment for these complications.

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