

Original Article

Manifestations of Polycystic Ovary Syndrome are Similar Regardless of the Degree of Menstrual Cycle Variation

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Abstract:

Background: Menstrual irregularities may predict over adverse consequences in polycystic ovary syndrome (PCOS). **Objective:** To observe the relation of variants of menstrual cycles with clinical and biochemical features of PCOS. **Methods:** This cross-sectional study encompassed 200 PCOS women diagnosed by Rotterdam criteria and 120 age-matched healthy controls. Subgroups were classified according to menstrual cycle length as: polymenorrheic (<21 days), eumenorrheic (21-35 days), oligomenorrheic (36 days-3 months) and amenorrheic (>3 months). Glucose was measured by glucose oxidase, lipid by glycerol phosphate dehydrogenase-peroxidase and all hormones by chemiluminescent immuno-assay method. **Results:** Around 86% of PCOS patients had menstrual irregularity, among which 75% had oligomenorrhea followed by amenorrhea (9%) and polymenorrhea (2%). All the subgroups of PCOS patients (polymenorrhea excluded from further analyses) had significantly poor metabolic manifestations than the control namely insulin resistance (IR), impaired glycaemic status, general and central obesity, metabolic syndrome and dyslipidaemia. Acanthosis nigricans (AN), hyperandrogenemia (HA) and IR had significant predictive association with PCOS patients with both irregular [OR (95% CI)- AN: 21.994 (6.427, 75.267), p<0.001; HA: 27.735 (8.672, 88.704), p<0.001; IR: 7.268 (2.647, 19.954), p<0.001] and regular cycle [AN: 16.449 (3.830, 70.643), p<0.001; HA: 24.635 (6.349, 95.590), p<0.001; IR: 6.071 (1.658, 22.234), p=0.006] in reference to control group. None of the variables had significant predictive associations with irregular cycle in reference to regular cycle in patients with PCOS. **Conclusion:** Oligomenorrhea was the most common variant of menstrual irregularity in PCOS patients. All menstrual variants including eumenorrhea had similar manifestations in PCOS women, but poorer than controls.

Keywords: PCOS, menstrual disturbance, hyperandrogenism, insulin resistance and metabolic syndrome.

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Introduction

Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder that implies various severe consequences to female health, including infertility, cutaneous complications

as well as several metabolic complications of insulin resistance. PCOS manifests with a range of menstrual irregularities that frequently occur throughout adolescence or later in the reproductive years.¹

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Regularity of menstrual cycle is regarded as a sign of women's reproductive health. Alterations in the menstrual cycle can occur for a variety of reasons and are frequently linked to ovaries-thyroid and pituitary axis dysfunctions. Menstrual irregularities constitute a prerequisite for the diagnosis of PCOS according to National Institute of Health and Androgen Excess- PCOS Society criteria, and one of the components of Rotterdam criteria.²⁻⁴ Thus, regular cycle PCOS and other cyclical abnormalities like polymenorrhea remained underdiagnosed for a long period. In a large series of patients diagnosed with PCOS, approximately 80% had clinically evident menstrual dysfunction appearing as abnormal uterine bleeding like oligomenorrhoea. Polymenorrhoea was relatively rare, present in only 3.2% of untreated patient, whereas, prevalence of regular cycle was about 16%.⁵ Previous research works have also found a link between severe cycle abnormalities and insulin resistance. When compared to controls, hyperinsulinemia was found to be substantially associated with amenorrhea in a retrospective, observational research.⁶ In another study, Legro et al. found that hyperandrogenic sisters of PCOS patients with regular menses and sisters with PCOS and oligo/amenorrhea had similar levels of insulin resistance.⁷ Thus this finding establishes the relation between IR and menstrual irregularities. If a relationship does exist between the degree of cycle irregularity and metabolic parameters in patients with PCOS, then menstrual dysfunction could be used as a simple clinical marker to identify patients at the greatest risk for metabolic abnormalities. The present study is designed to see the various pattern of menstrual disturbance and to clarify the significance of menstrual irregularities as predictor for adverse manifestations in PCOS.

Methods

This study was conducted in the Department of Endocrinology of BSMMU, Dhaka, Bangladesh. Sample size was estimated according to a previous study.⁸ Two hundred Bangladeshi women of age 16-35 years with PCOS diagnosed on the basis of Revised Rotterdam Consensus 2003 criteria were enrolled.³ Control group included 120 age-matched healthy women having regular menstrual cycle without clinical and biochemical hyperandrogenism and any known endocrine disease. Patients were not included if they had: primary amenorrhea, hyperprolactinemia (serum prolactin >25 ng/

ml), hypothyroidism (serum thyroid stimulating hormone, TSH >10 μ IU/ml) and non-classical congenital adrenal hyperplasia diagnosed in case of basal or adrenocorticotrophic hormone (ACTH) stimulated 17-hydroxyprogesterone greater than 10 ng/ml.⁹ Women on medication for ≤ 6 months prior to the study (including oral contraceptives, glucocorticoids, metformin, ovulation induction agents, and estrogenic or anti-androgenic drugs or any medication for dyslipidemia or anti-obesity drugs) or suffering from other systemic diseases (e.g. chronic kidney disease, liver diseases etc.) were also excluded from the study. The study was conducted according to the ethical standards of Helsinki's declaration. Prior to commencement, the research protocol was approved by the Institutional Review Board (IRB) of the university. Informed written consent was taken from all participants.

Anthropometric measurements were done by the same investigator and hirsutism was assessed using a modified Ferriman-Gallwey (mFG) score.¹⁰ Blood sample for total testosterone (TT), follicle-stimulating hormone (FSH), luteinising hormone (LH), TSH and prolactin were collected on any day between 2nd-5th of a spontaneous bleeding episode or randomly in the case of amenorrhea. Trans-abdominal (in unmarried) or trans-vaginal ultrasonography was performed in early follicular phase. Samples for glucose (fasting and 2 hours after 75gm glucose load) and lipid profile were taken to assay on the same day of collection whereas for fasting insulin (FI) blood was centrifuged, serum separated and preserved at -20°C until assay. Plasma glucose was assayed by glucose oxidase method, insulin by chemiluminescent microparticle immunoassay (CMIA, Architect Plus ci4100) and lipid profile by glycerol phosphate dehydrogenase-peroxidase method with automated analyzer (Architect Plus ci8200). Assay were verified by use of internal quality control (QC) method of the respective laboratory. Any missing or unusual data were verified immediately and there were no missing data.

Women with PCOS were grouped according to the interval between menstrual cycles and classified as polymenorrheic (<21 days), eumenorrheic (21 – 35 days), oligomenorrheic (36 days – 3 months) and amenorrheic (>3 months).¹¹ Clinical hyperandrogenism (mFG score of ≥ 8) or biochemical hyperandrogenism (TT >46 ng/dl), polycystic ovarian morphology on USG (any

ovarian volume $\geq 10 \text{ cm}^3$) were taken from a previous study.¹² Surrogate markers were used to define IR; fasting plasma insulin (FI) and HOMA-IR. IR was diagnosed by homeostasis model assessment of insulin resistance, $\text{HOMA-IR} \geq 2.6$; HOMA-IR was calculated using the formula = {fasting plasma glucose, FPG (mmol/L) \times FI ($\mu\text{U/ml}$)} $\div 22.5$.¹³ Metabolic syndrome (MetS) was defined by the harmonizing criteria for metabolic syndrome.¹⁴ Prediabetes was defined as follows: impaired fasting glucose (IFG) when fasting plasma glucose (FPG) was between 5.6–6.9 mmol/L and impaired glucose tolerance (IGT) when the 2-h plasma glucose (2-h PG) value during a 75 g oral glucose tolerance test (OGTT) was between 7.8–11.0 mmol/L. Diabetes mellitus was confirmed by FPG ≥ 7.0 mmol/L and/or a 2-h PG value during a 75 g OGTT of ≥ 11.1 mmol/L.¹⁵

Data were analyzed by SPSS software version 22.0. Qualitative values were expressed in frequency (percentages, %) and quantitative values were expressed in mean (\pm SD) or median (inter-quartile range, IQR) [waist hip ratio (WHR), mFG, FPG, 2H-OGTT glucose, TT, FI, HOMA-IR, HDL-cholesterol, triglyceride (TG)]. Comparison between groups was done by Chi-square/ Fisher's exact test with post-hoc analysis from adjusted residuals for qualitative variables. Quantitative variables with normal distribution were analyzed by independent-samples t-test or one-way ANOVA with post hoc Tukey test and skewed variables were analyzed by Mann-Whitney U test or Kruskal-Wallis one-way ANOVA with pairwise comparison by Dunn's test. Considering eumenorrhea as reference category, multinomial multivariate logistic regression analysis was done to see the predictive association of irregular and regular menstrual cycle of PCOS with different manifestations. P values < 0.05 were considered as statistically significant.

Results

This cross-sectional study included 200 newly diagnosed patients with PCOS and 120 age-matched healthy control [age (years): 22.50 ± 4.89 vs. 23.39 ± 4.12 , $p=0.093$; BMI (kg/m^2): 27.44 ± 5.54

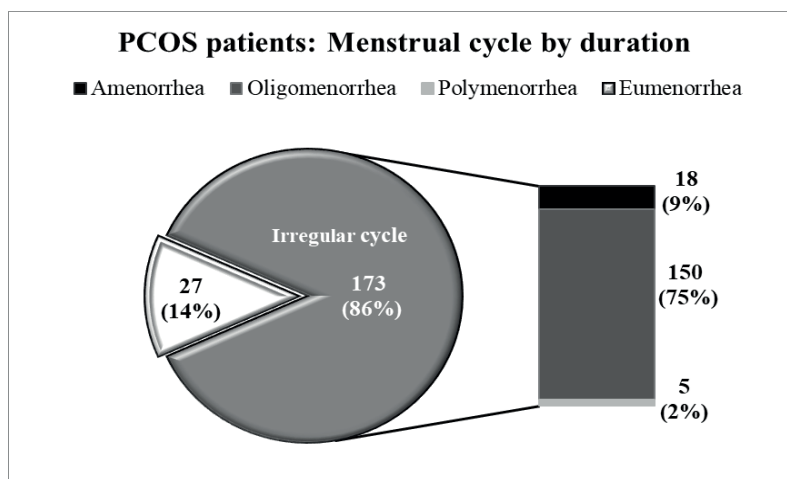


Figure 1. Pattern of menstrual cycle by duration in patients with PCOS (n= 200)

vs. 22.18 ± 4.04 , $p < 0.001$]. Figure-1 shows the pattern of menstrual cycle in patients with PCOS. Most of the patients had menstrual irregularity (86%). Among them 75% had oligomenorrhea followed by amenorrhea (9%) and only 2% had polymenorrhea.

The baseline characteristics of the study population with menstrual pattern are shown in Table 1 and Table 2. Polymenorrhea group was excluded from the analysis due to small number of patients. Age and age of menarche were statistically similar across the menstrual pattern [NS for all]. BMI [control vs. all groups of PCOS, $p < 0.001$], WC [control vs. amenorrhea and eumenorrhea: $p=0.001$; control vs. oligomenorrhea: $p < 0.001$], mFG score [control vs. all groups of PCOS, $p < 0.001$] along with fasting insulin [control vs. amenorrhea and oligomenorrhea: $p < 0.001$; control vs. eumenorrhea: $p=0.002$], HOMA-IR [control vs. amenorrhea and oligomenorrhea: $p < 0.001$; control vs. eumenorrhea: $p=0.001$] and TT [control vs. all groups of PCOS, $p < 0.001$] were significantly higher in all groups of PCOS than control. Patients with oligomenorrhea had significantly higher WHR [$p=0.012$], systolic [$p=0.010$] & diastolic BP [$p=0.020$] as well as 2h-OGTT glucose [$p=0.003$], TC [$p=0.002$] and LDL-cholesterol [$p < 0.001$] than control. Triglyceride was significantly higher in patients with amenorrhea [$p=0.023$] and oligomenorrhea than control [$p < 0.001$], whereas HDL-cholesterol was significantly lower in patients with oligomenorrhea [$p < 0.001$] and eumenorrhea [$p=0.005$] than control. Patients with oligomenorrhea [$p < 0.001$] and eumenorrhea [$p=0.018$] also had significantly higher FBG than control.

Table1. Characteristics of the study population (N= 315)

Variables	PCOS			Control	P	Post hoc significant
	Amenorrhea (a)	Oligomenorrhea (b)	Eumenorrhea (c)	Eumenorrhea (d)		
Age, years	21.33±4.94	22.53±4.94	22.93±4.73	23.39±4.12	0.235	–
Age of menarche, year	12.39±0.98	12.45±1.37	12.67±1.30	12.40±1.06	0.778	–
BMI, kg/m ²	28.01±6.04	27.54±5.76	26.50±3.91	22.18±4.04	<0.001	(a,b,c)>d
Waist circumference, cm	85.94±14.49	86.28±12.69	83.89±8.68	74.80±8.92	<0.001	(a,b,c)>d
Waist/hip ratio	0.84 (0.80, 0.88)	0.85 (0.81, 0.90)	0.85 (0.82, 0.88)	0.82 (0.79, 0.86)	0.012	b>d
Systolic BP, mm-Hg	108.89±12.31	111.62±14.28	107.41±12.59	106.58±11.88	0.017	b>d
Diastolic BP, mm-Hg	70.0±9.07	72.15±9.39	71.03±9.27	68.92±8.63	0.037	b>d
Modified F-G score	8.00 (3.75, 11.25)	8.0 (3.0, 12.0)	8.0 (5.0, 10.0)	1.0 (0.0, 2.0)	<0.001	(a,b,c)>d
Fasting blood glucose, mmol/L	4.95 (4.35, 5.40)	4.90 (4.50, 5.43)	4.90 (4.60, 5.30)	4.30 (3.70, 5.00)	<0.001	(b,c)>d
2H-OGTT glucose, mmol/L	6.55 (5.93, 8.78)	6.80 (5.90, 7.89)	6.50 (5.92, 7.60)	6.40 (5.40, 7.00)	0.005	b>d
Total cholesterol, mg/dl	179.11±34.59	176.26±32.84	161.99±31.37	161.91±30.21	0.001	b>d
LDL-cholesterol, mg/dl	108.56±30.33	111.55±28.46	102.91±23.68	97.87±23.35	<0.001	b>d
HDL-cholesterol, mg/dl	40.50 (34.75, 45.75)	39.0 (33.0, 46.0)	38.0 (34.0, 44.0)	45.0 (39.0, 51.0)	<0.001	(b, c)<d
Triglyceride, mg/dl	126.0 (95.75, 178.0)	115.0 (90.75, 158.75)	101.0 (69.0, 152.0)	91.0 (69.75, 117.75)	<0.001	(a, b)<d
Fasting insulin, µIU/ml	19.90 (12.33, 38.43)	17.20 (12.08, 24.18)	14.0 (7.80, 18.70)	8.40 (6.64, 10.88)	<0.001	(a,b,c)>d
HOMA-IR	4.38 (2.85, 8.31)	3.70 (2.49, 5.69)	3.05 (1.43, 4.31)	1.64 (1.17, 2.14)	<0.001	(a,b,c)>d
Total testosterone, ng/dl	74.13 (37.24, 99.17)	45.55 (32.16, 71.61)	46.97 (34.50, 66.93)	26.51 (21.18, 35.42)	<0.001	(a,b,c)>d

Data were expressed in mean±SD or median (IQR) as appropriate

One-way ANOVA with post hoc Tukey or Kruskal Wallis one-way ANOVA with pairwise comparison by Dunn's test were done as appropriate

PCOS patients with amenorrhea had significantly higher percentages of history of subfertility [33.0% vs. 0.0%, $p<0.001$] and family history of PCOS [38.9% vs. 0.0%, $p<0.001$] than control. On the other hand, patients with oligomenorrhea had significantly higher percentages of family history of irregular menstruation [28.0% vs. 5.0%, $p<0.001$] and subfertility [23.3% vs. 2.5%, $p<0.001$] than control. Family history of hirsutism was significantly higher in patients with both oligomenorrhea [22.0% vs. 1.7%, $p<0.001$] and eumenorrhea [33.3% vs. 1.7%, $p<0.001$] than control. General [62.7% vs. 23.3%, $p<0.001$] and central obesity [70.7% vs. 21.7%, $p<0.001$], significant hirsutism [56.7% vs. 0.0%, $p<0.001$], acanthosis nigricans [59.3% vs. 4.2%, $p<0.001$] all were present significantly with higher percentages

in patients with oligomenorrhea than control. While percentages of prediabetes was significantly higher in patients with oligomenorrhea [26.7% vs. 9.2%, $p<0.001$], DM was significantly higher in patients with amenorrhea [16.7% vs. 0.0%, $p<0.001$] than control. Patients with oligomenorrhea had significantly higher percentages of hypertriglyceridemia [29.3% vs. 10.8%, $p=0.001$], elevated insulin [76.0% vs. 15.0%, $p<0.001$], insulin resistance [72.0% vs. 12.5%, $p<0.001$] as well as metabolic syndrome [40.7% vs. 11.7%, $p<0.001$] than control. Hyperandrogenemia was present at a higher percentages in patients with amenorrhea [66.7% vs. 4.2%, $p<0.001$] and oligomenorrhea [49.3% vs. 4.2%, $p<0.001$] than control (Table 2).

Table 2. Characteristics of the study population

Variables		PCOS			Control	P	Post hoc significant
		Amenorrhea (a)	Oligomenorrhea (b)	Eumenorrhea (c)	Eumenorrhea (d)		
Personal history	Subfertility	6 (33.3)	18 (12.0)	4 (14.8)	0 (0.0)	<0.001	a>d
	MR/abortion	0 (0.0)	10 (6.7)	3 (11.1)	9 (7.5)	0.598	–
Family history	Irregular menstruation	7 (38.9)	42 (28.0)	7 (25.9)	6 (5.0)	<0.001	b>d
	Hirsutism	4 (22.2)	33 (22.0)	9 (33.3)	2 (1.7)	<0.001	(b, c)>d
	Subfertility	3 (16.7)	35 (23.3)	2 (7.4)	3 (2.5)	<0.001	b>d
	PCOS	7 (38.9)	22 (14.7)	4 (14.8)	0 (0.0)	<0.001	a>d
	Obesity	10 (55.6)	56 (37.3)	7 (25.9)	31 (25.8)	0.031	NS
	DM	10 (55.6)	85 (56.7)	11 (40.7)	56 (46.7)	0.256	–
	Hypertension	10 (55.6)	86 (57.3)	11 (40.7)	61 (50.8)	0.397	–
Obese (BMI ≥ 25 kg/m ²)		12 (66.7)	94 (62.7)	18 (66.7)	28 (23.3)	<0.001	b>d
Centrally obese (WC ≥ 80 cm)		11 (61.1)	106 (70.7)	19 (70.4)	26 (21.7)	<0.001	b>d
Hypertensive (BP ≥ 140 or 90 mm-Hg)		0 (0.0)	3 (2.0)	1 (3.7)	2 (1.7)	0.768	–
Significant hirsutism (mFG score ≥ 8)		11 (61.1)	85 (56.7)	14 (51.9)	0 (0.0)	<0.001	b>d
Acanthosis nigricans		12 (66.7)	89 (59.3)	14 (51.9)	5 (4.2)	<0.001	b>d
Glycemic status	NGT	12 (66.7)	103 (68.7)	22 (81.5)	109 (90.8)	<0.001	b<d
	Prediabetes	3 (16.7)	40 (26.7)	5 (18.5)	11 (9.2)		b>d
	DM	3 (16.7)	7 (4.7)	0 (0.0)	0 (0.0)		a>d
Lipid profile	High TC (≥ 200 mg/dl)	4 (22.2)	30 (20.0)	4 (14.8)	11 (9.2)	0.066	–
	High LDL-C (≥ 100 mg/dl)	10 (55.6)	92 (61.3)	12 (44.4)	54 (45.0)	0.043	NS
	Low HDL-C (< 50 mg/dl)	15 (83.3)	131 (87.3)	26 (96.3)	86 (71.7)	0.001	NS
	High TG (≥ 150 mg/dl)	5 (27.8)	44 (29.3)	8 (29.6)	13 (10.8)	0.001	b>d
Metabolic syndrome		6 (33.3)	61 (40.7)	8 (29.6)	14 (11.7)	<0.001	b>d
Elevated insulin (≥ 12 μ IU/ml)		14 (77.8)	114 (76.0)	18 (66.7)	18 (15.0)	<0.001	b>d
Insulin resistance (≥ 2.6)		14 (77.8)	108 (72.0)	17 (63.0)	15 (12.5)	<0.001	b>d
Hyperandrogenemia (TT > 46 ng/dl)		12 (66.7)	74 (49.3)	14 (51.9)	5 (4.2)	<0.001	(a, b)>d
Altered LH/FSH ratio (> 1.0)		14 (77.8)	125 (83.3)	22 (81.5)	Not done	0.893	–
Polycystic ovarian morphology		14 (77.8)	124 (82.7)	22 (81.5)	Not done	0.851	–

Data were expressed in frequency (%), within parentheses are percentages over column total

Pearson's chi-square/Fisher's exact test with post hoc analysis were done

Age group 21 – 30 years in comparison to age group 16 – 20 years, had significant predictive association with irregular cycle in PCOS patients [OR (95% CI): 0.398 (0.168, 0.940), $p=0.036$]. Acanthosis nigricans [irregular menstrual cycle: 21.994 (6.427, 75.267), $p<0.001$; PCOS with eumenorrhea: 16.449 (3.830, 70.643), $p<0.001$], hyperandrogenemia [irregular menstrual cycle: 27.735 (8.672, 88.704), $p<0.001$; PCOS with eumenorrhea: 24.635 (6.349, 95.590), $p<0.001$]

and insulin resistance [irregular menstrual cycle: 7.268 (2.647, 19.954), $p<0.001$; PCOS with eumenorrhea: 6.071 (1.658, 22.234), $p=0.006$] had significant predictive association with PCOS patients with both irregular and regular cycle in reference to control (Table 3). None of the variables had significant predictive associations with irregular cycle in reference to regular cycle in patients with PCOS.

Table 3. Multinomial multivariate logistic regression analysis of menstrual disturbance as dependent variable with control as reference group

Independent variables	Categories	Irregular cycle PCOS		Regular cycle PCOS	
		OR (95% CI)	p	OR (95% CI)	p
Age group	16 – 20 years	1		1	
	21 – 30 years	0.398 (0.168, 0.940)	0.036	0.455 (0.149, 1.392)	0.167
	31 – 40 ears	0.711 (0.110, 4.588)	0.720	0.414 (0.028, 6.203)	0.523
FH of menstrual disturbance	Absent	1		1	
	Present	3.426 (0.987, 11.897)	0.052	4.030 (0.890, 18.257)	0.071
FH of obesity	Absent	1		1	
	Present	0.938 (0.363, 2.428)	0.896	0.607 (0.167 2.199)	0.447
FH of DM	Absent	1		1	
	Present	0.431 (0.163, 1.140)	0.090	0.297 (0.08, 1.097)	0.069
FH of hypertension	Absent	1		1	
	Present	1.516 (0.650, 3.533)	0.335	1.075 (0.331, 3.496)	0.904
Body mass index	Non-obese	1		1	
	Obese	0.947 (0.355, 2.529)	0.913	2.156 (0.598, 7.769)	0.240
Blood pressure	Normotensive	1		1	
	Hypertensive	0.198 (0.010, 3.879)	0.286	0.724 (0.020, 25.669)	0.859
Acanthosis nigricans	Absent	1		1	
	Present	21.994 (6.427, 75.267)	<0.001	16.449 (3.830, 70.643)	<0.001
Androgenemia	Normoandrogenemia	1		1	
	Hyperandrogenemia	27.735 (8.672, 88.704)	<0.001	24.635 (6.349, 95.590)	<0.001
Glycemic status (glucose tolerance)	Normal GT	1		1	
	Abnormal GT	1.756 (0.577, 5.346)	0.322	1.257 (0.291, 5.426)	0.759
HOMA-IR	Insulin sensitive	1		1	
	Insulin resistant	7.268 (2.647, 19.954)	<0.001	6.071 (1.658, 22.234)	0.006
Metabolic syndrome	Absent	1		1	
	Present	1.825 (0.598, 5.569)	0.290	1.082 (0.265, 4.416)	0.912
Constant		B= -1.356	<0.001	B= -2.720	<0.001

Discussion

Menstrual irregularity is one of the key factors in diagnosing PCOS. Pattern of menstrual abnormalities in PCOS and its relationship with various manifestations of PCOS was evaluated in present study. It was revealed that all menstrual cycle variants had significantly adverse metabolic indices such as BMI, WC, fasting insulin, and HOMA-IR than control group.

Majority of patients (86%) had menstrual irregularity with a predominance of oligomenorrhea (75%), followed by amenorrhea (9%) and only 2% had polymenorrhea. On the

other hand, 14% PCOS women had regular cycle. These findings were almost similar with the study done by others.⁵ All the subgroups of PCOS patients had poor metabolic profile than the control namely IR, impaired glycemic status, general and central obesity, Mets, clinical and biochemical hyperandrogenemia and dyslipidemia, supported by similar findings found in a study done in Bangladeshi by our PCOS Study group.¹⁶

Normocyclic women with PCOS as defined by the Rotterdam criteria have a decreased risk of insulin resistance than women with various degrees of cycle abnormalities and PCOS.¹⁷ In the present

study, age group 21–30 years in comparison to age group 16–20 years had significant predictive association with irregular cycle in PCOS patients. This may indicate some effects of advancing age or the fact that pathophysiologic aberration of PCOS started in early age which was noticed and identified at some time after advancement of age thereby permitting elapse of time for menstrual abnormality be manifested. Hyperandrogenemia and IR had predictive association with PCOS patients with both irregular and regular cycle in reference to control. However, none of the variables had predictive associations with irregular cycle in reference to regular cycle in PCOS patients.¹⁷ Therefore it is pertinent from this study to assume that despite menstrual abnormality is a key manifestation of PCOS, it cannot apprehend over hyperandrogenemia and IR. Among metabolic and clinical manifestations in PCOS subgroups, general and central obesity, significant hirsutism, acanthosis nigricans, prediabetes, hypertriglyceridemia, IR as well as MetS were all present significantly with higher percentages in patients with oligomenorrhea than control. This would virtually indicate that PCOS is associated with menstrual irregularity which is considered as a key element in diagnosis is applicable in distinguishing between PCOS and control; but cannot be extrapolated for the discrimination among subtypes of PCOS. Percentages of T2DM was significantly higher in patients with amenorrhea than control along with history of subfertility and family history of PCOS. Likewise, hyperandrogenemia was present at a higher percentages in patients with amenorrhea and oligomenorrhea than control.

Several studies have found the overall prevalence of IR ranges from 44% to 70%; our study revealed around 78% in eumenorrheic, 72% in oligomenorrheic and 63% in amenorrheic group were insulin resistant.^{18,19} In the present study, the prevalence of MetS ranged from 30–40% in PCOS subgroups. This frequency is similar to that reported in the United States (43%–46%) but higher than that reported in Italy (8%–16%) and China (2.3%–12.2%).^{20,21} The variations in these metabolic findings could possibly be due to the influence of ethnic origin, genetic and environment, and dietary habits on the prevalence of PCOS and its comorbidities.

The study questionnaire did not use standard criteria to define regular menstruation. According to recommendations from International Federation

of Gynecology and Obstetrics (FIGO), normal menstrual cycle should be defined according to the: [i] frequency of menses (24–38 days), [ii] regularity of menses (variation ± 2 –20 days), [iii] duration of menstrual flow (4.5–8 days) and [iv] volume of monthly blood loss (5–80 ml).²² Thus, subjects might have experienced confusion regarding their menstrual pattern which may have led to inaccurate data. In the current study, after adjusting for BMI, age and race, women with PCOS were grouped according to the interval between menstrual cycles and classified as polymenorrheic, eumenorrheic, oligomenorrheic and amenorrheic respectively. Besides, the number of study participants in amenorrhea group was small, so the associations might not significant with other menstrual variants in PCOS group.

Conclusion

Our data suggest that one out of ten PCOS patients might present with regular menstrual cycle and oligomenorrhea was the predominant variant of irregular menstrual cycle in PCOS. Among different manifestations, acanthosis nigricans, insulin resistance and hyperandrogenemia were significantly associated with both irregular and regular menstrual cycle of PCOS patients in comparison to control. However, the manifestations were not different across different menstrual patterns in patients with PCOS.

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