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ORIGINAL ARTICLE

SCREENING OF PRE-DIABETES IN PATIENTS PRESENTING WITH POLYCYSTIC OVARIAN SYNDROME: A TERTIARY CARE EXPERIENCE

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ABSTRACT

OBJECTIVE: To screen the females presenting with Polycystic Ovarian Syndrome (PCOS) for underlying pre-diabetes and to correlate pre-diabetes with the various diagnostic criteria of PCOS.

METHODS: This descriptive cross-sectional study was conducted at Lady Reading Hospital Peshawar, Pakistan from March, 2020 till December, 2020. One hundred & fifty one cases of PCOS, ranging in age from 17-40 years, were selected through purposive sampling. The Rotterdam criterion was used to diagnose PCOS, the details of history, physical examination and biochemical investigations like luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, thyroid stimulating hormone (TSH), glycosylted hemoglobin (HBA1c), prolactin and pelvic ultrasound were recorded on a structured questionnaire.

RESULTS: Mean age of the patients was 23.42±4.88 years. Mean BMI was 33.27±26.98 kg/m^2. Pre-diabetes was detected in 19.2% (n=29) and overt diabetes in 4.0% (n=6) of the women with PCOS. Hypertension, dyslipidemia and hypothyroidism were reported by 11 (7.2%), 9 (5.9%) and 4 (2.6%) patients respectively. Delayed menstrual cycle was reported by 44.8% (n=52); 27.6% (n=8) & 33.3% (n=2) cases of normoglycemic, prediabetes and diabetes mellitus respectively. Oligomenorrhoea was present in 69.0% (n=20) of pre-diabetics. Moderate and severe hirsutism was present in 44.8% and 10.3% PCOS patients with pre-diabetes. There was no significant correlation between pre-diabetes and the criteria of PCOS diagnosis.

CONCLUSION: Women with PCOS are at increased risk of pre-diabetes and other metabolic complications like obesity, hypertension and dyslipidemia at an earlier age. However, there was no significant correlation between pre-diabetes and the criteria of PCOS diagnosis.

KEY WORDS: Polycystic Ovarian Syndrome (MeSH); Prediabetic State (MeSH); Diabetes Mellitus (MeSH); Dyslipidemias (MeSH); Hypertension (MeSH); Metabolic Complications (Non-MeSH); Obesity (MeSH).

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an endocrine disorder that affects women in their reproductive age group and could lead to different cosmetic, metabolic or reproductive consequences over the course of the disease and may ultimately affect the psychological wellbeing of the person as well as the economic productivity.[1] It is a multifactorial syndrome that initially appears after puberty; females with this disease are at a greater risk of several other diseases such as obesity, infertility, type 2 diabetes, hypertension, dyslipidemia, cardiovascular complications, non-alcoholic fatty liver disease, cancer, obstructive sleep apnea, musculoskeletal disorders and mental ill health.[2] The American Association of Clinical Endocrinologists has clearly recommended a yearly oral glucose tolerance test (OGTT) in patients with PCOS, particularly with a family history of type 2 Diabetes Mellitus (T2DM) and a body mass index (BMI) >30 kg/m^2. That is consistently supported by the PCOS Special Interest Group of the European Society of Endocrinology in favour of OGTT in all PCOS patients with a family history of T2DM or gestational diabetes.[3-4]

Likelihood of having T2DM diagnosed at the time of PCOS diagnosis is proposed to be substantially higher in overweight or obese PCOS patients than in normal-weight PCOS patients.[5,6] PCOS is known to be associated with an array of metabolic disorders; however, compromised glucose metabolism has been a topic in multiple prospective research studies that focused on the association between the higher prevalence and incidence of impaired glucose tolerance in PCOS patients.[7,8]

Insulin resistance (IR) is speculated to be the mainstay for having an increased risk for pre-diabetes among PCOS women. It is characterized by non-diabetic hyperglycemia and simultaneous presence of β-cell dysfunction even before any glucose changes become apparent.[9,10] With that rationale, this study was designed to screen pre-diabetes in females presenting with PCOS at a tertiary care hospital of Peshawar, Pakistan. Furthermore, this study also aimed to study the correlation of pre-diabetes with the different diagnostic criteria of PCOS diagnosis in terms of the menstrual cycle disorders, clinical hyperandrogenism (acne, hirsutism, alopecia) or biochemical hyperandrogenism (reversal of luteinizing

TABLE I: BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE ENROLLED PATIENT (N=151)

Variables		Frequency (%age)
Employment status	Employed	94 (61.84)
	Unemployed	57 (37.50)
Residence	Urban	100 (65.78)
	Rural	51 (33.6)
Educational Status	Illiterate	27 (17.8)
	Primary	24 (15.8)
	Secondary	51 (33.7)
	Higher secondary or Above	49 (32.4)
Marital Status	Married	56 (36.8)
	Unmarried	95 (62.5)
Hypertension	Yes	11 (7.2)
	No	140 (92.1)
Hypothyroidism	Yes	4 (2.6)
	No	147 (96.7)
Oral Contraceptive Use	Yes	55 (36.2)
	No	96 (63.2)
Dyslipidemia	Yes	9 (5.9)
	No	142 (93.4)
Galactorrhea	Yes	3 (2.0)
	No	148 (97.4)
Weight History	Steady	21 (13.8)
	Losing	6 (3.9)
	Gaining	124 (81.6)
Fertility	Previous Pregnancy	14 (9.2)
	Spontaneous Pregnancy	7 (4.6)
	Assisted Pregnancy	12 (7.9)
	Not Relevant	101 (66.4)
	Infertility	17 (11.2)
Acanthosis Nigricans	Axial	21 (13.9)
	Neck	63 (41.7)
	Not Present	67 (44.3)
Ferriman Gallway Score	1	1 (0.7)
	2	12 (7.9)
	3	75 (49.3)
	4	59 (38.8)
Pelvic Ultrasound	Polycystic Ovarian Synrome	97 (64.2)
	Normal	54 (35.8)

hormone (LH) & follicle stimulating hormone (FSH) ratio (LH:FSH) and serum Testosterone levels) and the presence of polycystic ovaries on ultrasound.

METHODS

This observational cross-sectional study was conducted from March, 2020 till December, 2020; at the Department of Diabetes and Endocrinology, Medical Teaching Institution, Lady Reading Hospital Peshawar, Pakistan. The Ethical Review Committee approval was obtained (Letter no: 401/LRH/MTI, Dated: 10/02/2020) before the commencement of the study.

The sample size of 151 was calculated using the WHO formula, considering 11% prevalence of PCOS among women of premenopausal age, with a confidence interval of 95% and absolute precision of 0.05%.

Post pubertal PCOS women between the ages 17-40 years, complaining of irregular menses and or infertility, oligomenorrhea (absence of menses for 35-182 days), amenorrhea (absence of menses for >182 days), symptoms or signs of hyperandrogenism, abdominal ultrasound showing at least 12 follicles (2-9 mm in diameter) were included in the study. The Rotterdam criterion[11] was used to diagnose PCOS with at least two of the three following criteria after excluding other etiologies, i.e. oligo/amenorrhea or amenorrhea, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasonography. The menstrual irregularity was assessed by the presence of chronic amenorrhea/oligomenorrhea, which is described as menstrual cycle length of fewer than 21 days or more than 35 days or more than four days variation between cycles. At the same time, clinical hyperandrogenism was assessed via the modified Ferriman Gallway (mFG) Scoring method for hirsutism and acne via the Global Acne grading system. HbA1c levels were obtained to confirm pre-diabetes (or diabetes), with levels between 5.7% and 6.4% considered as pre-diabetes and with ≥6.5 were considered as overt diabetes.

However, women with acute febrile or systemic illness or major surgery within the last three months, congenital adrenal hyperplasia, hyperprolactinemia, acromegaly, functional hypothalamic amenorrhea, menopause, any malignant disease, severe psychiatric illness, or pregnant lactating females or those receiving drugs for any other systemic illness e.g., steroids, immunosuppressive drugs etc. were excluded.

Written informed consent was taken from each patient enrolled and baseline demographic information, including marital status, education, and occupation, were noted on a structured questionnaire. A detailed history of the menstrual cycle, hirsutism, alopecia, acne, weight issue, and infertility were documented. The patients were also examined for acanthosis nigricans, alopecia, hirsutism, thyromegaly and striae. Biochemical investigations like LH, FSH, Testosterone, thyroid stimulating hormone (TSH), glycosylated hemoglobin (HbA1c), Prolactin and Pelvic Ultrasound were performed at the hospital facilities.

The statistical analysis was performed on SPSS version 25.0. The data were

TABLE II: PATIENT CHARACTERISTICS IN RELATION TO INCIDENCE OF PRE-DIABETES

Variables		Normal (n=116)	Pre-Diabetes (n=29)	Diabetes (n=6)	p-value
		Frequency (%age)	Frequency (%age)	Frequency (%age)	
Menstrual Cycle	Regular	28 (24.1)	11 (37.9)	1 (16.7)	0.525
	Delayed	52 (44.8)	8 (27.6)	2 (33.3)	
	Absent	13 (11.2)	5 (17.2)	2 (33.3)	
	Irregular	15 (12.9)	4 (13.8)	1 (16.7)	
Menstrual Flow	Normal	23 (19.8)	7 (24.1)	1 (16.7)	0.265
	Oligomenorrhea	84 (72.4)	20 (69.0)	3 (50.0)	
	Polymenorhagia	7 (6.0)	1 (3.4)	1 (16.7)	
Hirsutism	Upper Lips	108 (93.1)	26 (89.7)	5 (83.3)	0.599
	Chin	112 (96.6)	28 (96.6)	6 (100.0)	0.899
	Arms	43 (37.1)	8 (27.6)	3 (50.0)	0.482
	Chest	31 (26.7)	6 (20.7)	2 (33.3)	0.723
	Upper Abdomen	41 (35.3)	6 (20.7)	1 (33.3)	0.321
	Lower Abdomen	89 (76.7)	22 (75.9)	4 (66.7)	0.227
	Upper Back	14 (12.1)	2 (6.9)	2 (33.3)	0.190
	Lower Abdomen	15 (12.9)	1 (3.4)	2 (33.3)	0.095
	Thighs	94 (81.0)	21 (72.4)	5 (83.3)	0.573
Severity of Hirsutism	Mild	32 (27.6)	13 (44.8)	3 (50.0)	0.563
	Moderate	60 (51.7)	13 (44.8)	2 (33.3)	
	Severe	23 (19.8)	3 (10.3)	1 (16.7)	
Alopecia	None	67 (57.8)	25 (86.2)	-	<0.01*
	Grade 1	40 (34.5)	2 (6.9)	6 (100.0)	
	Grade 2	7 (6.0)	2 (6.9)	-	
	Grade 3	2 (1.7)	-	-	
Acne	Face	69 (59.5)	18 (62.1)	3 (50.0)	0.859
	Chest	30 (25.9)	11 (37.9)	1 (16.7)	0.355
	Back	32 (27.6)	10 (34.5)	2 (33.3)	0.745
Severity of Alopecia	No	65 (56.0)	25 (86.2)	-	<0.01*
	Mild	41 (35.3)	2 (6.9)	6 (100.0)	
	Moderate	7 (6.0)	2 (6.9)	-	
	Severe	3 (2.6)	-	-	
Weight History	Steady	16 (13.8)	4 (13.8)	1 (16.7)	0.988
	Losing	5 (4.3)	1 (3.4)	-	
	Gaining	95 (81.9)	24 (82.8)	5 (83.3)	
		(Mean±SD)	(Mean±SD)	(Mean±SD)	
Age (Years)		12.69±1.54	13.0±1.30	12.17±1.72	0.398
BMI (kg/m^2)		33.61±30.63	32.86±5.88	28.702±5.63	0.907
HbA1c (%)		5.10±0.33	5.94±0.19	6.60±0.12	<0.01*
LH (mIU/ml)		13.54±7.15	14.78±6.70	11.09±3.83	0.454
FSH (mIU/ml)		6.35±2.65	6.72±2.87	6.08±1.18	0.769
LH/FSH		2.34±1.34	7.03±25.28	1.77±0.54	0.121
Testosterone (ng/ml)		0.50±0.31	0.56±0.43	0.61±0.40	0.592
TSH (ulU/ml)		3.22±2.95	2.62±1.87	2.62±1.86	0.527

BMI=Body Mass Index; LH=Leutinizing Hormone; FSH=Follicle Stimulating Hormone; TSH= Thyroid Stimulating Hormone; HBA1c= Glycosylted Hemoglobin; *p-value< 0.05 is considered significant

presented as mean±standard deviation, frequency and percentages. Chi-square test and one-way ANOVA were used to assess the patient characteristics concerning the incidence of pre-diabetes, where $p < 0.05$ was considered significant. The incidence of pre-diabetes was correlated with the criteria of PCOS diagnosis in terms of the pattern of menstrual cycles, clinical hyperandrogenism (acne, hirsutism, alopecia) or biochemical hyperandrogenism (LH: FSH ratio and Testosterone) and the presence of polycystic ovaries on ultrasound, using Pearson's correlation.

RESULTS

Out of 151 females, 56 (36.8%) were married and 95 (62.5%) were unmarried. The mean age of the enrolled patients with the polycystic ovarian syndrome was 23.42±4.88 years, and mean age of menarche was 12.73±1.50 years. The

TABLE III: CORRELATION OF PRE-DIABETES INCIDENCE WITH PCOS DIAGNOSIS

	Pre-diabetes Incidence	Menstrual Cycle	Hirsutism	Acne	Alopecia	LH/FSH	Testosterone	Pelvic Ultrasound
Pre-diabetes Incidence	1	.002	.043	-.034	-.029	.106	.084	-.096
Menstrual Cycle		1	-.026	-.152	-.005	-.038	.005	.109
Hirsutism			1	-.040	.043	-.038	-.176*	.187*
Acne				1	-.026	.021	-.090	.022
Alopecia					1	-.076	-.038	.170*
LH/FSH						1	.450**	-.071
Testosterone							1	-.163*
Pelvic Ultrasound								1

LH= Leutinizing Hormone; FSH= follicle stimulating Hormone; * Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed).

mean weight was 74.99±14.79 kgs, height was 159.23±24.34 cm and BMI of the patients was 33.27±26.98 kg/m^2.

Mean values of LH, FSH, Testosterone, TSH and HbA1c in our study population were 13.68±6.97 mU/ml, 6.41±2.64 mU/ml, 0.52±0.34 ng/ml, 3.08±2.74 ulU/ml and 5.32±0.51% respectively.

Sixty two (41.1%) patients experienced a delayed menstrual cycle. Hypertension, hypothyroidism, dyslipidemia and galactorrhea were also reported by 11 (7.2%), 4 (2.6%), 9 (5.9%) and 3 (2.0%) of the patients respectively. Moreover, 124 (81.6%) patients had a history of weight gain, while 17 (11.2%) suffered from infertility. 84 (55.6%) had acanthosis nigricans, while half of the patients had moderate hirsutism and 97 (64.2%) had ultrasonic evidence of PCOS (Table I).

Overall, 19.2% (n=29) of the females presenting with PCOS were diagnosed with pre-diabetes, 4.0% (n=6) had overt diabetes, and 76.8% (n=116) were normoglycemic. There were no significant alterations in the hormones amongst diabetic and pre-diabetic patients with PCOS. While observing the menstrual cycle of the study patients, it was found that 27.6% (n=8/29) and 33.3% (n=2/6) of the pre-diabetic and diabetic patients were reported to have delayed menstrual cycles, respectively.

Overall, 27 (17.9%) patients had severe hirsutism and 75 (49.7%) had moderate hirsutism. Moderate and severe hirsutism in patients with pre-diabetes was observed in 13 (44.8%) and 3 (10.3%) cases respectively. Mean HbA1c was 5.10±0.33 %, 5.94±0.19 %, and 6.60±0.12 % in normoglycemic, pre-diabetes and diabetes mellitus patients respectively ($p<0.01$) [Table II].

There was no significant correlation between the incidence of pre-diabetes and the criteria of PCOS diagnosis in terms of the menstrual cycle, hirsutism, acne, alopecia, LH/FSH ratio, testosterone and pelvic ultrasound, as shown in table III.

DISCUSSION

Based on the existing literature, PCOS with pre-diabetes are closely correlated with a higher BMI.[10,12] The women between 19 to 30 years of age fulfilling the PCOS National Institutes of Health (NIH) criteria are at higher risk for developing subsequent diabetes, dyslipidemia, and hypertension.[13] Studies have shown that the risk of getting T2DM for the lifetime increased many folds in patients with PCOS as well. It is also well studied that an extensive amount of insulin causes trouble in two possible ways; firstly, it increases the chance of getting T2DM and also, it stimulates the ovaries to make and release more male hormones.[14] Moreover, obesity has a deep-rooted connection with PCOS and their aftermaths. Obese people are more vulnerable as compared to lean subjects.[15] Although, there are no such studies available that give a clear picture of the etiology, nature of the impact and the underlying mechanism that put obese women at the risk of getting PCOS and T2DM.[15] However, this is an established fact that PCOS, T2DM and obesity make a deadly triad that could adversely affect a person's life. A previous study suggested that obese patients with PCOS are at higher risk of T2DM than lean patients with PCOS.[2,3] The present study results seem to defy the fact, suggesting that pre-diabetic women with PCOS have comparatively low BMI than normal women with PCOS. The reason for this may be the considerable difference in the sample size of the three groups (normal, pre-diabetics and diabetics).

Out of the total, 19.2% of these were found to be pre-diabetic, 4.0% were diabetic, and 76.8% were normal, with a mean HBA1c (%) of 5.94±0.19, 6.60±0.12, 5.10±0.33, respectively. A similar study showed that pre-diabetes was prevalent among 12% of the total enrolled women with PCOS (n=239), which is comparatively lower than that observed in the present study.[16] While Legro RS, et al. compared the prevalence of impaired glucose tolerance (IGT) and T2DM amongst obese women with and without PCOS. He found that the obese females with PCOS had IGT in 30% and T2DM in 15.7% of subjects, whereas obese women without PCOS had IGT and T2DM in 4% and 0% of subjects, respectively.[17]

The findings from a large cohort study in the United States suggested that young PCOS women display higher odds of subsequent diabetes and dyslipidemia.[13] A significant association of PCOS with hypertension has been recognized in a few studies, Lo JC, et al. observed higher odds of hypertension among the PCOS females (OR 1.41, 1.31-1.51)[18] and

similarly, Wild S, et al. also reported an odds ratio of 1.4 (0.9-2.0) for PCOS and hypertension association.[19] Other studies also showed no significant difference in the incidence of hypertension among females with PCOS and without PCOS (26.9% vs. 26.3%; AOR 1.7, 0.83.3).[18,19] In the present study, hypertension and dyslipidemia were prevalent among 7.2% and 5.9% of the enrolled PCOS females.

Furthermore, there were no significant variations in the biochemical parameters among the normal, pre-diabetic and diabetic patients. Although the alterations in the mean LH and FSH (mIU/ml) levels are apparent between normal and pre-diabetic groups but no significant change could be seen, i.e. mean LH was 13.54±7.15 (normal) and 14.78±6.70 (pre-diabetic). While, FSH was 6.35±2.65, 6.72±2.87 and 6.08±1.18 among normal, pre-diabetic and diabetic patients, respectively. Also, the difference in the LH/FSH ratio was noteworthy among PCOS females with pre-diabetes (7.03±25.28) than those without pre-diabetes (2.34±1.34). In contrast, Velija et al. reported significantly lower levels of FSH among pre-diabetic women with PCOS than those without incident prediabetes, i.e. 5.26±0.88 vs. 6.05±2.19 ($p=0.05$), while the LH levels were comparable between the two groups. The reported LH/FSH ratio was significantly high among PCOS females with pre-diabetes than those without pre-diabetes, i.e. 2.99±0.54 vs. 2.78±0.96 ($p=0.031$).[16] Furthermore, it is evident from the existing data that the testosterone levels differ significantly among PCOS with pre-diabetes as compared to those with normal glucose tolerance (NGT).[20,21,22] Zhang B, et al. reported a median testosterone level of 1.0 (0.71.5) nmol/L among PCOS women with NGT, 1.1 (0.71.6) nmol/L among those with pre-diabetes and 1.4 (0.72.2) among PCOS women with T2DM ($p<0.05$).[23]

Ultrasonic polycystic ovaries were confirmed in 97(64.2%) of the PCOS females; 20.6% of these were pre-diabetic, 74.2% had normal glucose tolerance, and 5.2% were diabetic. Ibricevic and Asimi confirmed the prevalence of polycystic ovaries on pelvic ultrasound in 45% PCOS women,[24] while another study reports that it exceeds 70%.[6] Lastly, the frequency of menstrual flow, hirsutism, acne and alopecia were similar among the PCOS patients with pre-diabetes and those without pre-diabetes, which is also reported in another study. Zhang B, et al. reported no significant difference in the frequency of hyperandrogenism among PCOS women with different glucose metabolism statuses.[23] Whereas a contrasting study demonstrated a high prevalence of hyperandrogenic disorders like PCOS and hirsutism among diabetic women, it is well-known that hirsutism is itself significantly associated with PCOS.[25]

Furthermore, we found no significant correlation between the incidence of pre-diabetes and the criteria of PCOS diagnosis in terms of the menstrual cycle, hirsutism, acne, alopecia, LH/FSH ratio, testosterone and pelvic ultrasound, which is contradictory to the published literature.[1,2] But it can be seen that there was a significant inverse correlation between hirsutism and testosterone ($r=-0.176$; $p<0.05$) and a significant positive correlation between hirsutism and pelvic ultrasound ($r=0.187$; $p<0.05$). A strong positive correlation was also found between LH/FSH ratio and testosterone levels ($r=0.450$; $p<0.01$).

Although the study successfully presented the data of the single site, the detailed analysis including all relevant clinical parameters. Moreover, the association and correlation of covariates in terms of PCOS diagnostic criteria with the risk of diabetes were extensively studied. But there are certain limitations; first and foremost was that the prevalence was driven from a single-center population. Furthermore, we were unable to analyze the effect of other relevant significant covariates contributing to the risk of pre-diabetes among PCOS women.

CONCLUSION

This study showed a close association of dysglycemia and PCOS in women of reproductive age group. Our findings suggest that women with PCOS are at increased risk of developing pre-diabetes, at an earlier age which inadvertently leads to overt diabetes. There is also an increased risk of developing other metabolic complications like obesity, hypertension and dyslipidemia in the course of PCOS. However, there was no significant correlation between pre-diabetes and the criteria of PCOS diagnosis.

RECOMMENDATIONS

Further research is desirable not only to explore the tendency of metabolic disorders in patients with PCOS but also to screen PCOS in females of our population at an earlier age. Those patients must be advised measures for healthier lifestyles besides adequacy of their medical treatment. Preferably there should be PCOS awareness campaigns for females at a community level, so as to educate them about the necessary details of PCOS, as well as for early screening of their metabolic and hormonal disorders.

LIMITATIONS

This was a cross-sectional study where limited number of patients were selected and there was no control group. A prospective cohort study will give a more in-depth view and knowledge of prediabetes risk factors and their association with other metabolic disorders in PCOS patients.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

AH: Conception and study design, acquisition of data, Manuscript writing, approval of the final version to be published

SSA: Conception and study design, analysis and interpretation of data, critical review, approval of the final version to be published

IA: Conception, acquisition of data, critical review, approval of the final version to be published

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Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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DATA SHARING STATEMENT

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