Assessment of Quality of Life and Therapeutic Outcomes of Metformin, Pioglitazone with Myoinositol and Ethinylestradiol Cyproterone in Ethnic Pakistani Women with Polycystic Ovary Syndrome

Khan A* and Shahid A

Department of Pharmacy, Quaid-I-Azam University, Islamabad, Pakistan

*Corresponding author: Khan A

Department of Pharmacy, Quaid-i-Azam University, Islamabad, Pakistan

✉ akhan@qau.edu.pk

Tel: +92-51 9064-4181

Abstract

Background: Only a few studies are available on improvement in quality of life after reviewing treatment in Polycystic Ovary Syndrome (PCOS) patients and no study was found in ethnic Pakistani women. This study was aimed to compare the outcomes of metformin, pioglitazone and ethinylestradiol cyproterone as changes in Quality of Life (QoL), clinical features, and adverse drug reactions, in patients suffering from PCOS.

Methods: This observational study was carried out at 4 public and private sector infertility centers in Islamabad. Patients aged 18-43 yrs, as per Rotterdam criteria diagnosed as PCOS were included in the study. Chi-PCOSQ as a measure of HRQoL. Patients were stratified according to BMI, infertility and family history of diabetes mellitus to further analyze features of these groups. Paired-t-test and regression analysis was applied to study changes in patient's quality of life after 3 months of treatments given.

Findings: We recruited 160 patients (20.6% obese, 61.2% infertile, and 46.2% patient's presents with family diabetes history). Mean score of Chi-PCOSQ was 98.4 ± 24.2 with lowest in infertility (10.3 ± 7.9) domain. Metformin improved hair loss (p=0.015), pelvic pain (0.007), oligo menorrhea (p=0.001) and in Chi-PCOSQ depression domain score (p=0.002). Whereas pioglitazone improved acne (p=0.01), oligo menorrhea (p=0.031) and depression domain score (p=0.013). Ethinylestradiol cyproterone improved acne (p=0.003), menorrhagia (p=0.01) symptoms and in Chi-PCOSQ menstrual, acne and hair loss domain score (p=0.004 & p=0.001, respectively). A few of the patients also reported adverse drug reactions e.g. Ethinylestraiol cyproterone and metformin resulted in gastrointestinal upset in 21.4% and 11.5% patients, respectively.

Conclusion: Given drugs improved patients, clinical features and HRQoL while no drug significantly improved patient's hirsutism related problems. PCOS adversely affects patient's QOL and there was variation in clinical features from patient to patient. So, PCOS must be treated with drugs specifically considering their clinical features.

Keywords: Polycystic ovary syndrome; Quality of life; Pakistani; Metformin; Pioglitazone; Ethinylestradiol cyproterone

Abbreviations:

Chi-PCOSQ: Chinese version of health-related Quality-of-Life Questionnaire for women with Polycystic Ovary Syndrome; HRQoL: Health Related Quality of Life; PCOS: Polycystic Ovary Syndrome; PCOSQ: Health-related Quality-of-Life Questionnaire for women with Polycystic Ovary.

Background

According to World Health Organization (WHO) health is defined as, "A state of complete physical, mental, and social well-being not merely the absence of disease" [1]. Health cannot be measured only on the basis of changes in severity and frequency of disease symptoms and number of life savings it must be defined using properly designed tools i.e. Health Related Quality of Life (HRQoL) [2]. HRQoL in general point of view is an individual's or a group's perceived physical and mental health over time. Therefore nowadays, improvement in patient's quality of life is ultimate goal of healthcare professionals [3]. Specifically, in the case of chronic diseases HRQoL can give us

best idea about patient satisfaction and health status. It is also a best measure when we have to compare various treatment plans having similar impacts on patients life expectancy [4,5]. This study was aimed to compare the outcomes of metformin, pioglitazone with myoinositol and ethinylestradiol cyproterone, in terms of changes in clinical features and HRQoL of PCOS patients with different drugs. As stated by U.S.FDA guidance for industry, HRQoL is a measure to assess outcome of treatment. By using disease specific HRQoL tools we can estimate extent of improvement in disease symptoms [4].

One of most common endocrine-metabolic disorders in reproductive aged women is Polycystic Ovary Syndrome (PCOS). PCOS being a syndrome is frustrating and complex disorder [6,7]. Its prevalence is up to 26% worldwide, which varies with ethnicity and genetics in presentation of clinical features [7-10]. Mainly, PCOS can be defined as imbalance of hormones [10]. Firstly, in 1935 Stein and Leventhal reported a link between polycystic ovaries, oligomenorrhea and hirsutism [11]. After that different diagnostic criteria's reported including NIH/NICHD (National Institute of Health/National Institute of Child Health and Human Development), Rotterdam criteria and androgen excess society criteria [12,13]. These criteria's vary in phenotypes i.e. 1) Hyperandrogenism+oligo-anovulation+polycystic ovaries; 2) Hyperandrogenism+oligo-anovulation; 3) Hyperandrogenism+polycystic ovaries; and 4) Oligo-anovulation+polycystic ovaries without hyperandrogenism. However, in 2012 NIH recommended Rotterdam criteria as it includes all the phenotypes [14]. PCOS patients presents with different characteristics which can be, metabolic (obesity, insulin resistance, and diabetes), endocrinological (oligo/amenorrhea, hirsutism, acne, hair loss, infertility and darkened skin) and emotional derangements [12-14]. It is also associated with co-morbidities like diabetes mellitus, heart diseases, epilepsy, dyslipidemia etc. [14]. Treatment of PCOS depends on clinical features and complexity of disease. It starts from lifestyle modification (e.g. Atkins diet) to drugs (for example, clomiphene citrate, insulin sensitizing agents, oral contraceptives) and surgical procedures (laparoscopic drilling) depending upon the characteristics presented at the time of diagnosis [15-17].

Due to variation in presentation of symptoms and broad pathogenesis (genetics, ethnicity, environmental factors, insulin resistance, endocrine factors) [18-20] there are a myriad of treatment options. However, there is lack of research on effect of different treatment on patients QOL and moreover characteristics of PCOS patients and no such study is available in Pakistan. As, PCOS clinical features varies with culture and ethnicity. Therefore, treatment outcomes may also vary with ethnicity difference. As, Caucasians have more prevalence of hirsutism and obesity than Chinese women [21]. Therefore, due to eminent differences in genetics lifestyle and culture, it is important to assess the demographics and quality of life of Pakistani women.
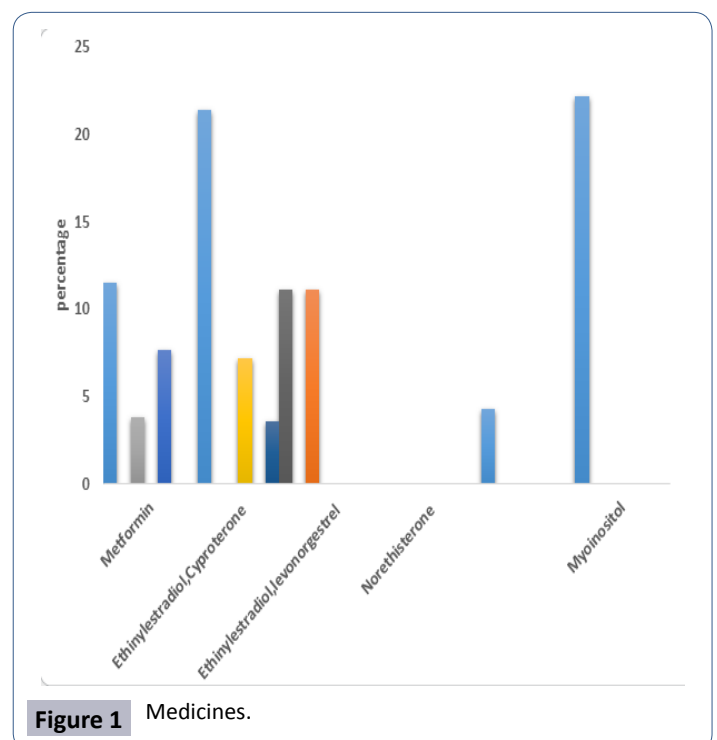
Methodology

It is a prospective, observational study. Study permission was taken from ethical and scientific research board of Quaid-i-

Azam University, Islamabad (BEC-FBS-QAU-111) and respective hospitals and infertility clinics. Schematic representation of methodology **(Figures 1 and 2)**.

Participants

We recruited 160 PCOS patients out of which we got follow-up of only 120 patients. The reason of not getting follow-up was patients started IVF/ICSI (*In-vitro* Fertilization/Intracytoplasmic Sperm Injection) protocols, switched the medicine, didn't come back for follow-up, had more than 12 ARMS (Adherence to Refills and Medication) score etc. Inclusion criteria for study was: Patients (1) aged between 18-43 yrs, (2) diagnosed with PCOS as per the Rotterdam criteria (existence of any 2 of the following): (i) oligo-anovulation (a cycle length of >35 days or amenorrhea), (ii) clinical hyperandrogenism (hirsutism recorded as m-FG score of ≥ 6 with/without acne or androgenic alopecia) and (iii) Polycystic Ovaries (PCO) on ultrasound, (3) on metformin, pioglitazone with myoinositol and ethinylestradiol cyproterone treatment were included in the study. Patients with hypothyroidism, hyper-prolactinemia, renal (adrenal insufficiency) or history of laparoscopy and IVF/ICSI before starting study were excluded from the study. All participated patient gave an informed consent for their willingness to participate in the study. The questionnaires were filled *via* face-to-face interview with each participant at the time of their first visit and after 3 months of treatment. All participants completed all study questionnaires and demographic questions on age, highest education, occupation, marital status, disease duration, comorbidities, exercise behavior, family history and clinical features. Patients were assessed for BMI, PCOS-specific clinical features at each visit.

After diagnosis of PCOS, metformin was being administered 500 mg TID for three months, ethinylestradiol 0.035 mg OD for three months and pioglitazone 45 mg OD for 3 months.
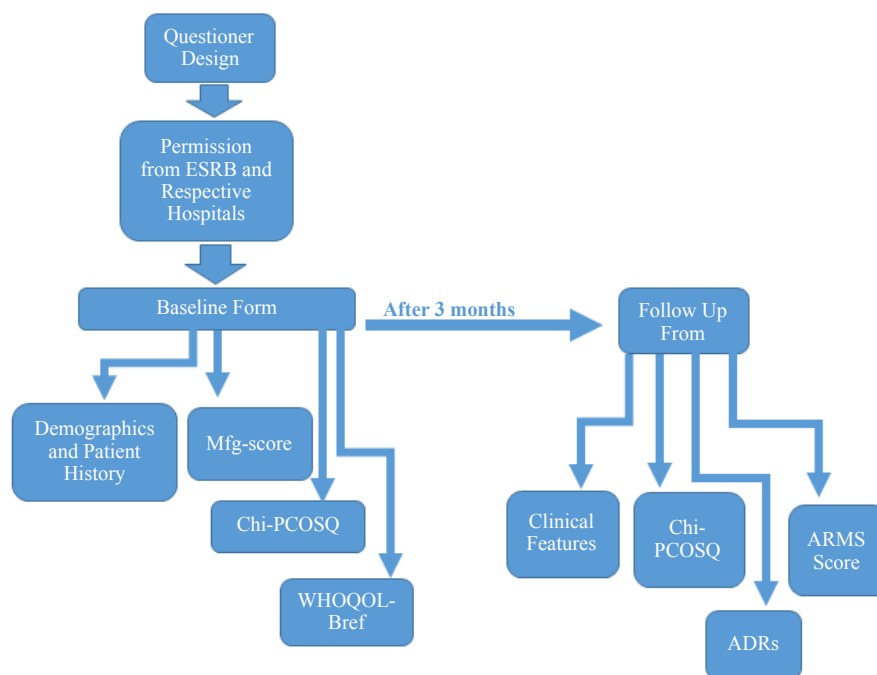

Figure 1 Medicines.

Figure 2 Schematic representation of methodology.

Abbreviation: Mfg-score: Modified ferrimen-gallway score; Chi-PCOSQ: Chinese version of PCOSQ; WHOQOL-Bref: WHO Quality of Life questioner brief version; ARMS: Adherence to Refills and Medication Score.

Study measurements

BMI was calculated by using weight to height ratio and categorized as ≤ 25, >25 and >30 kg/m^2 representing normal weight, overweight and obese patients, respectively. Permission for pre validated questioners was obtained from all respective researchers. Ferriman Gallway score was used to evaluate hirsutism [22]. PCOSQ is a disease specific questioner and it was used to assess quality of life of women with PCOS and improvement in quality of life. Chi-PCOSQ is Chinese version of PCOSQ with additional acne and hair loss domain. It consists of 30 questions with 7 no. scale i.e. 1 for maximum impairment and 7 for no impairment. It consists of 6 domains: emotions (7 items), hair growth (5 items), body weight (5 items), infertility (5 items), menstruation (4 items) and hair loss and acne (4 items) [23]. Its validity score was reliable and showed validity in Chinese women suffering from PCOS.

Patient's adherence to medications assessed by using Adherence to Refills and Medication (ARMS) Scale. It was a 7 question scale with score of 1 for full adherence and 4 for non- adherence. We included patients with less than 12 ARMS scale score and all others were excluded from the study. This scale was validated in 435 chronic disease patients in which it shows Cronbach's α=0.814 and when correlated with Mo risky scale it gives Spearman's rho= -0.651, p <0.01, and it correlated more strongly with measures of adherence than the Mo risky scale [24].

Statistical analysis

Descriptive analysis was done to analyze the demographics data of the study sample and ANOVA and t-test were used to measure relation between different variables and stratified groups. Similarly, by using ANOVA we did comparison of frequency measures of different clinical features and QOL measures with drugs. Study patients were stratified by BMI (Body Mass Index: overweight *vs.* normal), infertility and family history of diabetes mellitus. Outcome of treatments after 3 months was assessed by chi-square and paired-t tests. The IBM SPSS 22.0 was utilized for all above mentioned analyses.

Results

Total 160 women meeting the inclusion criteria were included in the study. Out of these after 3 months 120 patients meet criteria for follow-up. Majority of patients were 25.4 ± 6.0 yrs old; 20.6% were obese, 61.2% infertile, and 46.2% patient's presents with family diabetes history. Most of married patients were obese and overweight. Overweight patients BMI was significantly more than normal weight patients. Patients with family history of DM have significantly more BMI (28.2 ± 5.5) as compared to patients with no family DM history. Whereas overweight patients were married from longer duration than normal weight patients.

Majority of patients were not doing exercise. PCOS patients suffer from many co-morbidities while, in our data most of patients have history of hypotension (23.1%) and 14.4 % infertile patients had history of miscarriage. PCOS patients have many clinical features i.e. hirsutism 28.8%, oligomenorrhea (70.6%), menorrhagia (7.5%), acne (45.6%) and hair loss (58.8%). While in comparison of groups, more no. of overweight patients have hirsutism as compared to normal weight. The details of demographics and patient characteristics are given in **Table 1** as demographics and baseline findings of PCOS patients.

Table 1 Demographics and baseline findings of PCOS patients.

Characteristics	Subgroups					
	Normal Weight	Overweight	Obese	Infertility	Family history of Diabetes Mellitus	
BMI	All (n=160)	(BMI <25 kg/m²)	(BMI 25-30 kg/m²)	(BMI ≥ 30 kg/m²)	(n=98)	(n=74)
N Value		(n=61)	(n = 66)	(n = 33)		
Mean	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age	25.4 ± 6.0	22.6 ± 4.6	26.3 ± 5.4	28.7 ± 7.14	27.3 ± 5.9	26.6 ± 6.5
BMI	26.9 ± 5.2	22.1 ± 2.1	27 ± 1.5**	34.4±4.3	28.7 ± 5.1	28.2 ± 5.5*
mF-G score	5.2 ± 3.35	6.0 ± 3.8	5.0 ± 2.8	4.1 ± 3.1	4.6 ± 2.9	5.3 ± 3.3
Disease Duration (Year)	4.9 ± 4.7	3.0 ± 2.6	4.8 ± 4.4*	8.4 ± 6.3	6.4 ± 4.0	5.8 ± 5.25*
Marriage Duration (Year)	6.7 ± 5.1	5.0 ± 4.0	6.0 ± 4.1*	9.4 ± 6.4	6.5 ± 5.1	7.8 ± 5.2*
Mean	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Lab Findings						
FSH (mIU/mL)	5.3 ± 1.91	5.1 ± 2.1	5.3 ± 1.8	5.3 ± 1.5	5.3 ± 2.0	5.1 ± 1.7
LH (mIU/mL)	6.9 ± 3.84	7.3 ± 3.6	6.9 ± 4.1	6.2 ± 3.3	6.3 ± 3.9	6.4 ± 3.0
Prolactin (ng/mL)	17 ± 6.0	17.4 ± 5.4	16.2 ± 6.4	17.8 ± 6.0	17.1 ± 7.4	17.3 ± 5.8
TSH (µIU/mL)	1.9 ± 1.04	1.7 ± 0.6*	2.2 ± 1.4	2.0 ± 0.6	2.1 ± 1.2	2.1 ± 0.96
	n%	n%	n%	n%	n%	n%
Exercise						
No Exercise	97 (60.6)	36 (59.0)	40 (66.6)	21 (63.6)	59 (62.2)	48 (64.9)
5-10 Minutes	25 (15.6)	7 (11.5)	14 (21.2)	4 (12.1)	15 (15.3)	11 (14.9)
10-20 Minutes	19 (11.9)	9 (14.8)	5 (7.6)	5 (15.2)	11 (11.2)	8 (10.8)
20 Or More	19 (11.9)	9 (14.8)	7 (10.6)	3 (9.1)	13 (13.2)	7 (9.5)
Comorbidities n%						
Diabetes Mellitus	2 (1.3)	0 (0.0)	2 (3.0)	0 (0.0)	1 (1.0)	2 (2.7) 8 (10.8) 0 (0.0)
Hypertension	12 (7.5)	3 (4.9)	4 (6.10)	5 (15.2)	10 (10.2)	1 (1.4)
Dyslipidemia	2 (1.3)	0 (0.0)	0 (0.0)	2 (6.1)	2 (2.0)	9 (12.2)
Heart Disease	2 (1.3)	1 (1.6)	0 (0.0)	1 (3.0)	2 (2.0)	1 (1.4)
Emotional Depression	16 (10)	2 (3.3)	9 (13.6)	5 (15.2)	12 (12.2)	10 (13.5) 21 (28.4)
Endometriosis	3 (1.9)	0 (0.0)	2 (3.0)	1 (3.0)	3 (3.1)	1 (1.4)
Miscarriage History	16 (14.4)	3 (4.9)	10 (15.2)	3 (9.1)	11 (11.2)*	10 (13.5)
Hypotension	37 (23.1)	15 (24.6)	10 (15.2)	12 (36.4)	20 (20.4)	21 (28.4)
Clinical Features n%						
Hirsutism	46 (28.8)	22 (36.1)	20 (30.3)*	4 (12.1)	23 (23.5)	23 (31.1)
Pelvic Pain	73 (45.6)	26 (42.6)	30 (45.5)	17 (51.5)	45 (45.9)	30 (40.5)
Oligo Menorrhea	113 (70.6)	46 (75.4)	43 (65.2)	24 (72.7)	64 (65.3)	52 (70.3)
Menorrhegea	12 (7.5)	7 (11.5)	5 (7.6)	0 (0.0)	3 (3.1)	2 (2.7)
Acne	73 (45.6)	31 (50.8)	29 (43.9)	13 (39.4)	43 (43.9)	28 (37.8)*
Hair Loss	94 (58.8)	22 (36.1)	29 (43.9)	15 (45.5)	46 (46.9)	28 (37.8)
Darkened Skin	41 (25.6)	15 (24.6)	14 (21.2)	12 (36.4)	22 (22.4)	16 (21.6)
Ultrasound Findings n%						
Unilateral PCOS	41 (25.6)	22 (36.1)	13 (19.7)	6 (18.2)	27 (27.6)	18 (24.3)
Bilateral PCOS	115 (71.9)	39 (63.9)	50 (75.8)	26 (78.8)	67 (68.4)	539 (71.6)

Abbreviations: BMI: Body Mass Index; BP: Blood Pressure; LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone; E2: Estradiol; PRL: Prolactin; TT: Total Testosterone; mF-G: Modified Ferriman-Gallwey; SD: Standard Deviation.
*p<0.05; **p<0.001.

Overall chi-PCOSq score was 98.4 ± 24.2 with the lowest score in infertility domain i.e. 10.3 ± 7.9 in weight domain. Within BMI categories obese and overweight patients respectively had low score in weight, infertility and total score as compared to normal weight patients with p=0.000. Infertile patients were having low emotions, infertility and total chi-PCOSq score as compared to fertile group with p=0.03, p=0.00, p=0.004, respectively. In patients with family diabetes history within weight domain chi-PCOSq score was significantly different as compared to patients with no family diabetes history i.e. p=0.027. All other details of chi-PCOSq score of PCOS patients are given in **Table 2** as Baseline HRQoL scores of PCOS patients.

Average ARMS score of patients included in follow-up study was 7.56 ± 1.14 and we included patients with more than 12 ARMS score in study. Metformin significantly reduced acne, oligomenorrhea, infertility and BMI with p=0.002, 0.001, 0.004 and 0.000 respectively. It improved weight, menstrual, acne and

Table 2 Baseline HRQoL scores of PCOS patients.

Characteristics Chi-PCOSq	Groups					
	All (N=160)	Normal Weight	Overweight	Obese	Infertility	Family history of Diabetes Mellitus
		(BMI <25 kg/m²)	(BMI 25-30 kg/m²)	(BMI ≥30 kg/m²)	__	__
		(n=61)	(n = 66)	(n = 33)	(n=98)	(n=74)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Total score (30-210)	98.4 ± 24.2	109.6 ± 22.7	92.2 ± 22.5**	90 ± 22.4	90.4 ± 22.3*	100.9 ± 24.0
Weight domain (5-35)	14.3 ± 10.5	21.5 ± 12.1	10.8 ± 6.2**	7.9 ± 4.7*	12.0 ± 8.2*	12.3 ± 9.1*
Body hair domain (5-35)	19.0 ± 8.5	19.6 ± 8.7	17.7 ± 7.8	20.4 ± 9.5	18.3 ± 8.4	18.8 ± 8.2
Infertility domain (5-35)	10.3 ± 7.9	14.4 ± 7.9	8.0 ± 6.7**	7.4 ± 6.9	4.9 ± 3.4**	9.6 ± 7.74
Menstrual domain (4-28)	15.7 ± 6.0	14.7 ± 5.4	16.2 ± 6.4	16.5 ± 6.2	16.8 ± 6.4	15.6 ± 6.4
Emotions domain (7-49)	22.4 ± 6.2	23.3 ± 5.4	22.6 ± 6.7	20.2 ± 6.1	21.3 ± 6.0	21.9 ± 6.6
Acne & Hair loss domain (4-28)	16.6 ± 6.7	16.0 ± 7.0	16.8 ± 6.9	17.4 ± 5.9	16.9 ± 6.9	17.1 ± 6.1

hair loss Chi-PCOSQ domain score with p=0.000 and emotions domain score with p=0.002.

While, in case of pioglitazone+myoinositol hair loss, acne, pelvic pain and oligomenorrhea symptoms were improved with p=0.001, 0.01, 0.007, 0.031 respectively. It improved weight, depression, menstrual, acne and hair loss, and total Chi-PCOSQ scores too. Ethinylestradiol cyproterone improved acne (p=0.006) and menorrhagia (p=0.010) symptoms. It also significantly improved emotions, menstrual, acne and hair loss domain scores with no effect on infertility and weight domains. Details of treatment versus clinical features and Chi-PCOSQ scores in visit 1 representing baseline data and visit 2 for follow-up data are represented in **Table 3** and regression analysis for treatment outcome is given in **Table 4**.

Changes in clinical features and HRQOL of PCOS patients with different treatments **(Table 3).**

Regression analysis for different treatment effects on PCOS-specific quality of life by using Chi-PCOSQ **(Table 4).**

Discussion

No research is available on quality of life and treatment outcomes in Pakistani women. In our study, we found that clinical features and depression due to PCOS led to reduction in QOL score. Proper treatment selection can lead to improvement in patient symptoms and HRQoL. HRQoL is nowadays measure of therapeutic outcomes. As, by our study metformin was more effective in reducing BMI and infertility. While, ethinylestradiol cyproterone was more effective in improving acne and menorrhagia symptoms significantly, with more serious menorrhagia side effects in some patients. Only, few studies [25-29] are available on HRQoL improvement after treatment and no one in Pakistani women.

In 2006, a study conducted in Germany declared that metformin can improve patients, acne, BMI, menstrual disturbances and emotional distress which significantly correlates with our findings [26]. Other studies have also shown that metformin can improve clinical signs of acne in PCOS patients [30,31], which strongly correlates our findings where patients improved acne and HRQOL score too. A study reported that metformin increases ovulation rate leading to improvement in infertility rate. Studies conducted on metformin and troglitazone supports that these drugs can alleviate infertility issues of PCOS patients and improve pregnancy rate while in our study no significant values were observed [32,33]. Another study provides evidence that metformin only is not sufficient to counter PCOS symptoms so, it should be managed with lifestyle modifications [21]. Another study presents that 72.16% possess oligomenorrhea symptoms and most of infertile patients presents with this symptom which strongly correlates our findings according to which 65.3% patients with infertility have oligomenorrhea [10] and it was significantly improved by pioglitazone and ethinylestradiol cyproterone. Another study shows that 30% of women with PCOS will have normal menstruation [34]. Hirsutism presentation was reported in a study was about in 70% of women with PCOS [35]. However, in our study only 28.8% patients were presenting hirsutism clinical features. This can be due to PCOS clinical presentation differences among different ethnic groups. While, another study reported that 52% had clinical evidence of cutaneous hyperandrogenism and/or oligomenorrhea [36].

In a study about oral contraceptives impact on PCOS patient's QoL in 2012, it was reported that oral contraceptives improved emotions and hirsutism domain score. While in our study, emotions domain score was improved significantly, with no effect on hirsutism [25].

As reported in many studies, our study also revealed that ultrasound is one of significant measure in diagnosis [37-45]. Gastrointestinal disturbances due to vitamin B12 malabsorption are one of most common adverse drug reaction of metformin [46-52]. While, in our study 11.5% patients on metformin show GIT related adverse reactions with other symptoms like hypoglycemia and increased urine frequency in few patients.

Importance of study findings to clinicians and patient care

High prevalence of PCOS and variation in prevalence of symptoms presentation in ethnic Pakistani women requires specific research in Pakistan. HRQOL being one of the latest health assessment tools in modern days would be the best measure to assess disease burden and treatment outcomes. As we included multiple drugs in our study. Hence, it can be a baseline study to give an idea to

Table 3 Changes in clinical features and HRQOL of PCOS patients with different treatments.

Characteristics	Metformin n=40	pioglitazone+myoinositol n=38	Ethinylestradiol cyproterone n=42
Hirsutism n%			
(visit 1)	17 (42.5)	8 (21.0)	18 (42.8)
(visit 2)	17 (42.5)	8 (21.0)	18 (42.8)
Hair loss			
(visit 1)	34 (85.0)	28 (73.6)	39 (92.8)
(visit 2)	29 (72.5)	23 (60.5)**	28 (66.6)
Acne			
(visit 1)	23 (54.7)	8 (21.0)	27 (64.3)
(visit 2)	11 (27.5)**	5 (13.1)**	13 (35.1)*
Pelvic pain			
(visit 1)	12 (30.8)	12 (31.5)	22 (52.3)
(visit 2)	12 (30.8)	7 (18.4)**	9 (21.4)
Oligomenorrhea			
(visit 1)	32 (80.0)**	17 (43.5)	29 (92.8)
(visit 2)	23 (57.5)	7 (18.4)*	4 (9.5)
Menorrhegea			
(visit 1)	3 (7.5)	1 (4.3)	4 (11.9)
(visit 2)	0 (0.0)	1 (4.3)	3 (7.1)*
Infertility			
(visit 1)	17 (42.3)	38 (100.0)	9 (75.0)
(visit 2)	17 (42.3)	31 (80.7)	9 (75.0)
Darkened skin			
(visit 1)	13 (34.6)	5 (13.0)	9 (21.4)
(visit 2)	4 (11.5)	0 (0.0)	9 (21.4)
	Mean ± SD	Mean ± SD	Mean ± SD
BMI			
(visit 1)	26.5 ± 3.8	29.8 ± 5.0	24.1 ± 3.9
(visit 2)	25.9± 3.9*	28.6 ± 3.9	24.6 ± 4.8
Mfg_score			
(visit 1)	5.4 ± 3.4	4.8 ± 2.3	6.1 ± 2.8
(visit 2)	5.6 ± 3.7	4.8 ± 2.9	6.5 ± 3.1
Weight domain (5-35)			
(visit 1)	8.6 ± 4.8	10.0 ± 4.5	21.0 ± 12.1
(visit 2)	12.2 ± 5.9**	13.7 ± 4.4*	21.8 ± 11.9
Body hair domain (5-35)			
(visit 1)	19.9 ± 8.1	19.6 ± 7.7	16.5 ± 8.0
(visit 2)	19.9 ± 8.1	20.5 ± 8.2	18.3 ± 8.0
Infertility domain (5-35)			
(visit 1)	12.3 ± 8.1	3.8 ± 1.2	16.0 ± 7.2
(visit 2)	13.4 ± 8.4	4.9 ± 4.3	15.7 ± 7.6
Menstrual domain (4-28)			
(visit 1)	14.3 ± 6.1	19.9 ± 5.3	13.0 ± 5.0
(visit 2)	17.8 ± 6.8**	24.7 ± 4.0*	22.1 (4.7)*
Emotions domain (7-49)			
(visit 1)	24.1 ± 8.1	21.6 ± 6.9	22.7 ± 4.4
(visit 2)	26.8 ± 8.3**	25.0 ± 8.5*	31.7 ± 7.1*
Acne & Hair loss domain (4-28)			
(visit 1)	15.5 ± 7.2	19.2 ± 6.2	14.8 ± 5.3
(visit 2)	19.8 ± 6.2**	22.4 ± 5.0*	21.1 ± 4.0*
Total chi_PCOSq score (30-210)			
(visit 1)	94.8 ± 28.4	94.1 ± 17.5	104.1 ± 26.6
(visit 2)	109.7 ± 27.9	111.3 ± 20.4*	130.7 ± 30.9

Note Visit 1 is 1st hospital visit of PCOS diagnosed patients represented as baseline. Visit 2 represents the follow-up after taking 3 months treatment. The analysis was adjusted for the effect of medication adherence by using ARMS (Adherence to Refills and Medication Scale).

Abbreviation: HRQoL: Health Related Quality of life.

Table 4 Regression analysis for different treatment effects on PCOS-specific quality of life by using Chi-PCOSQ.

Chi-PCOSq	Drugs		
	Metformin	**Pioglitazone+myoinositol**	**Ethinylestradiol cyproterone**
	Coefficient (SE)	**Coefficient (SE)**	**Coefficient (SE)**
Total score			
Visit 2 (reference=visit 1)	0.86 (0.09)*	0.81 (0.18)**	0.93 (0.09)**
Weight domain			
Visit 2 (reference=visit 1)	0.91 (0.15)**	0.69 (0.09)**	0.94 (0.05)**
Infertility domain			
Visit 2 (reference=visit 1)	0.84 (0.12)**	1.73 (0.64)*	1.01 (0.02)**
Menstrual domain			
Visit 2 (reference=visit 1)	0.93 (0.14)	0.35 (0.13)*	0.50 (0.16)**
Emotions domain			
Visit 2 (reference=visit 1)	0.70 (0.15)**	0.83 (0.19)**	0.25 (0.24)
Body hair domain			
Visit 2 (reference=visit 1)	0.92 (0.07)**	0.99 (0.096)	0.84 (0.09)**
Acne and hair loss domain			
Visit 2 (reference=visit 1)	0.76 (0.08)**	0.67 (0.09)**	0.35 (0.09)**

*$p < 0.05$; **$p < 0.005$

healthcare professionals to treat clinical signs specific treatment selection.

Limitations of study

Firstly, it was an observational study not a clinical trial. Secondly, HRQOL questioners were filled by patients so, self-reporting bias will definitely be there. Thirdly, in Pakistan treatment in all centers was prescribed for 3 months only so, we didn't observe changes in hirsutism features of PCOS patients, as it requires a treatment of at least 6 months.

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Conclusion

This is the first study in Pakistan to assess PCOS patients HRQOL and treatment outcomes. Our, result can provide an important baseline data to further clinical associations and can pave a way to decisive guidelines for Pakistani PCOS patients. Further, studies on large scale are required to assess treatment outcomes and changes in HRQOL of PCOS patients.

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