



External Validation of PCOS Questionnaire in Assessing Quality of Life in Females with PCOS Based on Lifestyle Changes with Therapeutic Measures like OC Pills and Metformin

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Abstract

Background: The aim was to study the effect of metformin in a lifestyle modification program combined with oral contraceptive pills on quality of life parameters measured by PCOS questionnaire in women and validate PCOSQ.

Methodology: Total 50 willing patients with PCOS participated in this hospital based single centered pilot study. Patients had to rate the symptoms given in questionnaire concerning health and health related issues on a scale of 1-7. Random selection for treatment with OC pills with or without Metformin was made. Post treatment analysis of their quality of life was done with the same questionnaire and data was analyzed by SPSS statistical software.

Result: The patients taking metformin along with OC Pills showed significant improvement in menstrual irregularities, hirsutism and the psychological distress related to it. Neither the symptoms related to being overweight was improved significantly nor the Psychological and emotional conditions regarding the symptoms. Similar results were obtained when we compared pre and post therapy scores in patients taking placebo in place of metformin.

Conclusion: This study validated the PCOS questionnaire in Indian population which can be considered first of its kind. This can give us an objective method of response assessment in patients with PCOS and also showed no significant additional effect of metformin on improvement of symptoms in patients with PCOS, which could be secondary to either small sample size or short duration of action.

Keywords: Metformin, PCOS, hirsutism, acne, HRQL, Health-related quality of life, Overweight.

Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common reproductive endocrinological

disorders affecting about 6-8% of women in their reproductive years¹. Although there are limited studies in India, recently few studies reported

prevalence of PCOS ranging from 9.13% to 36% among adolescents². PCOS is a heterogeneous condition with varied signs and symptoms that include amenorrhoea, oligomenorrhoea, hirsutism, obesity, subfertility, anovulation and acne. Any of these symptoms can significantly affect the female's quality of life³. The greatest negative influences on quality of life were associated with hirsutism (especially under the age of 25 years old), being overweight, and infertility concerns (over age 25)⁴. Usually signs and symptoms of the disorder appear at puberty, however it may not be diagnosed until adulthood in some.⁵ PCOS accounts for 95% of cases of hyperandrogenism, 20% of all cases of amenorrhea and up to 75% of all cases of anovulatory infertility⁶. The treatment of PCOS proves to be effective if it can reduce the burden of these symptoms as well as the associated psychological distress and thus improve health-related quality of life (HRQL). It is found that mostly PCOS is the endocrine disorder in reproductive-aged women⁷. There are several clinical presentations associated with PCOS, such as hirsutism, acne, overweight/obesity, hair loss/ androgenic alopecia, oligomenorrhea, amenorrhea and infertility and can lead to mood disturbances, affect the emotional wellbeing as well as sexual satisfaction of women, and cause a reduction in the HRQoL of patients^{8,9}. Obesity, clinical signs of hyperandrogenism (i.e., acne, hair loss), and infertility are the main contributors to psychological morbidity¹⁰⁻¹². The HRQoL of women with PCOS has been investigated in several studies for some countries^{8,13,14}; however, data on the HRQL of Indian women with PCOS is limited. It has been recognized that clinical representations of PCOS vary with culture and ethnicity¹⁵, and may thus have different impacts on HRQL. For example, the prevalence of hirsutism and obesity in Chinese women with PCOS appears to be lower than that from Caucasians patients¹⁵; contrarily, acne and hair loss were common problems reported in ethnic Chinese women with PCOS¹⁶. Therefore, assessing the impact of PCOS on the HRQL of

patients across ethnic groups is important. Metformin, which increases insulin sensitivity, is one of common treatments for PCOS in Taiwan. Some studies showed that metformin decreases the body weight and improves insulin sensitivity, acne, hirsutism, and menstrual cycle of women with PCOS, and that the effects of metformin may vary depending on a patient's characteristics (i.e., obesity, hyperandrogenism)¹⁷⁻²⁰. However, other research found that, among obese women with PCOS, metformin may not lower body weight or improve the menstrual cycle and weight loss alone through lifestyle modifications improves menstrual function²¹. Of notice, previous research primarily focused on clinical effectiveness of metformin^{17,21}, but only a few studies^{8,22} have determined whether the amelioration of the clinical signs of PCOS achieved by treatment leads to improvement in the HRQL of patients. Till date, no study has been done among the Indian population regarding effects on psychological or emotional well-being after therapeutic interventions. There is paucity of data regarding the role of lifestyle modification and therapeutic interventions in emotional well-being of females with PCOS. An examination of the effect of treatment on quality of life in this, could provide additional insight into the appropriate treatment course. The PCOS questionnaire, validated for its use as a reliable instrument for measuring the HRQL in women with PCOS, requires an external validation due to ethnic variation in PCOS and lower BMI cut off in Indian women. So we are investigating the quality of life factors in Indian women with PCOS using the PCOS Questionnaire (PCOSQ) during a randomized trial of metformin or placebo, with concurrent LSM and OC treatment in deciding the therapeutic intervention in Indian women with PCOS, which will help to individualize the treatment protocol.

Materials & Methods

Identification of patient population

The study was conducted after getting clearance from the institutional ethical committee. Total

number of subjects recruited was 50 with 25 subjects in each treatment arm. Medical students, nursing students and patients from the department with PCOS who were willing to participate were recruited. Written informed consent from the patients was obtained before recruiting them.

Type of study

It was a prospective hospital based single centered interventional trial with follow up period of 2 months.

Women with PCOS who met following criteria were included

1. Women of reproductive age group (Age: 18-45 yrs)
2. Hyperandrogenism, elevation of total testosterone, moderate to severe facial hirsutism and/ or terminal hair growth on upper chest, back and infraumbilical area
3. Menstrual irregularities-oligomenorrhoea: menses every 6 weeks -6 months Amenorrhoea DUB (dysfunctional uterine bleeding) with documented anovulation

Women with following criteria were excluded

- 1) Diagnosis of hyperprolactinemia, non classical -21 hydroxylase deficiency
- 2) Linguistic or cognitive difficulties preventing reliable completion of the questionnaire

The demographic profile of involved patients was collected before drug intervention.

This includes year of birth, marital status, educational qualification, BMI and duration of PCOS and the frequency of each parameter is provided (Fig 1- Fig 4, Table 1).

Height, weight and BMI of all the patients obese or non obese.

Method of Randomization

Sealed opaque random codes by block method

Method of Allocation Concealment

Sealed opaque envelopes were used for allocation of the randomization sequences, which was opened after consent. Patients included in this trial were given the questionnaire concerning health and health related issues. The PCOSQ developed by Cronin et al¹¹ for the assessment of health-related quality-of- life (HRQL) consists of five

domains, each relating to the common symptoms of PCOS-pattern of hair growth on face and body, emotions, infertility, menstrual problems and weight. Patients rated the symptoms on a scale of 1-7, in accordance with the PCOSQ with 7 being worst (symptoms all of the time) and 1 best (symptoms none of the time). Questions were self administered and given in their own vernacular language. The questionnaire was administered and supervised by a single principal investigator. Questions were compiled and assessment of the quality of life was done. Patients were randomly selected in either OC pills with or without Metformin. Placebo was supplied to the patients with OC pills without metformin by our registered pharmacy. Menstrual data and pill counts of the subjects were collected by personal visit to the hospital. A proper diet chart was provided to the subjects by the registered dietician of our institute. Patients were encouraged to exercise for 20- 30 minutes per day of moderate-to-intense physical activity. Post treatment analysis of their quality of life was done with similar questionnaire. Data was analyzed by SPSS statistical software .The differences in mean scores were compared between groups by unpaired t-test and differences in means between pre and post therapy scores in a single group were analyzed by using paired t-test.

Result

Out of 50 patients recruited, 2 patients from placebo group didn't turn up for follow up and one patient from metformin group excluded due to lack of compliance. When we compared the effect of OC pills with metformin/ placebo on the 47 patients enrolled for the study, total scores of PCOSQ improved across almost all the domains, suggesting significant improvement in quality of life after treatment. We also tried to compare the pre and post therapy improvement in scores of symptoms separately in two randomized groups. As per table 2, the patients taking metformin along with OC Pills showed significant improvement in menstrual irregularities. Presence of visible hair on chin, upper lips and the psychological distress related to it have also

improved significantly after metformin treatment (Table 2). However there is no significant improvement in the symptoms related to being overweight. Psychological and emotional conditions regarding the symptoms haven't changed significantly after the therapeutic intervention. Similar results were obtained when we compared pre and post therapy scores in patients taking placebo in place of metformin. This showed most of the symptoms got improved significantly after treatment (Table 3). However in both the groups the confounding factor being the OC pills, we tried to compare the post intervention symptom scores among both the groups

(Metformin and placebo) directly. This is to show whether there is any additional statistically significant effect of metformin on improvement on quality of life or not. On analysis, as in table 4, it showed there is no significant difference in post symptom score improvement in any of the symptoms after therapeutic intervention (Table 4)

Table 1 Duration of PCOS symptoms of the patients attending during the study period

Sl. No.	Duration of PCOS	Number of patients
1	Less than 1 yr	23
2	1-5 yrs	19
3	>5 years	8

Table 2 Statistical significance of the effect of OC pills with metformin on PCOS patients.

Sl. No.	SYMPTOMS	MEAN \pm SD BEFORE MEDICATION	MEAN \pm SD AFTER MEDICATION	P VALUE
1.	Growth of visible hair on chin	4.25 \pm 1.85	3.83 \pm 1.49	0.005
2.	Depressed as a result of having pcos	4.71 \pm 1.16	4.17 \pm 1.13	0.012
3.	Concerned about being overweight	4.50 \pm 1.72	4.04 \pm 1.52	0.036
4.	Easily tired	4.75 \pm 1.33	4.00 \pm 1.14	0.000
5.	Concerned with infertility problems	4.04 \pm 1.65	3.46 \pm 1.44	0.001
6.	Moody as a result of having pcos	4.29 \pm 1.43	3.79 \pm 1.25	0.007
7.	Headaches	3.88 \pm 1.42	3.63 \pm 1.35	0.083
8.	Irregular menstruation	4.96 \pm 1.46	3.83 \pm 1.31	0.001
9.	Growth of visible hair on upper lip	4.63 \pm 1.50	3.88 \pm 1.23	0.009
10.	Had trouble dealing with your weight	4.63 \pm 1.69	4.17 \pm 1.55	0.069
11.	Had low self esteem as a result of having your pcos	4.17 \pm 1.20	4.04 \pm 1.16	0.450
12.	Felt frustration in trying to lose weight	4.42 \pm 1.47	4.21 \pm 1.53	0.233
13.	Felt afraid of not being able to have children	3.88 \pm 1.78	3.38 \pm 1.58	0.015
14.	Felt frightened of getting cancer	3.21 \pm 1.44	3.04 \pm 1.04	0.405
15.	Growth of visible hair on your face	4.50 \pm 1.59	3.79 \pm 1.44	0.000
16.	Embarrassment about excessive body hair	4.04 \pm 1.46	3.38 \pm 1.31	0.000
17.	Worried about having pcos	4.71 \pm 1.20	4.04 \pm 1.23	0.000
18.	Self conscious as a result of having pcos	4.29 \pm 1.37	3.88 \pm 1.08	0.116
19.	Abdominal bloating	4.21 \pm 1.25	3.79 \pm 1.14	0.067
20.	Late menstrual periods	4.92 \pm 1.72	3.67 \pm 1.31	0.000
21.	Menstrual cramps	4.21 \pm 1.77	3.71 \pm 1.49	0.043
22.	Feel like you are not sexy because of being overweight	4.00 \pm 1.53	3.88 \pm 1.65	0.479
23.	Feel a lack of control over the situation with PCOS	4.17 \pm 1.46	4.00 \pm 1.32	0.382
24.	Have difficulties staying at your ideal weight	4.58 \pm 1.59	4.17 \pm 1.46	0.022
25.	Feel sad because of infertility problems	3.88 \pm 1.73	3.46 \pm 1.38	0.096
26.	Growth of visible body hair	4.38 \pm 1.66	4.00 \pm 1.18	0.119

Table 3 Statistical significance of the effect of OC pills with placebo on PCOS patients

Sl. No.	SYMPTOMS	MEAN \pm SD BEFORE MEDICATION	MEAN \pm SD AFTER MEDICATION	P VALUE
1.	Growth of visible hair on chin	3.65 \pm 1.50	3.26 \pm 1.32	0.004
2.	Depressed as a result of having PCOS	3.87 \pm 1.36	3.57 \pm 1.16	0.216
3.	Concerned about being overweight	4.35 \pm 1.58	3.78 \pm 1.38	0.000
4.	Easily tired	4.04 \pm 1.40	3.43 \pm 1.24	0.000
5.	Concerned with infertility problems	3.91 \pm 1.76	3.52 \pm 1.56	0.119

6.	Moody as a result of having PCOS	4.35±1.34	3.65±1.23	0.000
7.	Headaches	3.74±1.21	3.48±1.16	0.186
8.	Irregular menstruation	5.13±1.10	3.91±1.56	0.000
9.	Growth of visible hair on upper lip	4.26±1.48	3.61±1.47	0.013
10.	Had trouble dealing with your weight	4.17±1.56	3.70±1.33	0.024
11.	Had low self esteem as a result of having your PCOS	3.87±1.58	3.52±1.34	0.029
12.	Felt frustration in trying to loose weight	4.04±1.49	3.57±1.41	0.018
13.	Felt afraid of not being able to have children	3.87±1.66	3.22±1.41	0.001
14.	Felt frightened of getting cancer	3.57±1.38	3.17±1.19	0.095
15.	Growth of visible hair on your face	4.04±1.49	3.13±1.14	0.000
16.	Embarrassment about excessive body hair	3.74±1.48	3.09±1.12	0.025
17.	Worried about having PCOS	4.13±1.10	3.39±1.12	0.000
18.	Self conscious as a result of having PCOS	4.17±1.15	3.52±1.12	0.001
19.	Abdominal bloating	3.70±1.55	3.17±1.15	0.056
20.	Late menstrual periods	4.74±1.10	3.87±1.29	0.004
21.	Menstrual cramps	3.87±1.55	3.35±1.19	0.004
22.	Feel like you are not sexy because of being overweight	3.74±1.36	3.35±1.37	0.165
23.	Feel a lack of control over the situation with PCOS	4.13±1.46	3.48±1.12	0.006
24.	Have difficulties staying at your ideal weight	4.04±1.33	3.61±1.16	0.171
25.	Feel sad because of infertility problems	3.70±1.61	3.39±1.31	0.110
26.	Growth of visible body hair	4.23±1.45	3.39±1.34	0.003

Table 4 statistical analysis of the scores achieved in both the groups after therapeutic intervention

SI No.	SYMPTOMS	MEAN +SD OF GROUP A AFTER MEDICATION	MEAN +SD OF GROUP B AFTER MEDICATION	P VALUE
1.	Growth of visible hair on chin	3.83±1.49	3.26±1.32	0.178
2.	Depressed as a result of having pcos	4.17±1.13	3.57±1.16	0.178
3.	Concerned about being overweight	4.04±1.52	3.78±1.38	0.622
4.	Easily tired	4.00±1.14	3.43±1.24	0.137
5.	Corcerned with infertility problems	3.46±1.44	3.52±1.56	0.567
6.	Moody as a result of having pcos	3.79±1.25	3.65±1.23	0.665
7.	Headaches	3.63±1.35	3.48±1.16	0.714
8.	Irregular menstruation	3.83±1.31	3.91±1.56	0.528
9.	Growth of visible hair on upper lip	3.88±1.23	3.61±1.47	0.905
10.	Had trouble dealing with your weight	4.17±1.55	3.70±1.33	0.224
11.	Had low self esteem as a result of having your pcos	4.04±1.16	3.52±1.34	0.137
12.	Felt frustration in trying to loose weight	4.21±1.53	3.57±1.41	0.067
13.	Felt afraid of not being able to have children	3.38±1.58	3.22±1.41	0.866
14.	Felt frightened of getting cancer	3.04±1.04	3.17±1.19	0.765
15.	Growth of visible hair on your face	3.79±1.44	3.13±1.14	0.137
16.	Embarrassment about excessive body hair	3.38±1.31	3.09±1.12	0.504
17.	Worried about having pcos	4.04±1.23	3.39±1.12	0.085
18.	Self conscious as a result of having pcos	3.88±1.08	3.52±1.12	0.188
19.	Abdominal bloating	3.79±1.14	3.17±1.15	0.050
20.	Late menstrual periods	3.67±1.31	3.87±1.29	0.318
21.	Menstrual cramps	3.71±1.49	3.35±1.19	0.354
22.	Feel like you are not sexy because of being overweight	3.88±1.65	3.35±1.37	0.226
23.	Feel a lack of control over the situation with pcos	4.00±1.32	3.48±1.12	0.076
24.	Have difficulties staying at your ideal weight	4.17±1.46	3.61±1.16	0.090
25.	Feel sad because of infertility problems	3.46±1.38	3.39±1.31	0.096
26.	Growth of visible body hair	4.00±1.18	3.39±1.34	0.073

Note: P value ≤ 0.05 denotes significant effects and P value ≥ 0.05 denotes no significant effects

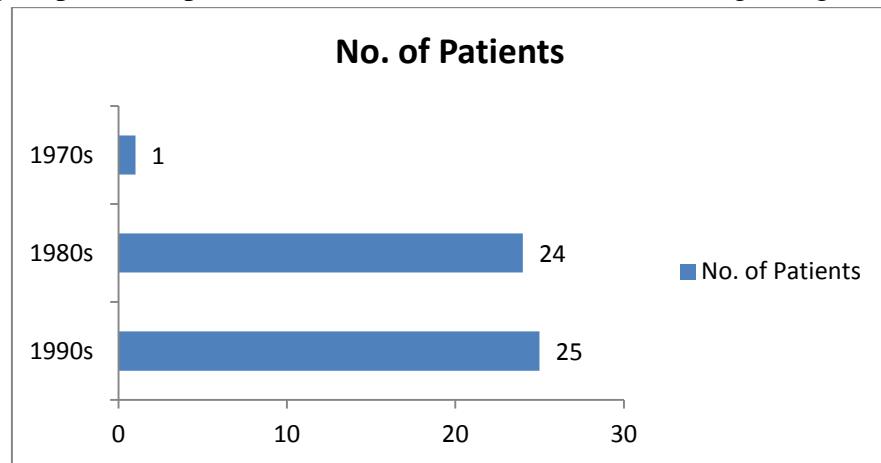
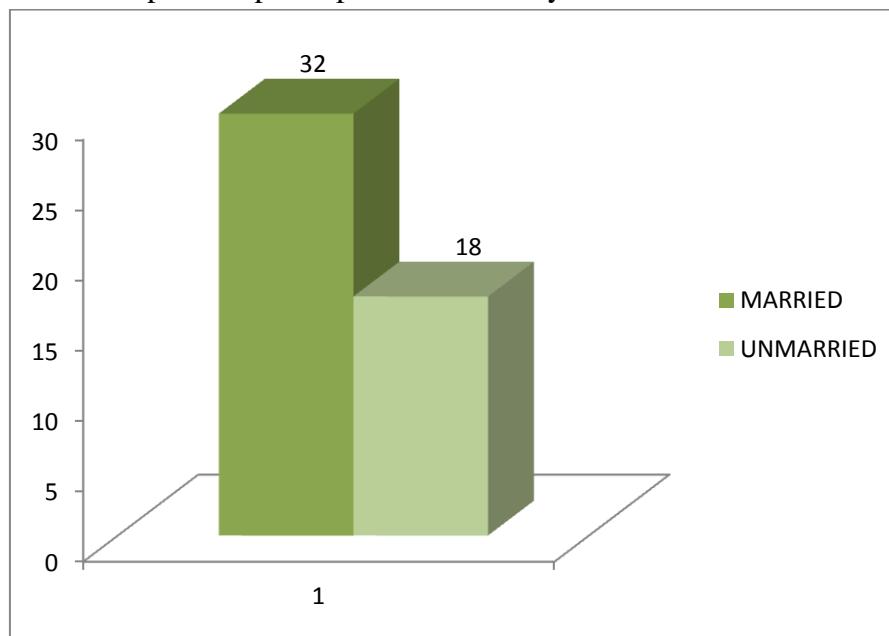
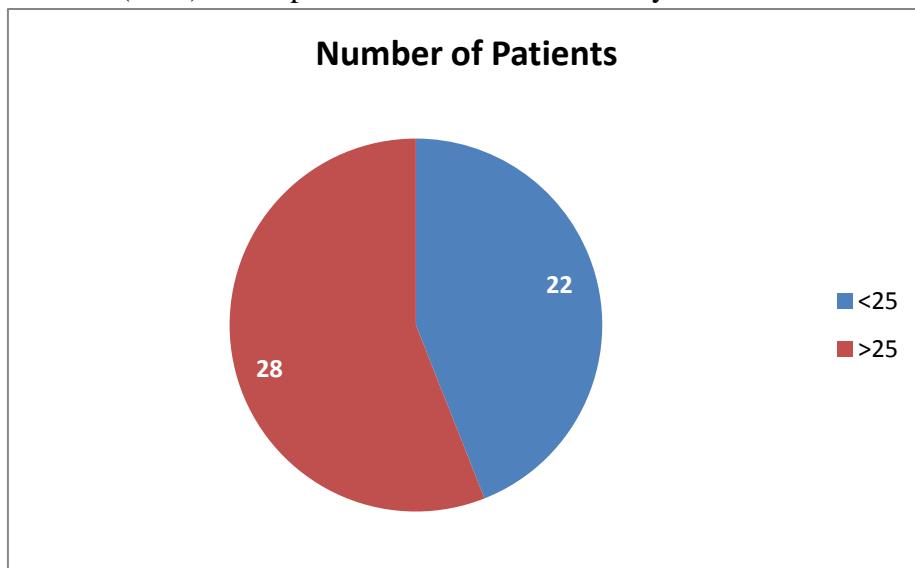
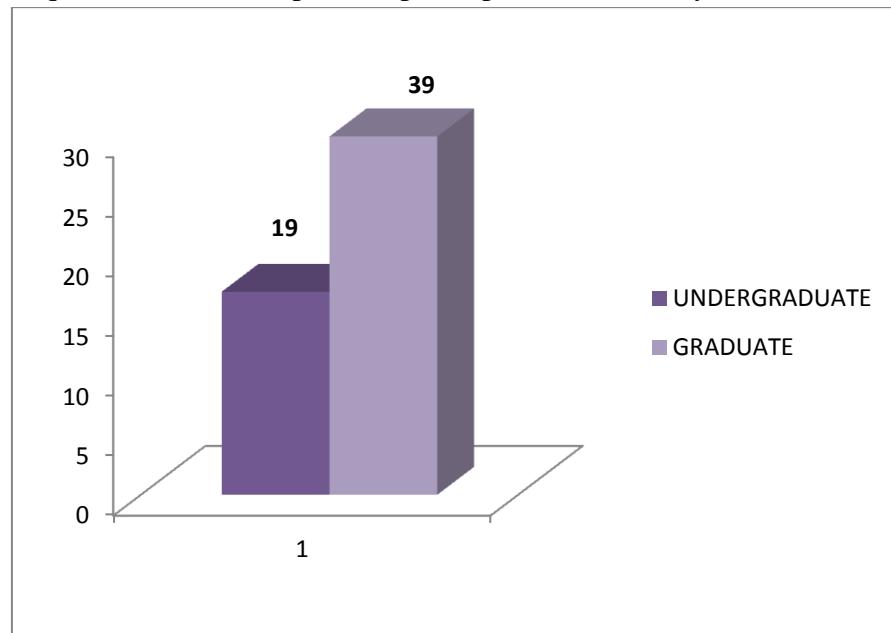
Figure 1 Demographic profile of patients with PCOS was recorded in the beginning of the trial**Figure 2** Marital status of the patients participated in the study**Figure 3** Body mass index (BMI) of the patients involved in the study

Figure 4 Educational qualification of the patients participated in the study

Discussion

The treatment of PCOS has been well established with OC pills^{5, 22}. The HRQL and emotional well-being improved significantly after metformin therapy in adult Women.²³ However interventions like life style modification, weight reduction have also shown to improve quality of life in many studies. As it is known that insulin resistance is commonly associated with PCOS, some physician tried to use metformin as a treatment option. Though, actual mechanism is not known, in some studies it showed to improve symptomatology in the patients^{24, 25}. But in a recent study, it is revealed that Metformin might improve health-related quality of life of polycystic ovary syndrome women by ameliorating psychological disturbances due to acne, hair loss and infertility problems, especially for overweight and hyperandrogenic patients²⁶. Previous research has supported that insulin sensitizers (e.g., metformin) provide fertility benefits to PCOS patients (i.e., improve pregnancy rate¹⁷, especially those with hyperinsulinemia or insulin resistance, which could be responsible for the abnormal ovarian response²⁷. Guyatt et al.'s study observed significant improvements in the infertility aspect of the PCOS-specific HRQoL (measured via PCOSQ) after 44 weeks of troglitazone treatment⁸. Troglitazone, an insulin sensitizer like

metformin, was previously used in PCOS. The present study also observed improved infertility aspect of PCOS-specific HRQoL, especially in hyperandrogenic patients. Thus, the amelioration of ovulation problems achieved by insulin sensitizers (i.e., troglitazone, metformin) may alleviate emotional distress due to infertility and thus contribute to the improvement of the HRQoL of PCOS patients. The infertility domain in Chi-PCOSQ consists of three items: "concerned about infertility problems", "afraid of not being able to have children", and "sad because of infertility problems". These items are associated with patient's psychological concerns about fertility. Although we did not find a significant increase in pregnancy rate in our reproductive-aged participants after treatment, however, patient's perceived benefits from metformin and reduced susceptibility to infertility after treatment²⁸ may lead to the improved fertility aspect of HRQoL. Metformin is recommended as one of treatment options in PCOS women, especially for those who present obesity, hyperandrogenism, insulin resistance or hyperinsulinemia¹⁹. Consistently, our results showed significant effects of metformin on HRQoL of PCOS patients, especially in overweight and hyperandrogenic patients. Also, insulin resistance is one of important characteristics for metformin efficacy²⁹. Our

previous study showed that with metformin treatment, overweight PCOS women ($BMI \geq 25 \text{ kg/m}^2$) had a significant reduction in body weight as compared to those with normal weight and patients with insulin resistance had a significantly improved 2-h insulin level as compared to those without insulin resistance²⁰. In the present study, we found that the prevalence of insulin resistance in the overweight group was higher than that in the normal weight group (85 versus 58 %). This may be another reason why positive effect of metformin on HRQoL outcomes was observed in overweight patients, but not in normal weight patients. Moreover, it has been argued that the combination of menstrual problems, hyperandrogenism and anovulation can be positively affected by metformin treatment¹⁹. This may explain our findings showing that metformin provided significant benefits in HRQoL outcomes for PCOS women with hyperandrogenism, especially in terms of mitigating the burden of acne and hair loss, and infertility associated psychological distress on the HRQoL of patients. But in our study we did not find statistically significant additional benefit of metformin in patients with PCOS taking OC pills alone, suggesting the former has only placebo effect. Another explanation in support of our finding could be the short duration of our study and metformin might need a longer duration to show its beneficial effect. As a part of our study we also tried to validate the PCOSQ in Indian population. This can be a quantification method for response assessment in these patients and can help to objectively evaluate the symptomatology of them. Either due to small sample size or short duration of metformin therapy, the present study does not show any statistically significant result, but we can plan to extrapolate the study to achieve the target sample size in the present trial.

Conclusion

This study validated the PCOS questionnaire in Indian population which can be considered first of its kind. This can give us an objective method of response assessment in patients with PCOS.

This pilot study also showed that there is no significant additional effect of metformin on improvement of symptoms in patients with PCOS, this could be secondary to either small sample size or short duration of action. For authentication of the drug metformin for improvement of the symptoms related to PCOS, sample size should be more (1000) and minimum 6 months of therapeutic intervention.

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