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Do anxiety and depression statuses differ in different polycystic ovary syndrome phenotypes?

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Background/aim: To evaluate psychological parameters and health quality profiles in women with reproductive polycystic ovary syndrome (PCOS) phenotypes and age matched controls.

Materials and methods: The study groups included 101 women with PCOS (54 with the National Institutes of Health [NIH] phenotype and 47 with the non-NIH phenotype) and 49 healthy female controls. The participants completed anxiety and depression scales and four quality of life domains.

Results: We identified the women with PCOS as having a 3.39 times increased risk for depression (subscale ≥ 7) and a 3.64 times increased risk for anxiety (subscale ≥ 10) compared to the controls. Both NIH and non-NIH phenotypes showed similar rates of depression (46.3% vs. 46.8%, respectively; P = 0.57) and anxiety (31.5% vs. 36.2%, respectively; P = 0.47). Regarding the quality of life scale, the women with NIH PCOS had significantly lower mental health scores compared to those with non-NIH PCOS (P = 0.03). Furthermore, while mental health scores were similar in the women with PCOS and the controls, physical health scores were significantly lower in the women with PCOS (P = 0.007).

Conclusion: Nearly half of the women with PCOS had higher depression scores and one third had higher anxiety scores. Thus, psychiatric evaluations appear necessary for PCOS patients in order to diagnose and treat clinical depression and anxiety.

Key words: Anxiety, depression, polycystic ovary syndrome, phenotype, quality of life

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-aged women, affecting 6–10% of women (1). The major reproductive features of PCOS include menstrual irregularity, anovulation, androgen excess symptoms, and infertility. However, many women with PCOS also have metabolic conditions including abdominal obesity, glucose intolerance, dyslipidemia, and elevated blood pressure. Furthermore, women with PCOS are at an increased risk for cardiovascular events. Recent studies have also indicated that women with PCOS have an increased prevalence for mood disorders (2). Especially symptoms such as hirsutism, acne, abdominal obesity, and subfertility might cause a reduction in self-esteem and sexual satisfaction and deterioration in quality of life (QoL). Although the exact etiology of the increased rate of mood disorders remains unknown, each of these factors might be speculated to cause emotional distress and psychological burden in young women with PCOS (3).

PCOS is a heterogeneous disease and, to date, several criteria had been introduced for its diagnosis. In 1990, PCOS was defined by the National Institutes of Health (NIH) criteria as requiring both the presence of menstrual irregularity and hyperandrogenism (4). In subsequent years, it was noted that women with PCOS might also present with a milder phenotype. Thus, the Rotterdam criteria were introduced in 2003, and now there are non-NIH phenotypes, such as normoandrogenic or ovulatory women with PCOS, who have also been included in the spectrum of this disease (5,6). In line with the recent guidelines, gynecologists and endocrinologists suggest the use of the Rotterdam criteria (1–7). Therefore, both women with mild phenotypes and those with the classic NIH phenotype are now evaluated together regarding reproductive, metabolic, and psychiatric problems.

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Previous studies have illustrated that women diagnosed with the NIH criteria had more cardiovascular risk factors compared to those with the non-NIH PCOS phenotypes (8–11). However, the association is not yet clarified as to whether the NIH and non-NIH phenotypes have similar risks regarding mood disorders and impaired QoL profiles (12). As far as we know, the most commonly reported psychiatric co-morbidity of PCOS women was depression and anxiety disorders. PCOS women presenting with these physical and psychiatric symptoms might also have impaired QoL profiles. Klimczak et al. also reported that, irrespective of phenotype, PCOS patients with high levels of androgens and lipids were at the increased risk for depression (13). PCOS patients presenting with hyperandrogenic symptoms might also have impaired QoL profiles.

Therefore, we aimed to assess the psychological parameters (depression and anxiety disorder) and QoL parameters in different phenotypes (NIH and non-NIH) of women with PCOS and healthy controls. The secondary aim was to analyze the impact of sociodemographic and reproductive features on depression in women with PCOS.

2. Materials and methods

2.1. Patients

This cross-sectional study was conducted in a specialized reproductive endocrinology clinic of a tertiary care center from January 2014 to July 2014. The study group included women aged 18–35 years who were newly diagnosed with PCOS (PCOS group). Patients for the control group were recruited from women who underwent routine gynecologic examinations during the same period (non-PCOS group). Women with other causes of hyperandrogenism such as congenital adrenal hyperplasia, Cushing syndrome and androgen producing tumor, diabetes mellitus, hypertension, thyroid dysfunction, history of psychiatric disease, and use of steroids, oral contraceptives, and other medications during the previous 3 months were excluded.

The hospital's local ethical committee approved this study and all participants gave their written informed consent prior to participation. All women who presented with the complaint of irregular menses or hirsutism had undergone the routine complete PCOS work-up. Participants who were confirmed to have PCOS according to the Rotterdam criteria were invited to participate in the trial. Women who were enrolled in the study were classified into two phenotypes by the two specialists (SA, FA) in this study. The two phenotypes included: 1) NIH phenotype: irregular cycles (O) and hyperandrogenism (H) with or without polycystic ovaries (P) (O + H + P and O + H); and 2) non-NIH phenotype: ovulatory phenotype with hyperandrogenism, polycystic ovaries, and regular cycles (H + P), or normoandrogenic phenotype: oligo-anovulation, polycystic ovaries, and normal androgen levels (O + P). Upon being accepted into this study, all women were asked to complete a data collection form to identify their sociodemographic and clinical features.

2.2. Clinical and biochemical assessments

All participants gave fasting venous blood samples in the early follicular period of the menstrual cycle. They were also analyzed for fasting glucose (FG), follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), prolactin (PRL), total testosterone (TT), and dehydroepiandrosterone acetate (DHEAS). All participants were weighed in the morning with light clothes and the body mass index (BMI) was calculated with the following formula: BMI = weight (kg)/height squared (m^2). Waist circumference (WC) was measured at the level of the midpoint between the lowest rib and the iliac crest.

2.3. Psychiatric assessment

The Hospital Anxiety and Depression Scale (HADS) is a reliable self-assessment scale specifically developed for detecting states of depression and anxiety in the setting of a hospital outpatient clinic. The scale comprises of 14 items consisting of HADS-A (anxiety, 7 questions) and HADS-D (depression, 7 questions) subscales. All items are rated on a four-point scale, from 0 to 3, resulting in maximum subscale scores of 21, with higher scores indicating greater levels of depression and anxiety. Aydemir et al. (14) previously established the validity and reliability of the Turkish version of this scale and determined cut-off points for the depression subscale and anxiety subscale as 7/8 and 10/11, respectively.

The World Health Organization Quality of Life (WHOQOL) - BREF is a shorter version of the original QoL questionnaire developed by the WHO. This scale has 26 items with a five-point Likert-type response for generic quality of life (QoL assessments with four broad domains, namely physical, mental, social relations, and environmental) (15,16). The instrument assesses satisfaction with life as well as the impact of disease or illness, and it captures positive and negative aspects of QoL. It was validated for the Turkish population by Eser et al. (17).

2.4. Statistical analysis

Statistical analysis was performed using SPSS 22.0 (IBM Statistics for Windows, IBM Corporation, Armonk, NY, USA) and $P < 0.05$ was considered statistically significant. Normal distribution of the data in the groups was tested with Kolmogorov–Smirnov tests. Variables were expressed as mean ± standard error for normally distributed data and proportions for the nonnormally distributed and categorical data. The differences in parametric and categorical variables were tested with Student's t-tests and Pearson chi-square tests, respectively. When investigating

the changes in variables by different groups, the effect of age and BMI was adjusted using analysis of covariance (ANCOVA) tests and logistic regression analyses. The power analysis of the study was done with reference to a previous study (18) that reported the differences in anxiety scores as 2.9 ± 3.5 and depression scores as 2.4 ± 3.2. The current study was sufficiently powered to detect the differences in anxiety between NIH and non-NIH phenotypes of PCOS (93.42% power, effect size = 0.71), the differences in depression between NIH and non-NIH PCOS phenotypes (80.33% power, effect size = 0.55), and the difference between PCOS and controls (80.15% power, effect size = 0.30).

3. Results

3.1. Patients' characteristics

A total of 172 patients were eligible for this study. Patients were excluded if they had a positive pregnancy test (n = 3), had used any hormonal and insulin sensitizing medication within the previous 3 months (n = 4), or had missing data (n = 15). The remaining 150 women were enrolled in the study for final analysis. The study group ultimately included 101 women with PCOS (n = 54 women with NIH, and n = 47 women with non-NIH phenotype) and the control group included 49 women without PCOS. The demographic and endocrinologic features of the participants are shown in Table 1.

3.2. Comparison of depression and anxiety statuses in the study and control groups (PCOS vs. non-PCOS)

When the depression and anxiety scores were compared, women with PCOS had significantly higher HADS-D and HADS-A scores compared to the controls (P < 0.001 and P = 0.001, respectively). According to HADS, the cut-off values for the depression and anxiety subscales are 7 and 10 points, respectively. By using these HADS cut-off values, the rates of depression and anxiety among women with PCOS were also significantly higher than those of the controls (46.5% vs. 20.0%; P = 0.002 and 33.7% vs. 12.2%; P = 0.005, respectively) (Table 2). Compared to the controls, the women with PCOS had a 3.39 times higher risk of depression (P = 0.005) and a 3.64 times higher risk of anxiety (P = 0.002).

Table 1. The demographic and endocrinologic characteristics of women with different PCOS phenotypes and controls.

	PCOS with NIH phenotype	PCOS with non-NIH phenotype	Control group (C)	P value (NIH vs. non-NIH)	P value (PCOS vs. C) (age/BMI adjusted)
Age (years)	24.70 ± 4.39	24.15 ± 4.08	26.29 ± 5.17	0.514	0.022
BMI (kg/m^2)	25.84 ± 4.81	23.88 ± 8.45	24.44 ± 3.88	0.399	0.021
WC (cm)	89.29 ± 11.80	83.73 ± 14.31	80.27 ± 11.67	0.055	<0.001
FG score	14.00 ± 3.00	7.00 ± 7.00	6.00 ± 2.00	<0.001	<0.001
Fasting glucose (mg/dl)	84.00 ± 11.00	82.00 ± 9.00	85.00 ± 8.00	0.276	0.196
FSH (IU/L)	5.50 ± 2.25	5.80 ± 1.90	6.49 ± 1.38	0.203	0.076
LH (IU/L)	7.60 ± 6.30	6.25 ± 9.20	4.10 ± 2.11	0.635	<0.001
E2 (pg/mL)	41.00 ± 23.00	41.50 ± 24.30	41.10 ± 13.76	0.29	0.410
PRL (ng/mL)	12.15 ± 7.45	13.00 ± 6.90	13.00 ± 4.60	0.574	0.406
TSH (μIU/mL)	1.90 ± 1.10	1.90 ± 1.10	1.99 ± 0.89	0.669	0.520
Testosteron (ng/mL)	0.75 ± 0.19	0.62 ± 0.20	0.46 ± 0.14	<0.001	<0.001
DHEAS (μmol/L)	263.0 ± 115.0	207.0 ± 120.0	180.0 ± 76.0	0.016	<0.001
Clinical HA n (%)	48 (88.9)	26 (55.3)	14 (28.6)	<0.001	<0.001
Biochemical HA n (%)	54 (100)	15 (31.9)	12 (24.5)	<0.001	<0.001

Data are shown as mean ± SD or number (percentage). Continuous data were analyzed with independent t-test with adjustment for age/BMI for all variables except the age and BMI variables. Categoric data were assessed with chi-square test. [1]Data are presented as mean ± SEM and [2]column percentage. NIH, National Institute of Health; BMI, body mass index; WC, waist circumference; FG, Ferriman–Gallwey; FSH, follicle stimulating hormone; LH, luteinizing hormone; E_2, estradiol; PRL, prolactin; TSH, thyroid stimulating hormone; DHEAS, dehydroepiandrostenedione sulfate; HA, hyperandrogenism

Table 2. Comparison of depression and anxiety status in women with different PCOS phenotypes and the controls.

Parameters	NIH PCOS	Non-NIH PCOS	P value (NIH vs. non-NIH)	Control	PCOS	P value (PCOS vs. control)
HADs-D scores[1]	7.00 ± 3.25	7.00 ± 4.00	0.67	6.00 ± 2.00	7.00 ± 4.00	<0.001
Rate of depression[2] (n%)	25 (46.3)	22 (46.8)	0.96	10 (20.4)	47 (46.5)	0.002
HADs-A scores[1]	10.00 ± 4.00	10.00 ± 4.00	0.47	8.00 ± 3.00	10.00 ± 5.00	0.001
Rate of anxiety[2] (n%)	17 (31.5)	17 (36.2)	0.62	6 (12.2)	34 (33.7)	0.005

Data are shown as mean ± SD or number (percentage). Continuous data were analyzed with independent t-test with adjustment for age/BMI for all variables except the age and BMI variables. Categoric data were assessed with chi-square test. [1]Data are presented as mean ± SEM and [2]column percentage. NIH, National Institute of Health; HADs-D, Depression subscale of hospital anxiety and depression scale; HADs-A, Anxiety subscale of hospital anxiety and depression scale. HADS-D ≥ 10 was used to suggest depression and HADS-A ≥ 7 was used to suggest anxiety disorder.

3.3. Comparison of the depression and anxiety statuses in different PCOS phenotypes (NIH vs. non-NIH)

The depression and anxiety scores were specifically assessed for the women with PCOS. When we compared these scores between the subgroups of women with PCOS with NIH and non-NIH phenotypes, the mean HADS-D and HADS-A scores were similar in the two groups (P = 0.67 vs. P = 0.47, respectively). Accordingly, by using the HADS cut-off value, the rates of depression and anxiety were also similar in NIH and non-NIH PCOS phenotypes (46.3% vs. 46.8%, P = 0.96 and 31.5% vs. 36.0%, P = 0.62, respectively) (Table 2).

3.4. The comparison of QoL in women with PCOS and controls, and between the NIH and non-NIH phenotypes

For the QoL scores, mental, social, and environmental domain scores were similar in the women with PCOS and the controls (P = 0.11, P = 0.75, and P = 0.92, respectively). However, physical health domain scores were significantly lower in the women with PCOS compared to the controls (P = 0.007). When the phenotypes were compared, there was no difference in physical, social, and environmental domain scores between NIH and non-NIH phenotypes (P = 0.82, P = 0.89, and P = 1.0, respectively). However, mental health domain scores were significantly lower in NIH phenotypes compared to non-NIH phenotypes (P = 0.03) (Table 3).

3.5. Regression analysis for anxiety and depression in women with PCOS

In the univariate analysis, all of the sociodemographic, clinical, and endocrinological variables were similar in the two groups of PCOS women (n = 101) who were depressed and not depressed (Table 4). Similarly, regression analysis for anxiety and depression also revealed no independent predictor for anxiety in PCOS women (data not shown).

4. Discussion

In this study, we investigated the psychological statuses and QoL profiles in women with different phenotypes of PCOS and healthy controls. We found that almost half of the PCOS women had higher scores for depression and one third had higher scores for anxiety. This relatively high prevalence for higher depression scores was

Table 3. Comparison of quality of life scores, assessed by WHOOL-Bref in women with different PCOS phenotypes and the controls.

Domains of WHOQOL-Bref scale	NIH PCOS	Non-NIH PCOS	P value (NIH vs. non-NIH)	Control	PCOS	P value (PCOS vs. control)
Physical domain scores	22.56 ± 3.61	22.72 ± 3.62	0.82	24.37 ± 3.71	22.64 ± 3.60	0.007
Mental domain scores	20.04 ± 3.85	21.55 ± 3.01	0.03	21.76 ± 3.88	20.74 ± 3.55	0.11
Social domain scores	11.02 ± 2.47	11.09 ± 2.22	0.89	11.18 ± 2.56	11.05 ± 2.35	0.75
Environmental domain scores	31.17 ± 4.50	31.17 ± 4.80	1.00	31.08 ± 5.97	31.17 ± 4.62	0.92

Data are shown as mean ± SD or number (percentage). Data were analyzed with independent t-test with adjustment for age/BMI for all variables except the age and BMI variables. [1]Data are presented as mean ± SEM. NIH, National Institute of Health; WHOQOL-Bref, World Health Organization quality of life scale

Table 4. Sociodemographic and endocrinologic characteristics of women with PCOS according to the depression status assessed by HADS.

Parameters	Not depressed	Depressed	P value
Sociodemographic parameter			
Age[1] (years)	24.11 ± 4.04	24.83 ± 4.46	0.398
BMI[1](kg/m^2)	26.35 ± 4.91	25.9 2 ± 5.83	0.685
Presence of marriage[2], n (%)	31 (57.4)	33 (70.2)	0.217
High school education[2], n (%)	43 (79.6)	29 (61.7)	0.052
Employee[2], n (%)	14 (25.9)	15 (32.6)	0.512
History of infertility[2], n (%)	27 (50)	29 (61.7)	0.316
Clinical parameters			
Waist circumference ≥ 88 cm[2], n (%)	23 (50)	23 (59)	0.513
FG score ≥ 8[2], n (%)	34 (63)	30 (63.8)	1.000
Oligo-anovulation[2], n (%)	44 (81.5)	42 (89.4)	0.198
Biochemical hyperandrogenism, n (%)	39 (72.2)	30 (63.8)	0.398
Clinical hyperandrogenism, n (%)	36 (66.7)	38 (80.9)	0.121
Biochemical parameters			
LH/FSH[1]	1.22 ± 1.17	1.22 ± 1.14	0.615
TSH[1] (μIU/mL)	1.99 ± 0.86	1.96 ± 0.85	0.854
PRL[1] (ng/mL)	13.57 ± 6.00	13.74 ± 4.82	0.879
Testosterone[1] (ng/mL)	0.70 ± 0.19	0.68 ± 0.175	0.639
DHEAS[1] (μmol/L)	224 ± 94	225 ± 129	0.842

Data are shown in mean ± SD or number (percentage). Data were analyzed with Student's t-tests and chi-square test in parametric and categoric variables. [1]Data are presented as mean ± SEM and [2]column percentage. BMI, body mass index; FG, Ferriman–Gallwey score; LH, luteinizing hormone; FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone; PRL, prolactin; DHEAS, dehydroepiandrosterone sulfate.

consistent with a recent meta-analysis that reported a fourfold increased risk of depression in PCOS women (2). Additionally several studies have reported a wide range of depression and anxiety levels for various populations of PCOS women (13,19,20). Population surveys conducted in 10 countries worldwide also reported the lifetime prevalence of depression varied from 3.0% to 16.9%. This high variation in depression rates in PCOS women might be attributed to their cultural backgrounds, differences in genetic predisposition, and the use of different scales for psychological assessments.

Whether the incidence of depression and anxiety differs among NIH and non-NIH PCOS women is still unclear. To the best of our knowledge, the only study published in the English language literature was carried out by Moran et al., who recruited 54 women with PCOS and 27 controls, and no difference was reported between the two phenotypes of PCOS (12). However, this study was insufficiently powered to detect the difference in depression between the PCOS phenotypes and controls. For the first time in the literature, with a powered study, we have demonstrated there is no difference in depression levels between PCOS phenotypes.

PCOS is the most common endocrinopathy of reproductive-aged women. The clinical features of this syndrome, such as menstrual irregularity and androgen excess symptoms, begin appearing during adolescence and continue through the reproductive years. With increasing age, young women with PCOS may also suffer from infertility, abdominal obesity, and glucose intolerance. Chronic exposure to all of these PCOS symptoms may impair the psychiatric status and the QoL

of these young women (22). However, not all women presenting with all of the PCOS signs develop depression, nor are the milder normoandrogenic phenotypes free of these mood disorders. Bazarganipour et al. investigated 300 Iranian women with PCOS and reported that the women with hyperandrogenism and polycystic ovaries had higher depression and anxiety symptoms than the other phenotypes (23). However, women with menstrual irregularities had higher psychological impairment in the quality of life than those with hyperandrogenism. An earlier study by these authors also showed that menstrual irregularities are the major concern in women with PCOS and lead to reduced feminine identity (24).

The pathophysiology of the increased depression and anxiety in women with PCOS is still unclear. Livadas et al. reported that the degree of anxiety was parallel to the degree of hyperandrogenemia and insulin resistance (25). However, in other studies, the increased risk of depression and anxiety among women with PCOS was attributed to poor self-esteem linked to hirsutism, acne, and health-related concerns (26), rather than the clinicobiochemical markers (27). Some studies in women have shown an association between high serum androgen levels and depression (28–30). On the other hand, some other studies have failed to demonstrate any association between free and total androgen levels with depression (31). Similarly, in this study, we found that serum testosterone and DHEA-S levels were not related to higher depression scores. This leads us to think that it is the body perception as to whether the young women are pleased with their body appearance in the mirror that predisposes the women to depression rather than an increased serum level of androgens. Another study from Turkey revealed that the FG score was an independent risk factor for depression in PCOS women and hirsutism was the major contributor to anxiety in the questionnaire (21). In contrast, studies from India, Australia, and the United States did not demonstrate any association between depression and hirsutism (12,31,32). This difference might be explained by cultural differences in conceptions of "beauty" or "hirsutism." Klimczak et al. also reported that PCOS patients with depression demonstrated higher blood lipids than the nondepressed ones (13). However, neither age nor BMI had an impact on the rate of depression in women with PCOS.

QoL questionnaires (e.g., WHOQOL-BREF) also yielded lower scores in both physical and mental fields in PCOS patients. Although physical scores in the two phenotypes were similar, mental scores were lower in the NIH phenotype. In our previous study, we found a significant inverse relationship between the FG scores and QoL scores in infertile PCOS patients (33). Similarly, in the current study, mental scores were also significantly lower in PCOS patients with the NIH phenotype, in which both clinical and biochemical hyperandrogenism were also more common. An interpretation of these results may be that, although the hyperandrogenism causes emotional disturbances, and has a significant impact on the psychological domain of the QoL, it does not always cause psychiatric problems like depression. However, improving the QoL is also an important issue for women with PCOS, since 14% of women with PCOS reported suicidal ideas (34). Current evidence suggested that psychological distress, impaired self-esteem, negative body image, and sexual dysfunction might be the targets to improve QoL.

Although this study has some strengths, there were also limitations. The first limitation is that this study was a single center study and does not represent whole PCOS population in this country. The second limitation is the cross-sectional study design that limits the report of a firm conclusion. Only a prospective study design could clarify the cause–effect relationship between mood disorders and PCOS. Therefore, future studies should investigate the possible etiologic factors for the development of mood disorders in women with PCOS and should be conducted in multiple centers in different countries and cultures.

In conclusion, we found that both depression and anxiety scores, evaluated by HADS, are higher in women with PCOS compared to controls. For the first time in the literature, with a sufficiently powered study, we demonstrated that NIH and non-NIH phenotypes have similar rates of depression and anxiety disorders. Although women with the NIH phenotype have lower scores in some aspects of the QoL scale, all PCOS women, regardless of their phenotype, might benefit from an investigation of psychiatric co-morbidities. It is known that, compared to family medicine physicians and general internists, gynecologists are less likely used to evaluating psychiatric co-morbidities. Since the majority of women with depression might be cured with appropriate treatment, endocrinologists and gynecologists should pay special attention to the psychological problems of women with PCOS and refer them to psychiatrists when necessary.

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