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Association between depression, symptom experience and quality of life in polycystic ovary syndrome

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Abstract

Background: Clinical stigmata of polycystic ovary syndrome include hirsutism, obesity, menstrual disturbances and infertility. These symptoms impair health-related quality of life. Depression is also common. The relationship between depression, symptom self-perception and quality of life in polycystic ovary syndrome is poorly understood.

Objective: To investigate the relationship between health-related quality of life and depression in women with polycystic ovary syndrome

Study Design: We conducted a secondary analysis of a multicenter, randomized clinical trial (Pregnancy in Polycystic Ovary Syndrome II,) comparing clomiphene citrate versus letrozole in the treatment of infertility. Subjects included 732 women ages 18–40 with polycystic ovary syndrome by modified Rotterdam criteria. The validated Polycystic Ovary Syndrome Health-Related Quality of Life survey was self-administered, assessing the following domains: emotions, body hair, body weight, menstrual problems and infertility; scores range from 1–7, with lower numbers indicating poorer quality of life. Depression was evaluated via the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire. Quality of life scores were compared between Depressed and Non-depressed women in unadjusted regression analyses. Multivariate linear regression models analyzed the association between depression and quality of life scores, controlling for age, body mass index, hirsutism score and duration of infertility.

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Presentation Information:

The findings were presented at the 73rd Annual Scientific Congress of the American Society for Reproductive Medicine in San Antonio Texas, October 28 – November 1, 2017.

Condensation: Depression may modulate symptom perception and is associated with reduced health-related quality of life in polycystic ovary syndrome.

Dr. Eisenberg reports no conflict of interest disclosures.

Results: Sixty-four women (8.4%) met criteria for depression. Depressed women reported reduced quality of life in all domains compared to Non-depressed women: mood (3.1 vs 4.6, p <0.001), body hair (3.5 vs 4.2, p = 0.002), weight (2.0 vs 3.5, p <0.001), menstrual problems (3.3 vs 4.1, p <0.001) and infertility (1.9 vs 3.0, p <0.001). Global quality of life score was reduced in Depressed women (2.8 vs 3.9, p <0.001). Impairments in quality of life in Depressed women persisted in all domains after controlling for objective parameters including age, body mass index, hirsutism score and infertility duration.

Conclusions: Depression is associated with reduced quality of life related to polycystic ovary syndrome symptoms. Disturbances in health-related quality of life in Depressed women are not explained by objective measures including body mass index, hirsutism scores and duration of infertility. Depression may color the experience of polycystic ovary syndrome symptoms and should be considered when there is significant discordance between subjective and objective measures in women with polycystic ovary syndrome.

Keywords

Depression; Health-Related Quality of Life; Polycystic Ovary Syndrome (PCOS); Quality of Life

Introduction

Up to 15% of reproductive age women are affected by polycystic ovary syndrome (PCOS) (1, 2). The diagnostic triad for PCOS comprises ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology on ultrasound (3). Hyperandrogenism may manifest biochemically (i.e. in the serum) or clinically in the form of hirsutism and acne. Metabolic dysfunction is common in PCOS (4, 5), related to insulin resistance (6), and embodied in increased rates of obesity. An estimated one in two women with PCOS is obese (7). Additionally, women with PCOS face an estimated 3–8x increased risk of depression (8–10). The pathophysiology explaining the elevated prevalence of depression in PCOS is unknown.

Health-related quality of life (HRQOL) may been defined as “the extent to which one’s usual or expected physical, emotional and social well-being are affected by a medical condition” (11), and is an increasingly emphasized patient-reported outcome (12). Women with PCOS have been shown to have decreased HRQOL (13, 14). Symptoms inherent in the disorder, including emotional disturbances, growth of body hair, increased body weight, menstrual problems and infertility are frequently cited as reasons for the perturbed HRQOL (13, 15–17). Depression is also common in PCOS (8). It has been suggested that PCOS somatic symptoms such as obesity and hirsutism are linked to depression risk, (18, 19), however the causal direction of this association is poorly understood. Indeed, while PCOS symptoms may reduce HRQOL and contribute to depression risk, it is possible that depression itself might modulate how women perceive their symptoms and thereby HRQOL.

Understanding the connections between depression and HRQOL is a critical step toward identifying opportunities to enhance overall well-being in the PCOS population. The objective of our study was to test the hypotheses that 1) depressed women perceive their PCOS symptoms more negatively or severely compared to non-depressed women, and 2)

that differences in symptom self-perception are not explained by differences in objective clinical measures.

Materials and Methods

We conducted a secondary analysis of data from a multicenter, double-blind, randomized clinical trial comparing clomiphene citrate versus letrozole in the treatment of infertility in 750 women with PCOS (PPCOSII) (20). Subjects provided written, informed consent to participate in the clinical trial. This secondary analysis utilized only de-identified data, and was exempt from Institutional Review Board approval accordingly.

Subjects

The study cohort included 732 female patients, ages 18–40, enrolled in the PPCOSII clinical trial at one of 11 centers. PCOS was diagnosed by modified Rotterdam criteria (21), requiring chronic ovulatory dysfunction in addition to hyperandrogenism, or polycystic appearing ovaries, or both. Ovulatory dysfunction was defined as oligomenorrhea (ie ≤8 menses annually), a spontaneous intermenstrual interval of ≥45 days, or chronic anovulatory bleeding with midluteal serum progesterone of < 3ng/dL. Hyperandrogenism included hirsutism (modified Ferriman-Gallwey (mFG) Score >8), or elevated serum testosterone or free androgen index. Polycystic morphology was defined per Rotterdam criteria as ≥12 antral follicles 2–9 mm in diameter, or increased ovarian volume >10 cm^3 in at least one ovary on transvaginal ultrasound. Related disorders were screened out by TSH, prolactin and 17-hydroxyprogesterone. Additional details regarding eligibility criteria are available publicly (22). Subjects who completed both the Polycystic Ovary Syndrome Questionnaire (PCOSQ) and Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ) at the screening visit were included in this analysis.

At the screening visit, thorough history and physical examination, including calculation of body mass index, was performed. The modified Ferriman-Gallwey (mFG) scoring system (23) was utilized to assess hirsutism.

Health-related Quality of Life

Validated instruments were self-administered at the screening visit. HRQOL was assessed using the Polycystic Ovary Syndrome Questionnaire (PCOSQ) survey (24). PCOSQ is a validated, Likert-type 26-item questionnaire, which examines five domains specifically targeted to quality of life in PCOS: emotional disturbance, body hair, weight, menstrual problems and infertility. Items query the severity and frequency of symptomatic distress related to PCOS. Reponses are coded from 1–7. Scoring of PCOSQ provides separate domain scores for each of the five domains, as the numeric mean of items in that domain, as well as a global score, as the mean of the five domain scores. Scores range from 1–7, with 1 indicating poorest function and highest distress, and 7 indicating optimal function and minimal distress.

Depression

The Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ) (25) was used to assess depression. The PRIME-MD PHQ is a validated, self-administered questionnaire designed to diagnose specific mental disorders in the primary care setting, in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (26). The sensitivity and specificity (73% and 94%, respectively) for diagnosing depressive disorders are considered excellent compared to the gold standard structured clinical interview (25). The survey assesses the frequency of nine symptoms of clinical depression over the preceding two weeks. “Depression” is indicated by experiencing at least three of nine symptoms on at least “more than half the days.” One of these symptoms must be “little interest or pleasure in doing things” or “feeling down, depressed, or hopeless” or both, in accordance with DSM-IV.

Statistical analysis

Descriptive statistics were provided. Baseline characteristics of Depressed versus Non-depressed women were compared using two-sided t-tests or chi-square as indicated; PCOSQ scores were compared using t-tests. Univariate and multivariate linear regression models assessed the association between Depression and PCOSQ domain and global scores. The multivariate model was adjusted for age, body mass index, mFG score, and duration of infertility. To determine whether the relationship between a woman’s BMI and her body weight PCOSQ score varied on the basis of whether or not she was Depressed, a linear regression model incorporating an interaction term between Depression and BMI was examined (outcome: body weight domain PCOSQ score). This analysis was repeated to evaluate potential interactions between Depression and hirsutism score as predictors of body hair domain PCOSQ score, and between Depression and duration of infertility as predictors of infertility domain PCOSQ score. Statistical significance was set at the level of $p<0.05$. Analyses were performed using STATA, version 14.2 (College Station, TX).

Results

Sixty-four of the 732 women (8.4%) met criteria for Depression by the PRIME-MD PHQ algorithm.

Baseline demographic and clinical characteristics are demonstrated in Table 1. On average, subjects were 28.9 years old, with a BMI of 35.2 kg/m^2. Most women were Caucasian (79%). While 20% had a prior live birth, average duration attempting conception was 42 months.

Health-related quality of life scores as determined by PCOSQ were lower (i.e. more distress) in all domains in the Depressed compared to Non-depressed subjects (Table 2). Quality of life scores were lowest in the infertility domain, followed by body weight in both groups. In Depressed women, the third most distressing domain was emotions, while the third most distressing domain for the Non-depressed subjects was menstruation. The global PCOSQ score in the Depressed women was 2.8 compared to 3.9 in the Non-depressed group ($p<0.001$), indicating lower overall health-related quality of life in women with depression.

Linear regression models further assessed the difference in PCOSQ scores between Depressed and Non-depressed women (Table 3). In unadjusted analyses, depression was associated with statistically significant reductions in quality of life (i.e. negative coefficients) in all domains and in the global score.

To assess whether clinically measurable parameters of PCOS symptom severity explained the impairment in health-related quality of life reported by the Depressed women, we conducted multivariate linear regression analyses controlling for age, BMI, mFG score and duration of infertility; the primary outcome was PCOSQ scores, and we considered Depressed vs Non-depressed group assignment as one predictor in the model (Table 3). The association of Depressed status with reduced quality of life in each of the five individual domains, as well as the global score, remained significant in the adjusted models. For example, after controlling for BMI, age, mFG and infertility duration, Depressed status was associated with a reduction in weight domain score by 1.23 points (95% CI −1.63, – 0.83, p <0.001), and a reduction in global health-related quality of life score by 0.98 points (95% CI −1.23, −0.73, p <0.001) (Table 3).

To visualize the relationship between objective clinical measurements and subjective ratings of quality of life distress, we constructed scatter plots with linear models by Depressed versus Non-depressed status (Figure 1a–c). Linear regression modeling incorporating interaction terms between Depression and clinical measurements as predictors of subjective symptom severity assessed whether the relationship between the following varied on the basis of Depression status: weight PCOSQ domain score versus body mass index, body hair PCOSQ domain score versus mFG score, and infertility PCOSQ domain score versus duration of infertility (Figure 1a–c).

Among Non-depressed women, weight-related quality of life declined significantly with increasing BMI, with each 1-kg/m^2 increase in BMI corresponding to a 0.10-point reduction in weight domain PCOSQ score (coeff = −0.10, 95% CI = −0.12, −0.09, p <0.001) (Figure 1a). Conversely, among Depressed women, the association between reported weight symptom distress and BMI was attenuated and non-significant (coeff = −0.03, 95% CI = −0.08, 0.02, p =0.23). The interaction term in the model confirmed the presence of an interaction between Depression and BMI (coeff 0.07, 95% CI 0.02, 0.13; p<0.01), indicating a differential impact of BMI on weight-related quality of life in Depressed versus Non-depressed women. Quality of life was higher across the range of BMIs in Non-depressed women.

Figure 1b depicts a similar analysis regarding body hair signs and symptoms. In both Non-depressed and Depressed women, body hair quality of life scores declined with increasing mFG scores (Depressed: coeff = −0.14, 95% CI −0.16, −0.13, p <0.001; Non-depressed coeff = −0.12, 95% CI −0.17, −0.08, p <0.001). An interaction was not observed between Depression and hirsutism score as predictors of body hair-related quality of life.

A comparison of infertility domain score versus duration of infertility showed increasing duration of infertility was associated with worsening quality of life among Non-Depressed women (coeff = −0.01, 95% CI −0.01, −0.00, p <0.001), while among Depressed women the

inverse association was non-significant (coeff = −0.00, 95% CI −0.01, 0.01, p = 0.68) (Fig 1c). However, there was no statistically significant interaction between Depression and infertility duration as predictors of infertility domain PCOSQ score (coeff 0.00, 95% CI −0.01, 0.01, p=0.40).

Comment

Health-related quality of life is increasingly emphasized as an essential patient-reported outcome; it constitutes one of four foundation health measures and overarching goals of Healthy People 2020 (27). HRQOL is multidimensional concept which includes physical, social and emotional functioning (27). Prior reports have shown a reduction in HRQOL in women with PCOS compared to controls (13, 14). It is conceivable that psychological dysfunction, namely depression, might affect the perception and experience of physical symptoms related to disease.

In our study, we identified a global reduction in HRQOL in Depressed women with PCOS compared to their Non-depressed counterparts. Reduced scores, indicating increased symptom-specific distress, were noted in each of the five queried domains (i.e. emotions, body hair, weight, menstruation, and infertility). These reductions in QOL reported by Depressed women are arguably clinically as well as statistically significant, as a 0.5-point differential in PCOSQ scores is considered clinically meaningful (28). The reported impairments in functioning in Depressed women were not accounted for by corresponding objective clinical measures including BMI, hirsutism scores and infertility duration in multivariate linear regression models.

Focusing further on the weight domain, we noted that the relationship between weight-specific HRQOL and BMI differed between Depressed and Non-depressed women. We identified a progressive reduction in weight domain QOL scores with increasing BMI in Non-Depressed women. Conversely, we failed to identify a statistically significant association in Depressed women. An interaction was noted between Depression and BMI, confirming that the effect of BMI on perceived weight distress differed on the basis of whether a woman was Depressed or not. While the vast majority of prior literature examining the interplay of BMI, depression, and HRQOL focuses on mutual correlations, the concept that an interaction may exist between obesity and depression as predictors of HRQOL is supported by a prior population-based study which observed a synergistic effect between obesity and mental health disorders in their detrimental impact on HRQOL (29).

Regarding the infertility domain, we again observed a statistically significant association between infertility-specific QOL scores and duration of infertility in Non-depressed women, but observed an attenuated, non-significant association in Depressed women; however the interaction term between Depression and infertility duration was not significant in our model. In the body hair domain, increasing severity of clinician-rated hirsutism was associated with worse QOL scores for both Depressed and Non-depressed women, however QOL was lower for Depressed women.

Our multivariate model (Table 3) identified persistent reductions in weight and infertility domain PCOSQ scores in the Depressed women, which were independent of BMI and infertility duration. Taken together, these findings suggest that depression might color the somatic symptom experience in PCOS, adding distress independent of objective findings. The alternative explanation – that women who viewed their PCOS symptoms more negatively increased the risk for depression – is also plausible.

Our data are consistent with a prior Turkish study which also observed impaired HRQOL functioning in Depressed compared with non-Depressed women with PCOS seen in an endocrinology clinic (17). Our study extends the prior findings by taking into account baseline differences between groups (for example, BMI and mFG scores) to address this potential source of confounding. Comparing depressed women across studies, we found that infertility and weight problems were the most serious concerns, while hair growth and menstrual disturbances were most distressing in the Turkish population (17), reflecting the differential clinical compositions and perhaps cultural differences. Another recent study investigating clinician versus patient self-rating of hirsutism in PCOS determined that while both ratings were associated with a negative quality of life impact, self-ratings alone were associated with the risk of depression (15), echoing our findings of the association between self-reported symptom-specific distress and depression.

Psychological well-being is paramount in PCOS. One prior investigation determined that PCOS had a greater negative impact on psychological HRQOL functioning compared to arthritis, back pain, epilepsy, and coronary heart disease, as measured by the SF-36 (14). Decreased psychological functioning may have critical implications for long-term health. Lifestyle modification including diet and exercise are primary treatment strategies to combat cardiometabolic risk in PCOS and may ameliorate some PCOS features, such as obesity, cycle irregularity and infertility. Depression can negatively impact the motivation required for efforts at self-care, further exacerbating the effects of PCOS (30). Indeed, cognitive theories of depression focused on “learned helplessness” suggest that depression might evolve when an individual, following repeated unpleasant experiences, no longer attempts to change their situation due to a sense of lacking control (31). Conversely, perceiving that one’s actions (for example, pursuing diet and exercise) could improve health is prerequisite for motivation to produce a change. Thus, depression might precipitate a vicious and compounding cycle in PCOS: a perception of lack of control to improve health status may lead to depression, which further impedes efforts to improve lifestyle habits, in turn resulting worsening symptoms and metabolic decline.

The results of our study underscore the importance of symptom self-report in the context of patient-centered care and suggest that clinicians should consider depression when encountering patients with a notable sign-symptom mismatch. Further, our findings suggest the possibility that adequate treatment of depression might improve PCOS symptom self-perception and HRQOL dysfunction. The converse, that treatment of distressing PCOS clinical symptomatology might improve depression, is also possible. Pharmacotherapy and psychotherapy are both effective treatment modalities for depression symptoms, and evidence supports a combined approach as most effective (32). In light of our findings demonstrating perturbations in symptom self-perception related to the PCOS disease state

among depressed women, therapies targeted at helping women re-evaluate their thinking about PCOS, such as cognitive behavioral therapy, should be strongly considered in a treatment approach to ameliorate depressive symptoms and improve HRQOL indices.

Strengths, Limitations and Future Directions

Strengths of our study include the large sample size representing 11 centers nationwide. Limitations inherent in the cross-sectional design restrict our interpretation of causal direction. While it is possible depression might result in heightened distress from somatic symptoms by coloring self-perception, it is also possible escalated perception of symptom burden might contribute to depression. In addition, the smaller sample size in the Depressed group may impact statistical power to detect associations between objective and subjective findings in the interaction models. However, with regards to the weight domain, the statistically significant interaction identified between Depression and BMI confirmed that the impact of BMI on weight-related QOL differs as a function of whether or not a woman is Depressed. Further, the findings from our multivariate regression models corroborate the overall concept that the reduction in HRQOL in the Depressed group is not fully explained by objective clinical measures. By nature of design, our study is limited to infertile women with PCOS; if and how our results might vary in fertile women with PCOS cannot be extrapolated from this report. Finally, the prevalence of depression in this cohort was low (8.4%) relative to prior reports in other PCOS populations (average 37%) (8). This may reflect the relative rigor of the PRIME-MD screening algorithm, and/or the selection of motivated individuals in pursuit of eligibility to participate in a clinical trial of fertility treatment. Studies which seek to replicate our findings in alternate clinical cohorts are needed.

In conclusion, we demonstrate an association between depression and HRQOL in PCOS unexplained by objective measures. Our data suggest that depression may color the perception of somatic symptoms of PCOS, uncoupling the subjective experience from objective clinical measurements. Our data indicate the utility of future prospective, interventional studies to ascertain whether the treatment of depression improves subjective assessment of PCOS-symptom related quality of life; or, alternatively, if treatment of PCOS symptoms improves depressed mood.

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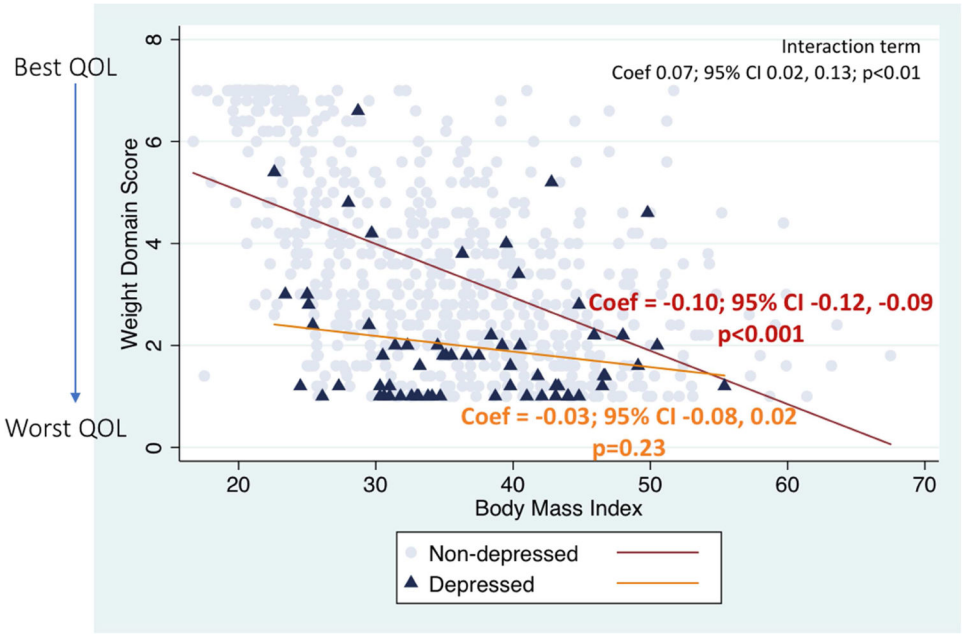
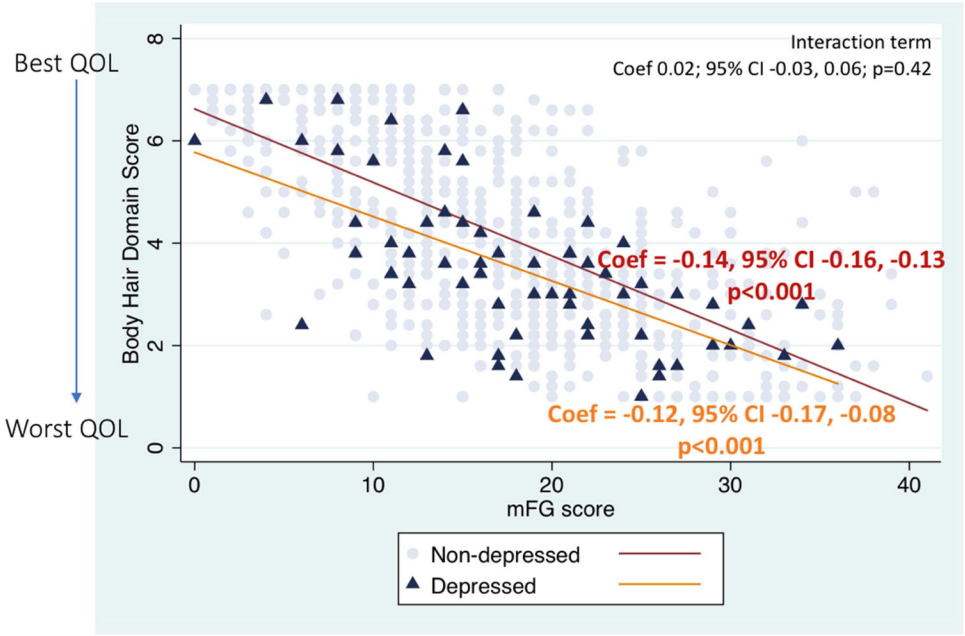
Implications and Contributions:

A. To examine the association between depression and health-related quality of life in polycystic ovary syndrome (PCOS).

B. Reduced quality of life was reported by depressed women for all PCOS-specific symptom domains, including: body hair, weight, infertility, menstrual disturbances and emotions, and, in depressed women, differences in symptom distress were not accounted for by objective measures of body mass index, hirsutism scores and infertility duration.

C. What this study adds to our knowledge: These findings suggest that depression may color how women experience PCOS symptoms and correspond to reduced quality of life.





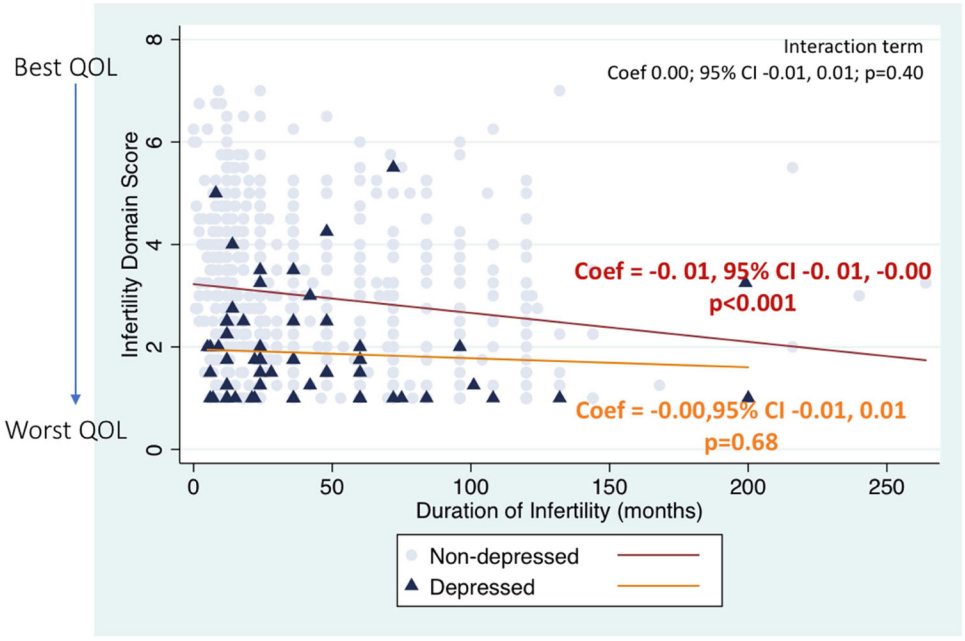


Figure 1.

Among depressed (navy blue triangles) and nondepressed (light gray circles) subjects, associations between Polycystic Ovary Syndrome Questionnaire(PCOSQ) domain scores and corresponding clinical measurements: A, weight domain and body mass index (kg/m2); B, body hair domain and modified Ferriman-Gallwey (mFG) score; C, infertility domain and duration of infertility (months). PCOSQ domain scores are plotted along y-axis with lower scores indicating lower QOL (or increased distress) related to each symptom. Corresponding objective clinical measurements are plotted along x-axis. Linear models are shown in red and orange, for nondepressed and depressed subjects, respectively, with regression coefficients (coef) shown by text. Co-efficient for interaction term between depressed status and objective clinical measurement (x-axis variable) as predictors of PCOSQ score (y-axis variable)are shown at top right of each plot.

Table 1.

Demographic and Clinical Characteristics of Study Population

Variable	Overall N=732	Non-depressed N=668	Depressed N=64	p
Age, yrs	28.9 (4.3)	29.0 (4.2)	27.5 (4.6)	<0.01
BMI, kg/m^2	35.2 (9.3)	35.0 (9.4)	36.8 (7.7)	0.15
Waist circumference, cm	105.9 (20.5)	105.4 (20.6)	111.2 (18.6)	0.03
Caucasian, %	79	79	77	0.27
Education, %				0.21
≤8th grade	1	1	0	
Some high school	4	4	5	
High school grad	18	17	23	
Some college	36	35	45	
College graduate	30	31	20	
Graduate degree	12	12	6	
Income, %				<0.01
<$25,000	11	10	22	
$25,000–49,999	29	29	34	
$50,000–74,999	27	28	14	
$75,000–100,000	14	15	11	
>$100,000	5	6	0	
Decline to state	14	13	19	
mFG score	17.0 (8.5)	16.9 (8.6)	18.4 (7.7)	0.17
Number of menses per year	4.3 (2.8)	4.3 (2.7)	5.1 (3.9)	0.04
Intermenstrual interval, days	95.7 (93.0)	98.3 (94.5)	68.3 (70.8)	0.12
Prior live birth, %	20	20	23	0.54
Duration of infertility, months	41.7 (37.9)	41.7 (37.7)	41.9 (40.3)	0.96

Mean (SD) or % as indicated

BMI (body mass index); mFG (modified Ferriman-Gallwey)

P-values were derived from two-sided t-tests or chi-square as indicated

Table 2.

PCOSQ Health-Related Quality of Life Scores

Domain	Overall N=732	Non-depressed N=668	Depressed N=64	p
Emotions	4.47 (1.26)	4.60 (1.19)	3.13 (1.09)	<0.001
Body hair	4.13 (1.81)	4.20 (1.82)	3.46 (1.48)	0.002
Weight	3.34 (1.86)	3.47 (1.85)	1.98 (1.27)	<0.001
Menstruation	4.05 (1.12)	4.13 (1.10)	3.26 (1.09)	<0.001
Infertility	2.92 (1.42)	3.02 (1.41)	1.95 (1.09)	<0.001
Global Score	3.89 (1.16)	3.99 (1.14)	2.81 (0.82)	<0.001

Mean (SD)

Lower scores indicate reduced quality of life

P-values were derived from two-sided t-tests

Table 3.

Association Between Depression and PCOSQ Health-Related Quality of Life

Domain	Unadjusted Coefficient, 95% CI	p	Adjusted Coefficient, 95% CI	p
Emotions	−1.47 (−1.78, −1.17)	<0.001	−1.29 (−1.58, −1.00)	<0.001
Body hair	−0.74 (−1.20, −0.27)	0.002	−0.47 (−0.81, −0.13)	0.008
Weight	−1.49 (−1.95, −1.02)	<0.001	−1.23 (−1.63, −0.83)	<0.001
Menstruation	−0.87 (−1.15, −0.59)	<0.001	−0.78 (−1.06, −0.50)	<0.001
Infertility	−1.07 (−1.43, −0.72)	<0.001	−0.87 (−1.21, −0.52)	<0.001
Global Score	−1.18 (−1.46, −0.90)	<0.001	−0.98 (−1.23, −0.73)	<0.001

A negative coefficient indicates a reduction in quality of life in the Depressed women compared to the Non-depressed women

Adjusted model includes: age, BMI, mFG score and duration of infertility

Univariate and multivariate linear regression models were used in the analyses, with Depressed group coded as 1 and Non-depressed as 0