Androgen Excess- Polycystic Ovary Syndrome Society: position statement on depression, anxiety, quality of life, and eating disorders in polycystic ovary syndrome

Anuja Dokras, M.D., Ph.D.,[a] Elisabeth Stener-Victorin, Ph.D.,[b] Bulent O. Yildiz, M.D.,[c] Rong Li, M.D.,[d] Sasha Ottey, M.H.A.,[e] Duru Shah, M.D.,[f] Neill Epperson, M.D.,[a,g] and Helena Teede, M.B.B.S., Ph.D.[h]

[a] Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, Pennsylvania; [b] Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; [c] Department of Internal Medicine, Division of Endocrinology and Metabolism, Hacettepe University School of Medicine, Hacettepe, Ankara, Turkey; [d] Department of Obstetrics and Gyneocology, Reproductive Medical Center, Peking University Third Hosptal, Bejing, People's Republic of China; [e] PCOS Challenge, Atlanta, Georgia; [f] Gynaecworld, Mumbai, India; [g] Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; and [h] Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University and Monash Health, Clayton, Victoria, Australia

Objective: To formulate clinical consensus recommendations for screening depression, anxiety, health-related quality of life (HRQoL), and disordered eating symptoms in women with polycystic ovary syndrome (PCOS) and review prevalence based on phenotypes and ethnicity, changes over time, etiology, and impact of treatment.
Design: Systematic reviews and preparation of position statement.
Setting: Not applicable.
Patient(s): Women with PCOS and controls screened using validated tools.
Intervention(s): None.
Main Outcome Measure(s): Depressive symptoms, anxiety symptoms, disordered eating, and HRQoL scores.
Result(s): Several studies demonstrate that women with PCOS have an increased prevalence of higher depression and anxiety scores and higher odds of moderate and severe depressive and anxiety symptoms compared with controls. Obesity, hyperandrogenism, and fertility have a weak association with these symptoms. HRQoL scores are consistently reduced in PCOS, with infertility and weight concerns having the most significant impact. Some studies suggest an increased prevalence of disordered eating in women with PCOS compared with controls. The few studies that have evaluated the impact of PCOS-related treatments (lifestyle interventions and pharmacotherapy) show no detrimental effect or some improvement in depressive and anxiety symptoms and HRQoL scores.
Conclusion(s): In women with PCOS, screening for depressive and anxiety symptoms should be offered at the time of diagnosis and screening for disordered eating should be considered. Further research is required across PCOS phenotypes, in longitudinal cohorts and on impact of therapy on depressive and anxiety syptoms, HRQOL, and disordered eating. (Fertil Steril® 2018;109:888–99. ©2018 by American Society for Reproductive Medicine.)
Key Words: PCOS, depression, anxiety, disordered eating, quality of life

Discuss: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/29692-25200

Received October 24, 2017; revised January 26, 2018; accepted January 29, 2018.
A.D. has nothing to disclose. E.S.-V. has nothing to disclose. B.O.Y. has nothing to disclose. R.L. has nothing to disclose. S.O. has nothing to disclose. D.S. has nothing to disclose. N.E. has nothing to disclose. H.T. has nothing to disclose.
Reprint requests: Anuja Dokras, M.D., Ph.D., 3701 Market Street, Suite 800, Philadelphia, Pennsylvania 19104 (E-mail: adokras@obgyn.upenn.edu).

Fertility and Sterility® Vol. 109, No. 5, May 2018 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2018.01.038

There has been a paradigm shift from recognizing polycystic ovary syndrome (PCOS) as a gynecological and dermatologic condition to international position statements and guidelines now presenting PCOS as a multisystem disorder with comorbidities (1–3). Reproductive (hyperandrogenism, anovulation, infertility, pregnancy complications) and metabolic features (insulin resistance, impaired glucose tolerance, type 2 diabetes, dyslipidemia) are well described (4). The health and economic burden due to the high prevalence of PCOS (12%–21%) (5) mandates greater recognition and understanding of this condition across the breadth of its clinical features including emotional well-being, mood disorders, and health-related quality of life (HRQoL) (6–9).

Depression and anxiety are the second leading causes of global disease burden (10, 11). Postpubertal females are twice as likely as males to meet the criteria for major depressive disorder (MDD) and dysthymia (12–14). In the general population, the 12-month prevalence of MDD ranges from 2.2% in Japan to 8.3% in the United States (15, 16). The recent United States Preventive Task Force statement recommends screening all adults in the general population including pregnant and postpartum women for depressive symptoms (17). The statement highlighted that adequate systems are needed to ensure accurate diagnosis, effective treatment, and appropriate follow-up with a pragmatic approach to subsequent screening based on risk factors. The American College of Physicians recommends selecting between either cognitive behavioral therapy (CBT) or second generation antidepressants after discussing impact of treatment, adverse effects, cost, and accessibility with patients with MDD (18). International entities such as the World Health Organization have also ramped up efforts to promote screening and treatment of depression worldwide (19).

Anxiety disorders also represent a major public health problem, with a 12-month prevalence of 6%–18% (20, 21). The incidence of generalized anxiety disorder (GAD) is highest in the thirties and forties, with the highest prevalence among women over 45 years (8%–10%). Female sex and presence of an anxiety disorder increases risk of later MDD and dysthymia (22). Anxiety disorders can interfere with daily activities including work performance, school work, social interaction, and relationships and are the sixth leading cause of disability (23). Risk factors associated with GAD are related to sociodemographic factors: age, ethnicity, stressful life events, personality, and parental history of mental disorders (24).

Several meta-analyses demonstrate increased depressive symptoms, anxiety symptoms, and reduced HRQoL scores in women with PCOS (6–9). Yet general population recommendations on screening for depression and anxiety symptoms do not recognize PCOS as an at-risk group, highlighting a clear gap. The Australian and Endocrine Society practice guidelines recommend routine screening for depression and anxiety symptoms in women with PCOS (1, 2). Despite these recommendations, <10% of surveyed women with PCOS in North America, Europe, and Australia were satisfied with information provided regarding long-term complications, <5% were satisfied with emotional support and counseling offered, and >50% did not recieve any information on these issues (25).

Given the high prevalence of PCOS and the health burden associated with its comorbidities including depression, anxiety disorders, lower HRQoL scores, and patient dissatisfaction, changes in clinical practice are needed that align with general population screening and treatment recommendations. There is an urgent need to update recommendations and to expand the scope of previous guidelines to address critical gaps related to PCOS. For example, within each of the four conditions, namely, depression, anxiety, HRQoL, and disordered eating, risk factors specific to PCOS such as phenotype, age, and impact of PCOS-related treatments are not well studied. In this context, the Androgen Excess-PCOS (AE-PCOS) Society commissioned a multidisciplinary panel to review current guidelines, systematic reviews, and meta-analyses and to update these with relevant new studies. In addition, the panel prioritized six specific questions related to the prevalence and/or severity of symptoms, racial and phenotypic differences, etiology and impact of PCOS related treatments on depressive and anxiety symptoms, HRQoL, and disordered eating. Based on their findings, the panel was charged with forumulating consensus recommendations in an evidence-based position statement and highlighting gaps in knowledge.

MATERIALS AND METHODS

Panel

The AE-PCOS Society Board appointed an international panel including a psychiatrist, medical and reproductive endocrinologists, a gynecologist, a basic scientist, and a consumer representative. No external funds were used. Authors met face to face and by video conference, identified priority areas and questions, sought relevant evidence, drafted the position statement, and achieved consensus. All recommendations represent the final consensus by all authors and were critically reviewed and endorsed by the AE-PCOS Society Board.

Data Acquisition

Six questions were prioritized for each of the four conditions, namely, depression and anxiety symptoms, HRQoL, and eating disorders (ED). An updated systematic review and meta-analysis (up to January 2016) of depressive and anxiety symptoms in PCOS was specifically commissioned to support this position statement (26). We also updated a QoL subscales systematic review up to March 2016 (27). Electronic searches were performed to identify longitudinal studies on anxiety and depressive symptoms in PCOS and prevalence of disordered eating and studies examining the impact of PCOS-related treatments. The MeSH terms used are shown in Supplemental Table 1. The electronic databases searched were Ovid (MEDLINE and MEDLINE in-process and other non-indexed citations), EMBASE, PsycINFO, and the Cochrane Reviews database. Searches were limited to human studies with no restrictions on language. We excluded secondary publications of the same patient populations and studies that included only adolescents. Each review was conducted by at least two investigators, and the criteria for inclusion/exclusion were

agreed upon by at least two reviewers in each area. The screening tools used in the identified studies are summarized in Supplemental Table 2. Institutional Review Board approval was not obtained as only published articles were reviewed by the panel.

Process

The position statement applied components of the Grading of Recommendations, Assessment, Development and Evaluation group criteria in which the strength of a recommendation was indicated by "recommend" or, if a weaker recommendation was indicated, by "suggest."

Depressive Symptoms and Depression in PCOS

Is there increased prevalence and/or severity of depressive symptoms and depression in women with PCOS? Several meta-analyses have shown that women with PCOS are more likely to have depressive symptoms or clinical depression than their healthy counterparts (6–8). A meta-analysis of 10 studies from eight countries reported increased depression scores in women with PCOS compared with controls (odds ratio [OR], 4.03, 95% confidence interval [CI], 2.96–5.5; $P<.01$) (6), and this risk persisted in studies matched for body mass index (BMI), with no evidence of heterogeneity between the included studies. Two other meta-analyses examined the standardized mean difference (SMD) in depression scores between groups (7, 8). Although the included studies did not show a significant heterogeneity, it was unclear whether the depression scores were clinically significant. In fact, the authors emphasized that scores for women with PCOS were not in a clinically significant range in one-half of the studies, whereas depression scores in the mild range were reported in the remaining studies. The most commonly reported symptoms of depression in women with PCOS were daily fatigue, sleep disturbances, and diminished interest (28). To distinguish between mild symptoms of depression versus an adjustment to the underlying chronic illness, we commissioned a meta-analysis with rigorous inclusion criteria including diagnosis of PCOS by a physician and not self-report and inclusion of studies that provided prevalence of abnormal depression scores (26) and specifically ascertained risk of moderate to severe depressive symptoms. The overall prevalence of abnormal depression scores was 36.6% (interquartile range [IQR], 22.3%, 50.0%) in the PCOS group and 14.2% (IQR, 10.7%, 22.2%) in the control group. Moreover, the odds of moderate and severe depressive symptoms in women with PCOS were increased compared with controls (OR, 4.18; 95% CI, 2.68–6.52), highlighting the clinical significance of these findings (26). This meta-analysis also confirmed that the increased risk of depressive symptoms was independent of obesity (OR, 3.25; 95% CI, 1.73, 6.09) (26). Several sensitivity analyses were performed to ascertain the robustness of the results, for example, both clinic- and community-based women with PCOS showed higher depression scores, compared with appropriately matched controls. Further, clinic recruits had higher odds of depressive symptoms, indicating a greater need to screen this population. We noted some limitations, including small study sizes and lack of interview-based confirmation of the diagnosis of depression. For example, depression was confirmed with further clinical assessment in individuals who had abnormal screening scores in only three studies (26). Nevertheless, two of these studies reported increased rates of clinically diagnosed depression in women with PCOS.

A large population-based study using national health registries in Sweden (n = 24,385) (29) reported a significantly increased adjusted risk of depressive disorders in women with PCOS (OR, 1.25 [1.1.9–1.31]). In another large hospital database in Western Australia, the incidence of depression in women with PCOS was significantly higher compared with women who did not have a diagnosis of PCOS (9.8% vs. 4.6%) (30). Overall these studies confirm that women with PCOS have a higher prevalence of clinically significant depressive symptoms.

Are there differences among PCOS phenotypes in the prevalence of depressive symptoms? Only one small study compared depression scores between women with the National Institutes of Health (NIH) phenotype (n = 29) and those with only the reproductive phenotype (n = 27) and reported no differences (31).

What are the associations between features of PCOS and depressive symptoms? Small studies have examined the association between androgens, obesity, and abnormalities in insulin insensitivity, lipids, and depression scores (31–34). There are limited data on the interaction among infertility, depressive symptoms, and PCOS status. In a cross-sectional study, medically diagnosed depression and depression scores were not significantly different between fertile (n = 25) and infertile (n = 22) women with PCOS (35). In a Chinese study, the depression subscales were significantly higher in women with PCOS with infertility compared with women with PCOS women without infertility (36). Neither of these studies had a control arm. Several studies have examined the relationship between BMI and depressive symptoms in PCOS, and in two meta-analyses depression scores positively correlated with BMI (8, 26). Data regarding association of clinical/biochemical androgen excess and depressive symptoms are mixed (37–40). However, the sensitivity analysis showed a weak positive correlation between depression scores and hirsutism scores (26). Smaller studies show that depression scores correlate with insulin resistance, lipid parameters, severity of metabolic syndrome (41), and level of physical activity (42, 43). However, the SMD values suggested that the effect size of all these associations was small. Overall, based on the current literature, infertility, obesity, and androgen excess do not seem to fully account for increased depressive symptoms in women with PCOS.

Does the prevalence of depressive symptoms in women with PCOS change over time? A small prospective U.S. study reported a persistently high rate of depressive symptoms in women with PCOS over a 2-year period (44). A cohort study from a Taiwanese national health insurance research database reported an approximately 30% increased risk of depression in women with PCOS (n = 5,431) compared with controls (n = 21,724; hazard ratio [HR], 1.2; 95% CI, 1.084–1.550) that

remained high over a 5-year period (45). In a longitudinal study of the population-based Northern Finland Birth Cohort 1966 (NFBC66) (46), the risk of reporting depression or being treated for depression was significantly increased at both age 31 and 46 in women with PCOS compared with controls.

Does treatment of PCOS symptoms also improve depressive symptoms?

Lifestyle intervention (LS). Lifestyle management including increased physical activity and dietary intervention is a component of primary management for PCOS (2). Few randomized controlled trials (RCT) have evaluated the benefits of LS on depressive symptoms (Table 1). Thomson et al. reported significant improvements in depressive symptoms in overweight/obese women with PCOS in three LS groups after 20 weeks. It should be noted that all three groups achieved similar weight loss and there was no control group (47). Galletly et al. reported significant reductions in depression scores with a high protein, low carbohydrate diet for 16 weeks compared with a low protein, high carbohydrate diet. All participants in this study attended a weekly exercise program, and there was no difference in weight loss between the study groups (48). In the OWL-PCOS study comparing oral contraceptive pills (OCPs), LS, and a combination of OCPs and LS for 4 months, the prevalence of abnormal depression scores decreased from 22.7% to 15.9% in the LS group (49). While the evidence in the general population shows improvement in depression scores with weight loss, none of the above studies included a control group and comparisons were made to baseline values only.

Acupuncture. Electroacupuncture has been found to improve some PCOS-related symptoms (50), partly mediated via modulation of sympathetic nerve activity (51). A secondary analysis of an RCT comparing acupuncture, exercise, and no intervention in 72 women with PCOS for 16 weeks reported a modest improvement in depression scores only in the acupuncture group (Table 1) (52).

Pharmacotherapy. OCPs are first-line pharmacotherapy for PCOS (2). In a prospective cohort study (n = 36), there was no significant change in depression scores after 6 months of OCPs in lean/overweight women with PCOS, despite improvement in hirsutism and menstrual irregularity (Table 1) (53). In the OWL-PCOS RCT described above, the prevalence of abnormal depression scores decreased significantly in the OCP group (13.3% to 4.4%, Table 1) (49). While there is some evidence that OCPs increase depression in the general population (54), OCP containing drosperinone are also prescribed for treatment of psychiatric conditions such as premenstrual depressive disorder (55). Only two studies have examined the effects of insulin-sensitizing agents on depressive symptoms with mixed results (56, 57). Kashani et al. found significant improvement in depression scores with pioglitazone treatment of women with PCOS and MDD (57).

CBT. We identified no published data using CBT to improve depressive symptoms in adult women with PCOS.

Treatment of hirsutism. In one RCT examining the effects of laser therapy on hirsutism in 88 women with PCOS, mean depression scores decreased significantly at the end of 6 months (Table 1) (58).

Summary of evidence, limitations, and recommendations. Our review indicates a significantly increased prevalence of moderate and severe depressive symptoms in women with PCOS compared with controls. Further, the increased prevalence of depressive symptoms is independent of BMI. However, very few studies have confirmed the diagnosis of depression based on clinical interviews and there are insufficient data to determine depressive symptoms across PCOS phenotypes, especially hyperandrogenic versus nonhyperandrogenic. No study comparing two or more ethnicities using the same PCOS selection criteria and screening tools for depression was identified. In a sensitivity analysis, studies from North America, Europe, Asia, and Australia all showed a higher prevalence of depression scores in women with PCOS compared with their geographically matched controls (26). In addition, limited studies have addressed our prioritized questions related to race, long-term follow-up, and treatment effects. A few longitudinal studies suggested a persistent high prevalence of depressive symptoms and depression over time. Similarly, a few studies with small numbers of subjects evaluated the impact of lifestyle management and pharmacotherapy for short durations on depression scores and showed no change or some improvement of depressive symptoms.

Based on these findings, we recommend that women with PCOS should be routinely screened for depressive symptoms at the time of diagnosis, using simple screening tools validated in the region of practice. If the screening test is positive, practitioners should further assess, refer appropriately, or offer treatment. If screening is negative, we suggest repeat screening in high-risk women such as those with anxiety, obesity, diabetes, and family history of depression and those in the postpartum period. Based on current data, treatment strategies for symptoms of PCOS should follow published guidelines in women who have concomitant depressive symptoms. Our review highlights that, moving forward, studies should include the diagnosis of clinical depression, explore PCOS phenotypes, and include a screen for depressive symptoms in all intervention studies.

Anxiety Symptoms and Disorders in PCOS

Is there an increase in prevalence and/or severity of anxiety symptoms and disorders in women with PCOS? Several meta-analyses have reported that women with PCOS have significantly higher anxiety scores compared with controls (7–9), however, there was heterogeneity among included studies and the clinical significance of the findings was unclear. A recent rigorous meta-analysis mentioned above (26) showed an increased odds of high anxiety scores (OR, 5.62; 95% CI, 3.22, 9.80, n = 10 studies) and also increased odds of moderate and severe anxiety scores (OR, 5.38; 95% CI, 2.28, 12.67) compared with controls (26). The median prevalence of anxiety symptoms was 41.9% (IQR, 13.6%, 52.0%) in the PCOS group and 8.5% (IQR, 3.3%, 12.0%) in the control group. There was, however, heterogeneity among studies. In a large population-based study in Sweden, women

TABLE 1

Randomized controlled trials and cohort studies assessing the effect of polycystic ovary syndrome (PCOS)-related treatments on depression and/or anxiety symptoms in women with PCOS.

Authors and intervention type	Inclusion criteria	Groups (no. of subjects)	Treatment length	Screening tool	Effect on depression (D)/ anxiety (A)
Galletly et al. (2007), life style intervention	Overweight women with PCOS. Two groups were matched on age, weight, and whether trying to conceive.	High protein low carbohydrate (HPLC) diet (n = 14). Low protein high carbohydrate (LPLC) diet (n = 14). Both groups, weekly group exercise and education program.	12 wk caloric restricted (~6,000 kJ/d), 4 wk of maintenance	HADS	Baseline/wk 16 scores: (D) HPLC: 5.6 ± 3.2/3.6 ± 2.8[b] LPHC: 4.8 ± 3.4/4.1 ± 3.3 (A) HPLC: 9.1 ± 3.3/7.8 ± 3.9 LPHC: 8.6 ± 3.9/9.1 ± 3.1
Thomson et al. (2009), LS	Overweight/obese women with PCOS	Diet (DO), ~6,000 kJ/ d energy restricted high protein (n = 30). Diet and aerobic exercise (DA) (n = 31). Diet and aerobic-resistance exercise (DC) (n = 33)	20 wk	CES-D	Week 0/wk 10/wk 20 depression scores: DO: 18.2 ± 2.5/13.0 ± 2.7[b]/16.6 ± 3.3 DA: 18.6 ± 2.2/10.6 ± 1.8[b]/14.0 ± 2.4 DC: 13.4 ± 1.7/9.3 ± 1.5[b]/ 12.8 ± 1.8
Stener-Victorin et al. (2013), acupuncture and LS	Women with PCOS, randomization stratified by age and BMI	Acupuncture (A), 14 treatments over 16 wk (n = 28). Exercise (E), 30 min at least 3 d/wk (n = 29). Control (C), no intervention (n = 15).	16 wk of intervention, scores repeated an additional 16 wk later	MADRS-S BSA-S	Difference in wk 16-baseline/wk 32 baseline scores (D) A: -0.96 ± 5.25/–1.00 ± 8.07[a] E: 0.52 ± 7.62/0.55 ± 8.00 C: 1.53 ± 5.33/1.00 ± 6.94 Time × treatment is not significant at both times (A) A: –1.61 ± 4.72/–1.74 ± 7.88*[b] E: 0.41 ± 5.62/1.41 ± 6.86[c] C: –0.13 ± 3.96/–1.53 ± 3.78. Time × treatment NS at week 16; time × treatment, *P*=.027 at week 32.
Dokras et al. (2016), LS/ pharmacotherapy	Overweight/obese women with PCOS	Lifestyle modification (LS), caloric restriction, physical activity ± weight loss medication (n = 44). OCP, 20 μg ethinyl estradiol/1 mg norethindrone acetate (n = 45). Combined LS + OCP (n = 43)	16 wk	Positive screen on Prime –MD and/or medication use	Prevalence baseline/week 16 scores (D) LS: 22.7%/15.9% OCP: 13.3%/4.4%[a] Combined: 11.6%/11.9% (A) LS: 15.9%/4.7%[a] OCP: 6.7%/2.2% Combined: 2.3%/0%

Dokras. Depression and anxiety symptoms in PCOS. Fertil Steril 2018.

TABLE 1

Continued.

Authors and intervention type	Inclusion criteria	Groups (no. of subjects)	Treatment length	Screening tool	Effect on depression (D)/ anxiety (A)
Clayton et al. (2005), laser treatment of facial hair	Women with PCOS with facial hirsutism	Intervention (I), five high-fluence laser hair treatments (n = 51) Control (C), five sham treatments at low fluence (n = 37)	6 mo	HADS	Mean baseline/mo 6 scores (D) I: 6.7 ± 4.5/3.6 ± 3.5 C: 6.1 ± 3.7/5.4 ± 3.8 Time × treatment $P<.05$ (A) I: 11.1 ± 3.5/8.2 ± 3.8 C: 9.6 ± 4.5/9.3 ± 4.9 Time × treatment $P<.05$
Kashani et al. (2013), pharmacotherapy	Obese women with MDD and PCOS	Metformin 750 mg twice daily (n = 38). Pioglitazone 15 mg twice daily (n = 38)	6 wk	HRDS	Mean difference (wk 3 to week 0/wk 6 to wk 0) in scores (D) Metformin: –0.3 ± 0.7/–1.3 ± 0.9 Pioglitazone: –3.3 ± 1.9/ 5.6 ± 2.1[b]
Cinar et al. (2012), pharmacotherapy	Lean/overweight	Cohort (n = 36) OCP, 30 μg ethinyl estradiol and 3 mg drosperinone	6 mo	BDI HADS	Mean scores baseline/mo 6 Scores (D) 10.2 ± 7.6/10.4 ± 7.1 (A) 13.5 ± 7.6/13.2 ± 8.4
Marsh et al. (2013), pharmacotherapy	Obese PCOS	Cohort (n = 7), metformin 1,500 mg	16 wk	BDI STAI	Mean scores baseline/ 16 wk (D) 5 ± 4.5/6 ± 9 (A) 31.5 ± 16.3/28 ± 6

Note: Modified from Cooney and Dokras (93). HADS = Hospital Anxiety and Depression Scale; CESD = Center for Epidemiologic Studies Depression scores; STAI = State-Trait Anxiety Inventory; MADRS-S = Montgomery Åsberg Depression Rating Scale; BSA-S = Brief Scale for Anxiety; HDRS = Center Hamilton Depression Rating Scale; DASS 21 = Depression, Anxiety, Stress Scales.

[a] $P < .05$ compared with baseline measurement within the same group.

[b] $P < .01$ compared with baseline measurement within the same group.

Dokras. Depression and anxiety symptoms in PCOS. Fertil Steril 2018.

diagnosed with PCOS matched for sex, year of birth, and county of residence to 10 individuals randomly selected from the general population had an increased adjusted OR for anxiety disorders including social phobia and obsessive-compulsive disorders (OR, 1.37; 95% CI, 1.32, 1.43) (30). In the large hospital database from Western Australia, the incidence of recorded clinical anxiety disorders in women with PCOS (14%) was significantly higher compared with women who did not have a diagnosis of PCOS (5.9%) (30). Collectively, these studies indicate increased anxiety symptoms and anxiety disorders in women with PCOS.

What are the associations between features of PCOS and anxiety symptoms? Several small studies have examined the associations among hyperandrogenism, obesity, and anxiety symptoms. Hirsutism and circulating T were not significantly related to effect size variations (8) or were positively but weakly associated with anxiety symptoms (26). These findings may be due to small study size and low sensitivity and specificity of T assays. In the Finnish NFBC66 study described above (46), BMI and hyperandrogenism were not associated with anxiety symptoms. In an experimental setting, maternal androgen exposure causes anxiety-like behavior in adult female and male rats (59). The anxiety-like behavior was accompanied by disordered androgen receptor function in the amygdala, together with changes in estrogen receptor-alpha, serotonergic, and GABAergic genes in amygdala and hippocampus. However, further studies are needed in humans to elucidate the etiology of increased anxiety symptoms in women with PCOS.

Are there differences among PCOS phenotypes in the prevalence of anxiety symptoms? Only one study has compared anxiety scores between NIH and reproductive PCOS phenotypes and did not detect significant differences (31).

Does the prevalence of anxiety symptoms in women with PCOS change over time? In the Finnish NFBC66 study, 16.1% of women with PCOS at age 31 years reported anxiety symptoms compared with 8.2% in women without PCOS (46). The same population was surveyed at 46 years of age, and 27.1% of women with PCOS reported anxiety symptoms compared with 16.3% of women without PCOS (60). In the Taiwanese longitudinal study, an approximately 40% increased risk of anxiety disorders was reported in women with PCOS compared with controls over a 5-year period (HR, 1.392; 95% CI, 1.121–1.729) (45).

Does treatment of PCOS symptoms also improve anxiety symptoms?

LS. Increasing evidence indicates that physical exercise or even increased physical activity improves many PCOS symptoms (61). There are very few RCTs comparing the impact of LS on anxiety symptoms. Intensive LS associated with weight loss in the OWL-PCOS study resulted in a significant reduction in the prevalence of anxiety symptoms (Table 1) (49). However, Stener-Victorin et al. did not find a significant difference in anxiety scores after 16 weeks of physical exercise, although it was not associated with weight loss (52).

Acupuncture. Although there are a few studies indicating that acupuncture may improve anxiety symptoms or disorders in non-PCOS patients (62), only one study has investigated the effects of acupuncture in women with PCOS (52) with nonsignificant improvement in anxiety scores.

CBT. We identified no published data using CBT to improve anxiety symptoms in adult women with PCOS.

Pharmacological treatment. In one cohort study, use of OCPs for 6 months in lean/overweight women with PCOS did not change anxiety scores (53). Similarly, in overweight/obese women with PCOS, randomized to the low-dose OCP arm for 4 months in the OWL-PCOS study, there was a nonsignificant decrease in anxiety scores (49). We identified only one study reporting the impact of metformin on anxiety scores, with no difference after 16 weeks (56).

Treatment of hirsutism. In one RCT, effective hair removal with laser therapy in women with PCOS was associated with significant decrease in anxiety scores after 6 months (58).

Summary of evidence, limitations, and recommendations. Our review indicates an increased prevalence of moderate and severe anxiety scores in women with PCOS compared with controls. Few studies, however, have reported on differences in specific anxiety disorders. Similar to the findings in depression, there are insufficient data to determine differences in prevalence of anxiety symptoms based on PCOS phenotypes, and we did not identify any study directly comparing subjects of different ethnicities/races recruited in the same manner and using the same screening tools. There are also very few longitudinal studies addressing changes in anxiety symptoms over time; however, these studies do suggest a persistent high prevalence of these symptoms. Only a few small studies conducted over relatively short time periods have evaluated the impact of current treatments of PCOS on anxiety symptoms, indicating that LS and pharmacotherapy have no detrimental effect or may improve anxiety scores.

Based on these findings, we recommend that anxiety symptoms should be routinely screened in all women with PCOS using simple screening tools validated in the region of practice. If the screening test is positive, practitioners should further assess, refer appropriately, or offer treatment. If the screen is negative, we suggest repeat screening in high-risk women such as those with depression and obesity. Treatment of symptoms of PCOS should follow published guidelines in women who have concomitant anxiety symptoms. Future research should include specific anxiety disorders as outcomes, compare the prevalence of anxiety symptoms in different PCOS phenotypes, examine changes over time, and include a screen for anxiety symptoms in all intervention studies.

HRQoL in Women with PCOS

HRQoL is an important health outcome in chronic disease (63) and relates to the physical, social, and emotional effects of a disease and its associated treatments (64). The commonly used tools for screening in women with PCOS are the PCOSQ scale, which includes domains to assess emotions, body hair, weight, infertility difficulties, and menstrual problems, and

the modified version (MPCOSQ), which includes an acne domain (65, 66).

Are HRQoL scores reduced in women with PCOS? Studies consistently demonstrate reduced HRQoL scores in women with PCOS, compared with control groups and normative population data (27,67–70). In women with PCOS, HRQoL occurs in the context of the multitude of clinical features and is affected by anxiety, poor body image and low self-esteem, depressive symptoms, delayed diagnosis, and inadequate education and information provision by health professionals (25, 71). Bazarganipour et al. in a meta-analysis showed that key domains with lower scores were hirsutism and menstruation (27). Here we updated this systematic analysis as shown in Table 2. A key challenge in data interpretation is the diversity of source populations studied including endocrine and (41, 69) gynecology clinics (27, 70) and baseline measures from infertility trials (72). This bias in recruitment is likely to impact on specific domains, with subjects recruited in an infertility setting more likely to be affected by infertility-related domains. Within these limitations, our updated analysis suggests that infertility and weight concerns generally have the most significant impact on HRQoL scores in PCOS.

Are there racial/Ethnic differences in HRQoL scores reported in PCOS? Comparisons between women with PCOS in Brazil and Austria found that Brazilian women had worse PCOS symptoms and lower HRQoL scores (73). In a study comparing South Asian women and Caucasians, those with PCOS had reduced HRQoL scores to similar levels (70). Another study in an Austrian infertility center identified lower HRQoL scores in all domains, especially infertility in PCOS Muslim immigrant women compared with women from the host country (74). This finding was attributed to significant reproductive pressure within the Muslim culture. Likewise, a study from Iran noted hirsutism as having the greatest impact on overall HRQoL (75).

Are there differences among PCOS phenotypes in HRQoL scores?. In one study, women with NIH-defined PCOS had lower HRQoL scores related to infertility, emotions, and weight compared with non-NIH phenotype (31). In a Turkish study (using the brief World Health Organization tool) (76), physical, spiritual, environmental, and overall HRQoL scores were lower in women with the hyperandrogenism and ovulatory disturbance phenotype.

Does treatment of PCOS symptoms improve HRQoL scores?

LS. In a 24-week LS cohort study consisting of diet, exercise, and psychological components, and although BMI did not change, HRQoL scores significantly improved compared with baseline (). In the OWL-PCOS RCT, overweight/obese women in the LS arm lost ~7% body weight and significantly improved HRQoL scores (49).

Acupuncture. Stener-Victorin et al. reported improvement in overall HRQoL scores in the exercise and acupuncture groups (52).

Pharmacotherapy. OCP use in lean women with PCOS for 6 months and obese women with PCOS for 4 months improved HRQoL scores, alongside improved hirsutism and menstrual disturbances (49, 53, 77). In a secondary analysis of a large infertility study including women with PCOS (78), HRQoL scores in the clomiphene plus metformin arm were significantly lower than in the clomiphene plus placebo arm. On the other hand, in an observational study in Taiwan, metformin use improved HRQoL scores, especially in women who were hyperandrogenic and overweight at baseline (79). In an RCT of gonadotropins versus laparoscopic electro cautery (n = 162), there was no impact on HRQoL scores in both groups (80).

Treatment of hirsutism. In the previously reported study, women with PCOS randomized to laser therapy had improved HRQoL scores compared with controls (58).

CBT. A large RCT on the impact of CBT and LS in PCOS is currently underway and will include all psychological endpoints and HRQoL (81).

Summary of evidence, limitations, and recommendations. HRQoL, reflecting patient reported outcomes, is consistently reduced in women with PCOS compared with controls. There are insufficient data to compare differences in HRQoL scores in women with different PCOS phenotyes. The dimensions assessed in PCOS-specific HRQoL measures are dynamic across the lifespan; however, there are very few studies specifically addressing change in HRQoL scores over time. A few studies show that weight management and OCP use may improve HRQoL scores. Given that patient-reported outcomes are important to guide treatment and PCOS-specific HRQoL measures can highlight features most relevant to affected women, assessment should be undertaken in all intervention studies and should also be considered in clinical care using tools such as PCOSQ and MPCOSQ. Dimensions of HRQoL most severely affected on screening should then be targeted in treatment.

Disordered Eating and ED in PCOS

ED like anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) have high rates of medical complications. The community prevalence of AN in women is 0.9%, of BN is 1.5%, and of BED is 3.5% (82). BN is typically characterized by recurrent episodes of binges (overeating), followed by extreme behavior to control body shape and weight, like vomiting, laxatives, fasting, and so on that takes place a minimum of twice weekly for $\geq$3 months. BED is defined as recurrent binge eating, marked distress about the binge eating, and absence of inappropriate weight-compensatory behavior that characterizes BN. AN is a condition of severe undernutrition, restrictive eating, and body image disturbance characterized by low BMI, fat, and lean mass. Disordered eating refers to the far more common eating and weight-related symptoms commonly associated with diagnosable ED and includes behavioral, cognitive, or emotional symptoms.

Is the prevalence of disordered eating or ED increased in PCOS? The prevalence for any ED diagnosis in women with PCOS ranges from 12% to 36% (67, 68). Two studies have reported an increase in the prevalence of BED (28) and diagnosis of any ED (21%) in women with PCOS compared

TABLE 2

Update on PCOSQ subscales in women with PCOS.

Study/country	Study type/no.	Setting	Age, mean ± SD	BMI, kg/m^2, mean ± SD	PCOSQ/MPCOSQ scores[a] mean ± SD (CI) or median and (IQR)					
					Emotional	Menstrual	Infertility	Hirsutism	Weight	Acne
Bazarganipour et al. (2015)/Iran[b]	CS/200	Infertility center/private gynecology clinic	26.49 ± 4.42	<25 = 84 ± 42; 25–30 = 83 ± 41.5; > 30 = 33 ± 16.5	4.21 ± 1.57	4.04 (1.42)	3.26 (1.66)	5.24 (1.93)	4.87 (1.88)	5.60 (1.59)
De Frene et al. (2015)/Belgium	CS/31	Reproductive medicine, infertility center	30.1 ± 5.1	All were overweight (BMI of ≥25)	4.1 (1.4)	3.3 (1.7)	3 (1.4)	4.8 (3.7)	2.7 (1.8)	
Khomami et al. (2015)/Iran	CS/796	Reproductive endocrinology research center	28.02 ± 6.02	26.63 ± 5.70	5.05 ± 1.41	4.61 ± 1.54	5.14 ± 1.74	5.02 ± 1.94	4.98 ± 1.88	
Legro et al. (2013)/United States	RCT/733	Academic center infertility clinical trial	28.9 ± 4.3	35.1 ± 9.3	4.5 ± 1.3	4.1 ± 1.1	2.9 ± 1.4	4.1 ± 1.8	3.3 ± 1.9	
Stefanaki(2015)/Greece	RCT/I = 23 C = 15	PCOS clinic division of endocrinology	23.4 ± 4.62 28.3 ± 7.20	I = 21.53 ± 2.15; C = 23.7 ± 4.4	I = 35.21 ± 11.7; C = 31.06 ± 14.5	I = 16 ± 6.63; C= 14.2 ± 6.1	I = 18.78 ± 8; C = 14 ± 8.1	I = 22.3 ± 9; C = 22.3 ± 9.19	I = 21.7 ± 10.21; C = 17 ± 10.6	
Turner-McGrievy (2015)United States[c]	RCT/18	Infertility cohort	27.8 ± 4.5	39.9 ± 6.1	3.0 ± 0.9	3.2 ± 1.1	1.5 ± 0.7	2.6 ± 1.6	1.8 ± 0.8	

Note: CS = cross-sectional.
[a] At baseline if an intervention study.
[b] Used MPCOSQ. All other studies used PCOSQ, where each item is associated with a seven-point Likert scale, in which a score of 7 suggest no problems or difficulties or concerns and 1 indicates high concern or maximum HRQoL impairment on that item.
[c] Did not use Rotterdam criteria to define PCOS.

Dokras. Depression and anxiety symptoms in PCOS. Fertil Steril 2018.

with controls. Hollinrake et al. reported an increased prevalence of BED in women with PCOS (n = 103, 12.6%) compared with controls (1.9%) (28). A case controlled study reported a high prevalence for the diagnosis of any ED (21%) based on clinical MINI international interviews in women with PCOS (n = 49) (85). On the other hand, several studies report higher disordered eating scores in women with PCOS (83–88). A recent survey of 148 women with PCOS reported an increased risk of abnormal ED questionnaire (EDE-Q) scores compared with controls (12.16% vs. 2.83%; OR, 4.75; 95% CI, 1.36, 16.58) (83). In the previously mentioned Swedish registry, study subjects with PCOS reported an increased risk of BN among women with PCOS, even after controlling for psychiatric comorbidity (adjusted OR, 1.21; 95% CI, 1.03, 1.41) (29). Although numerically small, collectively these studies suggest an increased risk of disordered eating and ED in women with PCOS.

What are the associations between features of PCOS and disordered eating and ED? In the general population, there is a well-established association between BED and obesity (82). Although data in the PCOS population are limited, some studies have identified a correlation between BMI and ED scores (83, 84). There is also a known relationship with psychiatric comorbidities such that presence of anxiety increased the risk of disordered eating by almost fivefold, after controlling for age and BMI in women with PCOS (84). After adjusting for BMI and age, Lee et al. reported women with PCOS and anxiety or depressive symptoms were at increased risk of having disordered eating compared with women with PCOS but without anxiety or depressive symptoms (83). Elevated EDE-Q scores were inversely correlated with lower HRQoL scores ($r = -0.57$; $P < .001$). Similarly, another study reported that depressed women with PCOS were more likely to have BED than nondepressed women with PCOS (28). Studies also show that overweight women with PCOS-related infertility have poor eating behaviors for achieving a healthy body weight and low HRQoL scores (89, 90).

Do treatments of PCOS symptoms improve disordered eating and ED in women with PCOS? There is no information on impact of PCOS-related treatments on disordered eating. In the general population, lifestyle modifications, exercise, dietary strategies, and CBT (91) have been prescribed for disordered eating and ED such as BN and BED. In the United States, the Food and Drug Administration has recently approved lisdexamfetamine dismesylate for pharmacotherapy of BED, but its use has not been specifically tested in women with PCOS.

Summary of evidence, limitations, and recommendations. Published studies indicate an increased prevalence of ED and disordered eating in women with PCOS compared with controls. The degree of risk is, however, unclear with relatively few studies. Further, there are no data regarding change in prevalence over time, differences in prevalence based on PCOS phenotype, race, or ethnicity, or impact of common PCOS-related treatments on these conditions. We suggest that disordered eating may be routinely screened in all women with PCOS at diagnosis using screening tools validated in the region of practice. If the screen is positive, practitioners should further assess, refer appropriately, or offer treatment. Further research is needed in all aspects of disordered eating and ED related to PCOS.

CONCLUSIONS

PCOS should be recognized as a condition associated with increased prevalence of depressive and anxiety symptoms and reduced HRQoL. Even when mild to moderate, these symptoms can affect a person's motivation to follow through with treatment and have been linked to adverse outcomes. We recommend screening for these conditions using simple validated tools at diagnosis and subsequently in women at higher risk. Consistent with NIH recommendations (92), further research is needed to determine the impact of PCOS phenotypes, race, ethnicity, and age on prevalence of depressive and anxiety symptoms, HRQoL, and disordered eating. Moving forward, all intervention studies in women with PCOS should assess the impact of treatment on depressive, anxiety, and HRQoL symptoms. There is early evidence suggesting that disordered eating and ED are associated with PCOS, a finding that can affect the choice of LS strategies recommended as first-line therapy.

REFERENCES

1. Teede HJ, Misso ML, Deeks AA, Moran LJ, Stuckey B, Wong J, et al. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. Med J Austral 2011;195:S65.
2. Legro R, Arslanian S, Ehrmann D, Hoeger K, Murad H, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metabol 2013;98:4565–92.
3. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, et al. The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. Eur J Endocrinol 2014;171:P1–29.
4. Group REA-SPCW. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–7.
5. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril 2016;106:6–15.
6. Dokras A, Clifton S, Futterweit W, Wild R. Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis. Obstet Gynecol 2011;117:145–52.
7. Barry JA, Kuczmierczyk AR, Hardiman PJ. Anxiety and depression in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod 2011;26:2442–51.
8. Veltman-Verhulst SM, Boivin J, Eijkemans MJ, Fauser BJ. Emotional distress is a common risk in women with polycystic ovary syndrome: a systematic review and meta-analysis of 28 studies. Hum Reprod Update 2012;18:638–51.
9. Dokras A, Clifton S, Futterweit W, Wild R. Increased prevalence of anxiety symptoms in women with polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril 2012;97:225–30.e222.
10. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJL, et al. Burden of depressive disorders by country, sex, age, and year. Findings from the global burden of disease study. PLOS Med 2013;10:e1001547.
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, D.C.: American Psychiatric Association; 2013.
12. Merikangas KR, He JP, Burstein M, Swanson SA, Avenevoli S, Cui L, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication–Adolescent Supplement (NCSA). J Am Acad Child Adolesc Psychiatry 2010;49:980–9.

13. Salk RH, Petersen JL, Abramson LY, Hyde JS. The contemporary face of gender differences and similarities in depression throughout adolescence: development and chronicity. J Affect Disord 2016;205:28–35.
14. Chien YL, Gau SS, Gadow KD. Sex difference in the rates and co-occurring conditions of psychiatric symptoms in incoming college students in Taiwan. Compr Psychiatry 2011;52:195–207.
15. Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, et al. Cross-national epidemiology of DSM-IV major depressive episode. BMC Med 2011;26:90.
16. Piccinelli M, Wilkinson G. Gender differences in depression: critical review. Br J Psychiatry 2000;177:486–92.
17. Siu AL, Bibbins-Domingo K, Grossman DC, Baumann LC, Davidson KW, Ebell M, et al. Screening for depression in adults: US Preventive Services Task Force recommendation statement. JAMA 2016;315:380–7.
18. Qaseem A, Barry MJ, Kansagara D. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med 2016;164:350–9.
19. World Health Organisation. mhGAP intervention guide, ver. 2.0. http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/.
20. Andlin-Sobocki P, Wittchen HU. Cost of anxiety disorders in Europe. Eur J Neurol 2005;12(Suppl 1):39–44.
21. Bale TL, Epperson CN. Sex differences and stress across the lifespan. Nat Neurosci 2015;18:1413–20.
22. Parker G, Hadzi-Pavlovic D. Is the female preponderance in major depression secondary to a gender difference in specific anxiety disorders? Psychol Med 2004;34:461–70.
23. Baxter AJ, Vos T, Scott KM, Ferrari AJ, Whiteford HA. The global burden of anxiety disorders in 2010. Psychol Med 2014;44:2363–74.
24. Moreno-Peral P, Conejo-Ceron S, Motrico E, Rodriguez-Morejon A, Fernandez A, Garcia-Campayo J, et al. Risk factors for the onset of panic and generalised anxiety disorders in the general adult population: a systematic review of cohort studies. J Affect Disord 2014;168:337–48.
25. Gibson-Helm M, Teede H, Dunaif A, Dokras A. Delayed diagnosis and a lack of information associated with dissatisfaction in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2017;102:604–12.
26. Cooney LG, Lee I, Sammel MD, Dokras A. High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod 2017;32:1075–91.
27. Bazarganipour F, Taghavi SA, Montazeri A, Ahmadi F, Chaman R, Khosravi A. The impact of polycystic ovary syndrome on the health-related quality of life: a systematic review and meta-analysis. Iran J Reprod Med 2015;13:61–70.
28. Hollinrake E, Abreu A, Maifeld M, Van Voorhis BJ, Dokras A. Increased risk of depressive disorders in women with polycystic ovary syndrome. Fertil Steril 2007;87:1369–76.
29. Cesta CE, Mansson M, Palm C, Lichtenstein P, Iliadou AN, Landen M. Polycystic ovary syndrome and psychiatric disorders: co-morbidity and heritability in a nationwide Swedish cohort. Psychoneuroendocrinology 2016;73:196–203.
30. Hart R, Doherty DA. The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage. J Clin Endocrinol Metab 2015;100:911–9.
31. Moran LJ, Deeks AA, Gibson-Helm ME, Teede HJ. Psychological parameters in the reproductive phenotypes of polycystic ovary syndrome. Hum Reprod 2012;27:2082–8.
32. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010;67:220–9.
33. Jedel E, Gustafson D, Waern M, Sverrisdottir YB, Landén M, Janson PO, et al. Sex steroids, insulin sensitivity and sympathetic nerve activity in relation to affective symptoms in women with polycystic ovary syndrome. Psychoneuroendocrinology 2011;36:1470–9.
34. Livadas S, Chaskou S, Kandaraki AA, Skourletos G, Economou F, Christou M, et al. Anxiety is associated with hormonal and metabolic profile in women with polycystic ovarian syndrome. Clin Endocrinol 2011;75:698–703.
35. Deeks AA, Gibson-Helm ME, Teede HJ. Anxiety and depression in polycystic ovary syndrome: a comprehensive investigation. Fertil Steril 2010;93:2421–3.
36. Shi X, Zhang L, Fu S, Li N. Co-involvement of psychological and neurological abnormalities in infertility with polycystic ovarian syndrome. Arch Gynecol Obstet 2011;284:773–8.
37. Naqvi SH, Moore A, Bevilacqua K, Lathief S, Williams J, Naqvi N, et al. Predictors of depression in women with polycystic ovary syndrome. Arch Women Ment Health 2015;18:95–101.
38. Annagur BB, Tazegul A, Uguz F, Kerimoglu OS, Tekinarslan E, Celik C. Biological correlates of major depression and generalized anxiety disorder in women with polycystic ovary syndrome. J Psychosom Res 2013;74:244–7.
39. Barry JA, Hardiman PJ, Saxby BK, Kuczmierczyk A. Testosterone and mood dysfunction in women with polycystic ovarian syndrome compared to subfertile controls. J Psychosom Obstet Gynaecol 2011;32:104–11.
40. Rahiminejad ME, Moaddab A, Rabiee S, Esna-Ashari F, Borzouei S, Hosseini SM. The relationship between clinicobiochemical markers and depression in women with polycystic ovary syndrome. Iran J Reprod Med 2014;12:811–6.
41. Cinar N, Kizilarslanoglu MC, Harmanci A, Aksoy DY, Bozdag G, Demir B, et al. Depression, anxiety and cardiometabolic risk in polycystic ovary syndrome. Hum Reprod 2011;26:3339–45.
42. Banting LK, Gibson-Helm M, Polman R, Teede HJ, Stepto NK. Physical activity and mental health in women with polycystic ovary syndrome. BMC Women Health 2014;14:51.
43. Lamb JD, Johnstone EB, Rousseau JA, Jones CL, Pasch LA, Cedars MI, et al. Physical activity in women with polycystic ovary syndrome: prevalence, predictors, and positive health associations. Am J Obstet Gynecol 2011;204:352.e1–6.
44. Kerchner A, Lester W, Stuart SP, Dokras A. Risk of depression and other mental health disorders in women with polycystic ovary syndrome: a longitudinal study. Fertil Steril 2009;91:207–12.
45. Hung JH, Hu LY, Tsai SJ, Yang AC, Huang MW, Chen PM, et al. Risk of psychiatric disorders following polycystic ovary syndrome: a nationwide population-based cohort study. PLoS One 2014;9:e97041.
46. Karjula S, Morin-Papunen L, Auvinen J, Ruokonen A, Puukka K, Franks S, et al. Psychological distress is more prevalent in fertile age and premenopausal women with PCOS symptoms—15-yr follow-up. J Clin Endocrinol Metab 2017;102:1861–9.
47. Thomson RL, Buckley JD, Lim SS, Noakes M, Clifton PM, Norman RJ, et al. Lifestyle management improves quality of life and depression in overweight and obese women with polycystic ovary syndrome. Fertil Steril 2009;94:1812–6.
48. Galletly C, Moran L, Noakes M, Clifton P, Tomlinson L, Norman R, et al. Psychological benefits of a high-protein, low-carbohydrate diet in obese women with polycystic ovary syndrome—a pilot study. Appetite 2007;49:590–3.
49. Dokras A, Sarwer DB, Allison KC, Milman L, Kris-Etherton PM, Kunselman AR, et al. Weight loss and lowering androgens predict improvements in health-related quality of life in women with PCOS. J Clin Endocrinol Metab 2016;101:2966–74.
50. Jedel E, Labrie F, Oden A, Holm G, Nilsson L, Janson PO, et al. Impact of electro-acupuncture and physical exercise on hyperandrogenism and oligo/amenorrhea in women with polycystic ovary syndrome: a randomized controlled trial. Am J Physiol Endocrinol Metab 2011;300:E37–45.
51. Stener-Victorin E, Jedel E, Janson PO, Sverrisdottir YB. Low-frequency electroacupuncture and physical exercise decrease high muscle sympathetic nerve activity in polycystic ovary syndrome. Am J Physiol Regul Integr Comp Physiol 2009;297:R387–95.
52. Stener-Victorin E, Holm G, Janson PO, Gustafson D, Waern M. Acupuncture and physical exercise for affective symptoms and health-related quality of life in polycystic ovary syndrome: secondary analysis from a randomized controlled trial. BMC Complement Altern Med 2013;13:413–6.
53. Cinar N, Harmanci A, Demir B, Yildiz BO. Effect of an oral contraceptive on emotional distress, anxiety and depression of women with polycystic ovary syndrome: a prospective study. Hum Reprod 2012;27:1840–5.
54. Skovlund CW, Mørch LS, Kessing LV, Lidegaard Ø. Association of hormonal contraception with depression. J Am Med Assoc Psychiatry 2016;73:1154–62.
55. Lopez LM, Kaptein AA, Helmerhorst FM. Oral contraceptives containing drosperinone for premenstrual syndrome. Cochrane Database Syst Rev 2012:CD006586.

56. Marsh CA, Berent-Spillson A, Love T, Persad CC, Pop-Busui R, Zubieta JK, et al. Functional neuroimaging of emotional processing in women with polycystic ovary syndrome: a case-control pilot study. Fertil Steril 2013; 100:200–7.
57. Kashani L, Omidvar T, Farazmand B, Modabbernia A, Ramzanzadeh F, Tehraninejad ES, et al. Does pioglitazone improve depression through insulin-sensitization? Results of a randomized double-blind metformin-controlled trial in patients with polycystic ovarian syndrome and comorbid depression. Psychoneuroendocrinology 2013;38:767–76.
58. Clayton WJ, Lipton M, Elford J, Rustin M, Sherr L. A randomized controlled trial of laser treatment among hirsute women with polycystic ovary syndrome. Br J Dermatol 2005;152:986–92.
59. Hu M, Richard JE, Maliqueo M, Kokosar M, Fornes R, Benrick A, et al. Maternal testosterone exposure increases anxiety-like behavior and impacts the limbic system in the offspring. Proc Natl Acad Sci U S A 2015;112:14348–53.
60. Piltonen T, Karjula S, Auvinen J, Morin-Papunen L, Miettunen J, Tapanainen JS. Population based cohort analysis reveals persistently high depression and anxiety rates at the age of 46 in women with PCOS and/or hirsutism—a 15-year follow-up study. Fertil Steril 2014;102:e27.
61. Thomson RL, Buckley JD, Brinkworth GD. Exercise for the treatment and management of overweight women with polycystic ovary syndrome: a review of the literature. Obes Rev 2011;12:e202–210.
62. Pilkington K, Kirkwood G, Rampes H, Cummings M, Richardson J. Acupuncture for anxiety and anxiety disorders—a systematic literature review. Acupunct Med 2007;25:1–10.
63. Goldney RD, Phillips PJ, Fisher LJ, Wilson DH. Diabetes, depression, and quality of life: a population study. Diabetes Care 2004;27:1066–70.
64. Moran L, Gibson-Helm M, Teede H, Deeks A. Polycystic ovary syndrome: a biopsychosocial understanding in young women to improve knowledge and treatment options. J Psychosom Obstet Gynecol 2010;31:24–31.
65. Taghavi SA, Bazarganipour F, Montazeri A, Kazemnejad A, Chaman R, Khosravi A. Health-related quality of life in polycystic ovary syndrome patients: a systematic review. Iran J Reprod Med 2015;13:473–82.
66. Malik-Aslam A, Reaney MD, Speight J, Malik-Aslam A, Reaney MD, Speight J. The suitability of polycystic ovary syndrome-specific questionnaires for measuring the impact of PCOS on quality of life in clinical trials. Value Health 2010;13:440–6.
67. Barnard L, Ferriday D, Guenther N, Strauss B, Balen AH, Dye L. Quality of life and psychological wellbeing in polycystic ovary syndrome. Hum Reprod 2007;22:2279–86.
68. Coffey S, Bano G, Mason HD. Health-related quality of life in women with polycystic ovary syndrome: a comparison with the general population using the Polycystic Ovary Syndrome Questionnaire (PCOSQ) and the Short Form-36 (SF-36). Gynecol Endocrinol 2006;22:80–6.
69. Ching HL, Burke V, Stuckey BG. Quality of life and psychological morbidity in women with polycystic ovary syndrome: body mass index, age and the provision of patient information are significant modifiers. Clin Endocrinol 2007; 66:373–9.
70. Jones GL, Palep-Singh M, Ledger WL, Balen AH, Jenkinson C, Campbell MJ, et al. Do South Asian women with PCOS have poorer health-related quality of life than Caucasian women with PCOS? A comparative cross-sectional study. Health Qual Life Outcomes 2010;8:1–8.
71. Deeks AA, Gibson-Helm ME, Paul E, Teede HJ. Is having polycystic ovary syndrome a predictor of poor psychological function including anxiety and depression? Hum Reprod 2011;26:1399–407.
72. Santoro N, Eisenberg E, Trussell JC, Craig LB, Gracia C, Huang H, et al. Fertility-related quality of life from two RCT cohorts with infertility: unexplained infertility and polycystic ovary syndrome. Hum Reprod 2016;31:2268–79.
73. Hashimoto DM, Schmid J, Martins FM, Fonseca AM, Andrade LH, Kirchengast S, et al. The impact of the weight status on subjective symptomatology of the polycystic ovary syndrome: a cross-cultural comparison between Brazilian and Austrian women. Anthropologischer Anzeiger 2003; 61:297–310.
74. Schmid J, Kirchengast S, Vytiska-Binstorfer E, Huber J. Infertility caused by PCOS—health-related quality of life among Austrian and Moslem immigrant women in Austria. Hum Reprod 2004;19:2251–7.
75. Khomami MB, Tehrani FR, Hashemi S, Farahmand M, Azizi F. Of PCOS symptoms, hirsutism has the most significant impact on the quality of life of Iranian women. PLoS One 2015;10:e0123608.
76. Dilbaz B, Çınar M, Özkaya E, Vanlı Tonyalı N, Dilbaz S. Health related quality of life among different PCOS phenotypes of infertile women. J Turkish-German Gynecol Assoc 2012;13:247–52.
77. De Frene V, Verhofstadt L, Lammertyn J, Stuyver I, Buysse A, De Sutter P. Quality of life and body mass index in overweight adult women with polycystic ovary syndrome during a lifestyle modification program. J Obstet Gynecol Neonatal Nurs 2015;44:587–99.
78. Moll E, van Wely M, Lambalk CB, Bossuyt PMM, van der Veen F. Health-related quality of life in women with newly diagnosed polycystic ovary syndrome randomized between clomifene citrate plus metformin or clomifene citrate plus placebo. Hum Reprod 2012;27:3273–8.
79. Huang T, Chen PC, Wu MH, Lin CY. Metformin improved health-related quality of life in ethnic Chinese women with polycystic ovary syndrome. Health Qual Life Outcomes 2016;14:119.
80. van Wely M, Bayram N, Bossuyt PM, van der Veen F. Laparoscopic electrocautery of the ovaries versus recombinant FSH in clomiphene citrate-resistant polycystic ovary syndrome. Impact on women's health-related quality of life. Hum Reprod 2004;19:2244–50.
81. Jiskoot G, Benneheij SH, Beerthuizen A, de Niet JE, de Klerk C, Timman R, et al. A three-component cognitive behavioural lifestyle program for preconceptional weight-loss in women with polycystic ovary syndrome (PCOS): a protocol for a randomized controlled trial. Reprod Health 2017;14:34.
82. Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry 2007;60:348–58.
83. Lee I, Cooney LG, Saini S, Smith ME, Sammel MD, Allison KC, et al. Increased risk of disordered eating in polycystic ovary syndrome. Fertil Steril 2017;107: 796–802.
84. Karacan E, Caglar GS, Gürsoy AY, Yilmaz MB. Body satisfaction and eating attitudes among girls and young women with and without polycystic ovary syndrome. J Pediatr Adolesc Gynecol 2014;27:72–7.
85. Mansson M, Holte J, Landin-Wilhelmsen K, Dahlgren E, Johansson A, Landen M. Women with polycystic ovary syndrome are often depressed or anxious—a case control study. Psychoneuroendocrinology 2008;33: 1132–8.
86. Larsson I, Hulthén L, Landén M, Pålsson E, Janson P, Stener-Victorin E. Dietary intake, resting energy expenditure, and eating behavior in women with and without polycystic ovary syndrome. Clin Nutr 2016;35:213–8.
87. Jeanes YM, Reeves S, Gibson EL, Piggott C, May VA, Hart KH. Binge eating behaviours and food cravings in women with polycystic ovary syndrome. Appetite 2017;109:24–32.
88. Bernadett M, Szemán NA. Prevalence of eating disorders among women with polycystic ovary syndrome. [Hungarian] Psychiatria Hungarica 2016; 2016:136–45.
89. Grievy GT, Davidson CR, Billings DL. Dietary intake, eating disorders and quality of life in women with polycystic ovary syndrome who are trying to conceive. Hum Fertil 2015;18:16–21.
90. Rodino IS, Byne S, Sanders KA. Disordered eating attitudes and exercise in women undergoing fertility treatment. Aus NZ J Obstet Gynecol 2015: 1–6.
91. Murphy R, Srtraebler S, Cooper Z, Faiburn CG. Cognitive behavior therapy for eating disorders. Psychiatr Clin North Am 2010;33:611–27.
92. NIH Evidence based workshop on polycystic ovary syndrome. 2012. Available at: http://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/pcos.
93. Cooney LG, Dokras A. Depression and anxiety in polycystic ovary syndrome: etiology and treatment. Curr Psychiatry Rep 2017;19:8.