

When not to treat depression in PCOS with antidepressants

Other medications may help women with hormone dysregulation and insulin resistance

Natalie Rasgon, MD, PhD

Associate professor
Departments of psychiatry and behavioral sciences
and obstetrics and gynecology
Stanford School of Medicine, Stanford, CA

Shana Elman, MA

Research assistant
Medical College of Wisconsin, Milwaukee

Women with depression and polycystic ovary syndrome (PCOS) can be trapped in a vicious cycle of hormonal dysregulation. Treating these patients appropriately—with or without antidepressants—requires an understanding of their underlying metabolic disorder.

This article presents a case¹ that exemplifies the association between depression and PCOS (*Box 1, page 48*).²⁻⁴ Based on our research and clinical experience, we offer recommendations to help you manage depression in patients with PCOS.

CHRONIC DEPRESSION WITH AMENORRHEA

Ms. K, age 30, presented for psychiatric evaluation of treatment-resistant recurrent major depression. Her symptoms included sad mood, sleep disturbance, decreased energy, anhedonia, poor concentration, and feelings of guilt and worthlessness. Her



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Box 1

Depression often accompanies PCOS

Polycystic ovary syndrome (PCOS) is the most common cause of menstrual disturbance in women of reproductive age, affecting approximately 5% of U.S. women.¹ Clinically, it is the association of hyperandrogenism with chronic anovulation, without specific underlying adrenal or pituitary gland disease.²

PCOS has been shown to be associated with depression, though little research has been done in this area. We conducted a pilot study (the first, to our knowledge) to examine the rate of depression among women with documented PCOS and to correlate Center for Epidemiological Studies Depression Scale (CES-D) scores indicative of depression with clinical and biochemical markers of PCOS. We found an increased prevalence of depression in women with PCOS and an association between depression, insulin resistance, and body mass index. Specifically, among 32 women with documented PCOS,³ 16 (50%) had CES-D scores indicating depression.

score of 28 on the Hamilton Rating Scale for Depression (HAM-D-21) indicated severe depression.

This was Ms. K's third episode of major depression, with the first two occurring at ages 24 and 26. She reported similar symptoms each time. Previous psychiatrists had tried a variety of antidepressants with no therapeutic benefit before she responded to citalopram, 40 mg/d, at age 27. With this selective serotonin reuptake inhibitor, her depressive symptoms resolved for >1 year, except for mild irritability and low mood the week before menses.

Her depressive symptoms returned, however, and her previous psychiatrist treated her for approximately 13 months with extended-release venlafaxine, 225 mg/d. When she remained depressed, she was referred to our clinic for evaluation. Based on her history, we could not determine whether she had become euthymic at age 27 or her symptoms had improved but still met criteria for a major depressive episode.

Ms. K reported having PCOS symptoms from age 19. These included amenorrhea since menarche, hirsutism, hair loss, alopecia, central fat distribution characteristic of PCOS, and male-pattern hair growth on her abdomen and thighs. She was not obese—with a body mass index (BMI) of approximately 25—but had gained 10 to 15 lbs while taking venlafaxine.

Ms. K had never been treated for PCOS but reported that her desire to become pregnant made her more concerned about her symptoms and possible infertility.

Diagnosis. PCOS is usually diagnosed using endocrinologic, clinical, and ultrasonographic criteria (*Table 1*). Obesity is not a presenting symptom in all women with PCOS. As with Ms. K, about 50% of patients have normal BMI.

Causes of depression in PCOS. Depressed mood in PCOS may be both physiologic and psychological:

- Hypothalamic, pituitary, and other end-organ system dysregulation occurs in both PCOS and affective disorders, which share clinical and biochemical markers including insulin resistance, obesity, and hyperandrogenism.
- PCOS' clinical sequelae—hirsutism, acne, obesity, hormonal disturbances, fear of infertility, and psychological distress—may damage their self-esteem and female identity.

PCOS' physical symptoms alone apparently do not account for patients' worsened mood states. Weiner et al⁵ found that women with PCOS and free testosterone (FT) of 10 to 26 pg/mL (just above normal range) were more depressed than women without PCOS (FT <10 pg/mL) and women with PCOS and FT >26 pg/mL. Women with PCOS with the lower and higher FT levels had similar demographic profiles, but those with the highest FT levels were not the most depressed.

Similarly, in a study of 32 women with PCOS, we found no association between depression and other possibly distressing PCOS symptoms, including hirsutism, irregular menses, acne, or alopecia.⁴

Testosterone and mood disorders. Women such as Ms. K with hyperandrogenic syndromes are at increased risk for mood disorders.⁶ Many metabolic changes associated with PCOS—insulin resistance, obesity, and hyperandrogenism—are also described in patients with affective disorders. Our investigation of reproductive status in women with bipolar disorder found no clinical or biochemical evidence of PCOS with mood-stabilizer treatment. We did find that menstrual disturbances were common, however, and sometimes preceded bipolar disorder onset.⁷

Insulin resistance and depression. Others have linked insulin resistance and depression;⁸ depression has been shown to be associated with impaired insulin sensitivity and hyperinsulinemia.⁹ Depressed persons also tend to eat more sweets, drink more alcohol, exercise less, and sleep fewer hours than the nondepressed—all of which contribute to insulin sensitivity and insulin resistance.¹⁰

WHAT LINKS ENDOCRINE, MOOD DISORDERS?

Insulin and serotonin. Insulin affects central serotonin (5-HT) levels.¹¹ Thus, central 5-HT system dysregulation that causes depression might also affect peripheral insulin sensitivity—or vice versa.⁹

Tryptophan, a serotonin precursor, competes with other large neutral amino acids for access to the transport system that moves them across the blood-brain barrier. Insulin stimulates uptake of the competing amino acids—but not tryptophan—into muscle tissue. The resulting increased tryptophan ratio in plasma affords it greater access to the transport system to contribute toward serotonin synthesis. Insulin also promotes central catecholaminergic activity, perhaps by sup-

Table 1

Diagnostic signs of PCOS

Endocrine

Chronically elevated plasma free and total testosterone levels

Increased luteinizing hormone (LH) secretion because of enhanced pituitary sensitivity to GnRH stimulation

Low or normal plasma follicle-stimulating hormone (FSH) levels

Hyperinsulinemia and peripheral insulin resistance

Metabolic abnormalities of hyperinsulinemia and peripheral insulin resistance, including obesity and increased susceptibility to type 2 diabetes and cardiovascular disease

Clinical

Hirsutism

Acne

Infertility

Anovulation or menstrual abnormalities

- amenorrhea
- oligomenorrhea
- dysfunctional uterine bleeding

Morphologic

Ovaries may appear to have multiple cysts 8 to 10 mm in diameter

pressing norepinephrine reuptake and prolonging its residence in the synaptic cleft.¹⁰

Several studies have found that insulin resistance and hyperinsulinemia can resolve after depression recovery.^{9,12} Because insulin resistance is a cardinal feature in PCOS pathophysiology,² insulin resistance may be a common link between depression and PCOS.

Weight gain and obesity also have been described in patients with affective disorders.¹³ Not known is whether the weight gain precedes the psychopathology or is caused by long-term exposure to drugs used to treat affective disorders.

continued



Box 2

Hormonal treatments with possible antidepressant effects in PCOS

CRH antagonists. Corticotropin-releasing hormone (CRH) receptor antagonists have been suggested as possible antidepressants.²⁶ Depression and anxiety scores have declined during treatment with the cortisol synthesis inhibitors metyrapone²⁷ and ketoconazole.^{28,29} These trials do not reveal whether these agents treat depression symptoms—rather than the underlying pathophysiology—or if the affective disorder will recur after long-term administration.²⁶

GR antagonists. Glucocorticoid receptor (GR) antagonists such as mifepristone (RU-486) have been suggested as antidepressants in depressed patients with elevated basal cortisol levels.³⁰ Mifepristone may be useful for treating psychotic depression, in which the HPA axis is particularly hyperactive.³¹ Mifepristone is contraindicated in most women with PCOS, however, as its progesterone antagonism would lead to infertility—already a common problem for women with PCOS.

MR antagonists. Spironolactone, a mineralocorticoid receptor (MR) antagonist, decreases insulin resistance and fasting insulin levels in PCOS patients.²⁵ We propose that insulin resistance may provide a common link in the pathophysiology of PCOS and depression. Therefore, treatment with insulin resistance-lowering medications such as spironolactone may induce antidepressant effects in women with depression and PCOS.

We reported a correlation between depression and BMI in women with PCOS.⁴ Depression might be independently associated with BMI, as weight gain and obesity are distressing symptoms associated with depression.¹⁴ However, we found no association between depression and other possibly distressing PCOS symptoms. Thus, the correlation between BMI and depression might more likely reflect the relationship between depression and insulin resistance, as degree of insulin resistance is known to correlate with BMI.

Elevated cortisol. Clearly, other factors—such as

hypothalamus-pituitary-adrenal (HPA) axis dysfunction—are known to link affective and endocrine disorders. Hypercortisolemia can lead to both insulin resistance and obesity. Cortisol is one of the glucocorticoids the body secretes in response to stress to mobilize energy by increasing blood glucose levels. Early life stress and chronic emotional stress:

- can impair the negative feedback system that limits cortisol production during stress
- are associated with depression.

Approximately one-half of individuals with depression have elevated serum cortisol.¹⁰ Epidemiologic data show a positive correlation between cortisol levels and insulin resistance,¹⁵ and an association between HPA dysfunction and obesity has been described.¹⁶ Insulin can trigger androgen production by enhancing adrenal sensitivity to adrenocorticotrophic hormone (ACTH).¹⁷

CASE: IMPROVING INSULIN RESISTANCE

We referred Ms. K to an endocrinologist for PCOS evaluation and treatment. Her serum glucose and insulin levels were 83 mg/dL (normal range 70 to 125 mg/dL) and 19.0 uIU/mL (normal range <10 uIU/mL), respectively. These values indicated insulin resistance as determined by the homeostasis model assessment (HOMA) ratio (fasting insulin x fasting glucose/22.5). Values >3.2 indicate insulin resistance, and Ms. K had a HOMA ratio of 3.9. The endocrinologist recommended:

- metformin, starting at 850 mg/d and gradually increased to 2,550 mg/d
- spironolactone, 100 mg/d.

Metformin, a biguanide approved for treating for type 2 diabetes, inhibits hepatic glucose production and increases peripheral insulin sensitivity, but it does not modify pancreatic insulin secretion. It

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may decrease insulin resistance by reducing gut absorption of glucose, improving glucose uptake by tissues, and/or increasing the number of insulin receptors.¹⁸ In treating PCOS, metformin can:

- restore ovulation¹⁹
- decrease insulin resistance, acne, hirsutism, total and bioavailable testosterone, BMI, and waist-hip ratio.^{20,21}

Although the link between insulin resistance and depression is unclear, insulin is known to contribute to 5-HT synthesis by promoting tryptophan influx into the brain.²² Therefore, drugs used to treat insulin resistance—such as metformin and alpha lipoic acid²³—might be useful in treating depression.

Spironolactone, a mineralocorticoid receptor (MR) antagonist, reduces hirsutism in women with PCOS.²⁴ It also can decrease insulin resistance and fasting insulin levels in PCOS patients and reduce serum testosterone.²⁵

Evidence on treating mood disorders with hormonal agents such as spironolactone is scarce, although treatment-resistant depression has been reported to resolve with antigluco-corticoid use (*Box 2, page 50*).²⁵⁻³¹ Modulating HPA axis activity to treat affective disorders has been investigated.

CASE: GOING ANTIDEPRESSANT-FREE

At first, Ms. K said she wanted to continue taking venlafaxine with the PCOS treatment. After 2 weeks of combined therapy, however, she chose to stop the antidepressant after her depressive symptoms persisted, and her HAM-D-21 score remained at 28.

During the next 4 weeks, as we tapered off the venlafaxine, Ms. K's HAM-D-21 score dropped to 7, indicating depressive symptom resolution. Despite

slow venlafaxine titration, withdrawal symptoms of excessive crying, not feeling “present,” and tingling sensations occurred. Three days of fluoxetine, 20 mg/d, alleviated these symptoms.

We continued Ms. K's treatment without antidepressants, and her mood continued to improve with metformin, 2,550 mg/d, and spironolactone, 100 mg/d.

TREATMENT RECOMMENDATIONS

PCOS therapy may take up to 6 months to resolve symptoms such as anovulation or hirsutism, but affective symptoms may improve during the first 6 weeks, as this case shows. Choosing medications to treat depression in patients such as Ms. K depends on whether their PCOS is being treated when they present for psychiatric evaluation.

Patient not being treated for PCOS. Refer her to an endocrinologist for PCOS treatment with an insulin-sensitizing medication, such as metformin (*Table 2*). Treating the insulin resistance associated with PCOS may also resolve the depression. PCOS drug therapy may also include antiandrogens such as spironolactone to treat hirsutism, male-pattern baldness, and acne. We suggest that spironolactone's antiandrogen effects may help reduce depressive symptoms.

Table 2

Insulin-sensitizing medications used to treat PCOS

Medication	Normal dosage	Common side effects
Metformin	500 mg tid	Headache, GI effects (nausea, diarrhea, flatulence) at start of therapy, weight loss, taste disturbances
Pioglitazone	15 to 45 mg once daily	Swelling, headache, respiratory infection, abdominal discomfort, muscle soreness
Rosiglitazone	4 to 8 mg once daily	Headache, mild weight gain

continued



If your patient is not taking an antidepressant at presentation, try PCOS treatment first. If depressive symptoms persist after 3 months, consider adding an antidepressant. If your patient is taking an antidepressant at presentation but continues to be depressed, offer two options:

- taper off the antidepressant while starting PCOS treatment
- continue the antidepressant while starting PCOS treatment.

The first option allows you to try PCOS treatment alone. If the depression is caused by a common underlying pathophysiology—such as insulin resistance—treating PCOS alone may alleviate her depressive symptoms. Monitor for withdrawal symptoms, which may be minimized with a short-term SSRI, such as fluoxetine.

The second option may help patients who have responded to antidepressants in the past. Adjunctive PCOS treatment may “jump-start” the antidepressant response without withdrawal symptoms, but you will not be sure whether the antidepressant response was caused by PCOS therapy alone or the combination therapy.

Patient being treated for PCOS. Treat her with antidepressants, and consult with her endocrinologist to consider more-aggressive insulin-sensitizing medications, especially if she exhibits high levels of insulin resistance.

Other interventions that increase insulin sensitivity and improve glycemic control—such as improving dietary management and sleep habits, reducing alcohol consumption, and increasing physical activity—might have an antidepressant effect. Therefore, recommend these health practices to patients as adjuncts to drug therapies.

CASE: DEPRESSION IN REMISSION

At the 3-month follow-up visit, Ms. K scored zero on the HAM-D-21 scale. With metformin treatment, she had lost approximately 10 lbs and resumed menstruating approximately every 33 days. She reported experiencing low mood, decreased energy, and irritability during the week before her periods, but these symptoms resolved with menses onset.

Serum glucose was within normal range at 89 mg/dL, and serum insulin was 15.0 uIU/ml. Her HOMA ratio had dropped to 2.8 (below the 3.2 cut-off for insulin resistance).

Ms. K’s endocrinologist monitored her spironolactone and metformin therapy for approximately 1 year, when she became pregnant.

Discussion. PCOS treatment duration depends on the patient’s response and her goals for therapy. Whether or not she continues PCOS treatment, her primary care physician or endocrinologist should continue to monitor her for insulin resistance’s metabolic consequences, including increased risk of type 2 diabetes and cardiovascular disease.

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Depression in PCOS may be caused by hormonal pathophysiology, such as insulin resistance. Even without antidepressant therapy, depression may improve with metformin to reduce insulin resistance, spironolactone for antitestosterone effects, and diet and exercise to improve insulin sensitivity and glycemic control.

BottomLine



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Related resources

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DRUG BRAND NAMES

Citalopram • Celexa	Mifepristone • Mifiprex
Fluoxetine • Prozac	Pioglitazone • Actos
Ketoconazole • Nizoral	Rosiglitazone • Avandia
Metformin • Glucophage	Spirolactone • Aldactone
Metypalone • Metopirone	Venlafaxine • Effexor XR

DISCLOSURES

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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