REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Polycystic Ovary Syndrome: Update on Diagnosis and Treatment

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ABSTRACT

Polycystic ovary syndrome is now a well-recognized condition affecting 6%-25% of reproductive-aged women, depending on the definition. Over the past 3 decades, research has launched it from relative medical obscurity to a condition increasingly recognized as common in internal medicine practices. It affects multiple systems, and requires a comprehensive perspective on health care for effective treatment. Metabolic derangements and associated complications include insulin resistance and diabetes, hyperlipidemia, hypertension, fatty liver, metabolic syndrome, and sleep apnea. Reproductive complications include oligo-/amenorrhea, sub-fertility, endometrial hyperplasia, and cancer. Associated psychosocial concerns include depression and disordered eating. Additionally, cosmetic issues include hirsutism, androgenic alopecia, and acne. This review organizes this multi-system approach around the mnemonic "MY PCOS" and discusses evaluation and treatment options for the reproductive, cosmetic, and metabolic complications of this condition.

 • *The American Journal of Medicine (2014) 127, 912-919*

KEYWORDS: Hirsutism; Insulin resistance; Irregular menses; Oligomenorrhea; PCOS; Polycystic ovary syndrome; Treatment

The diagnosis of polycystic ovary syndrome has emerged from relative medical obscurity over the past 25 years. It is only since the late 1980s that focused research efforts have attempted to unravel this common yet complex syndrome. In that time, and particularly over the past decade, the once-underdiagnosed condition has gained the attention of practitioners and patients. The result is that more women are receiving the diagnosis appropriately, and evidence about effective treatments is being evaluated. This article provides an update on the care of women with polycystic ovary syndrome. The discussion will be organized around the mnemonic "MY PCOS" in order to emphasize the multiple separate issues to be addressed in managing this condition.[1]

Funding: None.

Conflicts of Interest: None.

Authorship: The authors meet criteria for authorship. The final copy of this article has been approved by both of the authors. Both authors accept responsibility for the scientific content of the manuscript.

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0002-9343/$ -see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjmed.2014.04.017

DIAGNOSIS

There are several diagnostic guidelines for polycystic ovary syndrome, and although different, each relies on combinations of 3 major elements to make the diagnosis: ovulatory dysfunction, hyperandrogenism (clinical or biochemical), and ovarian morphology (see **Table 1**[2-5]). The National Institutes of Health (NIH)[2] and Androgen Excess Society[3] criteria emphasize the importance of androgen excess in the diagnosis, noting that this identifies a phenotype at greater risk for metabolic complications. In contrast, the Rotterdam definition includes a phenotype that does NOT exhibit androgen excess: anovulation and polycystic ovarian morphology, but no hirsutism.[4] Because the name polycystic ovary syndrome focuses on a relatively minor and inconsistent component of the syndrome, a recent NIH Workshop on polycystic ovary syndrome called for considering a name change.[6]

There are several nuances to consider in the diagnosis.

- Polycystic ovarian morphology, as defined by the Rotterdam criteria, requires transvaginal ultrasonography, which must demonstrate 12 or more follicles measuring 2-9 mm in diameter in each ovary, or increased ovarian

volume (>10 mL) in the absence of a dominant follicle >10 mm.
- Testosterone measurements are often inaccurate in the normal female and polycystic ovary syndrome range, and the definition of "hyperandrogenemia" is often vague.
- While ovulatory dysfunction typically results in oligomenorrhea, many women with irregular ovulation have "regular" menses. Thus, a history of regular menses does not rule out polycystic ovary syndrome.[3]
- New diagnostic tools may be on the horizon. Anti-Müllerian hormone (made by antral follicles, which are numerous in polycystic ovaries) in combination with luteinizing hormone levels has high sensitivity and specificity for the diagnosis of polycystic ovary syndrome.[7]

CLINICAL SIGNIFICANCE

- Recognition of polycystic ovary syndrome allows providers to work with patients to help prevent and adequately treat metabolic complications such as type 2 diabetes, hyperlipidemia, hypertension, fatty liver, and sleep apnea.
- Cycle control, prevention of endometrial hyperplasia, and fertility planning are important issues to be addressed in women with polycystic ovary syndrome.
- Providers should discuss the cosmetic concerns as well as explore the impact of polycystic ovary syndrome on self-image and psychological well-being.

PATHOGENESIS

The pathogenesis of polycystic ovary syndrome is not known, and potential etiologies are explored in a recent review.[8] Both genetic and lifestyle factors contribute to the development of the polycystic ovary syndrome phenotype. Studies have evaluated potential contributors, including abnormal gonadotropin secretion, insulin resistance, and ovarian factors.

ASSESSMENT

Women presenting with the typical signs and symptoms of polycystic ovary syndrome almost always have polycystic ovary syndrome.[9] Other causes of chronic anovulation and hyperandrogenism are relatively unusual, and a diagnosis of polycystic ovary syndrome can be made with a careful history combined with targeted laboratory evaluation (see **Table 2**).

A key feature of polycystic ovary syndrome is the time course of symptoms. Symptoms are typically chronic, start in adolescence, and progress gradually over time. Certain events can cause an atypical pattern of symptom development. For instance, weight gain can exacerbate anovulation and hirsutism, and weight loss in overweight and obese women with polycystic ovary syndrome can increase ovulatory frequency. Long-term hormonal contraception can prevent hyperandrogenism, and symptoms may only develop when oral contraceptives (OCPs) are stopped.

Even with a typical time course, other causes of oligo/anovulation and hyperandrogenism need to be considered. Hyperprolactinemia and abnormal thyroid function should both be ruled out because both can cause anovulation (although hirsutism would be unusual in these conditions). Two important but uncommon causes of oligo/anovulation and hirsutism include nonclassical congenital adrenal hyperplasia and Cushing syndrome. Found in fewer than 5% of hyperandrogenic women,[10] nonclassical adrenal hyperplasia can be ruled out with a morning 17-hydroxyprogesterone <200 ng/dL. Cushing syndrome may be present in up to 5.8% of women with symptoms of polycystic ovary syndrome.[11] This diagnosis can be difficult to make, in part because the condition can be episodic or subtle. Multiple tests and repeated measurements are often needed.

Hypothalamic amenorrhea is another condition to consider in evaluating symptoms of polycystic ovary syndrome. Both may present with amenorrhea and some degree of hirsutism. In hypothalamic amenorrhea, central nervous system suppression of gonadotropin-releasing hormone secretion results in low follicle-stimulating hormone, luteinizing hormone, and estradiol. This is in contrast to polycystic ovary syndrome, where these values are not suppressed. Laboratory testing readily shows these patterns. However, OCP use is common in both conditions, and distinguishing the diagnoses while on hormonal agents is challenging. In both conditions, OCP use results in low

Table 1 Polycystic Ovary Syndrome Diagnostic Criteria

	1990 National Institute of Health[2]	2003 Rotterdam[4]	2009 Androgen Excess & Polycystic Ovary Syndrome Society[3]
	Both Criteria Required	Two of the Three Criteria Required	Both Criteria Required
Criteria	1) Hyperandrogenism* 2) Oligo-anovulation	1) Hyperandrogenism* 2) Oligo-anovulation 3) Polycystic ovaries (by ultrasound)	1) Hyperandrogenism* 2) Ovarian dysfunction (oligo-anovulation or polycystic ovaries)
Prevalence[5]	6%-8%	15%-25%	10%-15%

*Clinical or biochemical, or both.

Table 2 Laboratory Testing to Exclude Other Causes of Ovulatory Dysfunction and Hyperandrogenism

Lab	Evaluation For:	Comment
Total or bioavailable testosterone	Androgen-secreting tumor	Measure if there are symptoms concerning for an androgen-secreting tumor or if biochemical evidence of hyperandrogenism is needed to make the diagnosis of polycystic ovary syndrome. Rapid progression or a total testosterone >200 ng/dL should prompt a work-up for an androgen-secreting tumor.
Dehydroepiandrosterone sulfate	Androgen-secreting tumor	Measure if there are symptoms concerning for an androgen-secreting tumor. Although modest elevations in dehydroepiandrosterone sulfate can be seen in polycystic ovary syndrome, rapid progression or greater elevations should prompt a work-up for an adrenal androgen-secreting tumor.
Morning 17-hydroxyprogesterone	Late-onset congenital adrenal hyperplasia	This disorder is caused by a partial adrenal enzyme defect that leads to impaired cortisol production, compensatory elevation in adrenocorticotropic hormone, and subsequent excess androgen production. Symptoms may mimic polycystic ovary syndrome. Normal values <200 ng/dL. If higher than this, adrenocorticotropic hormone stimulation test recommended.
24-hour urine for cortisol and creatinine; dexamethasone suppression test; salivary cortisol	Cushing syndrome	Consider ruling out Cushing syndrome in women with an abrupt change in menstrual pattern, later-onset hirsutism, or other evidence of cortisol excess such as hypertension, facial plethora, supraclavicular fullness, hyperpigmented striae, and fragile skin.
Prolactin	Hyperprolactinemia	May be accompanied by galactorrhea. Consider ruling this out in all women with irregular menstrual cycles.
Thyroid function studies	Hyper- or hypothyroidism	Consider ruling out thyroid dysfunction in all women with irregular menstrual cycles.

gonadotropins and estradiol. Clues for hypothalamic amenorrhea include a history of significant athleticism, life stress, or disordered eating.

MANAGEMENT

Polycystic ovary syndrome is a heterogeneous syndrome in which a key challenge is to support patients' engagement in self-care with the goal of reducing their morbidities. In a previous book chapter, we introduced the mnemonic "MY PCOS" as a way to organize multisystem care of women with polycystic ovary syndrome.[1] The elements are shown in Table 3 and each will be described below.

Metabolic

An important reason to make the diagnosis of polycystic ovary syndrome is to start engaging affected women in prevention and treatment measures early. Multiple metabolic issues have been identified, including early diabetes, obesity, high blood pressure, dyslipidemia, and fatty liver. Results from studies addressing the risk of developing these complications are summarized in Table 4.[12-19] Metabolic screening includes:

- Oral glucose tolerance test. This is particularly important in women with another risk factor for diabetes or body mass index >30. However, some studies show a significant proportion of polycystic ovary syndrome women with prediabetes or diabetes and no other risk factors, suggesting that all women with polycystic ovary syndrome should undergo an oral glucose tolerance test.[20]
  - Hemoglobin A1c can be used to screen for diabetes, but it is insensitive for prediabetes.[20]
- Lipid profile.
- Transaminases, if the patient has other risk factors such as metabolic syndrome that are concerning for fatty liver disease.

Lifestyle modification is first-line therapy with weight loss (if overweight), a healthy diet, and regular exercise. Even without weight loss, moderate-intensity exercise can improve the metabolic status of women with polycystic ovary syndrome.[21] Bariatric surgery may also be an effective method for weight loss, but this should be reserved for patients unable to obtain goals via lifestyle changes.

For those with prediabetes or diabetes, metformin therapy may be considered, particularly in those who do not reach goals with lifestyle intervention alone. In this situation, metformin is the first-line pharmacologic therapy, if tolerated and not contraindicated. The use of metformin to treat insulin resistance alone (without prediabetes or diabetes) is theoretically useful, but not supported by studies evaluating clinical outcomes. Thiazolidinediones have been shown to slow the progression of prediabetes to diabetes, but cost, safety concerns, and possible adverse fetal effects limit their use. Statin therapy for dyslipidemia should be considered in individuals who otherwise meet criteria (per Adult Treatment Panel-III or American College of Cardiology/

Table 3 MY PCOS: Mnemonic for Assessment and Management of Polycystic Ovary Syndrome (PCOS)

	Assessment	Management
Metabolic	2-hour glucose tolerance test with 75 g oral glucose, measuring serum glucose at time 0 and 120 minutes.	Lifestyle intervention: diet, exercise, and weight loss (if overweight or obese)
	Lipid profile	Metformin for abnormal glucose tolerance not controlled with lifestyle
	Liver function tests (if other risk factors for nonalcoholic fatty liver disease)	Statin therapy if patient meets criteria (Adult Treatment Panel-III or American College of Cardiology/American Heart Association guidelines)
CYcle control	Ask about menstrual pattern; normal cycle length is 28 days (range 21-35)	If amenorrhea for 3 months or more, induces withdrawal bleed with progesterone (after negative pregnancy test) Hormonal therapy Examples: • Estrogen-containing oral contraceptives (monthly cycling, seasonal cycling, continuous use) • Vaginal ring • Patch • Progestin-only pill • Progestin-eluting intrauterine device (Mirena) • Progesterone as needed to induce withdrawal bleeding (medroxyprogesterone acetate 10 mg daily for 10-14 days, micronized progesterone 400 mg daily for 10-14 days) Metformin (second-line therapy)
Psychosocial	Screen for depression, disordered eating Affirm that polycystic ovary syndrome is an important medical issue; provide nonjudgmental support Discuss stress management Reinforce self-care behaviors	Mental health referral or antidepressant therapy may be warranted if depression or disordered eating is identified
Cosmetic	Ferriman-Gallwey score as guide to assess hirsutism Evaluate for acne and male pattern hair loss	Estrogen-containing hormonal contraception Anti-androgens such as spironolactone or finasteride. Teratogenic; only use with contraception
	Serum androgen levels if uncertain about degree of hirsutism or atypical symptoms	Cyproterone acetate (not available in the US) Eflornithine hydrochloride 13.9% cream Laser or electrolysis Topical treatment for acne Minoxidil 2.5 or 5% for male pattern hair loss
Ovulation and fertility	Counsel that fertility is reduced in polycystic ovary syndrome, but patients typically not infertile	If subfertility an issue, consider referral to reproductive endocrine for possible clomiphene citrate therapy
	Assess fertility goals	Metformin has limited role
Sleep apnea	Screen for sleep apnea: daytime somnolence, morning headache, reflux symptoms, snoring, observed interrupted breathing	Refer for sleep study Continuous positive airway pressure therapy recommended if sleep apnea diagnosed

American Heart Association guidelines). Recent studies have suggested that statins may inhibit theca cell growth and decrease ovarian testosterone production.[22] However, further studies are needed to evaluate the role of statin therapy in polycystic ovary syndrome before recommending it for treating anything besides dyslipidemia. Other relatively benign treatments such as fish oil or psyllium fiber may also be useful in some patients. Interestingly, a small study in polycystic ovary syndrome women treated with 4 g/day omega-3 fatty acids demonstrated improvement in triglycerides, blood pressure, and hepatic fat content on imaging.[23]

CYcle Control

Women with polycystic ovary syndrome have many of the established risk factors for endometrial cancer and its precursor, endometrial hyperplasia. These include irregular menses, lack of progesterone, unopposed estrogen exposure, obesity, insulin resistance, and diabetes. Women with polycystic ovary syndrome appear to have an almost threefold increased risk for endometrial cancer (2.70; 95% confidence interval [CI], 1.0-7.29).[24] Routine ultrasound screening to assess endometrial thickness is not recommended,[25] however, menstrual cycles should be regulated

Table 4 Metabolic Complications in Polycystic Ovary Syndrome

Abnormal glucose tolerance (impaired glucose tolerance or type 2 diabetes)	30% of obese polycystic ovary syndrome women have impaired glucose tolerance and 10% have type 2 diabetes by age 40 years. In thin women with polycystic ovary syndrome, 10% have impaired glucose tolerance and 1.5% have type 2 diabetes.[12]
Obesity	Prevalence of obesity varies considerably in women with polycystic ovary syndrome. Previously, prevalence rates of obesity were estimated based on populations of women with polycystic ovary syndrome seeking care. A recent study comparing patients presenting for care in a polycystic ovary syndrome clinic with an unselected population evaluated during a pre-employment physical suggests that obesity and overweight may not be more common in polycystic ovary syndrome.[13] In that study, 63.7% of polycystic ovary syndrome clinic patients were obese, compared with 28% of unselected women with polycystic ovary syndrome identified during screening, and 28% of nonpolycystic ovary syndrome controls. Polycystic ovary syndrome symptoms, including hyperandrogenism and oligo-ovulation are exacerbated by obesity.
Metabolic syndrome	33%-50% of US women with polycystic ovary syndrome have metabolic syndrome compared with only 12% in a similarly aged National Health and Nutrition Examination Survey population.[14] In contrast, only 8.2% of women with polycystic ovary syndrome in Italy met criteria for metabolic syndrome.[15] Thus, metabolic syndrome varies by geographic location, a finding likely related to different body mass index, although other causes, including genetics and diet, could also be playing a part.
High blood pressure	Data have been conflicting, but a large Kaiser Permanente study demonstrated that hypertension or elevated blood pressure was more than twice as common in women with polycystic ovary syndrome (27% vs 12%).[16]
Dyslipidemia	Dyslipidemia is more prevalent in women with polycystic ovary syndrome compared with controls (15% vs 6%).[16] In a meta-analysis, triglyceride values were 26 mg/dL higher (95% confidence interval [CI], 17-35), low-density lipoprotein cholesterol was 12 mg/dL higher (95% CI, 10-16), and high-density lipoprotein cholesterol was 6 mg/dL lower (95% CI, 4-9) in women with polycystic ovary syndrome compared with controls.[17] Women with polycystic ovary syndrome also have higher concentrations and proportions of small low-density lipoprotein cholesterol.
Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis	Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis have recently been recognized as a potential complication in women with polycystic ovary syndrome.[18] Prevalence of fatty liver disease in polycystic ovary syndrome women has been estimated to be 15%-55%,[18,19] depending on the diagnostic parameter used (level of serum alanine aminotransferase or ultrasound). Individuals that may be at higher risk of nonalcoholic fatty liver disease including nonalcoholic steatohepatitis include those with metabolic syndrome, insulin resistance, and possibly hyperandrogenemia.
Cardiovascular disease	Many studies demonstrate abnormal surrogate markers of cardiovascular disease in women with polycystic ovary syndrome. However, data about cardiovascular disease risk are conflicting with some studies suggesting an increased risk in women with polycystic ovary syndrome, whereas other studies have not found this difference in cardiovascular risk. While it is important to recognize and treat cardiovascular risk factors in this population, further research of cardiovascular risk and complications is still needed to clarify the long-term risk.

CI = confidence interval.

such that menses occur at least every 3 months (unless a therapy designed to induce amenorrhea is used).

Various methods can be used to manage menses, and are described in **Table 3**. The first-line approach is with hormonal contraceptives, the risks and benefits of which are discussed below ("Cosmetic" section). Because metformin increases ovulation rate,[26] it can be considered second-line treatment for cycle control. However, whether the improved ovulation rate is adequate to prevent endometrial hyperplasia is unknown.

Psychosocial

Although studies evaluating psychosocial issues are small, women with polycystic ovary syndrome appear to have a prevalence of depressive disorders that is about 3 times higher than seen in controls (35% vs 11%, respectively, $P < .001$).[27] Eating disorders are also more common in women with polycystic ovary syndrome,[28] particularly binge eating (12.6% of women with polycystic ovary syndrome vs 1.9% in controls, $P < .01$).[27]

Thus, it is important to screen for depression and eating disorders in women with polycystic ovary syndrome. Patients can be effectively screened for depression by asking 2 simple questions about mood and anhedonia (see **Table 5**[29]). In our experience, many women with polycystic ovary syndrome describe experiences with providers in which they did not feel their diagnosis and its associated symptoms were viewed as important medical issues. Therefore, providing nonjudgmental support, focusing on positive messages about healthy behaviors and self care, and validating that polycystic ovary syndrome and its associated complications are important to diagnose and treat, are important aspects of the clinic visit.

Cosmetic

Hirsutism occurs in up to 75% of American women with polycystic ovary syndrome.[30] Acne and androgenic alopecia (male-pattern hair loss) are other manifestations of hyperandrogenism.

Hormonal therapies can substantially improve hirsutism and acne. Estrogen-containing OCPs suppress gonadotropin secretion, thereby decreasing ovarian androgen production. The estrogen component in OCPs increases sex hormone-binding globulin, reducing bioavailable androgens. There have been small studies investigating the efficacy of different formulations of OCPs in women with polycystic ovary syndrome, but there currently is no consensus on preferred agents. Using formulations with lower doses of ethinyl estradiol may minimize adverse estrogen effects. The choice of progestin is more complex. Some newer progestins (including desogestrel, norgestimate gestodene, drospirenone) provide the advantage of lower androgenic activity compared with the older progestin levonorgestrel. However, they are also associated with an increased (although still low) risk of venous thromboembolism.[31] Although it is estimated that it would require about 2000 women to shift from using OCPs containing one of these agents to an OCP with levonorgestrel to prevent one venous thromboembolism event in 1 year, the significance of this increased risk is not known specifically in women with polycystic ovary syndrome. This population may already be at higher risk of venous thromboembolism than unaffected women.[32] Thus, the choice of OCP must be individualized based on the patients' symptoms, past experience with OCPs, and other metabolic risk factors.

Anti-androgens are often used off label to treat hirsutism and acne. They are potentially teratogenic and could result in pseudohermaphroditism in male fetuses. Reliable birth control is essential. Spironolactone is the anti-androgen most commonly used in the US. At doses of 50-200 mg daily, it blocks the androgen receptor at the hair follicle. Finasteride (2.5-5 mg daily) inhibits 5-alpha reductase, the enzyme that converts testosterone to the more potent dihydrotestosterone and is as effective as spironolactone.[33] Flutamide is an androgen receptor blocker that is similarly effective, but its use is limited by serious hepatotoxicity. Although it is not available in the US, cyproterone acetate, a potent androgen blocker, is effective in treating hirsutism and acne and is generally well tolerated.

Other treatments of hirsutism include laser, electrolysis, manual removal (waxing, shaving, threading), bleaching, and depilatory creams. Laser and electrolysis both induce permanent hair reduction, but still often require periodic maintenance treatments. Laser relies on the contrast between skin color and hair pigment for effectiveness, and thus works well on light-skinned women with dark terminal hair growth. It is not effective for vellus hair ("peach fuzz"). Darker-skinned patients and those who are heavily tanned require higher-energy pulses, increasing the risk of burns, and therefore are treated with specialized lasers that have cooling devices and adjusted energy levels. Electrolysis requires insertion of an electrode into individual hair follicles to destroy them and may be an option for patients that have a limited area to treat. Eflornithine hydrochloride cream (Vaniqa, Allergan Inc., Irvine, CA) improves facial hirsutism in 58% of women with unwanted hair growth, with marked improvement in 32% of women, compared with 8% with placebo.[34]

Hormonal therapy with estrogen-containing oral contraceptives or anti-androgens as above can be very effective for treating acne as well. In addition, topical agents for treating acne, retinoids, antibacterials, benzoyl peroxidase, and salicylic acid can be useful. Topical minoxidil (2% or 5%) can be used to treat male pattern hair loss.

Table 5 Two-Question Depression Screen[29]

Over the last 2 weeks, how often have you been bothered by little interest or pleasure in doing things?
Over the last 2 weeks, how often have you been bothered with feeling down, depressed, or hopeless?

Ovulation and Fertility

There are few published data about the spontaneous ovulation rate in women with polycystic ovary syndrome. However, in the placebo arm of a relatively large randomized clinical trial of women with polycystic ovary syndrome, spontaneous ovulation occurred in 32% of cycles.[35] In addition to decreased ovulation, alterations in the endometrium related to insulin resistance, reduced implantation, and increased miscarriage rates, may contribute to subfertility.

If fertility is desired, ways to increase ovulation frequency should be discussed. If the patient is obese, weight loss is recommended. Although there are no long-term, controlled trials of the effects of weight loss on pregnancy and live birth rates, several small studies in women with polycystic ovary syndrome report improvement in menstrual cycles and ovulation with weight loss. Thus, given the other benefits of diet, exercise, and weight loss in overweight and obese individuals, healthy lifestyle changes are recommended.

Clomiphene Citrate

Clomiphene citrate (CC) is first-line pharmaceutical therapy for ovulation induction in women with polycystic ovary syndrome. The anti-estrogen action blocks negative feedback of endogenous estrogens in the hypothalamus and pituitary. This results in an increase of follicle-stimulating hormone and ultimately, ovulation. Ovulation occurs in 60%-85%, with a pregnancy rate of 30%-50% after 6 ovulatory cycles.[36]

Metformin

Metformin improves ovulation rate in women with polycystic ovary syndrome.[26] However, the largest randomized

controlled trial of 626 infertile polycystic ovary syndrome women demonstrated better live birth rates with CC alone (22.5%) or in combination therapy (CC plus metformin) (26.8%), compared with metformin alone (7.2%, $P < .001$ for metformin alone vs both CC alone and combination therapy).[37] There was no benefit of combination therapy vs CC alone. Further, a recent Cochrane review reported no benefit in live birth rate with metformin compared with placebo, or metformin combined with CC vs CC alone.[26]

The use of metformin to prevent miscarriages or pregnancy complications has also been investigated. Compared with placebo, metformin alone does not appear to affect miscarriage rates (odds ratio 0.36; 95% CI, 0.09-1.47).[26] Further, comparing metformin plus CC vs CC alone, there is a nonsignificant trend toward increased miscarriage rate in combination therapy (odds ratio 1.61; 95% CI, 1.00-2.60).[26] Thus, despite initial reports of metformin's potential to decrease miscarriage risk, prevention of miscarriage is not currently an indication for metformin use in women with polycystic ovary syndrome.

Women with polycystic ovary syndrome have a higher risk of gestational diabetes, pregnancy-induced hypertension, preeclampsia, and preterm birth.[38] Although initial studies suggested that metformin may decrease pregnancy complications in women with polycystic ovary syndrome, a subsequent larger multicenter, randomized controlled trial of metformin vs placebo did not find any differences in the primary outcomes of preeclampsia (7.4% in metformin vs 3.7% in placebo, $P = .18$), preterm delivery (3.7% metformin vs 8.2% placebo, $P = .12$), gestational diabetes (17.6% metformin vs 16.9% placebo, $P = .87$), or a composite of these 3 outcomes (25.9% metformin vs 24.4% placebo, $P = .78$).[39] Thus, metformin does not appear to prevent pregnancy complications in women with polycystic ovary syndrome.

Sleep Apnea

Obstructive sleep apnea is associated with insulin resistance and type 2 diabetes as well as polycystic ovary syndrome. A retrospective study demonstrated an increase in sleep-disordered breathing (17.0% vs 0.6%, $P < .001$) and excessive daytime sleepiness (80.4% vs 27.0%, $P < .001$) in 53 polycystic ovary syndrome women compared with 452 premenopausal controls.[40] The risk and severity of obstructive sleep apnea in polycystic ovary syndrome is strongly correlated with insulin resistance. Treatment with at least 4 hours per night of continuous positive airway pressure improves insulin sensitivity, decreases norepinephrine levels and diastolic blood pressure, and lowers cardiac sympathetic activity.[41] Thus, it is important to screen patients with polycystic ovary syndrome for symptoms of sleep apnea (daytime sleepiness, snoring, witnessed apneic episodes, morning headaches), and refer for a sleep study if indicated. Adherence to continuous positive airway pressure treatment may improve metabolic parameters in these patients.

CONCLUSION

Recognizing polycystic ovary syndrome in women presenting with oligo-ovulation and hyperandrogenism offers an important opportunity to begin a life-long conversation about prevention and treatment of a condition that has a multi-system impact on affected women. Recognition offers the chance for providers and patients to engage in discussions about prevention and early treatment of metabolic derangements. It leads to discussions about cycle control both for convenience and to prevent endometrial hyperplasia, and opens the door to conversations about mood, eating, and body image, as well as cosmetic concerns, fertility, and sleep. Each of these is critically important to the health and well-being of patients with this common condition.

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