Exploring new frontiers in the management of polycystic ovary syndrome associated obesity

For the past 5 years, several landmarks worldwide are lit up in teal each September to celebrate polycystic ovary syndrome (PCOS) awareness month. With each passing year, we recognize the tremendous progress made since the publication by Drs. Stein and Leventhal almost 90 years ago describing a case series of seven women presenting with irregular or absent menses and signs of hyperandrogenism. They described enlarged cystic ovaries seen during laparotomy and performed wedge resections in all these patients, six of whom were in their twenties. Over the past few decades, supported by evidence from both human and animal models, we have witnessed remarkable advances in understanding the genetics, pathophysiology, and clinical presentations of this chronic condition. Data from populations around the world suggest a high prevalence (10%–20%) and a shared genetic background. Polycystic ovary syndrome is now recognized as a heterogeneous endocrine condition with reproductive, cardiometabolic, and psychological components. Despite these remarkable advances, patient surveys indicate significant frustration with the management and counseling related to this syndrome (1).

The epidemic of obesity altered patient symptomatology related to PCOS and increased reproductive and long-term cardiovascular risk. The prevalence of obesity in some PCOS cohorts is now as high as 50% to 70%, depending on geography and ethnicity. Adolescents with a high body mass index are at increased risk of developing PCOS, and the prevalence of PCOS increases with each body mass index strata. Therefore, prevention and management of weight gain, with lifestyle interventions as the initial approach, are recommended as first-line treatments in conjunction with hormonal therapy (2).

However, does lifestyle management improve the symptoms of PCOS? Short-term yet well-conducted studies suggest that weight loss is associated with improving menstrual regularity, decreasing androgen levels, and lowering cardiovascular disease risk and anxiety and depression scores. Weight loss may also result in increased ovulation rates and ultimately higher live birth rates. For example, in the oral contraceptive pills versus weight loss-PCOS study, intensive lifestyle modifications, using meal replacements and orlistat, resulted in significant weight loss, higher ovulation rates, and increased live birth rates than the direct use of ovulation induction medications (3). Despite these findings, it is well recognized that most people are unable to engage in sustained dietary changes or exercise regimens.

There are additional challenges to weight management that are unique to PCOS and need to be recognized. The underlying hyperinsulinemia and hyperandrogenism predispose patients to central obesity. Despite social media propagating "PCOS-friendly" diets, no single approach works better for this population. This is particularly frustrating for patients with PCOS who report that they have a more difficult time losing weight, even when they engage in similar dietary interventions as their friends and family members. Additionally, the high prevalence of anxiety and depressive symptoms associated with PCOS makes it more difficult to sustain lifestyle modifications. Restrictive dietary recommendations are typically initiated at an early age, leading to a vicious cycle of disordered eating and reduced self-image. Because weight management is one of their leading concerns, patients are seeking clear guidance—and more importantly, effective therapies.

Metformin, a suboptimal choice for weight management, is often prescribed starting in adolescence. Despite significant gastrointestinal side effects, patients take it for extended durations with limited information on its long-term benefit. The lack of new pharmacologic options for comprehensively managing PCOS has compounded patient frustrations. Although a radical intervention for a young population, bariatric surgery in patients with PCOS offers remarkable benefits (4). Cohort studies report that most patients lose substantial weight, resulting in improved menstrual cyclicity and normalization of serum androgens. Data from the general population clearly demonstrate the resolution of diabetes and improvement in cardiometabolic profiles. However, conception during the period of rapid weight loss may be associated with a negative impact on the fetus and pregnancy, leading to recommendations to defer pregnancy for 1 to 2 years after surgery. It is, indeed, encouraging that many of these patients can maintain their lower weight for extended durations.

Obesity is now recognized as a chronic disease. The arrival of glucagon-like peptide receptor agonists (GLP1RAs) on the market offers an exciting new opportunity to meet the tremendous unmet need for the management of obesity in PCOS and its related symptoms. Glucagon-like peptide receptor agonists act on the gut and brain to increase satiety and regulate appetite. With careful titration, the common side effects of constipation, bloating, and nausea can be managed, and most patients tolerate dose escalation and maintenance for long durations. The Food and Drug Administration has approved the use of GLP1RAs for type 2 diabetes, obesity, and cardiovascular disease risk reduction, whereas recent clinical trials show wide ranging benefits in patients with metabolic dysfunction–associated steatotic liver disease, heart failure, and obstructive sleep apnea. The use of GLP1RA is associated with 10% to 20% weight loss in most clinical trials, an effect size much greater than that reported with lifestyle changes and use of metformin in the PCOS population. Moreover, although not specifically indicated for use in PCOS, small cohort studies report improvements in PCOS symptoms with GLP1RA use. The significant impact of these medications led to three scientists—Joel Habener, Svetlana Mojsov, and Lotte Bjerre Knudsen—receiving the 2024 Lasker-DeBakey Clinical Medical Research Award.

What does the future look like for the management of obesity associated with PCOS? Many of our patients are wanting to use GLP1RAs and are seeking our guidance. This

class of weight loss medications is remarkably effective and tolerated by a large majority with high compliance, supporting their inclusion in PCOS management pathways. However, there are several challenges: a paucity of data on use during reproductive years; supply-demand mismatch; cost; gastrointestinal side effects; and depression, to name a few.

Glucagon-like peptide receptor agonists could fulfill a useful niche in managing patients with PCOS and obesity where lifestyle intervention has proved frustrating. Because some of these medications are approved by the Food and Drug Administration for use in patients with obesity alone—no additional comorbidities such as diabetes and dyslipidemia—several patients with PCOS will be appropriate candidates. For those women not seeking pregnancy, we recommend combining the use of GLP1RAs with a hormonal contraception because weight loss could lead to a higher chance of unwanted fertility. Recently, reports about "Ozempic infants" or "O" infants hit the news worldwide. It is not surprising that some anovulatory patients may become pregnant if their GLP1RA-related weight loss is associated with the resumption of menses. We, however, currently do not know whether GLP1RAs reduce the efficacy of the oral contraceptive pill because most clinical trials to date have excluded patients at risk of pregnancy. In the meantime, the use of implants or progestin intrauterine devices can effectively offer contraception and manage other PCOS symptoms in conjunction with GLP1RA use.

Because the diagnosis of PCOS is made in adolescence and early adulthood, how long can young patients continue these medications? Moreover, once they have achieved adequate weight loss, do they need to be on long-term maintenance doses? Experts in bariatric medicine remind us that obesity is a chronic disease, and thus, we should counsel patients regarding the potential for prolonged treatment. Should this give us pause regarding the liberal use of GLP1RAs in the PCOS population, especially because discontinuation is associated with weight regain? The answers to these important questions are essential as we consider GLP1RAs in the pharmacologic choices for managing PCOS. For now, patients on prolonged antiobesity medications should be closely monitored and recommended concomitant exercise to prevent muscle loss.

Healthcare providers also need to counsel patients with PCOS on the impact of obesity on reproductive outcomes. Long-term strategies including behavioral interventions especially initiated when they are not actively seeking pregnancy will provide the most benefit. Acute weight loss in the immediate prepregnancy period has been associated with detrimental effects on pregnancy. Moreover, the issue of potential embryonic or fetal harm in the case of inadvertent concurrent treatment with GLP1RAs remains unresolved, although a recent registry-based study does not suggest an increase in birth defects (5). Although we do not know the optimal interval, the recommendation to stop GLP1RA for 1 to 2 months before trying to conceive seems prudent. We should counsel patients that weight regain and increased hunger may return rapidly on cessation. For those patients requiring in vitro fertilization, one can initiate treatment while on GLP1RA and freeze embryos for later use. Although there are currently no data to cause concern, there is limited information about the effects of these agents on oocytes. It is recommended to stop GLP1RA 1 week before egg retrieval in patients receiving monitored anesthesia care because of a higher risk of aspiration related to decreased gastric emptying.

In addition, other intriguing questions remain: could we use GLP1RA before puberty to reduce the risk of developing PCOS? What is their role in adolescence, where weight gain frequently exacerbates symptoms? Will their use in pregnancy, if deemed safe for use, help reduce gestational diabetes and hypertension? Can we successfully defend any legal claims arising from congenital abnormalities concurrent with but not due to the use of GLP1RAs?

Comprehensive care for patients with PCOS includes weight management through lifestyle changes, pharmacotherapy, or bariatric surgery. Because obesity is a chronic disease, we need to offer patients resources and up-to-date information for long-term management. It is not often we encounter a radically new treatment option that may be successfully used in reproductive endocrinology practice. The advent of these drugs could revolutionize the treatment of PCOS, although some questions remain to be answered. Despite consensus recommendations and federal guidance, the default approach is to exclude women at risk of pregnancy or currently pregnant from pharmaceutical trials. We have summarized critical unanswered questions related to the use of GLP1RA, highlighting the urgent need to include these populations in future trials to provide patients and healthcare providers with additional information.

CRediT Authorship Contribution Statement

Anuja Dokras: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Robert Norman:** Data curation, Writing – original draft, Writing – review & editing.

Declaration of Interests

A.D. has nothing to disclose. R.N. has nothing to disclose.

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