

Fertility Nurses First

ISSUE 32

Metabolic Concerns in Polycystic Ovary Syndrome: Innovative Approaches to Medical Management

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Background

Among the infertility disorders, polycystic ovary syndrome (PCOS) is one of the most common, affecting approximately 4 million women in the U.S. and more than 100 million women worldwide.¹ PCOS is characterized by both reproductive and metabolic dysfunctions with familial clustering.² From a reproductive perspective, PCOS is a heterogeneous syndrome characterized by hyperandrogenism (diagnosed clinically/biochemically) with oligomenorrhea and chronic anovulation in the absence of specific ovarian, adrenal and pituitary gland diseases.³⁻⁵

Most women with PCOS also manifest insulin resistance and alterations in β -cell function.⁶⁻¹² PCOS is viewed by some as a clinical phenotype of the metabolic syndrome. Obesity, particularly abdominal obesity, plays a central role in the development of PCOS, and exacerbates the reproductive and metabolic dysfunction.¹³⁻¹⁶

The incidence of glucose intolerance, gestational diabetes and type 2 diabetes (DM2) is increased in women with PCOS.^{2,6,15,17} Like most prediabetic states, PCOS is associated with an increased risk of cardiovascular disease, dyslipidemia, hypertension, and endometrial cancer.¹⁸ There is clearly a long-term need for prevention of diabetes mellitus, heart disease and cancer in this population.

PCOS is the most common endocrine disturbance in women.^{19,20} Insulin resistance, secondary to genetic and lifestyle factors, is integral to the pathogenesis of PCOS, as well as its metabolic features and long-term sequelae. The recognition that insulin resistance has a pivotal role in the pathogenesis of PCOS revolutionized our understanding of this complex disorder.¹⁷ There is now a greater focus on the management of the metabolic consequences of PCOS, and an emphasis on lifestyle intervention to achieve

weight loss and increase physical activity. Both hyperinsulinemia and the hyperandrogenism can be reduced with weight loss, resulting in better regularity of menses and fertility potential.²¹⁻²⁵ Formerly, standard treatment of PCOS had focused on oral contraceptives to address the clinical signs and symptoms.²⁶ Today, therapeutic strategies target insulin resistance in PCOS to ameliorate the clinical signs and potentially reduce long-term sequelae, including diabetes.²²

Therapeutic strategies

Lifestyle changes

Lifestyle modification is a key component in the improvement of reproductive function for overweight, anovulatory women with PCOS.^{25,27,28} Because obesity correlates with an increased rate of menstrual cycle disturbance and infertility, weight loss by dietary restriction and regular exercise is the recommended treatment.^{29,30} Reduction in weight improves the endocrine profile, insulin sensitivity, menstrual regularity, the frequency of spontaneous ovulation and the chance of pregnancy.^{21,23-25,31} Even a modest weight loss of 5 percent to 10 percent of total body weight may result in a 30 percent loss of visceral adipose tissue, the fat type associated with insulin resistance and hyperinsulinaemia.³² Waist circumference has been shown to have a higher correlation with visceral fat, with a >88 cm circumference in women indicative of increased metabolic risk.³²

Aerobic exercise improves menstrual cyclicity in obese women with PCOS independent of weight loss, according to recent research.³³ This suggests that the observed improvement in insulin sensitivity may mediate the improved reproductive function in PCOS. Indeed in a 16-week aerobic exercise study by Redman and Elkind-Hirsch,

women with PCOS had reduced fasting insulin and increased insulin-stimulated glucose disposal during a hyperinsulinemic euglycemic clamp without a consistent change in body weight.³⁴ This is compatible with findings that insulin sensitizers improve both hyperandrogenemia and ovulatory function in women with PCOS.²²

Use of medications

The mainstay for improving insulin resistance is lifestyle change; however, its feasibility and sustainability remain concerns. Several studies have demonstrated that reproductive responsiveness to weight loss (shown by improved menstrual cyclicity or ovulation) only occurs in 60 percent of previously anovulatory overweight women.^{23,25,27,28,35} In addition, insulin sensitivity and androgen concentrations are unlikely to improve in patients who lose less than 5 percent of their initial weight.^{23,36}

The use of metformin and other insulin-lowering or -sensitizing agents has excited much interest in the management of PCOS. These “antidiabetic” medications ameliorate reproductive abnormalities, restore ovulation and regular menses, increase pregnancy rates and reduce androgenic symptoms in affected women with PCOS. Accordingly, these agents, specifically metformin, have been widely adopted as therapy for this condition.³⁷

Metformin therapy certainly appears beneficial in certain circumstances and may alone improve menstrual cyclicity, ovulation and hyperandrogenism in some women. Lord *et al* published a systematic review in the Cochrane Database which concluded that metformin has a beneficial effect for women with PCOS by reducing serum insulin concentrations and thereby lowering androgen levels and improving reproductive outcomes.³⁷

Yet there remain a number of unanswered questions concerning the use of metformin in women with PCOS, including which parameters may best predict a response and the appropriate dose for a given body mass. The effect of metformin in women with PCOS is reduced as obesity increases.³⁸⁻⁴⁰ A recent, large, randomized, multicenter, clinical trial that assessed live-birth rates rather than surrogate end points suggested that metformin alone is inferior to clomiphene citrate in treating infertility associated with PCOS.⁴¹ There is, furthermore, no evidence to support the use of metformin during pregnancy to prevent spontaneous abortions or gestational diabetes mellitus in women with PCOS.⁴²

Moreover, studies involving metformin have tended to be small and produce varying results. Indeed, in a systematic review by Costello and Eden, nine out of 12 published studies on the effects of metformin alone on the menstrual cycle in women with PCOS had a sample size of <30 women.⁴³

A first choice treatment in hyperandrogenic women with PCOS who do not desire conception are oral hormonal contraceptives (OC). Addition of insulin sensitizers might counteract unfavorable metabolic consequences of OC monotherapy and could result in additional benefits. Among the thiazolidinediones, a novel class of insulin-sensitizing agents, troglitazone was the first available compound that resulted in effectively correcting menstrual and metabolic abnormalities in PCOS.^{44,45}

Currently the two available thiazolidinediones (pioglitazone and rosiglitazone) also seem to ameliorate the metabolic disturbances and clinical symptoms characterizing PCOS, but more randomised, controlled trials are needed before clinical guidelines can be determined.^{46,47}

In addition, recent studies reporting increased cardiovascular morbidity have renewed safety concerns about the use of thiazolidinediones. These concerns might preclude their use in otherwise healthy women.

Managing the risk of DM2

While progressive insulin resistance plays a key role in the predisposition to diabetes in PCOS, subtle alterations in insulin secretion may also contribute.^{6,7,9} Some investigators have shown a defective glucose-stimulated insulin secretion indicating a primary defect in β -cell function.⁷⁻¹⁰ Women with PCOS have significantly higher basal insulin secretory rates, reduced insulin clearance rates, and attenuated secretory responses to meals.⁶⁻⁹ The decreased postprandial response in these patients resembles the β -cell dysfunction of DM2 and may account for the increased incidence of impaired glucose tolerance in this population. The progression to diabetes is characterized by peripheral insulin resistance and progressive failure of pancreatic β -cell function, ultimately resulting in deficient insulin secretion. Furthermore, excessive glucagon secretion and an impaired incretin response to meals contribute to the metabolic derangement of DM2.⁴⁸

Glucagon-like peptide (GLP)-1 is an incretin hormone secreted from the intestinal mucosa in response to meal ingestion.⁴⁹ GLP-1 stimulates glucose-dependent insulin secretion but is significantly reduced postprandially in people with DM2 or impaired glucose tolerance.⁵⁰ In normal subjects, the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are responsible for 70 percent of the insulin response during a meal; but in diabetic subjects and other insulin-resistant conditions, the incretin effect is impaired.⁵¹⁻⁵⁴ The pathophysiologic mechanisms behind PCOS resemble those of

DM2; therefore, women with PCOS may have alterations in the incretin hormone response.

A novel antidiabetic medication, exenatide, is an incretin mimetic that shares similar glucoregulatory properties of the hormone GLP-1 including glucose-dependent enhancement of insulin secretion.⁵⁵⁻⁵⁷ Among the primary actions of exenatide in subjects with DM2 is the ability to restore first- and second-phase insulin secretion, which is attenuated in this population.⁵⁸ Therapy with exenatide often results in weight loss, which further assists in decreasing insulin resistance.⁵⁹⁻⁶¹ Optimal treatment of PCOS would not only correct specific clinical consequences of anovulation, but also reduce the comorbidities such as obesity and DM2 linked to this syndrome.

We recently published the results of a comparative study of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with PCOS.⁶² Combination treatment was more effective than either exenatide or metformin monotherapy in improving menstrual cyclicity, body weight, abdominal girth, hyperandrogenism and metabolic profiles. The marked decrease in central adiposity partially explains the improvements in reproductive function, insulin-glucose parameters, and adiponectin observed in these overweight women with PCOS treated with combination therapy.

Discussion

The management of PCOS is complex and includes lifestyle modification combined with dietary-induced weight loss, oral contraceptives, clomiphene citrate, gonadotropins, antiandrogens and anti-diabetic agents. More novel pharmacological treatment with the incretin mimetic exenatide, statins or combination therapies have been shown to improve menstrual cyclicity and reduce body weight, hyperandrogenism and insulin resistance in overweight women with PCOS. Diagnosed and managed properly, women with PCOS can benefit from the reduction or even reversal of the reproductive and metabolic morbidities and from the reduction of the risk factors for cardiovascular disorders.

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