The Androgen Excess Society guidelines on glucose intolerance in the polycystic ovary syndrome: what do they mean and what should we do?

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The polycystic ovary syndrome (PCOS) is a common disorder, affecting 5–10% of women of child-bearing age, and is the most common cause of infertility due to anovulation in developed countries. The polycystic ovary syndrome is a clinical diagnosis characterized by the presence of two or more of the following features: chronic oligo- or anovulation; clinical or biochemical androgen excess; and polycystic ovary on ultrasonography [1]. The diagnosis of PCOS requires that hyperprolactinemia, thyroid dysfunction and adrenal hyperplasia be excluded.

Arguably, the most important advance in the field has been the recognition that most, if not virtually all, women with PCOS exhibit insulin resistance. The lean woman with PCOS has a form of insulin resistance that is intrinsic to the syndrome, whereas the obese woman with PCOS suffers from both the insulin resistance intrinsic to PCOS and the insulin resistance due to excess adiposity. The obese woman with PCOS is markedly insulin resistant – as insulin resistant as a patient with type 2 diabetes [2,3].

A consequence of the association of insulin resistance with PCOS is that affected women are at a high risk for the development of glucose intolerance. In the United States, the prevalence of type 2 diabetes among women with PCOS is 10 times higher than in normal women [4,5]. Similarly, a woman with severe oligomenorrhea, most of whom would be expected to have PCOS, has a two-fold higher risk of developing type 2 diabetes than a eumenorrheic woman, and the increased risk is independent of weight [6]. Moreover, 20–30% of women with PCOS, on oral glucose tolerance testing, will exhibit impaired glucose tolerance (IGT). This is important, since IGT is a risk factor for both the development of type 2 diabetes and for cardiovascular disease.

To assist physicians in practice, the Androgen Excess Society (renamed the Androgen Excess and PCOS Society; http://www.androgenexcesssociety.org/), recently issued a position statement on glucose intolerance in PCOS [7]. The position statement comprehensively reviews the pertinent literature and provides a rationale for its guidelines, which address the evaluation and treatment of women with PCOS for glucose intolerance. The timeliness of the position statement cannot be overstated, since it is likely that the increasing incidence of obesity worldwide will be accompanied by a marked increase in the incidence of PCOS as well.

What are the most important features of the Androgen Excess Society (AES) guidelines? First, it is recommended that all women with PCOS, regardless of weight, be screened with an oral glucose tolerance at the time of diagnosis. The emphasis on using an oral glucose tolerance test (OGTT) is an important one. Multiple studies have shown that women with PCOS may have normal fasting serum glucose levels or glycated hemoglobin levels even when an OGTT reveals IGT or overt type 2 diabetes.

If it is deemed important to detect IGT as early as possible, because early intervention may be more successful in preventing progression to diabetes, then an OGTT is the most appropriate test.

Second, no study has defined the appropriate interval for re-testing with an OGTT. Nonetheless, given the high annual rate of conversion from normal glucose tolerance to IGT in women with PCOS (estimated to be between 16–19% in the United States), it was the expert opinion of the AES committee that a woman with PCOS undergo testing with an OGTT every 2 years if baseline testing revealed normal glucose tolerance, and yearly if baseline testing revealed IGT. These recommendations appear prudent, although without concrete data there is obviously some latitude and several unanswered questions.

For example, while a glycated hemoglobin may not be sufficiently sensitive in detecting IGT, could it be useful for detecting a deterioration in glucose tolerance in some women? If a woman with PCOS has normal glucose tolerance and a distinctly normal glycated hemoglobin level at baseline testing, could one simply follow the glycated hemoglobin level, and re-test with an OGTT only if the glycated hemoglobin level has risen? If that woman were placed on metformin, could the testing interval be prolonged to every 3 or 4 years?

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At this time, the answers to these questions are unknown; carefully designed studies are needed to answer them. Presently it is best to adhere to the AES guidelines. If testing at baseline indicates normal glucose tolerance, it is my practice to retest all women with PCOS with an OGTT at least every 2–3 years, regardless of the glycated hemoglobin level or type of treatment they are receiving.

The guidelines do not address screening for glucose intolerance when a woman with PCOS is placed on an oral contraceptive pill (OCP). Oral contraceptive pill's may aggravate insulin resistance and induce IGT [8], and may also induce hypertriglyceridemia [9].

Therefore, I check an OGTT (and level of serum triglycerides) 3–4 months after initiating treatment with an OCP to exclude these adverse consequences. I then check serum triglyeride levels annually and retest with an OGTT every 2 years. The AES guidelines wisely indicate that, in terms of reducing the risk for progression to IGT or diabetes, lifestyle modification consisting of a weight-loss diet and regular exercise should be the mainstay of treatment. In multiple studies, diet and exercise have been the most successful intervention, reducing progression to diabetes in individuals with IGT at baseline by as much as 58% [10,11]. Unfortunately, despite the clear efficacy of lifestyle modification, many women with PCOS lack the motivation or are unable to comply with suggested lifestyle changes. Hence, an earnest and persistent reenforcement of lifestyle modification is an important aspect of the care of women with PCOS.

Pharmacologic intervention can also reduce progression to diabetes, as demonstrated in two large-scale randomized, controlled trials in individuals with IGT at baseline who were treated with metformin [10,11]. The AES guidelines recommend that women with PCOS and IGT initially be treated with intensive lifestyle modification; however, if attempts at weight loss are unsuccessful, they recommend that treatment with metformin be considered.

No randomized controlled trial has specifically assessed the effect of metformin on progression to diabetes in women with PCOS and normal glucose tolerance at baseline. Nonetheless, given the extraordinarily high risk for glucose intolerance (both IGT and diabetes) in PCOS, it seems reasonable that women with PCOS and normal glucose tolerance should derive a protective benefit from metformin. A single small and uncontrolled retrospective study suggests that is the case [12]. Fifty women with PCOS were treated with metformin for an average of 43 months and no woman developed diabetes. The annual rate of progression from normal glucose tolerance to IGT was reduced by 90% compared to the annual rate reported in the literature for women with PCOS not on metformin. For this reason, many physicians treat women with PCOS with metformin [13]. In recognition of the potential role of metformin to prevent type 2 diabetes in women with PCOS and normal glucose tolerance, the AES guidelines note that treatment with metformin may be considered but should not be mandated until there have been well-designed randomized, controlled trials demonstrating efficacy specifically in women with PCOS.

Of note, it is likely that physicians will see an increasing number of adolescents with incipient or well established PCOS, as a regrettable consequence of the increasing incidence of obesity among children. The number of pertinent studies conducted in the adolescent population, with or without PCOS, is limited. Nonetheless, it was the expert opinion of the AES committee that adolescent girls with PCOS be evaluated and treated in a manner analogous to adult women with PCOS. I believe this was a prudent decision, especially since early intervention may prove more effective and successful.

Finally, it should be noted that the AES guidelines are not devoid of controversy. While the presence of PCOS itself confers risk for glucose intolerance, that risk is further aggravated by obesity. Which contributes more to glucose intolerance in an individual woman with PCOS: PCOS or obesity? If it is the obesity, then do lean women with PCOS need to be screened in the same manner as obese women with PCOS, or can they forego the inconvenience and expense of repetitive OGTT's? These questions warrant attention and further study. Presently however, until future studies indicate otherwise, it seems prudent to screen all women with PCOS, regardless of weight, with an OGTT at baseline and every 2–3 years thereafter.

All in all, the AES has contributed an important and valuable service to the medical community by issuing its position statement and guidelines. It has placed into clear perspective the scope of the problem of glucose intolerance in PCOS, and offered practical guidelines that can easily be put into practice by physicians and will contribute to improving the health of women with PCOS.

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