Hyperandrogenism

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When Stein and Leventhal characterized polycystic ovary syndrome(PCO) as a disease in 1935, the pathognomonic feature was that of enlarged sclerocystic or polycystic ovaries. Some time after this, it was realized that this syndrome is extremely heterogeneous from a clinical standpoint. It soon became apparent that this syndrome could be characterized from a biochemical point of view and characteristic gonadotropin aberrations suggested a central or hypothalamic-pituitary pathophysiology. Most recently, several investigators have suggested that this diagnosis be made on the ultrasonographic appearance of ovaries. Nevertheless, it remains clear that while typical findings are often seen on ultrasonography or magnetic resonance imaging, there is heterogeneity of these findings as well. A certain number of "normal" women can exhibit such ovarian changes and the characteristic ultrasound picture is not uniform. It has been documented that women with adrenal enzymatic defects and androgen-producing neoplasia may exhibit polycystic ovaries.

From a clinical vantage point, it is most appropriate to diagnose this syndrome according to the hallmark features, which are chronic anovulation and hirsutism and/or hyper-androgenemia. Chronic anovulation is typically perimenarchial in onset. It is most useful to find elevations in luteinizing hormone(LH), particularly bioactive LH, and an elevated LH·FSH ratio but this need not be present. The presence of obesity or being overweight is common but not essential. All patients exhibit hyperestrogenism on the basis of elevated estrone level and a relative unbound or "free" estradiol. The importance of the related hyperestrogenism is more that it is associated with endometrial pathology(e.g., hyperplasia and even carcinoma) than that it contributes to enhanced LH and prolactin secretion and also adrenal abnormalities. Prolactin may be mildly elevated in up to a third of patients, but the level should not be more than twice normal.

The hyperandrogenemia of PCO, while a hallmak feature, need not be accompanied by hirsutism. This hyperandrogenism may be either ovarian, adrenal or combined in origin. Because of the heterogeneity of this syndrome, both ovary and adrenal are not always involved. Those investigators who point out that the adrenal is not involved in PCO have characteristically studied only those patients with morphologic ovarian changes who have a pure ovarian source of hyperandrogenism. For this and other reasons, we have suggested that PCO be renamed and called the syndrome of hyperandrogenic chronic anovulation(HCA). This includes the cardinal features of this heterogeneous syndrome and excludes the need for specific ovarian or gonadotropin findings. While HCA presents with poly-

cystic ovaries on ultrasound most of the time(70%), this is not a diagnostic criterion.

From a pathophysiological standpoint, there is no clearcut etiology. There is some evidence for hypothalamic-pituitary dysfunction in PCO. While dopaminergic and opioid dysregulation have been suggested as an etiology for the LH disturbance, neither of these defects can be consistently demonstrated in all patients. However, some or all of this could be secondary to abnormal ovarian feedback. A primary ovarian defect has not been demonstrated either. Nevertheless, certain ovarian abnormalities may be found such as alterations in the production of insulin-like growth factor-1(IGF-1) binding proteins. Responsivity to FSH and inhibin levels, however, are probably normal. Yet all of these changes may be secondary to chronic anovulation and the hyperandrogenism of the syndrome. A popular notion to explain PCO is that patients exhibit a dysregulation of the cytochrome P450 17α-hydroxylase/17-20 desmolase enzymes in both the ovary and adrenal. However, this too may be secondary to other factors, although there could be a genetic predisposition.

Recent data implicate insulin and insulin resistance in the pathophysiology of PCO. This includes a possible reduction in growth hormone secretion, an increase in "free" IGF-1 levels and an increased stimulation by insulin and IGF-1 of ovarian androgens. Total serum IGF-1 levels are normal but IGF-1 binding protein levels in the circulation(particularly binding protein-1) may be decreased. Both insulin and IGF-1 stimulate ovarian androgen production. It remains unclear, however, what causes the insulin resistance. A genetic propensity for these and other findings seems likely.

Patients with HCA/PCO have alterations in metabolism. These specifically put patients at increased cardiovascular risk. Apart from insulin resistance, perhaps related to this, patients commonly have lipoprotein abnormalities. These include elevated triglycerides, total and low-density lipoprotein-cholesterol and decreased high-density lipoprotein-cholesterol levels. Current evidence suggests that this is more related to hyperinsulinemia than to androgen excess. Long-term follow-up of patients with PCO who had wedge resections suggests a high prevalence of diabetes and hypertension during the perimenopausal years.

Treatment of HCA/PCO depends on the presenting complaint. Patients may complain of dysfunctional uterine bleeding or infertility due to chronic anovulation and relative hyperestrogenism or symptoms related to androgen excess(hirsutism or acne). For the latter complaints, treatment is directed at suppressing abnormal ovarian and/or adrenal androgen production. Use of low-dose, nonandrogenic, oral contraceptives are a mainstay, but in severe cases, the gonadotropin-releasing hormone agonist with add-back therapy has been shown to be effective. Dexamethasone suppression is least effective for hirsutism and additional benefit for hirsutism requires an antiandrogen such as spironolactone.

For dysfunctional uterine bleeding, a progestin alone or oral contraceptives are highly effective. For infertility, while clomiphene citrate renders excellent ovulation and pregnancy rates(70% at 6 months by life-table analysis), 5% of patients may be clomiphene resistant. These patients have resistance which is due to a lack of an ovarian response. Under these circumstances, low-dose gonadotropin therapy is highly effective. Under some circumstances, a laparoscopic ovarian cautery(laser or unipolar current) may be appropriate for

clomiphene resistant patients ; particularly if gonadotropin treatment consistently results in hyperstimulation.

One of the mainstays of all treatment for PCO is weight reduction. It has been shown that many of the androgen and metabolic abnormalities of PCO may be improved with weight loss.

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