Polycystic ovary syndrome: Symptomatology, pathophysiology, and epidemiology

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Women with polycystic ovary syndrome seek health care for 3 major reasons: infertility, menstrual irregularity, and androgen excess. The infertility is associated with anovulation. The menstrual irregularity is typically chronic, beginning with menarche. Although amenorrhea may sometimes occur, the more common presentation is irregular bleeding characteristic of anovulation. Androgen excess may be manifested by varying degrees of hirsutism. Patients may also report acne. The rapid development of virilizing signs, such as deepening of the voice, increased muscle mass, and temporal balding, should prompt a search for a tumor and lead one away from a diagnosis of polycystic ovary syndrome. Typically treatment is directed at alleviating the symptoms: ovulation induction for infertility, oral contraceptives or a progestin for menstrual irregularity, and oral contraceptives or spironolactone for hirsutism. On the basis of recent epidemiologic data suggestive of increased cardiovascular risk among women with polycystic ovary syndrome, such treatment might be complemented by a long-term approach that addresses the underlying pathophysiology of insulin resistance. (Am J Obstet Gynecol 1998;179:S89-93.)

Key words: Cardiovascular risk, polycystic ovary syndrome, epidemiology

Polycystic ovary syndrome is characterized clinically by a history of chronic anovulatory bleeding in combination with some evidence of androgen excess, such as hirsutism, acne, elevated serum androgen concentrations, or a combination of these. This clinical definition is reflective of a 1990 National Institutes of Health–National Institute of Child Health and Development consensus conference[1] in which "definite or probable" criteria for polycystic ovary syndrome included menstrual dysfunction and androgen excess and excluded congenital adrenal hyperplasia and other causes. It is interesting to note that the 58 experts at the National Institutes of Health conference who completed a questionnaire on diagnostic criteria showed poor agreement; no single criterion was endorsed as "definite or probable" by more than 64% of respondents.[1] Factors such as insulin resistance, elevated ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) and ovaries appearing polycystic on ultrasonography were considered to be "possible" criteria.

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0002-9378/98 $5.00 + 0 ***6/0/94973***

Presenting symptoms

In clinical practice, women with polycystic ovary syndrome are seen for 3 major reasons: infertility (mean incidence 74%), menstrual irregularity (mean incidence of dysfunctional bleeding 29%, mean incidence of amenorrhea 51%), and androgen excess (mean incidence of hirsutism 69%, mean incidence of virilization, 21%).[2]

Because polycystic ovary syndrome is typically characterized by oligo-ovulation rather than amenorrhea, women with polycystic ovary syndrome sometimes conceive on their own without ovulation induction. In the absence of other male or female infertility factors, however, a clinically useful working hypothesis for an infertile woman with polycystic ovary syndrome is that the infertility is due to anovulation. Indeed, in 40% of women with polycystic ovary syndrome, infertility is a presenting problem.[3] Moreover, if ovulation is successfully induced in women with polycystic ovary syndrome, the infertility can be successfully treated: a cumulative pregnancy rate of 80% has been reported after 9 ovulatory cycles.[4]

The menstrual irregularity of polycystic ovary syndrome is chronic, typically beginning at menarche.[5] Although amenorrhea may occur, the more typical presentation is irregular bleeding characteristic of anovulation.

Because progesterone is produced by the ovary only after ovulation, women with polycystic ovary syndrome often have chronic estrogen exposure unopposed by progesterone. Women who have had long-standing

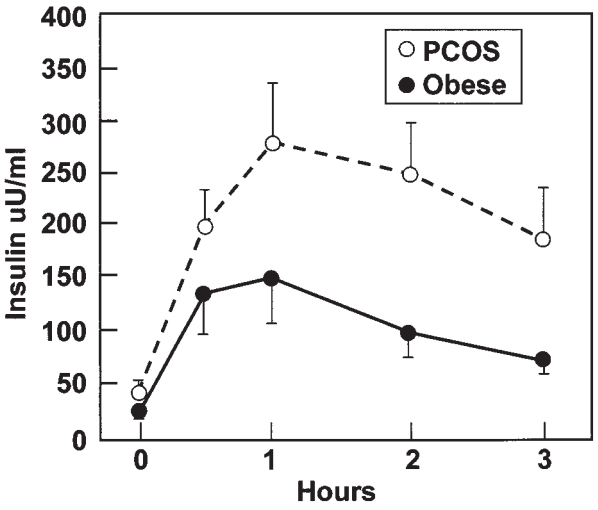

Fig 1. Insulin response to glucose challenge, suggestive of insulin resistance among women with polycystic ovary syndrome *(PCOS).* Reprinted with permission from Chang RJ, Nakamura RM, Judd HL, Kaplan SA. Insulin resistance in nonobese patients with polycystic ovarian disease. J Clin Endocrinol Metab 1983;57:356-9.

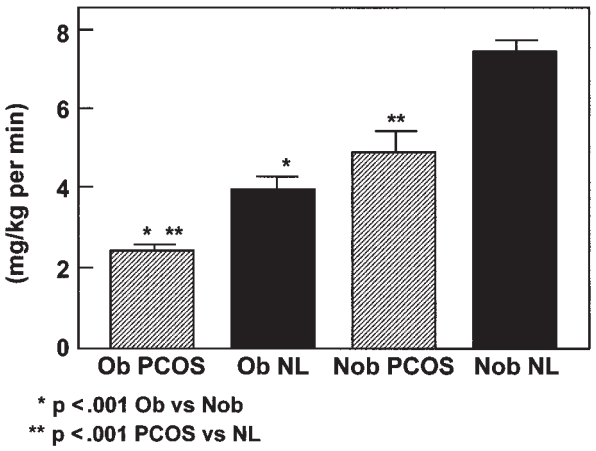

Fig 2. Glucose clamp results showing lower insulin sensitivity (greater insulin resistance) in patients with polycystic ovary syndrome than in weight-matched control subjects. *Ob PCOS,* Obese patients with polycystic ovary syndrome; *Ob NL,* obese control subjects; *Nob PCOS,* nonobese patients with polycystic ovary syndrome; *Nob NL,* nonobese control subjects. *Asterisk* indicates $P < .001$ for obese versus nonobese; *double asterisk* indicates $P < .001$ for patients with polycystic ovary syndrome versus control subjects. Reprinted with permission from Dunaif A, Segal KR, Futtereweit W, Drobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes 1989;38:1165-74.

chronic anovulation without periodic progestin exposure thus may have endometrial hyperplasia or endometrial cancer. Such women should be evaluated by means of endometrial sampling, uterine ultrasonography, or both.

The androgen excess of polycystic ovary syndrome is usually manifested by varying degrees of hirsutism. Patients may also report acne. Such symptoms are usually associated with serum total testosterone concentrations >60 ng/dL and androstenedione concentrations >200 ng/dL. More advanced signs of androgen excess, such as clitorimegaly and loss of female body contour, can be associated with hyperthecosis. The rapid development of virilizing signs, such as deepening of the voice, increased muscle mass, and temporal balding, should prompt a search for a tumor and lead one away from a diagnosis of polycystic ovary syndrome.

Typically treatment is directed at alleviating the presenting symptoms: ovulation induction for infertility, oral contraceptives or a progestin for menstrual irregularity, and oral contraceptives or spironolactone for hirsutism. On the basis of accumulating epidemiologic data, however, such treatment might ultimately be complemented by a long-term approach that addresses the underlying pathophysiology of insulin resistance by means of insulin-lowering drugs.

Pathophysiology

The fundamental pathophysiologic defect of polycystic ovary syndrome remains unknown and is a source of controversy and ongoing study. There is a growing consensus, however, that the key features include insulin resistance, androgen excess, and abnormal gonadotropin dynamics.

With respect to insulin resistance, approximately 60% to 70% of women with polycystic ovary syndrome are obese, and it is well known that obesity is associated with insulin resistance. However, women with polycystic ovary syndrome have evidence of insulin resistance beyond that of obese women in the general population. In an early study by Chang et al,[6] insulin response to an oral glucose challenge was significantly greater in patients with polycystic ovary syndrome than in obese control subjects without polycystic ovary syndrome (Fig 1). The same conclusion has been reached by many investigators by means of a more definitive glucose clamp study. Dunaif et al,[7] for example, found that the greater insulin resistance of patients with polycystic ovary syndrome compared with that of control subjects was true for both lean and obese patients with polycystic ovary syndrome (Fig 2).

There is a linear correlation between serum androgen levels and measures of hyperinsulinemia, such as fasting insulin level.[8] What is the direction of causation in polycystic ovary syndrome? On balance, the weight of the evidence indicates that the direction of causation is from insulin to androgen, rather than the reverse. For example, when androgens are suppressed with a gonadotropin-releasing hormone analog in patients with polycystic ovary

syndrome, insulin resistance does not decline.[9] When hyperinsulinemia is reduced with diazoxide, however, androgen levels decline.[10]

A provocative model of polycystic ovary syndrome, in which gonadotropin-dependent ovarian hyperandrogenism is central, has been proposed by Barnes et al[11] and Rosenfield et al.[12] They presented data suggesting that women with polycystic ovary syndrome demonstrate increased formation of 17β-hydroxyprogesterone and androstenedione in response to LH[11] because of abnormal enzymatic regulation of steroidogenesis.[12]

With respect to gonadotropins, circulating LH concentrations tend to be higher in women with polycystic ovary syndrome and FSH levels tend to be in the low to normal range. The frequency of LH pulses (as a reflection of gonadotropin-releasing hormone pulsatility) is often found to be increased in patients with polycystic ovary syndrome in comparison with normally cycling women (Fig 3.)[13] Controversy exists regarding whether these gonadotropin alterations represent a primary or secondary defect.

Epidemiology

The prevalence of polycystic ovary syndrome cannot be determined with precision because it depends on the definition. A strict, research-based definition that relies on endocrine characteristics is associated with a 3% prevalence of polycystic ovary syndrome,[14] whereas a definition that is based purely on ultrasonographically defined morphologic characteristics is associated with a 22% prevalence.[3] For the clinical definition used here, chronic anovulation plus androgen excess, the prevalence is probably in the 5% range.[15] Incidence data have not been reported.

During the past decade, increased attention has been paid to the possibility that the pathophysiologic features of polycystic ovary syndrome (anovulation, androgen excess, and hyperinsulinemia) are associated with a shift toward a male pattern of cardiovascular risk. In an early study by Dahlgren et al,[16] women who underwent ovarian wedge resection and who had histologic confirmation of polycystic type ovarian tissue were followed up for a variety of health outcomes. These patients were found to have higher rates of type 2 diabetes and hypertension (Fig 4). A subsequent study[17] used a statistical risk factor model to predict an increase of several times in the risk of myocardial infarction among women with polycystic ovary syndrome (Fig 5). It is important to note that long-term follow-up studies of patients with polycystic ovary syndrome with respect to cardiovascular events have not been reported.

Wild et al[18] performed several studies that investigated cardiovascular risk in patients with polycystic ovary syndrome. In 1 of these studies, patients with polycystic ovary syndrome were matched by weight with cycling control subjects. Although the sample size was small, the results suggested an adverse lipid profile in patients with polycystic ovary syndrome compared with that in control subjects (Table I).

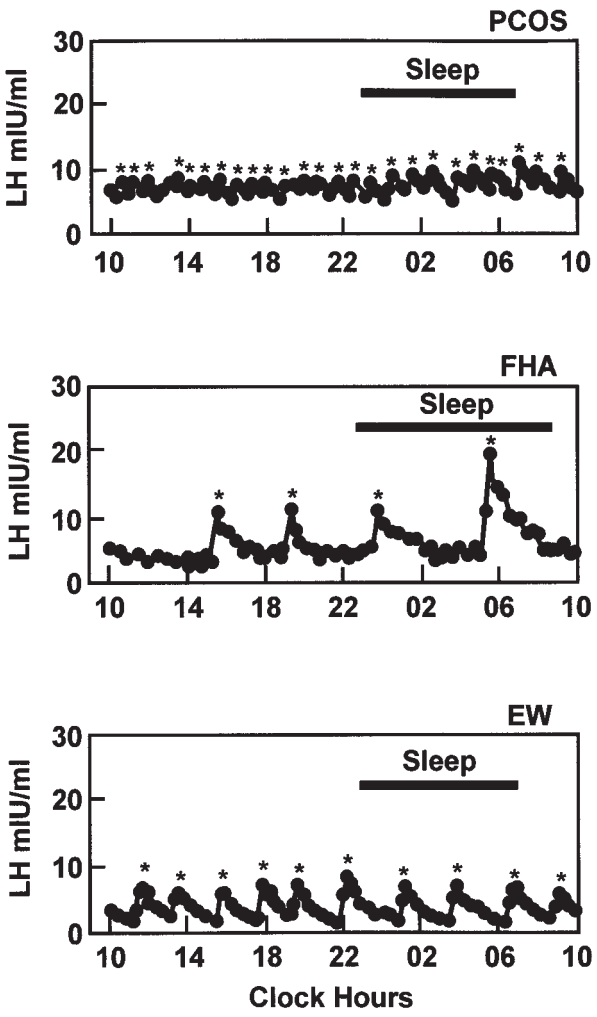

Fig 3. LH pulse patterns in women with polycystic ovary syndrome *(PCOS),* women with functional hypothalamic amenorrhea *(FHA),* and eumenorrheic control women *(EW). Asterisks* represent LH pulses. Reproduced permission from Berga SL, Daniels TL. Use of the laboratory in disorders of reproductive neuroendocrinology. J Clin Immunoassay 1991;14:23-8.

An ongoing study of cardiovascular risk in patients with polycystic ovary syndrome, involving >200 patients with polycystic ovary syndrome and control subjects, offers further support to the hypothesis that women with polycystic ovary syndrome are at increased risk for cardiovascular disease.[19] Patients with polycystic ovary syndrome were found to have an adverse lipid profile after controlling for body-mass index and other potentially confounding variables. Moreover, preliminary data suggest increased intima-media thickness of the carotid artery among patients with polycystic ovary syndrome[20]; these data have been confirmed in a larger sample, con-

Fig 4. Increased risk of hypertension and diabetes among women with polycystic ovary syndrome *(PCOS)* previously diagnosed by ovarian wedge resection. Reprinted with permission from Dahlgren E, Janson P, Johansson S, Mattson L, Lindstet G, Crona N, et al. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. Fertil Steril 1992;57:505-13.

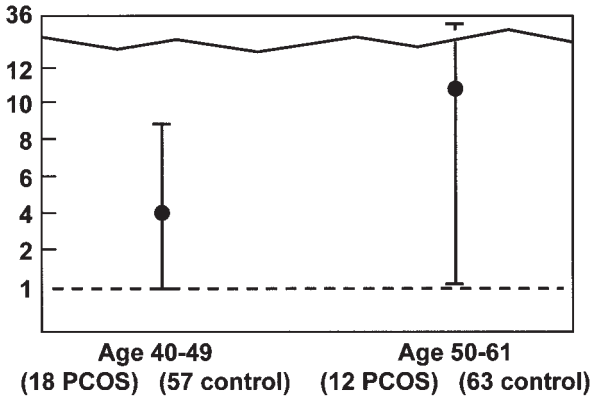

Fig 5. Risk factor statistical model indicative of an increased relative risk for myocardial infarction among women with polycystic ovary syndrome *(PCOS)*. Reprinted with permission from Dahlgren E, Janson P, Johansson S, Lapidus L, Oden A. Polycystic ovary syndrome and risk for myocardial infarction: evaluated from a risk factor model based on a prospective population study of women. Acta Obstet Gynecol Scand 1992;71:599-604.

Table I. Lipid profiles in women with polycystic ovary sydrome

Lipid profile (mg/dL)	*PCOS (N = 206)*	*Control (N = 206)*	*t*	*Significance*
TC	195.4 ± 33.5	185.6 ± 37.8	2.61	$P = .01$
HDLT	51.1 ± 14.5	57.8 ± 14.5	–4.05	$P < .0001$
HDL_2	7.8 ± 6.22	11.7 ± 7.34	–5.11	$P < .0001$
LDL	118.4 ± 31.5	110.7 ± 34.6	2.17	$P = .32$
Triglycerides	129 ± 88.8	85.9 ± 63.4	5.58	$P < .001$

Results are expressed as mean ± SD. Modified with permission from Talbott E, Guzick D, Clerici A, Berga S, Detre K, Weimer K, et al. Coronary heart disease risk factors in women with polycystic ovary syndrome. Arterioscler Thromb Vasc Biol 1995;15:821-6. *PCOS,* Polycystic ovary syndrome; *TC*, total cholesterol; *HDLT,* total high-density lipoprotein; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein.

trolling for body mass index and other variables (Talbott E, et al, unpublished data, 1998). Confirmation of cardiovascular risk must be accomplished through prospective cohort studies, with cardiovascular events as end points.

In view of the role of insulin resistance as a fundamental element in the pathophysiology of polycystic ovary syndrome and also of the possible long-term consequences of polycystic ovary syndrome with respect to cardiovascular disease, the use of insulin-lowering drugs in the treatment of polycystic ovary syndrome has begun to be studied. These promising investigations are reviewed elsewhere in this supplement.

Summary

Women with polycystic ovary syndrome are typically seen with symptoms of infertility, menstrual irregularity, and androgen excess. The fundamental pathophysiologic defect is not known, but important features include insulin resistance, androgen excess, and altered gonadotropin dynamics. Accumulating evidence suggests the possibility that women with polycystic ovary syndrome may be at increased risk for cardiovascular disease. It will be important to test this hypothesis by means of long-term follow-up of patients with polycystic ovary syndrome with respect to actual cardiovascular events.

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