

# Polycystic Ovary Syndrome

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Women with polycystic ovarian syndrome have chronic anovulation and androgen excess not attributable to another cause. This condition occurs in approximately 4% of women. The fundamental pathophysiologic defect is unknown, but important characteristics include insulin resistance, hyperandrogenism, and altered gonadotropin dynamics. Inadequate follicle-stimulating hormone is hypothesized to be a proximate cause of anovulation. Obesity frequently complicates polycystic ovarian syndrome but is not a defining characteristic. The diagnostic approach should be based largely on history and physical examination, thus avoiding numerous laboratory tests that don't contribute to clinical management. Women with polycystic ovarian syndrome typically present because of irregular bleeding, hirsutism, and/or infertility. These conditions can be treated directly with oral contraceptives, oral contraceptives plus spironolactone, and ovulation induction, respectively. However, women with polycystic ovarian syndrome also have a substantially higher prevalence of diabetes and increased risk factors for cardiovascular disease. They should also be screened, therefore, for these conditions and followed closely if any risk factors are uncovered. For obese women with polycystic ovarian syndrome, behavioral weight management is a central component of the overall treatment strategy. (Obstet Gynecol 2004;103:181-193. © 2004 by The American College of Obstetricians and Gynecologists.)

The basic pathophysiologic defect in polycystic ovarian syndrome is not known, and opinions differ about its evaluation and management. An extensive literature has therefore developed about this complex condition. True to the spirit of this series, there will be no attempt here to provide an exhaustive summary of the polycystic ovarian syndrome literature. Recognizing that many bits of evidence in support of one idea or another will not be included or referenced, my goal is to present a distilled view of the field that I hope will be of value to the practitioner.

## DEFINITION

Since its first description in 1935 by Stein and Leventhal,<sup>1</sup> a variety of histologic, biochemical, sonographic,

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and clinical characteristics has been associated with polycystic ovarian syndrome. There is no general agreement, however, about its definition. A 1990 consensus conference on the diagnostic criteria for polycystic ovarian syndrome, convened by the National Institute of Child Health and Development, revealed that there was no consensus.<sup>2</sup> Rather, as shown in Table 1, there was a wide variety of views among the assembled experts regarding the clinical and endocrinologic features that characterize polycystic ovarian syndrome.

That said, a practical and useful clinical definition of polycystic ovarian syndrome has emerged in the United States. Women are defined to have polycystic ovarian syndrome if they have chronic anovulation and evidence of androgen excess for which there is no other cause. This is often referred to as the "NIH Conference" definition, despite the variability in the responses shown in Table 1.

## PREVALENCE

Most studies of the prevalence of polycystic ovarian syndrome yield unreliable results because of the selection bias that occurs when a referral center for polycystic ovarian syndrome reports on its experience. The best prevalence study, reported in 1998, was based on an unselected sample of white and African-American women between the ages of 18 and 45 years who presented for a University employment physical in Alabama.<sup>3</sup> Of 277 women who consented to a history, physical examination, and hormonal evaluation, the overall prevalence of polycystic ovarian syndrome by using the above definition was 4-4.7% for white women and 3.4% for African American women. Although this is less than previous estimates of 5-10%, the 4% figure still implies that approximately 3 million reproductive-aged women in the United States have polycystic ovarian syndrome.

## CLINICAL IMPORTANCE

In clinical gynecologic practice, women with polycystic ovarian syndrome are seen primarily for menstrual irregularity, androgen excess, and infertility. Treatment is largely directed at the immediate presenting complaint. During the past decade, women with chronic anovula-



**Table 1.** Polycystic Ovary Syndrome Research Diagnostic Criteria (National Institutes of Health, April, 1990)

Definite or probable	Possible
Hyperandrogenemia, 64%	Insulin resistance, 69%
Exclusion of other etiologies, 60%	Perimenarchal onset, 62%
Exclusion of CAH, 59%	Elevated LH/FSH, 55%
Menstrual dysfunction, 52%	Polycystic ovary syndrome by ultrasound, 52%
Clinical hyperandrogenism, 48%	Clinical hyperandrogenism, 52%
	Menstrual dysfunction, 45%

LH = luteinizing hormone; FSH = follicle-stimulating hormone. Percentage refers to the fraction of participants who endorsed that criterion ( $n = 58$ ).

tion and hyperandrogenism have been observed to have an increased prevalence of diabetes and increased risk factors for coronary heart disease (CHD). Specifically, many women with polycystic ovarian syndrome are similar to those with metabolic cardiovascular syndrome (ie, Syndrome X), a CHD-associated clustering within the same individual of hyperinsulinemia, glucose intolerance, dyslipidemia, and hypertension. In addition, the chronic anovulation of polycystic ovarian syndrome implies unopposed estrogen and, therefore, an increased risk of endometrial cancer. These factors have led to a different clinical perspective about polycystic ovarian syndrome—one that recognizes the importance of addressing the immediate issues of irregular bleeding, hirsutism, and infertility, but also emphasizes the long-term goals of preventing diabetes, heart disease, and cancer.

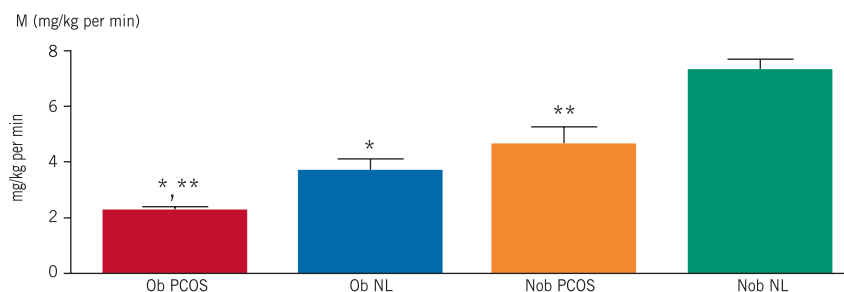
## PATHOPHYSIOLOGY

Although the fundamental pathophysiologic defect in polycystic ovarian syndrome is unknown, these women have several interrelated characteristics, including insu-

lin resistance, hyperandrogenism, and altered gonadotropin dynamics. We will consider each of these in turn, and conclude with a discussion of the hypothesis that inadequate follicle-stimulating hormone (FSH) stimulation is a proximate cause of anovulation in polycystic ovarian syndrome.

Insulin resistance can be defined as a subnormal biological response to insulin. The gold standard for determining insulin resistance is the euglycemic hyperinsulinemic clamp technique. Insulin is administered intravenously at a fixed dose while simultaneously infusing sufficient glucose to maintain circulating glucose concentrations at a predefined normal level. In this manner, the amount of glucose taken up by tissue at equilibrium in the presence of specified doses of insulin can be calculated. A low tissue glucose concentration signifies low insulin sensitivity, ie, high insulin resistance.

It is well known that obesity is associated with insulin resistance. Because women with polycystic ovarian syndrome are often obese, it is not surprising that they would have some element of insulin resistance. However, the extent of insulin resistance among women with polycystic ovarian syndrome cannot be explained entirely by obesity. This was demonstrated in a now classic study reported by Dunaif et al.<sup>4</sup> In Figure 1, taken from this study, the total body glucose concentration at 100  $\mu\text{U/mL}$  of insulin is shown for women with polycystic ovarian syndrome and controls, stratified according to whether subjects were obese. Among nonobese women, those with polycystic ovarian syndrome had lower insulin sensitivity (ie, greater insulin resistance) than cycling controls. Indeed, the nonobese women with polycystic ovarian syndrome had a level of insulin resistance that approached that of obese controls. However, among obese women, who already have a certain degree of insulin resistance, those with polycystic ovarian syndrome had more insulin resistance than cycling controls.



**Figure 1.** Insulin sensitivity (the inverse of insulin resistance) in Obese (Ob) and nonobese (Nob) women with polycystic ovarian syndrome (PCO) and in cycling controls (NL). Copyright ©1989 American Diabetes Association. From *Diabetes*, Vol. 38, 1989:1165–74. Reprinted with permission from The American Diabetes Association.

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It had been repeatedly shown that there is a strong correlation between insulin resistance and hyperandrogenism. This relationship dates back to a 1921 observation by Achard and Thiers,<sup>5</sup> who reported on a bearded woman who was also diabetic. The connection between hyperandrogenism and insulin resistance was further highlighted by 3 cases of hyperandrogenism, insulin resistance and acanthosis nigricans, which Barbieri and Ryan<sup>6</sup> later described as the “HAIR-AN” syndrome.<sup>7</sup> In young women who do not have an adenocarcinoma, acanthosis nigricans (a dermatologic disorder characterized by velvety hyperpigmented skin, usually over the nape of the neck, in the axillae, or beneath the breasts), strongly suggests insulin resistance.

What is the directionality of the relationship between insulin resistance and hyperandrogenism? Does hyperandrogenism cause insulin resistance, does insulin resistance cause hyperandrogenism, or is there a bidirectional relationship? Most of the evidence would suggest that the direction of causation is from insulin to androgen and not the reverse. For example, administration of diazoxide, which specifically reduces insulin concentrations, results in a reduction in circulating androgen concentrations.<sup>8</sup> Weight loss and insulin sensitizers, which also lead to a reduction in insulin, similarly are associated with a reduction in androgens, particularly testosterone and androstenedione. However, administration of a gonadotropin-releasing hormone analog, which reduces androgen secretion from the ovary by suppressing gonadotropins, does not result in a reduction in insulin.<sup>9</sup> The *in vivo* effect on ovarian androgens by insulin is consistent with a number of *in vitro* studies that have shown that insulin synergizes with LH to promote androgen production by the thecal cells. That insulin can promote androgen production in ovarian tissue in the face of insulin resistance in peripheral tissues is a paradox that has not been fully explained. Some authors speculate that this can occur because of multiple actions of insulin and insulin growth factors, and because insulin and insulin-like growth factor may signal through several different intracellular pathways in the ovary.

Another key pathophysiologic feature of polycystic ovarian syndrome is altered gonadotropin-releasing hormone dynamics. Landmark experiments in primates by Knobil et al<sup>10</sup> in the early 1970s demonstrated that luteinizing hormone (LH) is secreted in a pulsatile manner. These investigators and others subsequently showed that the menstrual cycle is fundamentally regulated by the rhythmic release of the neuropeptide gonadotropin-releasing hormone, which came to be known as the “GnRH pulse generator.” Yen et al<sup>11</sup> conceptualized a cascade of 3 components: the central nervous system-hypothalamic complex responsible for pulsatile gonado-

tropin-releasing hormone release (signal generator), which stimulates the pituitary to secrete LH (signal transmitter), which results in cyclical ovarian steroid output (signal modulator).

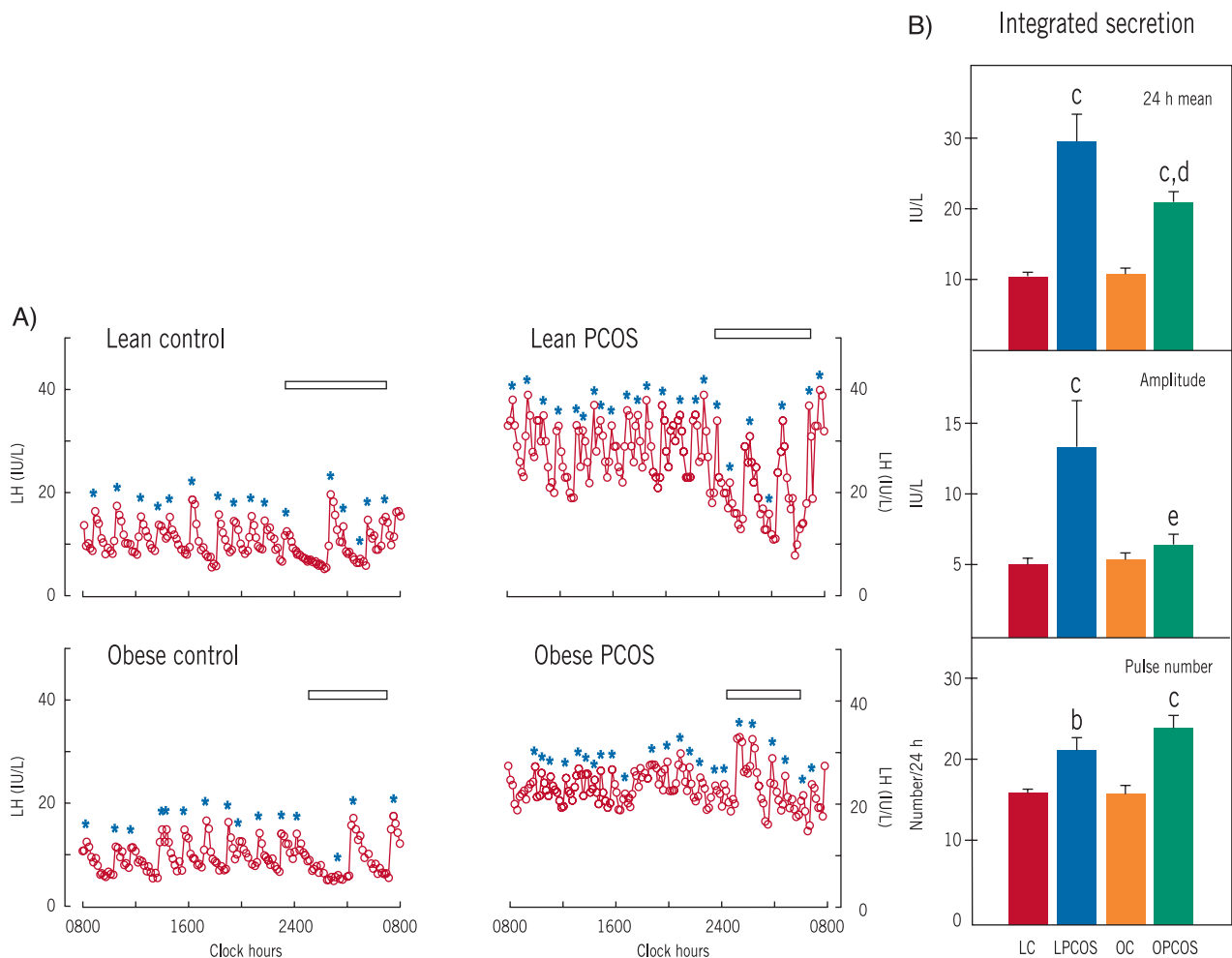
Both lean and obese women with polycystic ovarian syndrome have increased LH pulse frequency and amplitude, leading to increased 24-hour mean concentrations (Figure 2). A recent literature review shows that women with polycystic ovarian syndrome have LH pulse frequencies that are generally one-third to one-half again as fast as the LH pulse frequency for eumenorrheic control women.<sup>12</sup>

Because androgen production by theca cells is LH dependent,<sup>13</sup> it would seem to follow that the elevated levels of LH seen in women with polycystic ovarian syndrome are responsible for the excess androgen production. Indeed, suppression of LH by gonadotropin-releasing hormone analogs or by oral contraceptives reduces circulating testosterone and androstenedione. However, the role of LH in the ovarian hyperandrogenism is probably more permissive than etiologic. For example, women with isolated FSH deficiency have markedly increased LH concentrations because of a lack of feedback inhibition by estradiol ( $E_2$ ), but do not develop ovarian hyperandrogenism or polycystic ovaries.<sup>14,15</sup>

Although increased androgen production in women with polycystic ovarian syndrome is augmented by increased LH and is associated with anovulation, it can be argued that the proximate cause of the anovulation may be insufficient FSH. Follicles in the ovaries of women with polycystic ovarian syndrome do not mature fully, and the granulosa cells in these arrested follicles are low in number and in aromatase activity. Therefore,  $E_2$  production by these follicles is limited, generally in the range of 70–80 pg/mL higher than early follicular  $E_2$  and capable of suppressing FSH, but never reaching the levels needed to initiate an LH surge. Clinically, it is recognized that granulosa cells in the ovaries of polycystic ovarian syndrome patients are capable of proliferating and secreting large amounts of  $E_2$  in response to exogenous FSH injections. Thus, it is not surprising that *in vitro* studies have shown these granulosa cells to be functionally intact, with the full FSH-signaling mechanism needed to stimulate the aromatization of androstenedione to  $E_2$ .<sup>16</sup>

If the granulosa cells of polycystic ovarian syndrome patients have all of the machinery they need to proliferate and to make  $E_2$ , and if there is no blockade to FSH action within the follicle, as evidenced by follicular responsiveness to exogenous FSH, we might then infer that the problem is inadequate concentrations of endogenous FSH. Based on the work of Zeleznik<sup>17</sup> in monkeys, as well as subsequent studies in women,<sup>18</sup> absolute





**Figure 2.** Luteinizing hormone (LH) dynamics in lean and obese women with and without polycystic ovarian syndrome (A) and integrated, 24-hour values of LH concentration, amplitude, and pulse frequency (B). Reprinted from Morales AJ, Laughlin GA, Büttow T, Maheshwari H, Baumann G, Yen SSC. Insulin, somatotropic, and luteinizing hormone axes in lean and obese women with polycystic ovary syndrome: common and distinct features. *J Clin Endocrinol Metab* 1996;81:2854–64. Copyright 1996. The Endocrine Society.

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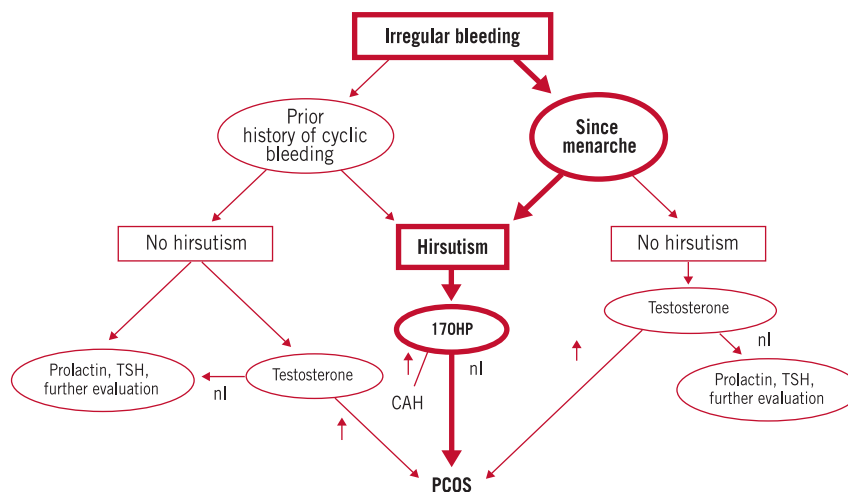
concentrations of FSH above a specified threshold are essential for both the initiation of preovulatory follicle development as well as the selection of a single preovulatory follicle. In the case of polycystic ovarian syndrome, the concentration of FSH may simply not rise above levels seen in the mid-follicular range of the normal menstrual cycle, which are insufficient to stimulate preovulatory follicle development. The low FSH concentrations may in part reflect the rapid gonadotropin-releasing hormone pulses seen in polycystic ovarian syndrome, but a more likely explanation is that FSH is also constrained by negative feedback inhibition of  $E_2$ , which never exceeds mid-follicular levels.

In support of this FSH hypothesis is the fact that most women with polycystic ovarian syndrome ovulate in

response to clomiphene citrate, which works by interfering with estrogen feedback on FSH. That is, when the feedback system is intact, the tonic mid-follicular levels of  $E_2$  seen in polycystic ovarian syndrome keep FSH suppressed below the necessary threshold level. When the negative feedback loop is opened by clomiphene, however, FSH rises sufficiently to initiate preovulatory follicle development. Similarly, gonadotropin-releasing hormone analogs or laparoscopic ovarian drilling, which reduce estrogen as well as androgen, can release FSH suppression and thereby promote ovulation.

We currently lack a satisfactory integrative model of polycystic ovarian syndrome pathophysiology that takes into account all of the key foregoing elements. It is likely that genetic factors are at the root of the condition; in





**Figure 3.** Initial diagnostic evaluation of polycystic ovarian syndrome (PCOS). The pathway in bold is the most common scenario. ↑ Testosterone is defined as more than 60 ng/dL. ↑ 17-Hydroxyprogesterone (17OHP) is more than 2 ng/mL. TSH = thyroid-stimulating hormone; CAH = congenital adrenal hyperplasia; n1 = cycling controls.

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view of characteristics such as insulin resistance and gonadotropin changes that do not appear to be linked, however, it is also likely that there is more than one genetic “hit.” Moreover, clinical manifestation of polycystic ovarian syndrome, given a genetic predisposition, may be influenced by environmental factors.

### DIAGNOSTIC APPROACH

When the combination of chronic anovulation and androgen excess is used as a working definition of polycystic ovarian syndrome, the clinician will be on relatively safe ground from the standpoint of avoiding over-diagnosis or making the wrong diagnosis. Let’s consider the 2 components of this definition in turn.

First, with respect to ovulatory history, women with polycystic ovarian syndrome classically give a history of irregular menstrual cycles dating to menarche. As a rule of thumb, they generally report 6 or fewer episodes of spontaneous vaginal bleeding per year. A woman with a history of cyclic, predictable menstrual cycles followed by secondary amenorrhea, however, especially in the absence of androgen excess, probably does not have polycystic ovarian syndrome. This individual should be evaluated for other causes of amenorrhea, beginning with thyroid stimulating hormone, prolactin, and FSH.

Oily skin and acne are subtle signs of androgen excess, but hirsutism is the most common manifestation of the androgen component of polycystic ovarian syndrome. The clinician should inquire about, and examine for, the presence “male-pattern” hair, ie, hair located on the upper lip, chin, chest, lower abdomen, and inner aspects

of the thighs. In the prevalence study of unselected women undergoing a pre-employment physical examination described earlier,<sup>3</sup> 7.6% of women had a Ferriman-Gallaway score<sup>19</sup> greater than 5, which can be taken as a reasonable definition of hirsutism. In evaluating whether hair growth is outside of the “normal range,” consideration must also be given to the ethnic background.

There are differing opinions on the question on what laboratory studies should be ordered in evaluating a woman with polycystic ovarian syndrome. In my judgment, polycystic ovarian syndrome is primarily a clinical diagnosis; few laboratory studies are needed. Given a history of chronic anovulation and androgen excess, the only condition that needs to be excluded to secure the diagnosis of polycystic ovarian syndrome is nonclassical congenital adrenal hyperplasia, which is very uncommon. This diagnostic pathway, which reflects the most common clinical scenario, as shown in bold in Figure 3.

To become comfortable with the minimalist approach to the evaluation of polycystic ovarian syndrome shown in Figure 3, let’s review some laboratory tests that are often advocated as important in the diagnostic evaluation of polycystic ovarian syndrome. In the absence of progression from hirsutism to virilization, there is no need to draw testosterone or dehydroepiandrosterone sulfate to rule out an ovarian or adrenal tumor.

A ratio of LH to FSH greater than 2:1 is certainly consistent with polycystic ovarian syndrome, and as noted above, FSH may play a key role in pathophysiology. As a diagnostic test, however, the LH:FSH ratio is

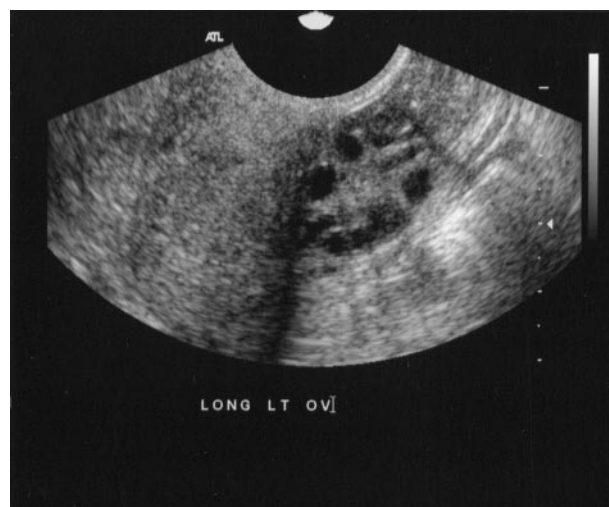


often in the “normal range,” and therefore is insensitive. This is because of the pulsatile nature of gonadotropins, resulting in a broad range of LH:FSH ratios in polycystic ovarian syndrome when a single blood sample is drawn. In addition, the double-sandwich immunofluorometric assays currently used for LH determinations are associated with lower LH:FSH ratios than earlier radioimmunoassays.

Thus, in my own practice, when evaluating a woman with chronic anovulation since menarche and hirsutism, the only blood sample I obtain is 17-hydroxyprogesterone concentration to rule out 21-hydroxylase-deficient nonclassical adrenal hyperplasia. To maximize sensitivity, this sample should be obtained in the follicular phase, and between 7:00 and 9:00 AM.<sup>20</sup> If the result is less than 2 ng/mL, nonclassical adrenal hyperplasia is safely excluded; if the result is greater than 2 ng/mL, the sensitivity for detecting the disorder is virtually 100%, but the positive predictive value is low; therefore, referral to a reproductive endocrinologist for provocative testing with adrenocorticotropic hormone is warranted. This should only occur in about 70% of cases.<sup>20</sup>

Although testosterone is not necessary for diagnosis when clear hirsutism is present, I sometimes obtain a baseline serum total testosterone concentration if I will be initiating management directed at reducing testosterone. Testosterone is also helpful in evaluating a woman with chronic anovulation but who does not have clinical evidence of hirsutism or other signs of androgen excess (Figure 3). In this regard, consideration of ethnicity is an important aspect of the diagnostic evaluation. Thus, women of Asian or Scandinavian descent may not express high circulating concentrations of androgen at the end organ (hair follicle), while women of Mediterranean descent, for example, may express some degree of hirsutism constitutionally even with normal levels of circulating androgens. Among cycling women, circulating total testosterone concentration of 60 ng/dL is about 2 standard deviations above the mean. Thus, in women who have a history of chronic anovulation but who do not have clinical signs of androgen excess on physical examination, the finding of a total testosterone concentration greater than 60 ng/dL is consistent with polycystic ovarian syndrome.

It should be noted that most laboratories report a “normal” upper limit for total testosterone considerably higher than 60 ng/dL. This is likely due to the use of “healthy volunteers” for the establishment of the normal range, without regard to menstrual history. One might argue that obtaining a “free” testosterone concentration, which takes into account the fact that less androgen is bound to sex hormone binding globulin in androgenized individuals, is a more accurate representation of biolog-



**Figure 4.** Transvaginal ultrasound image of an ovary from a woman with polycystic ovarian syndrome. Note “string-of-pearls” appearance of subcapsular cysts and hyperechoic stroma.

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ically important testosterone in polycystic ovarian syndrome. Free testosterone is more expensive than total testosterone, however, and clinical assays of free testosterone vary considerably in their reliability. Androstenedione is probably similar to total testosterone in diagnostic accuracy, but there are fewer data on the use of androstenedione in the evaluation of polycystic ovarian syndrome. In my experience, total testosterone concentration is simple, inexpensive, and adequate to the task of evaluating and monitoring androgen concentrations in the small fraction of women with polycystic ovarian syndrome for whom such monitoring is helpful.

What about ovarian anatomy in the evaluation of women for polycystic ovarian syndrome? A cross-section of an ovary with polycystic ovarian syndrome shows multiple, small, subcapsular cysts, reflecting repeated episodes of incomplete follicular growth. A dense, hyperplastic stroma is also present, reflecting an active thecal component that is over-secreting androgens.

The ovaries of women with polycystic ovarian syndrome typically show an ultrasound picture that reflects this morphology. Numerous, small (8–10) subcapsular cysts are classically found adjacent to one another in a manner that produces a “string of pearls” sign on ultrasound (Figure 4). The hyperechoic stroma reflects the hyperplastic thecal component seen in the histologic sections. Currently, many European centers make the diagnosis of polycystic ovarian syndrome based on ultrasound features of small subcapsular cysts and hyperechoic stroma. Although two thirds of women with



polycystic appearing ovaries based on ultrasound criteria also have clinical signs and symptoms, approximately one third of women with such findings will not have the clinical syndrome of chronic anovulation and androgen excess. Moreover, among normally cycling women, 15–30% have polycystic-appearing ovaries. Thus, polycystic-appearing ovaries are often, but not always, found in women with this clinical syndrome, and polycystic-appearing ovaries often occur in cycling women.

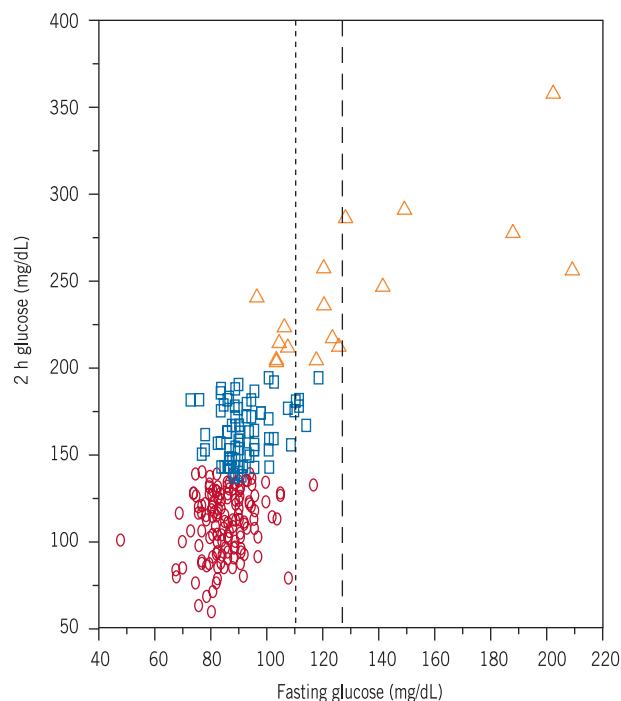
In summary, in my opinion, polycystic ovarian syndrome is best diagnosed clinically with a minimum of laboratory tests, as shown in Figure 3. The vast majority of patients will have a history of chronic anovulation dating since menarche and evidence of androgen excess, principally hirsutism. In such women, a blood sample for serum 17-hydroxyprogesterone concentration can be drawn to rule out 21-hydroxylase-deficient nonclassical adrenal hyperplasia; the diagnosis of polycystic ovarian syndrome is then secure. In cases of chronic anovulation without evidence of hirsutism, a serum testosterone greater than 60 ng/dL also suggests a diagnosis of polycystic ovarian syndrome. Women who currently have anovulatory bleeding but who have a history of cyclic menses can be similarly evaluated.

The presence of obesity in conjunction with anovulation and androgen excess increases further one's suspicion of polycystic ovarian syndrome. In cases in which the clinical diagnosis is not clear (ie, chronic anovulation without hirsutism or hirsutism with a history of cyclic menses), the presence of obesity increases the clinical suspicion of polycystic ovarian syndrome.

### LONG-TERM RISKS OF POLYCYSTIC OVARIAN SYNDROME

Women with polycystic ovarian syndrome usually present to the office because of the clinical symptoms of irregular bleeding, infertility, and hirsutism. Treatment for these symptoms will be discussed below. In addition, we have long known about the increased risk of endometrial cancer in women with polycystic ovarian syndrome, due to unopposed estrogen that results from chronic anovulation. In recent years, however, we have also learned that women with polycystic ovarian syndrome are more likely to develop diabetes and have a set of risk factors that may increase their likelihood of developing cardiovascular disease.

In view of the peripheral insulin resistance that characterizes women with polycystic ovarian syndrome, it would be reasonable to hypothesize that such women have impaired glucose tolerance and an increased prevalence of diabetes. Yet it wasn't until 1987 that evidence appeared to support this hypothesis, in the form of a



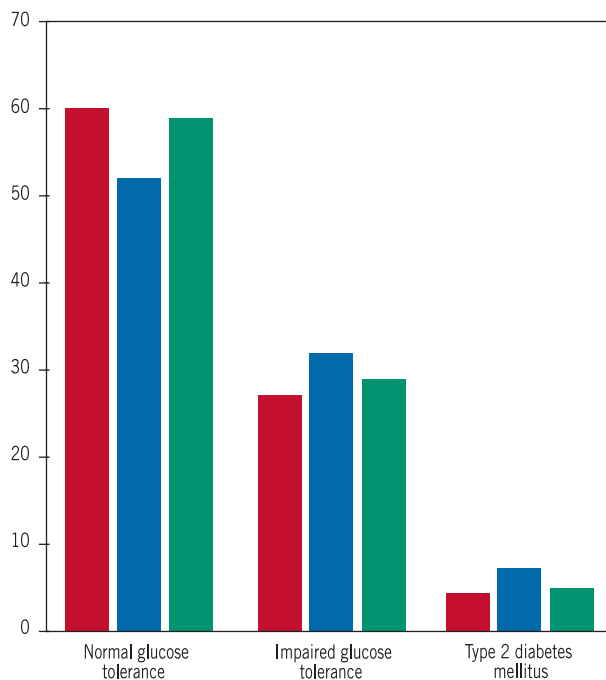
**Figure 5.** Scattergram of fasting blood glucose levels vs 2-h glucose stimulated levels in 254 women with polycystic ovary syndrome (PCOS). Dotted line = threshold for impaired fasting glucose (110/dL) by the 1997 American Diabetes Association criteria; dashed line (126 milligram/dL) = threshold for non-insulin-dependent diabetes mellitus by the same criteria. Circle = normal glucose tolerance based on WHO OGTT status; square = impaired glucose tolerance; triangle = Non-insulin-dependent diabetes mellitus. Reprinted from Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 1999;84: 165–9. Copyright 1999. The Endocrine Society.

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study by Dunaif et al<sup>21</sup> which showed that obese women with polycystic ovarian syndrome had significantly higher glucose concentrations during an oral glucose tolerance test than weight-matched ovulatory hyperandrogenic and control women.

We have now learned that women with polycystic ovarian syndrome have a dramatically increased risk of impaired glucose tolerance and non-insulin-dependent diabetes mellitus, and that fasting glucose concentrations are poor predictors of non-insulin-dependent diabetes mellitus in this group.<sup>22</sup> As shown in Figure 5, most women with polycystic ovarian syndrome have normal fasting glucose concentrations, but a substantial percentage have impaired glucose tolerance or frank non-insu-





**Figure 6.** Prevalence of glucose intolerance in 3 U.S. cities: Solid bar = New York City; hatched bar = Chicago, IL; open bar = Hershey, PA. NGT = normal glucose tolerance; IGT = impaired glucose tolerance; DM = diabetes mellitus. Reprinted from Legro RS. Diabetes prevalence and risk factors in polycystic ovary syndrome. Guzik DS, editor. *Polycystic Ovarian Syndrome. Obstetrics and Gynecology Clinics of North America*. Vol. 28, No. 1. Philadelphia (PA): W.B. Saunders; 2001:99–109. (Data from Ehrmann DA, Barnes RB, Rosenfield RL, et al. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care* 1999;22:141–6; and Legro RS, Kunselman AR, Dodson WC, et al. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 1999;84:165–9.)

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lin-dependent diabetes mellitus based on a 2-hour oral glucose tolerance test value. Indeed, women with polycystic ovarian syndrome in a variety of communities have been found consistently to have a prevalence of 30% for impaired glucose tolerance, and the rate of undiagnosed non-insulin-dependent diabetes mellitus in these women approaches 8–10% (Figure 6).

Beginning in the mid-1980s, Wild et al<sup>23,24</sup> and Slowinska-Srzednicka et al<sup>25</sup> began to consider whether the insulin resistance, androgen excess, and chronic anovulation that characterize polycystic ovarian syndrome might increase the risk of cardiovascular disease. Data from small samples of women with polycystic ovarian

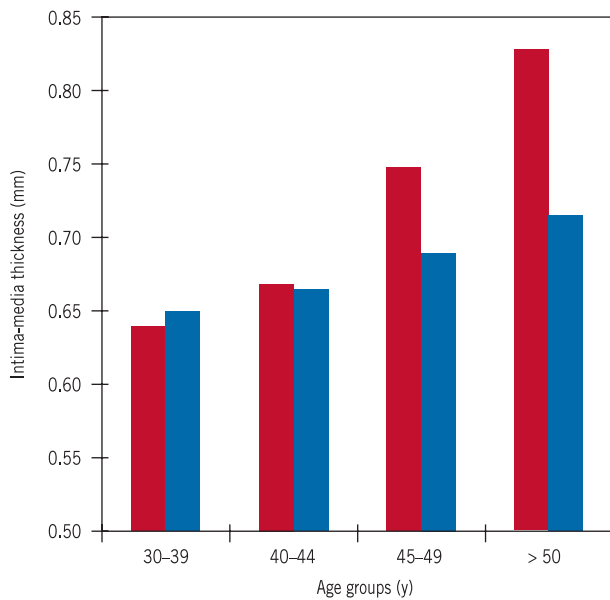
syndrome and controls were suggestive that polycystic ovarian syndrome was associated with lipid abnormalities, was independent of obesity, and correlated with insulin resistance.<sup>23–25</sup> In 1992, a team of reproductive endocrinologists and epidemiologists led by Evelyn Talbott<sup>26</sup> at the University of Pittsburgh initiated a large-scale epidemiologic study of cardiovascular risk factors in women with polycystic ovarian syndrome, which is still ongoing. In the first report by a cohort of 244 polycystic ovarian syndrome cases and 244 age- and neighborhood-matched controls, it was found that, controlling for body mass index, insulin, and smoking, women with polycystic ovarian syndrome had significantly lower high-density lipoprotein 2 and higher total cholesterol, low-density lipoproteins, and triglycerides.<sup>26</sup>

This cohort of women with polycystic ovarian syndrome has also been found to have an increase in blood pressure, plasminogen activator inhibitor, and coronary artery calcification, as summarized in a recent review.<sup>27</sup> Subsequent follow-up has indicated that the lipid differences between polycystic ovarian syndrome cases and controls are mainly seen in women aged less than 45 years, but that the carotid artery changes are seen mainly in women aged more than 45 years (Figure 7). These findings suggest that lipid alterations occurring early in women with polycystic ovarian syndrome translate into preclinical atherosclerosis later in life.

Do the diabetes, adverse lipid profile, and preclinical atherosclerotic changes seen in women with polycystic ovarian syndrome translate into an increase in actual cardiovascular events? Thus far, such evidence is limited and inconsistent. In the Pittsburgh cohort, among 126 Caucasian polycystic ovarian syndrome cases who were followed-up for cardiovascular events, 5 women reported myocardial infarction, angina pectoris, and/or coronary bypass or angioplasty. No events were observed among 142 control women who were similarly followed.<sup>27</sup> Similar findings of a 4-fold increase in the risk cardiac events among polycystic ovarian syndrome women were reported from the Czech Republic.<sup>28</sup>

On the other hand, Pierpoint et al<sup>29</sup> found no increase in the rate of deaths due to circulatory disease among a large sample of women with polycystic ovarian syndrome as compared with expected death rates based on age- and sex-specific national rates of mortality. This latter study is important because of the negative finding, but interpretation of these data is constrained by the fact that polycystic ovarian syndrome cases were diagnosed mainly on the basis of hospital records related to wedge resection and by the absence of a matched control cohort. As discussed below, wedge resection can correct the anovulation and metabolic changes that are seen in polycystic ovarian syndrome for long periods of time,





**Figure 7.** Intima-media thickness (IMT) of carotid arteries in women with polycystic ovary syndrome (solid bar) and in control women (hatched bar), by age, in Pittsburgh, PA, longitudinal cohort. Reprinted from Talbott EO, Guzick DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zborowski JV, Remsberg KE, Kuller LH. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. *Arterioscler Thromb Vasc Biol* 2000;20:2414–21.

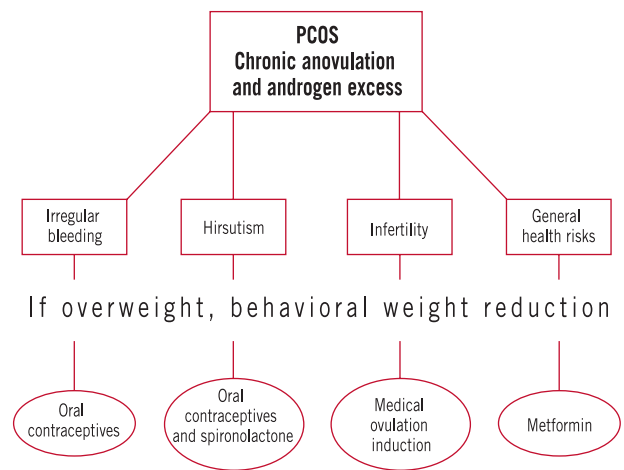
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and this method of case ascertainment may substantially underestimate the syndrome of polycystic ovarian syndrome as defined by chronic anovulation and androgen excess. There is a clear need for a prospective study of a large sample of nonsurgically treated women with polycystic ovarian syndrome and matched controls with respect to the incidence of cardiovascular events during a prolonged follow-up period.

## TREATMENT

As shown in Figure 8, women with polycystic ovarian syndrome typically present because of irregular bleeding, hirsutism, or infertility. In recent years, because of the publicity surrounding the long-term health risks associated with polycystic ovarian syndrome, some women with this condition seek physician consultation to learn about their options in managing these risks.

Regardless of the reason for presentation, it is prudent at the first visit to obtain the patient's height and weight to calculate her body mass index and to obtain her blood pressure. In addition, it is a reasonable practice to obtain a fasting lipid panel to evaluate cardiovascular risk and



**Figure 8.** Treatment algorithm for women with polycystic ovarian syndrome (PCOS). OCs = oral contraceptives.

*Guzick. Polycystic Ovary Syndrome. Obstet Gynecol* 2004.

also a fasting glucose concentration to evaluate the possibility of impaired glucose tolerance (IGT) or non-insulin-dependent diabetes mellitus. As noted above, because a substantial proportion of women with polycystic ovarian syndrome with normal fasting glucose values have abnormal 2-hour values, a 2-hour oral glucose tolerance test is preferable, especially if the patient is obese. If fasting plasma glucose is between 110 and 125 mg/dL, the diagnosis of IGT is made, and if it is 126 mg/dL or more, the patient has diabetes. For the 2-hour test, the reference values are 140–199 mg/dL for IGT and 2200 mg/dL for diabetes. Abnormalities in any of these areas will have implications for all subsequent counseling and treatment sessions, regardless of the reason for presentation.

If the patient is overweight (body mass index 26 or higher), a major component of any treatment should be directed at weight reduction. Both diet and exercise are needed for any long-term success in a weight reduction program. Most gynecologists are not equipped to provide the necessary counseling and structure. Therefore, success stories in gynecologist offices are few and far between. It is strongly recommended that each practitioner who sees women with polycystic ovarian syndrome establish a working relationship with an established weight reduction program in his or her community that can show data on long-term success in maintaining losses in weight.

Experience with very-low-calorie diets show short-term success in losing upward of 15 kg, which is helpful for research purposes in measuring the impact of weight loss on insulin, androgens, and ovulation. However, from a clinical standpoint, such diets are not useful in



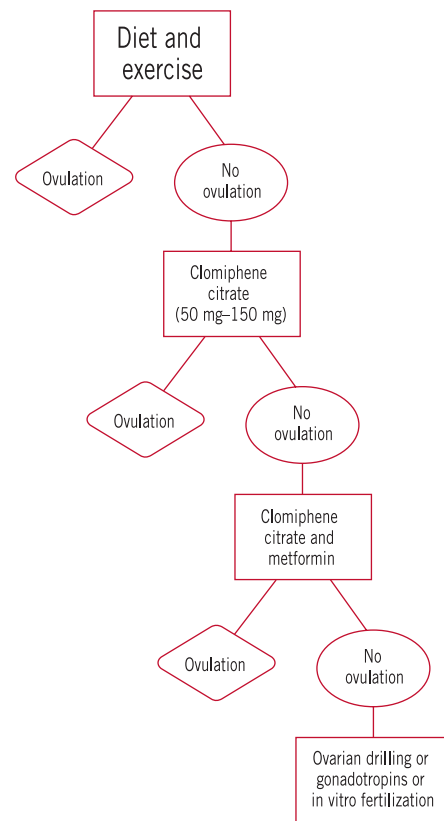
long-term management of women with polycystic ovarian syndrome, because there is invariably a regaining of the lost weight within 6–12 months.

In my experience, the best weight loss strategy is an integrated behavioral program that includes exercise and moderate caloric restriction. Even modest amounts of weight loss can result in a significant favorable impact on insulin, androgens, and ovulation if exercise is included in the program. For example, in a lifestyle modification program that did not involve significant caloric restriction, resulting in 2–5% weight loss, the free testosterone index declined by 21%, 9 of 18 women with irregular cycles resumed regular ovulation, and 2 women became pregnant.<sup>30</sup> We currently have no data on the long-term outcomes of such lifestyle modification programs or on their relative efficacy in comparison with pharmacologic treatments as reviewed below. Because behavioral weight control plays such a potentially critical role in the long-term management of what we now view as a chronic metabolic condition, there is a compelling need for such data.

As suggested in Figure 8, the initial therapeutic strategy in the management of polycystic ovarian syndrome, once the issue of behavioral weight management in obese patients has been addressed, follows directly from the patient's chief complaint. Weight loss programs don't work for everyone; long-term follow-up data, which are currently lacking, may or may not show efficacy in women with polycystic ovarian syndrome. Moreover, even although polycystic ovarian syndrome is characterized by insulin resistance, the best treatment for particular symptoms may still involve strategies that address those symptoms directly, rather than a global treatment of the underlying insulin resistance. In other words, metformin is probably not the silver bullet for all aspects of polycystic ovarian syndrome treatment.

Often, the first contact with a health care provider by a woman with polycystic ovarian syndrome is during her teenage years when she seeks treatment for unpredictable menstrual periods. The typical response is to administer oral contraceptives. As a treatment for pure anovulation, without the additional concerns of hirsutism or infertility, oral contraceptives remain an excellent choice. If hirsutism is also present, the addition of spironolactone, at a dose of 200 mg/d, remains the standard in the United States.

Although oral contraceptives have been associated with adverse effects on oral glucose tolerance tests results in some studies,<sup>31</sup> it is not clear whether the biochemical effects measured have a discernable clinical impact. On the other hand, oral contraceptives have several clear benefits in the treatment of irregular menstrual cycles in women with polycystic ovarian syndrome. These in-



**Figure 9.** Approach to ovulation induction in women with polycystic ovarian syndrome. IVF = in vitro fertilization.

*Guzick. Polycystic Ovary Syndrome. Obstet Gynecol 2004.*

clude: 1) regular withdrawal bleeding, 2) reduction in the risk of endometrial hyperplasia or cancer because of progestin opposition of estrogen, 3) reduction in LH secretion and consequent reduction of ovarian androgens, 4) increased sex hormone binding globulin production and consequent reduction in free testosterone, and 5) improvement in hirsutism and acne. A recent randomized trial of oral contraceptives and metformin showed that regular menstruation occurred more frequently with oral contraceptives than with metformin.<sup>32</sup> Oral contraceptives were also associated with a greater reduction in free testosterone; moreover, oral contraceptives were associated with a measurable decline in hirsutism after 6 months of treatment, while no effect on hirsutism was seen with metformin.

A common reason for a physician consultation by a woman with polycystic ovarian syndrome is infertility. The treatment, assuming a normal semen analysis, is ovulation induction. A recommended approach is shown in Figure 9. Hysterosalpingography, to confirm a normal genital tract, is indicated if there is a history suggestive of pelvic infection, endometriosis, or previous abdominal surgery.



As shown in Figure 9, the most physiologic approach to ovulation induction is weight loss. Failing that, clomiphene citrate provides an excellent initial pharmacologic strategy. Unlike the use of clomiphene citrate for unexplained infertility, where the purpose is to initiate follicular development of multiple ovulatory follicles, the strategy for the woman with polycystic ovarian syndrome is to use the lowest clomiphene citrate dose that will initiate the smallest number of ovulatory follicles (hopefully, only one!). The starting dose is 50 mg/d, for 5 days (usually days 5–9). Approximately 50% of women with polycystic ovarian syndrome will ovulate on 50 mg, and a majority of patients refractory to 50 mg will ovulate if higher doses and/or durations are used.

An ultrasound on day 13 should be performed to assess follicle development. If there are more than 2 preovulatory follicles on day 13, the dose in subsequent cycles can be reduced to 25 mg/d. If there is no follicle development, the dose or duration of treatment can be increased. Although dosage regimens that use more than 100 mg/d of clomiphene citrate for 5 days are not recommended by the manufacturer, regimens that use higher doses or durations are widely and safely used to establish ovulation. In my own practice, I virtually never exceed 150 mg/d for 5 days before moving on to other treatments as discussed below. A recent review of the science and art of ovulation induction with clomiphene citrate in women with polycystic ovarian syndrome, including a variety of strategic interventions to improve outcome, is available.<sup>33</sup> Once a regimen that induces ovulation is established, if there is no pregnancy the clinician should repeat that regimen and not increase the dose in subsequent cycles. The goal is ovulation, not superovulation. Overall, approximately 80% of women with polycystic ovarian syndrome will ovulate on clomiphene citrate.

How should ovulation be induced in the 20% of women who are refractory to clomiphene citrate? Until recently, the alternatives were injectable gonadotropins or laparoscopic ovarian drilling. However, due to the pioneering work of Nestler et al,<sup>34</sup> the use of metformin hydrochloride has now become a common and effective strategy in this situation. Metformin has been used extensively in the treatment of non-insulin-dependent diabetes mellitus. It helps with glycemic control by reducing hepatic glucose output and, to a lesser extent, by increasing peripheral uptake of glucose.

Recently, in a small group of women with polycystic ovarian syndrome who had failed to ovulate in response to 150-mg/d clomiphene citrate, 8 of 11 women ovulated on a regimen of metformin (500 mg 3 times daily) plus clomiphene citrate, while only 3 of 14 ovulated on a regimen of placebo plus clomiphene citrate.<sup>35</sup> Indeed, because Nestler's studies have shown substantial ovula-

tion rates on metformin alone in women with polycystic ovarian syndrome, a randomized trial between metformin and clomiphene citrate is currently being conducted by the Reproductive Medicine Network of the National Institute of Child Health and Development. A small number of women who have taken metformin have developed lactic acidosis. Therefore, patients who have conditions that increase the risk of lactic acidosis (eg, kidney or liver disease, alcoholism, heart failure treated with furosemide) should not take metformin. The medication is normally begun at a dose of 500 mg/d to minimize gastrointestinal side effects, and increased gradually as tolerated. An extended release form often improves compliance.

In the small percentage of women with polycystic ovarian syndrome (about 5–10%) who are refractory to clomiphene citrate alone and to metformin + clomiphene citrate or who cannot tolerate these medications, the alternatives are laparoscopic ovarian drilling or injectable gonadotropins. Like ovarian wedge resection, which can induce a regular menstrual pattern in the majority of patients for up to 25 years,<sup>36</sup> laparoscopic ovarian drilling results in a persistence of endocrine changes and ovulation in long-term follow-up.<sup>37</sup> However, the potential for postoperative adhesions is a concern. There are no published data on the efficacy of ovarian drilling in this highly selected subset of patients with polycystic ovarian syndrome who are refractory to both clomiphene citrate alone and clomiphene citrate plus metformin. Because women with polycystic ovarian syndrome are often hypersensitive to exogenous FSH, the use of gonadotropins in these women is fraught with the risk of multiple pregnancy and hyperstimulation syndrome. In my opinion, if gonadotropins are to be used in this clinical situation, they should be used in conjunction with in vitro fertilization, so that the number of embryos that are transferred to the uterine cavity can be controlled.

Finally, women with polycystic ovarian syndrome may seek consultation because of concerns about health risks. If the patient is overweight, counseling about the importance of lifestyle management, diet, and exercise should be emphasized, and a referral should be given to a behavioral weight management program in her community. As noted above, such a patient should be screened for diabetes, dyslipidemia, and hypertension. Depending on what is found, specific pharmacologic treatment for these conditions should be initiated, probably in conjunction with her internist. Metformin may play a role in the overall management of these women, due to its favorable impact on insulin and lipids. However, long-term data are not available. Assessment of individual risk for each patient, and individualization of



the treatment strategy on the basis of her risk profile, provides a rational management strategy.

## FOLLOW-UP

Women with polycystic ovarian syndrome who are being seen for infertility are followed closely with regards to ovulation induction. Evidence for the presence or absence of ovulation each month is documented, which serves as the basis for decisions about treatment strategies during the subsequent month. If there is no pregnancy after 6 months of documented ovulation, additional infertility evaluations are performed if they had not been done already. If there is no pregnancy after 9–12 months of documented ovulation, and if no other infertility factors are present, the infertility diagnosis begins to blend with “unexplained infertility” and intrauterine insemination is added to the ovulation induction regimen. As noted above, if a lack of pregnancy despite multiple cycles of ovulation induction and intrauterine insemination leads to consideration of the use of gonadotropins, I typically recommends in vitro fertilization as the safest and most effective strategy.

For women with polycystic ovarian syndrome who are not interested in pregnancy, follow-up at 6-month intervals is helpful. This frequency of contact encourages maintenance of the treatment strategy chosen (eg, weight management, oral contraceptives, metformin, etc), and allows for monitoring of weight and blood pressure. It also provides a level of connection of the patient with the physician’s office that increases her likelihood of calling if there are side effects or if there are other reasons for which she might change or discontinue the regimen. As data accumulate on the efficacy of lifestyle management, insulin sensitizers, or other treatment strategies for polycystic ovarian syndrome, these can be discussed with the patient. As well, if the patient has impaired glucose tolerance, diabetes, hypertension, or dyslipidemia, these office visits could be used to introduce advances in the management of these conditions as part of an overall primary care, prevention strategy.

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