Polycystic ovary syndrome (PCOS), characterized as a common endocrinopathy, is a significant cause of distress to most women affected by it. Reducing PCOS-associated signs and symptoms in the individual patient requires early recognition of the syndrome and the adoption of preventive and ameliorative treatment strategies tailored to the symptom profile. However, PCOS is difficult to diagnose and manage, in part because of its clinical and pathophysiologic heterogeneity and the variable manner in which it is defined. This paper discusses the epidemiology, clinical manifestations, and pathophysiology of PCOS.
In Europe, PCOS is generally defined as a polycystic ovary in the presence of at least one clinical sign of endocrine dysfunction (eg, menstrual irregularity, hirsutism, infertility). A polycystic ovary—defined as the presence of at least 10 subcapsular follicular cysts, each measuring 2 to 8 mm in diameter and arranged around or within thickened ovarian stroma—is diagnosed by pelvic ultrasonography and is not synonymous with PCOS. The European and NIH definitions of PCOS are consistent in specifying that, by itself, a polycystic ovary does not signify a pathologic condition. Polycystic ovaries are present in approximately 20% of women in the general population. As many as 1 in 4 of women with a polycystic ovary have no other known endocrine abnormalities or clinical manifestations of the syndrome.

**Prevalence**

The prevalence of PCOS has not been definitively established; in part because PCOS is inconsistently defined from study to study, prevalence estimates vary widely. The prevalence of PCOS among women of reproductive age in the general population has been estimated at 4% to 12%. Not surprisingly, the prevalence of PCOS appears to be higher—from 37% to 90%—in women with menstrual abnormalities and also is increased in the presence of certain diseases. The prevalence of PCOS in women with epilepsy, for example, exceeds that in women without epilepsy.

**Clinical Manifestations and Correlates**

PCOS is characterized by a remarkable spectrum of clinical manifestations and correlates, not all of which are present in all PCOS sufferers. Apart from the hallmark features of hyperandrogenism and anovulation, diseases or conditions that have been associated with PCOS include type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, and malignancies, including endometrial, breast, and ovarian cancer (Table).

**Hyperandrogenism**

Hyperandrogenism, a cardinal feature of PCOS, can be detected by measuring the serum concentration of androgens, including testosterone, androstenedione, and the androgen precursor dehydroepiandrosterone sulfate. It is suggested by clinical signs, such as acne and hirsutism. The etiology of hyperandrogenism in PCOS is unknown but has been hypothesized to be attributed to abnormalities such as inborn defects in ovarian steroidogenesis, hyperinsulinemia-stimulated excessive steroidogenesis by the ovaries, and LH stimulation of excessive steroidogenesis by the ovaries.

Several findings are consistent with a central role for persistent LH stimulation in the etiology of hyperandrogenism in PCOS. First, serum LH levels relative to FSH levels are elevated in 30% to 90% of women with PCOS. In addition, women with PCOS who are administered gonadotropin-releasing hormone (which, when endogenously released from the hypothalamus, stimulates LH secretion) show enhanced LH secretion compared with women without PCOS. Finally, women with PCOS do not show the normal waxing and waning in frequency of LH pulse secretions across the menstrual cycle. Rather, women with PCOS demonstrate rapid, consistent pulses of LH secretion throughout the menstrual cycle. The reasons for these LH abnormalities in women with PCOS are unknown but are hypothesized to result from abnormalities in gonadotropin-releasing hormone secretion from the hypothalamus. The abnormal gonadotropin-releasing hormone secretion could be attributed to a primary defect in the hypothalamus or could be secondary to abnormal circulating levels of estrogen, androgens, or insulin in PCOS.

**Menstrual Irregularity and Infertility**

Consistent with these abnormalities in ovarian hormonal function, anovulation—usually chronic and often first manifested as oligomenorrhea or amenorrhea around the time of onset of menstruation—is

<table>
<thead>
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<th>Table. Conditions Associated with PCOS</th>
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<tr>
<td>▶ Insulin resistance</td>
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<tr>
<td>▶ Type 2 diabetes</td>
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<td>▶ Hypertension</td>
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<td>▶ Dyslipidemia</td>
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<td>▶ Cardiovascular disease</td>
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<td>▶ Cancer (endometrial, breast, ovarian)</td>
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PCOS = polycystic ovary syndrome.
present in most women with PCOS. This aspect of PCOS has been difficult to characterize because of reliance on patients’ self-reports and inconsistencies between studies in the means of assessing and defining anovulation. Although most conceptualizations of PCOS include anovulation as a defining characteristic, it would be more accurate to state that women with PCOS are oligo-ovulatory, because women with PCOS will ovulate on occasion.

**OBESITY**

Obesity is often described as a characteristic of PCOS. However, obesity is not observed in all women with PCOS. The prevalence of obesity in women with PCOS ranges from 1% to 80% across studies and varies with the definition of obesity as well as with women’s race and cultural group. In the general population, the prevalence of overweight and obesity exceeds 50%. The degree to which obesity and its metabolic correlates exacerbate PCOS and/or contribute to its development is being actively researched.

**TYPE 2 DIABETES AND INSULIN RESISTANCE**

An association between PCOS and insulin resistance and type 2 diabetes has been observed independent of obesity, but the effect of a family history of diabetes has not been fully explored. The prevalence of type 2 diabetes has been reported to be higher among women with PCOS (15% to 33% across studies) compared with women without PCOS (2% to 24%), but the magnitude of this difference depends upon the criteria used to make the diagnosis. If elevated fasting blood glucose is used as the sole criterion, the prevalence of type 2 diabetes in women with PCOS is close to that in women without PCOS. If abnormal 2-hour glucose with normal fasting glucose following a 75-g glucose challenge is used as the criterion, then the prevalence of type 2 diabetes in women with PCOS is much higher than in women without PCOS.

Insulin resistance in PCOS is important in the pathogenesis of hyperandrogenemia and anovulation. Both hyperandrogenemia and polycystic ovaries cluster in families, a finding that suggests a genetic component to these disorders. In a study of 217 sisters of PCOS sufferers compared with 47 women with normal reproductive function who were not sisters of PCOS sufferers, regardless of whether they had PCOS or hyperandrogenism, the sisters of PCOS sufferers had significantly reduced glucose/insulin ratios and elevated total cholesterol and low-density lipoprotein (LDL) cholesterol levels. The authors concluded that both insulin resistance and elevated LDL levels cluster in families with PCOS, a finding that suggests that these traits have a genetic component.

**BLOOD LIPID ABNORMALITIES**

Women with PCOS have higher levels of total cholesterol, LDL cholesterol, very-low density lipoprotein cholesterol, and triglycerides, as well as lower levels of high-density lipoprotein (HDL) and HDL2 compared with healthy women. The effect of obesity independent of PCOS on these lipid abnormalities remains to be determined.

**CARDIOVASCULAR DISEASE**

Most of the clinical abnormalities in women with PCOS constitute risk factors for cardiovascular disease. Dyslipidemia, type 2 diabetes, obesity, and hypertension are established risk factors for cardiovascular disease. Chronic anovulation, hyperandrogenemia, and insulin resistance are also associated with increased cardiovascular risk.

In an epidemiologic case-control study of coronary heart disease risk factors in women with PCOS (defined as chronic anovulation with clinical and/or biochemical evidence of androgen excess), women with PCOS, when compared with age-, race-, and neighborhood-matched controls, had: significantly higher body mass indexes (BMIs) and waist-hip ratios; poorer lipid profiles, including higher levels of total cholesterol, LDL cholesterol, and triglycerides and lower levels of HDL and HDL2; thicker carotid arteries as measured by carotid artery ultrasonography assessment of intima-media thickness, which is a pre-clinical measure of atherosclerosis (observed in women ≥45 years of age); and more extensive coronary artery calcification as measured by electron beam computed tomography (coronary calcification, which occurs in the presence of atherosclerosis, predicts the occurrence of cardiovascular events). Although these converging lines of evidence support the hypothesis that PCOS increases cardiovascular risk, women with PCOS have not been shown to experience a higher incidence of cardiovascular events compared with women without PCOS. Results of a United Kingdom study, which followed women diagnosed with PCOS between 1939 and 1979, showed that death rates or cir-
cerebrovascular disease death rates in the women with PCOS did not differ from expected death rates (using standardized UK mortality ratios). The odds of coronary heart disease were not significantly different between women with PCOS and those without PCOS in a follow-up assessment of a sample of women from this study. However, the odds of cerebrovascular disease were higher for women with PCOS compared with those without PCOS. The discrepancy between the cardiovascular mortality data and the data showing heightened cardiovascular risk in women with PCOS highlights the need for prospective studies to evaluate the incidence of cardiovascular events in women with PCOS.

CANCER

Several studies have suggested a link between PCOS and cancer (eg, endometrial, breast, and ovarian cancers), but these studies were generally small, retrospective, and did not employ adequate controls. Although an association between PCOS and endometrial cancer has been reported in these studies, use of progestins and/or oral contraceptive pills by the women was not determined. The hypothesized links between PCOS and breast and ovarian cancer have not been consistently supported by studies conducted to date.

ETIOLOGY

Although the etiology of PCOS has not been determined, it is thought to be multifactorial and to include endocrine, metabolic, genetic, neurologic, and environmental factors. Endocrine abnormalities thought to cause PCOS include increased LH/FSH ratio, increased insulin concentrations, and/or increased 17-hydroxyprogesterone levels in thecal cells. All of these abnormalities result in the androgen excess that may underlie many of the clinical manifestations of PCOS. For example, elevated insulin concentrations resulting from insulin resistance may stimulate the ovaries to overproduce androgens and lead to lipid abnormalities. Insulin resistance decreases the release of sex hormone-binding globulin in the liver with a resultant increase in free androgen levels.

Obesity or marked weight gain may cause or exacerbate PCOS by inducing insulin resistance. In addition to a hypothesized indirect effect on androgen production by inducing insulin resistance, obesity can contribute to hyperandrogenism by stimulating steroid production by adipose tissue. Although obesity is thought to be an important contributor to reproductive endocrine abnormalities in women with PCOS, hyperandrogenism and PCOS also occur in lean women.

Environmental factors have also been implicated in causing or exacerbating PCOS independent from the endocrine and metabolic factors. Medications, such as antiepileptic drugs, have been postulated to lead to a condition mimicking PCOS. In particular, the anticonvulsant valproate, which is used to treat bipolar disorder as well as epilepsy, has been suggested to create a PCOS-like condition, primarily on the basis of several studies conducted by Isojärvi and colleagues in the mid-1990s. More recent data and assessments of the evidence suggest the prevalence of PCOS is no greater with valproate compared with other antiepileptic drugs.

PCOS AND ANTIEPILEPTIC DRUGS

Data suggesting a link between valproate and PCOS evolved from 3 nonrandomized, observational studies, 2 of which were retrospective analyses. In the first study, which included 238 women with epilepsy and 51 healthy untreated controls, menstrual disturbances were reported by 45% of 29 women receiving valproate, 19% of 120 women receiving carbamazepine, 25% of 12 women receiving a combination of carbamazepine and valproate, 13% of 62 women receiving other medications, and 0% of the untreated women. Vaginal ultrasonography performed on the 98 women with epilepsy and a history of menstrual abnormalities revealed polycystic ovaries in 43% of valproate-treated patients, 22% of carbamazepine-treated women, and 19% of a control group of healthy women. Fasting insulin levels were slightly higher in the valproate-treated group (16.9 ± 10.5) compared with the carbamazepine group (15.4 ± 10.5) and the control group (9.6 ± 5.1), and half of the valproate-treated women had marked, progressive weight gain (mean, 21.0 kg) associated with hyperinsulinemia and low serum levels of insulin-like growth factor protein I.
In a third study, switching 12 obese patients from valproate to lamotrigine improved serum insulin, testosterone, and HDL concentrations with a concomitant reduction in BMI.\textsuperscript{20}

Very recently, Morrell and colleagues reported on the results of a multicenter study that included women without epilepsy (controls; \(n = 23\)), women with localization-related epilepsy (\(n = 59\)), and women with idiopathic (primary) generalized epilepsy.\textsuperscript{21} Subjects were not randomized to different drug treatments because they were already undergoing treatment with either a cytochrome p450 enzyme-inducing antiepileptic drug (carbamazepine, phenytoin, or phenobarbital), a cytochrome p450 enzyme-inhibiting drug (valproate), or an antiepileptic drug with a mechanism of action that does not affect p450 enzymes (lamotrigine or gabapentin). Women were to have been on monotherapy for 6 months or longer before being studied for 3 menstrual cycles. Anovulatory cycles were observed in 10.9% of cycles in control patients, in 14.3% of cycles in women with localization-related epilepsy, and in 27.1% of cycles in women with idiopathic generalized epilepsy. Of women who were currently taking valproate or who had taken the drug in the preceding 3 years, 38.1% had at least 1 anovulatory cycle, in contrast to 10.7% of women not taking valproate within the preceding 3 years. Women who had taken valproate or lamotrigine had a significantly higher BMI.

In the study by Morrell et al., it was clear that valproate was the most commonly prescribed neuroleptic drug for women with idiopathic generalized epilepsy. What remained unclear was whether the condition of idiopathic generalized epilepsy was more likely to cause anovulatory cycles in the untreated state.\textsuperscript{21} In a study by Herzog et al., which included 50 women with temporal lobe epilepsy, 20 women did not receive treatment, and 30 women received treatment.\textsuperscript{22} Of the untreated women, 60% had menstrual disturbances compared with 53% of the treated women. Polycystic ovaries or hyperandrogenism were diagnosed in 30% of the untreated women and 13% of the treated women.

Studies of menstrual cycle disturbances in epileptic women using antiseizure medication have not been controlled, especially for BMI, and patients have not been randomized to treatment groups; use of the NIH criteria for defining PCOS does not often occur. It is therefore difficult to draw conclusions about the data, and several subsequent investigations have produced conflicting results. In a prospective cohort analysis of 93 women with epilepsy and PCOS defined by NIH criteria, PCOS was present in 2 of 18 valproate-treated patients (11%), 2 of 20 carbamazepine-treated patients (10%), none (0%) of the patients on antiepileptic polytherapy, and 11% of an untreated control group over a 6-month follow-up period (Figure).\textsuperscript{23} The authors concluded that the results suggest that manifestations of PCOS in patients with focal epilepsy are not related to the administration of either valproate or carbamazepine.

Reproductive endocrine disorders, including PCOS, were not associated with the use of any antiepileptic drugs or with type of epileptic syndrome in a study of 50 women with epilepsy who underwent clinical endocrinologic evaluation, hormonal assessment, and ovarian ultrasonography.\textsuperscript{24} One third (32%) of women experienced reproductive endocrine disorders, most commonly PCOS (\(n = 13\)) followed by hypothalamic amenorrhea (\(n = 2\)) and luteal-phase deficiency (\(n = 1\)). Valproate also was not associated with an excess risk of PCOS relative to other antiepileptic drugs in another sample of 43 women with epilepsy who had received treatment for at least 2 years.

\begin{figure}[h]
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\caption{Incidence of PCOS in Women Treated or Not Treated with Antiepileptic Drugs Over a 6-month Follow-up Period}
\end{figure}
years or in a sample of 105 women with epilepsy who had received valproate monotherapy (n = 52) or carbamazepine monotherapy (n = 53) for at least 2 years. Thus, although a high percentage of patients with epilepsy experienced reproductive endocrine abnormalities in some studies, these abnormalities were not more likely to be associated with valproate than with any other antiepileptic drug.

The high incidence of reproductive endocrine abnormalities in patients with epilepsy is consistent with a possible role of epilepsy in the development of PCOS. It is hypothesized that epileptic discharges involving the amygdala and hippocampus may alter release of gonadotropin-releasing hormone, which in turn alters release of FSH and LH to cause the hyperandrogenism characteristic of PCOS. Alternatively, the pathophysologic substrate of PCOS could be the same as that of epilepsy. Most studies of epileptic women taking valproate have reported increased weight gain or BMI coupled with hyperinsulinemia believed to be secondary to the weight gain. Weight loss with lowered fasting insulin levels was also reported when women with epilepsy who were taking valproate were switched to lamotrigine.

Findings in patients with bipolar disorder treated with antiepileptic drugs do not support a role of the drugs in causing PCOS. In a study of 22 outpatients with bipolar disorder, none of the 10 women receiving divalproex, 10 women receiving lithium, or 2 women receiving both divalproex and lithium for a mean duration of 12 months developed clinical or endocrinologic symptoms associated with PCOS. Ultrasound revealed an increased number of ovarian follicles in 1 patient taking lithium and in none of the patients taking divalproex. Women's self-reports revealed a high incidence of menstrual disturbances regardless of which antiepileptic medication was used, a finding that the authors suggested might be attributed to a dysfunctional hypothalamic-pituitary-gonadal axis in women with bipolar disorder.

A high incidence of menstrual disturbances among women with bipolar disorder was also found in a study of 32 women (17 received valproate and 15 did not receive valproate). Menstrual abnormalities were reported by significantly more women receiving valproate (47%) than women not receiving valproate (13%) compared with a control group of women (n = 22) with no psychiatric disorder. PCOS was determined to be present in all of the 7 women in the valproate group who reported current menstrual problems and who were assessed for PCOS. Because this study was an observational study and patients were not randomized, it is difficult to draw conclusions from the results. In addition, the incidence of PCOS was assessed only among the subset of patients who were using valproate and who reported current menstrual problems. The incidence of PCOS in the women with bipolar disorder not receiving valproate and in the healthy control subjects was not determined.

Considered in aggregate, the findings to date on the relationship between antiepileptic drugs and PCOS provide conflicting data on valproate use and the development of PCOS, although patients with epilepsy may be more likely to have PCOS compared with those without epilepsy. Studies suggesting an association between antiepileptic drug use and epilepsy are often small, and are retrospective and poorly controlled. To date, there are no data that contraindicate the use of valproate in women with epilepsy or bipolar disorder, but additional study is warranted. The relationship between use of valproate and weight gain is deserving of further study. Monitoring body weight during treatment, with institution of weight-loss methods if excessive weight gain occurs, seems to be a practical recommendation, as has been previously recommended.

Conclusions and Implications for Care of Patients

The multifarious clinical manifestations of PCOS necessitate a comprehensive approach to patient management. The clustering of cardiovascular and metabolic risk factors in women with PCOS underscores the importance of managing PCOS as a chronic disease. Women with PCOS typically consult physicians for infertility, menstrual irregularity, or androgen excess. Treatment strategies, focusing on short-term improvement, are usually targeted at addressing one or more of these complaints. However, the syndrome also needs to be conceptualized and managed as a chronic condition. Reduction of insulin resistance constitutes a key component of long-term treatment strategies. Nonpharmacologic measures, when appropriate, include diet, exercise, and weight reduction. Pharmacologic measures include insulin sensitizers, oral contraceptives, antiandrogen medications, and glucocorticoids.
REFERENCES


