

REVIEW ARTICLE

MEDICAL PROGRESS

# Polycystic Ovary Syndrome

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**I**N 1935, STEIN AND LEVENTHAL PUBLISHED A PAPER ON THEIR FINDINGS in seven women with amenorrhea, hirsutism, obesity, and a characteristic polycystic appearance to their ovaries — one of the first descriptions of a complex phenotype today known as the polycystic ovary syndrome.<sup>1</sup> Insight into the pathogenesis and treatment of the polycystic ovary syndrome has increased substantially in the decade since this topic was last addressed in the *Journal*.<sup>2</sup> The condition is now well recognized as having a major effect throughout life on the reproductive, metabolic, and cardiovascular health of affected women. This review addresses current knowledge regarding the diagnosis, cause, and treatment of the polycystic ovary syndrome.

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## DEFINITION AND DIFFERENTIAL DIAGNOSIS

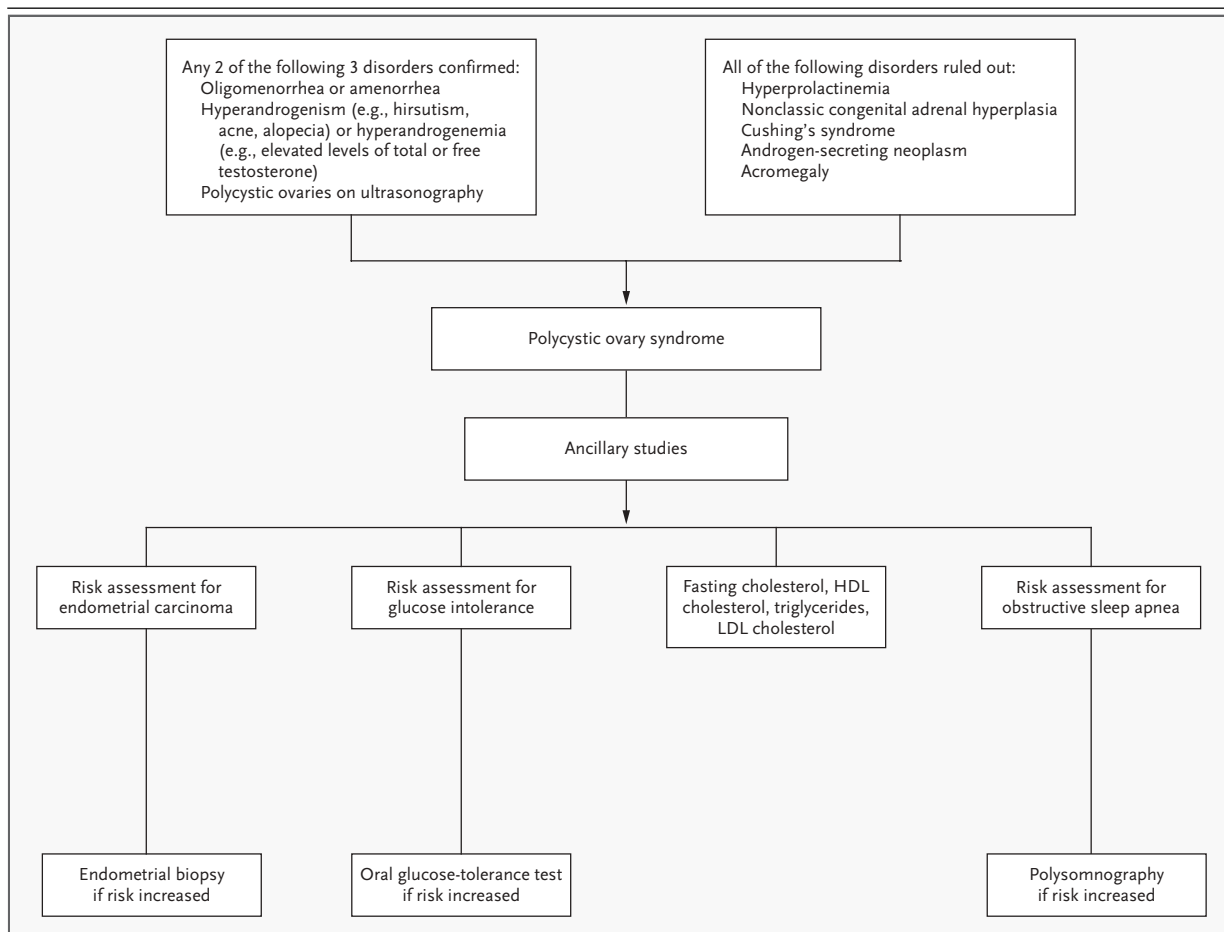
Several factors contribute to difficulties in the diagnosis of the polycystic ovary syndrome. Presenting signs and symptoms are heterogeneous and vary over time; in addition, a precise and uniform definition of the syndrome has been lacking. An international consensus group<sup>3</sup> recently proposed that the syndrome can be diagnosed after the exclusion of other medical conditions that cause irregular menstrual cycles and androgen excess (Fig. 1 and Table 1) and the determination that at least two of the following are present: oligoovulation or anovulation (usually manifested as oligomenorrhea or amenorrhea), elevated levels of circulating androgens (hyperandrogenemia) or clinical manifestations of androgen excess (hyperandrogenism), and polycystic ovaries as defined by ultrasonography.<sup>4</sup> These criteria acknowledge the condition as functional: polycystic ovaries need not be present to make a diagnosis of the polycystic ovary syndrome,<sup>5</sup> and conversely, their presence alone does not establish the diagnosis.<sup>6,7</sup>

Women with the polycystic ovary syndrome almost always have some aberration in gonadotropin secretion as compared with women who have normal menstrual cycles.<sup>8</sup> However, since gonadotropin concentrations vary over the menstrual cycle and are released in a pulsatile fashion into the circulation, a single measurement of luteinizing hormone and follicle-stimulating hormone provides little diagnostic sensitivity. Thus, in routine clinical practice, abnormal gonadotropin levels (an elevated level of luteinizing hormone or an elevated ratio of luteinizing hormone to follicle-stimulating hormone) need not be documented to diagnose the polycystic ovary syndrome.

Chronic anovulation most often manifests as oligomenorrhea (fewer than nine menses per year) or amenorrhea. Anovulatory cycles may lead to dysfunctional uterine bleeding and decreased fertility. Cutaneous manifestations of hyperandrogenemia in the polycystic ovary syndrome include hirsutism, acne, and male-pattern hair loss (androgenic alopecia), whereas acanthosis nigricans is a cutaneous marker of hyperinsulinemia.

A substantial proportion of women with the polycystic ovary syndrome are overweight; many are obese, some extremely so.<sup>9</sup> Although obesity itself is not considered the inciting event in the development of the syndrome, excess adiposity can exacerbate associated reproductive and metabolic derangements.

The symptoms of the polycystic ovary syndrome usually begin around menarche,<sup>10</sup>



**Figure 1. Diagnostic Algorithm for the Polycystic Ovary Syndrome.**

Single measurements of serum prolactin and 17-hydroxyprogesterone are usually sufficient to rule out hyperprolactinemia and nonclassic congenital adrenal hyperplasia due to deficiency of 21-hydroxylase. It is important to measure the 17-hydroxyprogesterone level in a blood sample taken in the early morning, when endogenous corticotropin levels peak. As an alternate test, 17-hydroxyprogesterone can be measured in response to a single dose of exogenously administered corticotropin. Risks for glucose intolerance include an elevated body-mass index, an increased waist circumference, a history of gestational diabetes, a family history of type 2 diabetes, and certain racial or ethnic backgrounds (including black, Caribbean Hispanic, and Mexican American). HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

but onset after puberty may also occur as a result of environmental modifiers such as weight gain. Premature pubarche, the result of early secretion of adrenal steroids, may be a harbinger of the syndrome.<sup>11</sup> In addition, an aberrant intrauterine environment has been implicated in the condition's pathogenesis, particularly its metabolic components.<sup>12-15</sup>

#### PATHOGENESIS

No single etiologic factor fully accounts for the spectrum of abnormalities in the polycystic ovary syndrome. In response to stimulation by luteinizing

hormone, the ovarian theca cell synthesizes androgens (Fig. 2). Androgen biosynthesis is mediated by cytochrome P-450c17, an enzyme with 17 $\alpha$ -hydroxylase and 17,20-lyase activities, both of which are required to form androstenedione. The androgenic steroid is then converted by 17 $\beta$ -hydroxysteroid dehydrogenase (17 $\beta$ -HSD) to form testosterone or is aromatized by the aromatase enzyme (cytochrome P-450arom) to form estrone. Studies performed both in vivo and in vitro (in cultured theca cells) consistently suggest that ovarian theca cells in affected women are more efficient at converting androgenic precursors to testosterone than are normal theca cells.<sup>16,17</sup>

**Table 1. Conditions for Exclusion in the Diagnosis of the Polycystic Ovary Syndrome.**

Condition	Hyperandrogenemia, Hyperandrogenism, or Both	Oligomenorrhea or Amenorrhea	Distinguishing Features	
			Clinical	Hormonal or Biochemical
Nonclassic congenital adrenal hyperplasia due to deficiency of 21-hydroxylase	Yes	Not often	Family history of infertility, hirsutism, or both; common in Ashkenazi Jews	Elevated (basal) level of 17-hydroxyprogesterone in the morning or on stimulation
Cushing's syndrome	Yes	Yes	Hypertension, striae, easy bruising	Elevated 24-hr urinary free cortisol level
Hyperprolactinemia or prolactinoma	None or mild	Yes	Galactorrhea	Elevated plasma prolactin level
Primary hypothyroidism	None or mild	May be present	Goiter may be present	Elevated plasma thyrotropin and subnormal plasma thyroxine level; prolactin level may also be increased
Acromegaly	None or mild	Often	Acral enlargement, coarse features, prognathism	Increased plasma insulin-like growth factor I
Premature ovarian failure	None	Yes	May be associated with other autoimmune endocrinopathies	Elevated plasma follicle-stimulating hormone and normal or subnormal estradiol level
Simple obesity	Often	Not often	Diagnosed by exclusion	None
Virilizing adrenal or ovarian neoplasm	Yes	Yes	Clitorimegaly, extreme hirsutism, or male-pattern alopecia	Extremely elevated plasma androgen level
Drug-related condition*	Often	Variably	Evidence provided by history	None

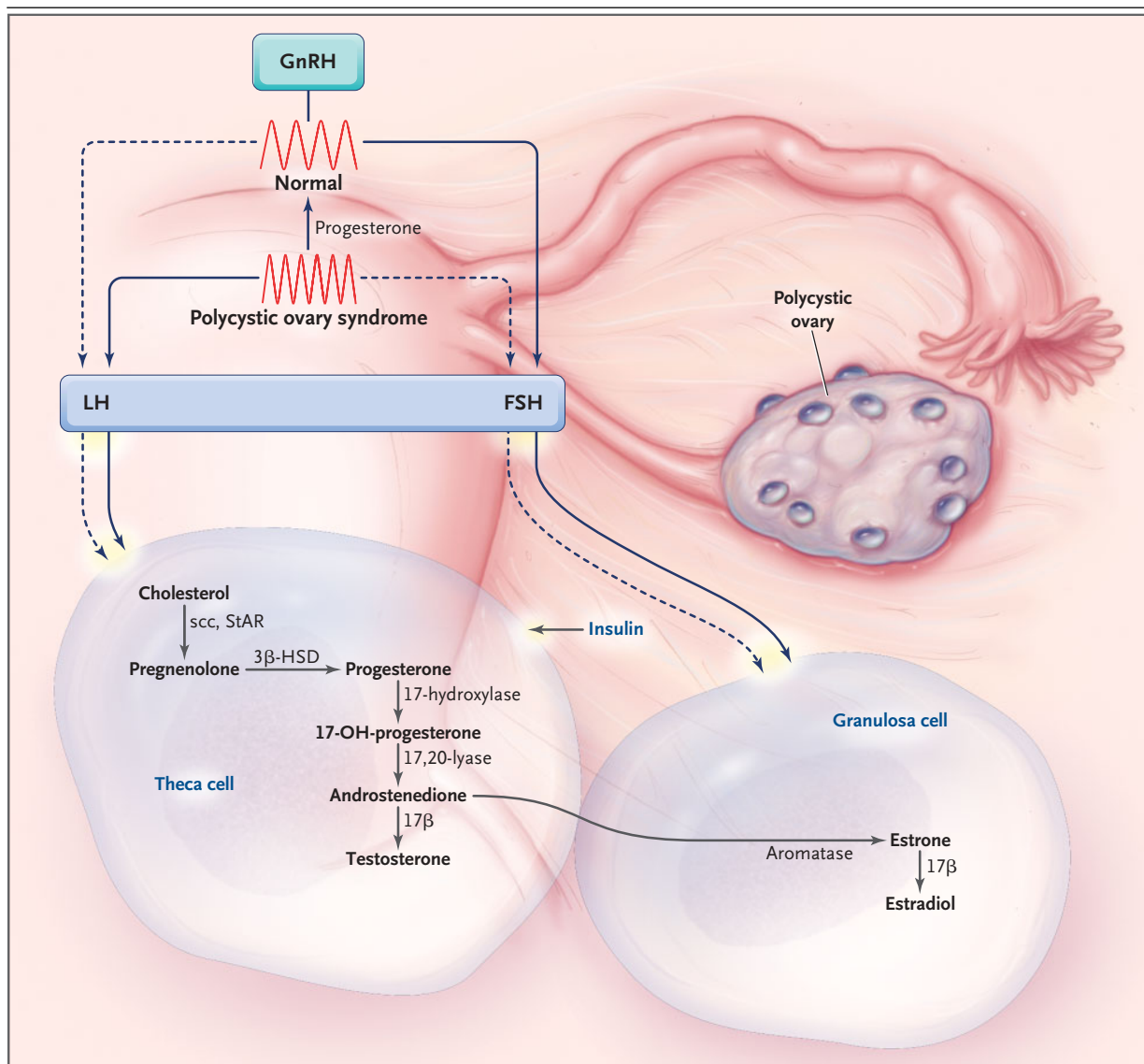
\* A drug-related condition is a condition due to the use of androgens, valproic acid, cyclosporine, or other drugs.

Whereas luteinizing hormone regulates the androgenic synthesis of theca cells, follicle-stimulating hormone is responsible for regulating the aromatase activity of granulosa cells, thereby determining how much estrogen is synthesized from androgenic precursors. When the concentration of luteinizing hormone increases relative to that of follicle-stimulating hormone, the ovaries preferentially synthesize androgen.

The frequency of the stimulus of hypothalamic gonadotropin-releasing hormone (GnRH) determines, in part, the relative proportion of luteinizing hormone and follicle-stimulating hormone synthesized within the gonadotrope (Fig. 2). Increased pulse frequency of hypothalamic GnRH favors transcription of the  $\beta$ -subunit of luteinizing hormone over the  $\beta$ -subunit of follicle-stimulating hormone; conversely, decreased pulse frequency of GnRH favors transcription of the  $\beta$ -subunit of follicle-stimulating hormone, which decreases the ratio of luteinizing hormone to follicle-stimulating hormone.<sup>18</sup>

Because women with the polycystic ovary syndrome appear to have an increased luteinizing hormone pulse frequency<sup>8</sup> (Fig. 2), it has been inferred that the pulse frequency of GnRH must be accelerated in the syndrome. It is not clear whether this accelerated pulse frequency is due to an intrinsic abnormality in the GnRH pulse generator or is caused by the relatively low levels of progesterone resulting from infrequent ovulatory events. Since progestins slow the GnRH pulse generator, low circulating progestin levels in women with the polycystic ovary syndrome may lead to an acceleration in the pulsatility of GnRH,<sup>19</sup> increased levels of luteinizing hormone, and overproduction of ovarian androgen.

Insulin plays both direct and indirect roles in the pathogenesis of hyperandrogenemia in the polycystic ovary syndrome (Fig. 2). Insulin acts synergistically with luteinizing hormone to enhance the androgen production of theca cells. Insulin also inhibits hepatic synthesis of sex hormone-binding globulin, the key circulating protein that binds to



**Figure 2. The Hypothalamic–Pituitary–Ovarian Axis and the Role of Insulin.**

Increased ovarian androgen biosynthesis in the polycystic ovary syndrome results from abnormalities at all levels of the hypothalamic–pituitary–ovarian axis. The increased frequency of luteinizing hormone (LH) pulses in the polycystic ovary syndrome appears to result from an increased frequency of hypothalamic gonadotropin-releasing hormone (GnRH) pulses. The latter can result from an intrinsic abnormality in the hypothalamic GnRH pulse generator, favoring the production of luteinizing hormone over follicle-stimulating hormone (FSH) in patients with the polycystic ovary syndrome, in whom the administration of progesterone can restrain the rapid pulse frequency. By whatever mechanism, the relative increase in pituitary secretion of luteinizing hormone leads to an increase in androgen production by ovarian theca cells. Increased efficiency in the conversion of androgenic precursors in theca cells leads to enhanced production of androstenedione, which is then converted by  $17\beta$ -hydroxysteroid dehydrogenase ( $17\beta$ ) to form testosterone or aromatized by the aromatase enzyme to form estrone. Within the granulosa cell, estrone is then converted into estradiol by  $17\beta$ . Numerous autocrine, paracrine, and endocrine factors modulate the effects of both luteinizing hormone and insulin on the androgen production of theca cells; insulin acts synergistically with luteinizing hormone to enhance androgen production. Insulin also inhibits hepatic synthesis of sex hormone–binding globulin, the key circulating protein that binds to testosterone and thus increases the proportion of testosterone that circulates in the unbound, biologically available, or “free,” state. Testosterone inhibits and estrogen stimulates hepatic synthesis of sex hormone–binding globulin. The abbreviation scc denotes side-chain cleavage enzyme, StAR steroidogenic acute regulatory protein, and  $3\beta$ -HSD  $3\beta$ -hydroxysteroid dehydrogenase. Solid arrows denote a higher degree of stimulation than dashed arrows.

testosterone, and thus increases the proportion of testosterone that circulates in the unbound, biologically available, or free, state. Because women with the polycystic ovary syndrome typically have hyperinsulinemia, the concentration of free testosterone is often elevated when the total testosterone concentration is at the upper range of normal or only modestly elevated.

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#### THE ROLE OF GENETIC AND ENVIRONMENTAL FACTORS

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The polycystic ovary syndrome remains one of the most common hormonal disorders in women, with a prevalence estimated between 5 and 10 percent.<sup>20-22</sup> Variance in prevalence among populations may reflect the effect of ethnic origin, race, and other environmental factors on the phenotype.<sup>23,24</sup>

Several lines of evidence suggest that the polycystic ovary syndrome is heritable,<sup>25-29</sup> and various approaches have been initiated to attempt to define a specific genetic cause.<sup>30,31</sup> In rare instances, single-gene mutations can give rise to the phenotype of the syndrome.<sup>32</sup> Current understanding of the pathogenesis of the syndrome suggests, however, that it is a complex multigenic disorder. Candidate genes that may regulate the hypothalamic–pituitary–ovarian axis, as well as those responsible for insulin resistance and its sequelae, have been the principal focus of linkage and case–control studies. Microarray analyses of target tissues in the polycystic ovary syndrome<sup>31</sup> have been used to identify novel candidate genes involved in the condition, and a number of them appear to contribute modestly to the phenotype (Table 2).<sup>30,57,58</sup>

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#### METABOLIC, CARDIOVASCULAR, AND OTHER CLINICAL COMPONENTS

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The consequences of the polycystic ovary syndrome extend beyond the reproductive axis; women with the disorder are at substantial risk for the development of metabolic and cardiovascular abnormalities similar to those that make up the metabolic syndrome.<sup>59</sup> This finding is not surprising, since both the polycystic ovary syndrome and the metabolic syndrome share insulin resistance as a central pathogenetic feature (Fig. 2). The polycystic ovary syndrome might thus be viewed as a sex-specific form of the metabolic syndrome,<sup>60</sup> and the term “syndrome XX” has been suggested as an apt term to underscore this association.<sup>61</sup>

#### OBESITY

The cause of obesity in the polycystic ovary syndrome remains unknown, but obesity is present in at least 30 percent of cases; in some series, the percentage is as high as 75.<sup>62</sup> Women in the United States with the polycystic ovary syndrome generally have a higher body weight than their European counterparts.<sup>62-65</sup> This fact has been cited as an explanation for the increase in the incidence of the polycystic ovary syndrome in the U.S. population—an increase that parallels the increase in obesity.<sup>66</sup>

Increased adiposity, particularly visceral adiposity that is reflected by an elevated waist circumference (>88 cm [35 in.]) or waist-to-hip ratio, has been associated with hyperandrogenemia, insulin resistance, glucose intolerance, and dyslipidemia.<sup>60</sup> Attenuation of insulin resistance, whether accomplished by weight loss or with medication, ameliorates (but not necessarily normalizes) many of the metabolic aberrations in women with the polycystic ovary syndrome.

#### IMPAIRED GLUCOSE TOLERANCE AND TYPE 2 DIABETES

Thirty to 40 percent of women with the polycystic ovary syndrome have impaired glucose tolerance, and as many as 10 percent have type 2 diabetes by their fourth decade.<sup>9,67</sup> These prevalence rates are among the highest known among women of similar age.<sup>68</sup> An enhanced rate of deterioration in glucose tolerance is also evident in the polycystic ovary syndrome.<sup>9,69</sup> Seminal studies by Dunaif et al.<sup>70-72</sup> indicated that women with the polycystic ovary syndrome are more insulin resistant than are unaffected counterparts matched for body-mass index, fat-free body mass, and body-fat distribution. A defect in the insulin signaling pathway appears to be present in both the adipocyte and skeletal muscle, the primary target tissues of insulin action.<sup>71,72</sup>

Insulin resistance alone cannot fully account for the predisposition to and development of type 2 diabetes among patients with the polycystic ovary syndrome. In patients with normal glucose tolerance, insulin secretion is (by definition) sufficient for the degree of insulin resistance; when the pancreatic  $\beta$  cell is no longer able to compensate sufficiently, glucose tolerance begins to deteriorate.<sup>73,74</sup> Most women with the polycystic ovary syndrome are able to compensate fully for their insulin resistance, but a substantial proportion (particularly those with a first-degree relative with type 2 diabetes<sup>27</sup>) have a disordered and insufficient  $\beta$ -cell response to meals



**Table 2. Representative Candidate Genes with Evidence of Linkage, Association, or Both, with the Polycystic Ovary Syndrome (PCOS).**

Pathway and Protein (Gene)	Comments
<b>Insulin secretion and action</b>	
Insulin receptor ( <i>INSR</i> ) region	D19S884, an anonymous marker 1 cM centromeric to <i>INSR</i> ; evidence for linkage and association with PCOS <sup>26,33</sup>
Insulin variable-number tandem repeats ( <i>VNTR</i> )	Region involved in transcriptional regulation of insulin gene; evidence for linkage and association with class III allele <sup>34-36</sup>
Insulin receptor substrate 1 ( <i>IRS-1</i> )	Post-receptor molecule in insulin signaling pathway; association with PCOS <sup>37,38</sup>
Insulin receptor substrate 2 ( <i>IRS-2</i> )	Post-receptor molecule in insulin signaling pathway; association with PCOS <sup>37,38</sup>
Calpain 10 ( <i>CAPN10</i> )	Cysteine protease with effect on insulin action and secretion; linkage and association with type 2 diabetes <sup>39,40</sup>
Peroxisome-proliferator-activated receptor $\gamma$ ( <i>PPAR\gamma</i> )	The Pro12Ala polymorphism in the <i>PPAR\gamma</i> gene is a modifier of insulin resistance in PCOS <sup>41-43</sup>
Protein phosphatase 1 regulatory subunit ( <i>PPP1R3</i> )	Variant of regulatory subunit of the glycogen-associated form of protein phosphatase-1 derived from skeletal muscle; associated with insulin resistance <sup>44</sup>
<b>Gonadotropin secretion and action</b>	
Follistatin ( <i>FST</i> )	Acts to inhibit ovarian follicular maturation and androgen production; enhances follicle-stimulating hormone and insulin secretion <sup>26,45</sup>
<b>Androgen biosynthesis, secretion, transport, and metabolism</b>	
Androgen receptor ( <i>AR</i> )	Number of CAG repeats associated with androgen levels in PCOS <sup>46</sup>
Sex hormone-binding globulin ( <i>SHBG</i> )	Association of the pentanucleotide (TAAAA) n repeat polymorphism with PCOS <sup>47,48</sup>
Cytochrome P-450c17 ( <i>CYP17</i> )	Possible association with PCOS <sup>49-53</sup>
Cytochrome P-45011 $\alpha$ ( <i>CYP11\alpha</i> )	Early analyses revealed association with hyperandrogenemia and PCOS <sup>54,55</sup> ; more recently, strength of association has been questioned <sup>56</sup>
11 $\beta$ -Hydroxysteroid dehydrogenase ( <i>11\beta-HSD</i> ) and hexose-6-phosphate dehydrogenase ( <i>H6PD</i> )	Mutations in both <i>11\beta-HSD</i> and <i>H6PD</i> in a triallelic digenic model of inheritance result in low <i>11\beta-HSD</i> expression and NADPH generation with loss of <i>11\beta-HSD</i> 1 oxo-reductase activity <sup>32</sup>

or a glucose challenge.<sup>27,75-78</sup> Before the development of frank glucose intolerance, defects in insulin secretion may be latent and revealed only in circumstances that augment insulin resistance, as with the development of gestational diabetes in pregnancy<sup>79</sup> or glucose intolerance associated with glucocorticoid administration.<sup>77</sup>

#### HYPERTENSION AND VASCULAR DYSFUNCTION

Hypertension develops in some women with the polycystic ovary syndrome during their reproductive years,<sup>59,80</sup> and sustained hypertension may develop in later life in women with the disorder.<sup>81,82</sup> Reduced vascular compliance<sup>83</sup> and vascular endothelial dysfunction were noted in most,<sup>83-86</sup> but not all,<sup>87</sup> studies of women with the polycystic ovary syndrome. Furthermore, the degree of impairment in vascular reactivity is significantly greater than can be explained by obesity alone.<sup>83</sup> Insulin-lowering therapies appear to improve the vascular endothelial dysfunction in patients with the polycystic ovary syndrome.<sup>85</sup>

#### CORONARY AND OTHER VASCULAR DISEASE

A predisposition to macrovascular disease and thrombosis<sup>88,89</sup> in women with the polycystic ovary syndrome has also been described. A recent study of premenopausal women showed that those with the polycystic ovary syndrome had a higher prevalence of coronary-artery calcification as detected by electron-beam computed tomography.<sup>90</sup> Increased levels of plasminogen-activator inhibitor type 1 may contribute to this risk.<sup>91-93</sup> Levels of plasminogen-activator inhibitor type 1 in patients with the polycystic ovary syndrome may exceed those typically seen in type 2 diabetes.<sup>91</sup> A reduction in insulin levels<sup>91</sup> decreases levels and activity of plasminogen-activator inhibitor type 1.

Hypertriglyceridemia, increased levels of very-low-density lipoprotein and low-density lipoprotein cholesterol, and decreased levels of high-density lipoprotein cholesterol<sup>94</sup> also predispose patients to vascular disease in the polycystic ovary syndrome. Both insulin resistance and hyperandrogenemia contribute to this atherogenic lipid profile. Testosterone decreases lipoprotein lipase activity in abdominal fat cells, and insulin resistance impairs the ability of insulin to exert its antilipolytic effects. Although these abnormalities would be expected to increase the morbidity and mortality from coronary artery disease and other vascular disorders in women with the polycystic ovary syndrome, this has been difficult to establish.<sup>95-97</sup>

#### OBSTRUCTIVE SLEEP APNEA

Recent studies indicate that the prevalence of obstructive sleep apnea in the polycystic ovary syndrome is higher than expected and cannot be explained by obesity alone.<sup>98-100</sup> In two studies,<sup>98,100</sup> the severity of sleep apnea did not correlate with

body-mass index; in a third study,<sup>99</sup> even after controlling for body-mass index, the risk of sleep-disordered breathing was increased by a factor of 30. Insulin resistance appears to be a stronger predictor of sleep-disordered breathing than is age, body-mass index, or the circulating testosterone concentration.<sup>98</sup>

#### ASSOCIATION WITH CANCER

There is an increased prevalence of endometrial hyperplasia and carcinoma in women with the polycystic ovary syndrome.<sup>101,102</sup> This increase has been attributed largely to the persistent stimulation of endometrial tissue by estrogen (mainly estrone) without the progesterone-induced inhibition of proliferation and differentiation to secretory endometrium that occurs after ovulation. Endometrial carcinoma has also been associated with obesity and type 2 diabetes, both of which are common in the polycystic ovary syndrome.

Breast and ovarian cancer have been variably associated with the polycystic ovary syndrome<sup>102</sup>; obesity, anovulation, infertility, and the hormonal treatment of infertility are so frequent in the polycystic ovary syndrome that the condition is difficult to isolate as an independent risk factor for these types of cancer.

### TREATMENT

#### CUTANEOUS MANIFESTATIONS OF ANDROGEN EXCESS: HIRSUTISM AND ACNE

Medical treatment of hirsutism and acne in the polycystic ovary syndrome generally aims to reduce androgen levels, attenuate their effects by lowering androgen production, augment androgen binding to specific plasma-binding proteins, and block androgen action at the level of the target tissue.

##### *Oral Contraceptives*

Estrogen–progestin combination therapy (with the use of the combination oral-contraceptive pill) remains the predominant treatment for hirsutism and acne in the polycystic ovary syndrome. The estrogenic component of the oral contraceptive suppresses luteinizing hormone and thus ovarian androgen production. Estrogen also enhances hepatic production of sex hormone–binding globulin (Fig. 2), thereby reducing the free, or unbound, fraction of plasma testosterone available to occupy the androgen receptor.

The choice of oral contraceptive is important,

since most progestins also possess variable androgenic effects. Norgestimate and desogestrel are virtually nonandrogenic progestins.<sup>103</sup> Drospirenone, an analogue of spironolactone with unique antiminer- alocorticoid and antiandrogenic activities,<sup>104</sup> has been approved for use in combination with ethinyl estradiol; thus, it is potentially ideal for the treatment of women with the polycystic ovary syndrome.<sup>105</sup>

Controversy persists regarding the use of oral contraceptives as first-line therapy in women with the polycystic ovary syndrome.<sup>106</sup> These agents clearly improve hirsutism and acne and protect against unopposed estrogenic stimulation of the endometrium, but their potential adverse effects on insulin resistance, glucose tolerance, vascular reactivity, and coagulability are a concern, particularly since insulin-lowering agents are now available (see below).

##### *Antiandrogens*

The antiandrogen cyproterone acetate competitively inhibits the binding of testosterone and its more potent conversion product, 5 $\alpha$ -dihydrotestosterone, to the androgen receptor. Although not available in the United States, cyproterone acetate effectively treats hirsutism and acne<sup>107</sup> and is used throughout Canada, Mexico, and Europe.

Spironolactone, typically used as an antiminer- aloccorticoid, possesses moderate antiandrogenic effects when administered in large doses (100 to 200 mg daily).<sup>108</sup> Adverse effects seem to be minimal, with the exception of occasional vaginal bleeding resulting from progestin-like properties at a high dose. Spironolactone and oral contraceptives appear to be synergistic. For these reasons, and because antiandrogens should not be administered to women desiring pregnancy, a combination of estrogen and progestin is often prescribed in conjunction with spironolactone.

Flutamide is a potent nonsteroidal antiandrogen that is effective in the treatment of hirsutism.<sup>109-111</sup> Concern about inducing hepatocellular dysfunction, however, has limited its use.

##### *Glucocorticoids*

Some women with the polycystic ovary syndrome have elevated adrenal androgen levels,<sup>5,112</sup> though the contribution to ovulatory dysfunction appears modest.<sup>113</sup> Unless a woman with the polycystic ovary syndrome has marked adrenal androgen excess, prolonged use of glucocorticoids is not advised.

### Other Agents

Finasteride, a 4- $\alpha$  steroid and competitive inhibitor of type 2 5 $\alpha$ -reductase,<sup>114</sup> has been reported to treat hirsutism.<sup>115</sup> However, the prominence of type 1 5 $\alpha$ -reductase in the pilosebaceous unit makes it unlikely to be an optimal treatment for the androgen-related cutaneous manifestations associated with the condition.

Eflornithine hydrochloride, an inhibitor of the enzyme ornithine decarboxylase in human skin, has been approved for topical use in treating facial hirsutism. The inhibition of hair growth is its primary action, but clinical data are too limited to recommend its routine use.

### MANAGEMENT OF OLIGOMENORRHEA AND AMENORRHEA

Chronic anovulation is associated with an increased risk of endometrial hyperplasia and carcinoma, as discussed. Thus, it is prudent to consider endometrial biopsy in patients with the polycystic ovary syndrome who have not had menstrual bleeding for a year or longer. Some investigators have advocated the use of ultrasonography to determine endometrial thickness in deciding whether to biopsy the endometrium.<sup>102</sup> Endometrial proliferation can be inhibited by administering either cyclic progestin or oral contraceptives with a combination of estrogen and progestin. The latter approach, which also reduces ovarian androgen production, may be particularly beneficial in this setting.

The induction of ovulation is a complex issue in the polycystic ovary syndrome that is beyond the scope of this review but has been discussed elsewhere.<sup>116-119</sup> It is important to note, however, that modest reductions in body weight (2 to 7 percent) through lifestyle modification have been associated with reductions in androgen levels and improved ovulatory function in patients with the polycystic ovary syndrome.<sup>120,121</sup> In addition, numerous studies have shown that the lowering of insulin levels may increase ovulatory events, potentially restoring cyclic menses and fertility.<sup>122,123</sup> The long-term outcomes of pregnancies associated with the use of insulin-lowering medications remain unknown.

### INSULIN RESISTANCE AND GLUCOSE INTOLERANCE

Weight reduction is important in treating overweight patients with the polycystic ovary syndrome. No unique weight-loss regimen targets excess adiposity specific to the syndrome. Restricting carbohydrates as compared with fats is generally perceived

to be advantageous in this patient population. However, several recent studies designed to address this issue have not shown a distinct benefit from calorie-restricted diets limiting carbohydrates rather than fat.<sup>123,124</sup>

A reduction in insulin levels pharmacologically ameliorates sequelae of both hyperinsulinemia and hyperandrogenemia. The place of insulin-reduction therapies in treating the polycystic ovary syndrome is evolving and should be viewed in context with all available therapies (Table 3). These therapies can effectively manage the established metabolic derangements in the polycystic ovary syndrome, but whether they can prevent them is not yet established.

Both metformin (a biguanide) and the thiazolidinediones pioglitazone and rosiglitazone have been used to reduce insulin resistance. Although metformin appears to influence ovarian steroidogenesis directly,<sup>125,126</sup> this effect does not appear to be primarily responsible for the attenuation of ovarian androgen production in women with the polycystic ovary syndrome. Rather, metformin inhibits the output of hepatic glucose, necessitating a lower insulin concentration and thereby probably reducing the androgen production of theca cells.

Subject characteristics and control measures for effects of weight change, dose of metformin, and outcome vary widely among published studies of metformin in the polycystic ovary syndrome. A recent meta-analysis of 13 studies in which metformin was administered to 543 participants<sup>127</sup> reported that patients taking metformin had an odds ratio for ovulation of 3.88 (95 percent confidence interval, 2.25 to 6.69) as compared with placebo and an odds ratio for ovulation of 4.41 (95 percent confidence interval, 2.37 to 8.22) for metformin plus clomiphene as compared with clomiphene alone. Metformin also improved fasting insulin levels, blood pressure, and levels of low-density lipoprotein cholesterol. These effects were judged to be independent of any changes in weight that were associated with metformin, but controversy persists as to whether the beneficial effects of metformin are entirely independent of the weight loss<sup>128</sup> that is typically seen early in the course of therapy. Finally, the rates of spontaneous miscarriage and gestational diabetes are reportedly lower among women with the polycystic ovary syndrome who conceive while taking metformin.<sup>129-132</sup> The long-term effects of metformin in pregnancy are unknown.

The thiazolidinediones improve the action of insulin in the liver, skeletal muscle, and adipose tissue



**Table 3. Drug Treatments.\***

Agent	Mechanism of Action	Advantages or Disadvantages	Examples	Uses
Combinations of estrogen and progestin	Increase SHBG, suppress LH and FSH, suppress ovarian androgen production; progestin can act as an antiandrogen	Cyclic exposure of endometrium to estrogen and progestin; effective for hirsutism and acne; may increase risk of thrombosis and metabolic abnormalities; beneficial antiandrogenic effects of drospirenone	Ethinyl estradiol and norgestimate (Ortho-Cyclen); ethinyl estradiol and desogestrel (Orthocept); ethinyl estradiol and drospirenone (Yasmin)	Hirsutism, Acne X Oligomenorrhea or Amenorrhea X Ovulation Induction X Insulin Lowering X
Antiandrogens	Inhibit androgens from binding to the androgen receptor	Effective for hirsutism and acne; risk of hyperkalemia (spironolactone) or hepatitis (flutamide)	Cyproterone acetate, spironolactone, flutamide	X
Glucocorticoids	Suppress corticotropin and thus adrenal androgen production	Attenuate adrenal component of androgen excess; long-term risks of glucose intolerance, insulin resistance, osteopenia, weight gain	Prednisone, dexamethasone	X X
5 $\alpha$ -Reductase inhibitors	Inhibit 5 $\alpha$ -reductase	Do not specifically target the isoenzyme of 5 $\alpha$ -reductase in the pilosebaceous unit	Finasteride (Propecia)	X
Ornithine decarboxylase inhibitors	Inhibit ornithine decarboxylase	Minimal documented efficacy; used topically	Eflornithine hydrochloride (Vaniqa)	X
Antiestrogen	Induces rise in FSH, LH	Moderately effective as monotherapy, less effective in obese patients; may be useful in conjunction with insulin-lowering therapies	Clomiphene citrate	X
Biguanide	Reduces hepatic glucose production, secondarily lowering insulin levels; may have direct effects on ovarian steroidogenesis	Substantial efficacy in restoration of menstrual cycling, less effective for hirsutism; usually associated with initial weight loss; may have untoward gastrointestinal effects	Metformin (Glucophage, Glucophage XR)	X X X
Thiazolidinediones	Enhance insulin action at target-tissue level (adipocyte, muscle); may have direct effects on ovarian steroidogenesis	Extremely effective at lowering levels of insulin and androgens, modest effects on hirsutism; associated with weight gain	Pioglitazone (Actos), rosiglitazone (Avandia)	X X X X

\* SHBG denotes sex hormone-binding globulin, LH luteinizing hormone, and FSH follicle-stimulating hormone.

and have only a modest effect on hepatic glucose output. As with metformin,<sup>125,126</sup> the thiazolidinediones are reported to affect ovarian steroid synthesis directly,<sup>133</sup> although most evidence indicates that the reduction in insulin levels is responsible for decreased concentrations of circulating androgen.

Obese women with the polycystic ovary syndrome who took troglitazone had consistent improvements in insulin resistance, hyperandrogenemia, and glucose tolerance.<sup>91,134</sup> In addition, troglitazone treatment was associated with a relative improvement in pancreatic  $\beta$ -cell function and a reduction in levels of the prothrombotic factor plasminogen-activator inhibitor type 1.<sup>91</sup> These findings led to a double-blind, randomized, placebo-controlled study of troglitazone in the polycystic ovary syndrome.<sup>62</sup> Ovulation was significantly greater for women who received troglitazone than for those who received placebo; free testosterone levels decreased, and levels of sex hormone-binding globulin increased in a dose-dependent fashion. Nearly all glycemic measures showed dose-related decreases with troglitazone treatment. Although troglitazone is no longer available, subsequent studies using rosiglitazone<sup>135,136</sup> and pioglitazone<sup>137</sup> have had similar results. Because of concern about using thiazolidinediones in pregnancy, the drugs have been less readily adopted for routine clinical use.

#### CONTROVERSIES

Several unresolved controversies persist regarding the evaluation and treatment of women with the polycystic ovary syndrome. One issue surrounds the question of whether all women with the polycystic ovary syndrome should be screened for glucose intolerance, insulin resistance, or both. Screening is supported by evidence that the combined prevalence of impaired glucose tolerance and type 2 diabetes approaches 45 percent by the fourth decade,<sup>9,67</sup> that both impaired glucose tolerance and type 2 diabetes are associated with significant morbidity, and that there is a substantial rate of conversion from impaired glucose tolerance to diabetes in the absence of intervention among women with the polycystic ovary syndrome<sup>9,69</sup> and those without the condition.<sup>138,139</sup> The American Diabetes Association recognizes the polycystic ovary syndrome as a risk factor that justifies screening for type 2 diabetes.<sup>140</sup>

On the other hand, it may be argued that since

only a subgroup of women with the polycystic ovary syndrome go on to have glucose intolerance, just that high-risk subgroup should be screened. Factors that augment the risk are increased body weight (particularly if body fat is distributed in an android pattern), a history of gestational diabetes, type 2 diabetes in a first-degree relative, and Caribbean-Hispanic,<sup>141</sup> Mexican-American,<sup>23</sup> or African-American<sup>39</sup> heritage.

Integral to this issue is whether the measurement of fasting glucose, with or without simultaneous measurement of fasting insulin, is sufficient to assess the risk of glucose intolerance. Although a supranormal fasting glucose concentration increases the likelihood that a patient will have an abnormally elevated glucose concentration at two hours during a formal oral glucose-tolerance test, a normal fasting glucose concentration does not necessarily predict normal glucose tolerance and is insufficient to distinguish between women who have normal glucose tolerance and those who have impaired glucose tolerance.<sup>9,62,67</sup> Thus, if the goal is to detect impaired glucose tolerance for the purpose of intervening to reduce the risk of conversion from impaired glucose tolerance to type 2 diabetes, an oral glucose-tolerance test should be performed.

Although insulin resistance is virtually inherent in the phenotype of the polycystic ovary syndrome, there is little to support its formal assessment outside the context of a clinical study. First, insulin resistance is not a diagnostic criterion, nor is it recommended as a factor to be used in determining treatment<sup>3</sup> in the polycystic ovary syndrome. These recommendations relate to the observation that the clinical response to insulin-lowering therapies does not appear to be related to the magnitude of insulin resistance. Insulin resistance is virtually universal and maximal once the body-mass index (the weight in kilograms divided by the square of the height in meters) exceeds 30<sup>73</sup>; thus, there appears to be little value gained by formal measurement of insulin sensitivity in obese patients. Finally, it is important to note that the simple and readily available methods proposed as tests to quantify insulin resistance — the ratio of fasting glucose to insulin<sup>142</sup> or the homeostatic model assessment index<sup>143</sup> — may be misleading, since both have been shown to lack precision when compared with the gold-standard method for quantifying whole-body insulin resistance (i.e., the hyperinsulinemic–euglycemic clamp).<sup>144</sup>

## SUMMARY

The polycystic ovary syndrome is one of the most common hormonal disorders affecting women. As a syndrome, it has multiple components — reproductive, metabolic, and cardiovascular — with health implications across the life span. Androgen excess and insulin resistance, both of which have strong genetic components, underlie much of the clinical presentation. The insulin resistance of the polycystic ovary syndrome appears to impart an increased risk of glucose intolerance, diabetes, and lipid abnormalities and may enhance the development of macrovascular disease. Obstructive sleep apnea is emerging as important in the polycystic ovary syndrome. A better understanding of the

pathogenesis of insulin resistance that is associated with complications of the polycystic ovary syndrome has led to novel therapies — chiefly insulin-lowering medications. Research that is focused on the genetic and environmental determinants of the polycystic ovary syndrome may provide the basis for new treatment methods and possible prevention of the syndrome and its sequelae.

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