Chapter 33
Polycystic Ovary Syndrome

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Definition, Clinical Manifestations, and Prevalence

Polycystic ovary syndrome (PCOS) is a common disorder affecting (depending on the population studied and the definition of the syndrome) between 5 and 20% of reproductive age women.1 If the middle of this range is considered as a realistic prevalence, then PCOS may be the most prevalent endocrine disorder in women. In spite of the widespread presence of PCOS, its precise definition still eludes both investigators and practitioners. Most consensus definitions describe PCOS as a disorder characterized by chronic anovulation and the presence of some degree of hyperandrogenism, with the exclusion of specific disorders that may lead to similar phenotypes, particularly, 21-hydroxylase deficiency and other forms of congenital adrenal hyperplasia. The definition proposed in 1990 by the National Institutes of Health Conference on PCOS requires a minimum of two criteria: menstrual abnormalities due to oligo- or anovulation, and hyperandrogenism of ovarian origin. Other disorders, such as 21-hydroxylase deficiency, androgen secreting tumors, hypothyroidism, Cushing’s syndrome, and hyperprolactinemia, must be excluded.2 In 2003 in Rotterdam a revised consensus on the diagnosis of PCOS was proposed. The new criteria require two out of the three following features once exclusion of other causes of hyperandrogenism has been made: oligo- or amenorrhea, hyperandrogenism (clinical or biochemical), and polycystic ovary morphology on ultrasound.3,4

Clinical manifestations vary widely among women with this disorder. Chronic anovulation may present as infertility or some form of menstrual irregularity, such as amenorrhea, oligomenorrhea, or dysfunctional uterine bleeding. Signs of hyperandrogenism include hirsutism, seborrhea, acne, and alopecia. Evidence of virilization, including clitoromegaly, may be present in severe cases. Obesity and acanthosis nigricans are clinical features that are commonly seen in PCOS women and are associated with insulin resistance.

Epidemiological data and prospective controlled studies have reported an increased prevalence of insulin resistance, impaired glucose tolerance, and undiagnosed type 2 diabetes mellitus in these women.5 Increased risk for dyslipidemia, cardiovascular disease, and endometrial carcinoma has also been observed in this population.6,7 In this chapter, we will discuss the role of insulin resistance in the pathogenesis of PCOS, the risk of diabetes mellitus in this population and the role of insulin-sensitizing agents, oral contraceptive pills and antiandrogens in treating patients with polycystic ovary syndrome.

Stein–Leventhal Syndrome

Although reports of disorders resembling PCOS date prior to the seventeenth century, the first clear description belongs to Chereau, who in 1844 described “sclerocystic degeneration of the ovaries.”8 The modern era of PCOS began with a report by two gynecologists, Irving F. Stein and Michael L. Leventhal, who in 1935 described a
syndrome of amenorrhea, hirsutism, and enlarged polycystic ovaries in anovulatory women. After observing the restoration of menstruation following ovarian biopsies in patients with this syndrome, Stein and Leventhal performed one-half to three-fourths wedge resection of each ovary in seven women. During the operation the ovarian cortex containing the cysts was removed. All of the patients who underwent wedge resection in Stein and Leventhal’s series experienced the return of their menses and two became pregnant.

Stein and Leventhal established both the term “polycystic ovary syndrome” and the theory attributing the origin of this disorder to endocrine abnormalities. In 1949, Culiner and Shippel coined the term “hyperthecosis ovarii” for polycystic ovaries comprised of nests of theca cells. Wedge resection performed in patients with this condition did not result in amelioration of hyperandrogenism. These women were masculinized, and often had diabetes and hypertension. The hyperthecosis ovarii was characterized by familial clustering. The polycystic ovaries in these patients were found to have not only hyperplasia of the theca cells but also atretic follicles.

Hormonal studies in PCOS women were performed only after the clinical manifestations and anatomical abnormalities of this disorder were well reported. In one of the first studies that measured hormone levels in PCOS patients, McArthur et al., in 1958, reported increased urinary levels of luteinizing hormone (LH). Reports of elevated circulating androgen levels followed.

During the last two decades PCOS has been identified as a metabolic disorder in which underlying insulin resistance and consequent hyperinsulinemia contribute to hyperandrogenism.

**Genetics in PCOS**

It has been proposed that the development of PCOS is dependent on the combination of both genetic and environmental factors. Familial aggregation of PCOS phenotypes has been reported in as early as the 1960s. Multiple studies have evaluated the association of various genes and PCOS. Some of these studies support the association while others do not. The genes that have been evaluated can be divided into those involved in adrenal or ovarian steroidogenesis; gonadotropin action and regulation; insulin action and secretion; chronic inflammation; and energy homeostasis. The genes which are potential candidates for the pathogenesis of PCOS are CYP 11a, CYP 17, sex hormone-binding globulin (SHBG), insulin (with variable tandem repeats [VNTR] polymorphism), peroxisome proliferator-activated receptor-gamma (PPAR-γ), and plasminogen activator inhibitor-1 (PAI-1). In summary, studies evaluating the genetic association of PCOS, have presented conflicting results. Further research is required to have a more conclusive proof of the relationship between genetic inheritance and PCOS (Table 33.1).

**Table 33.1** Genes implicated in polycystic ovary syndrome and linked to insulin signaling pathway or insulin resistance

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Genes</th>
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<tr>
<td>Insulin action and secretion</td>
<td>Insulin (VNTR polymorphism)</td>
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<td>Insulin receptor</td>
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<td></td>
<td>Insulin receptor substrate (IRS-1 or IRS-2)</td>
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<tr>
<td>Energy homeostasis</td>
<td>Leptin gene and receptor</td>
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<td></td>
<td>Adiponectin</td>
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<td>PPAR-γ (Pro12Ala polymorphism)</td>
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**Main Hormonal Abnormalities**

The two main endocrine theories of PCOS attribute its pathogenesis to the primary role of either central (hypothalamic, pituitary) or ovarian hormonal abnormalities.

The central theory proposes that the initial pathogenic event is an abnormally increased pulsatile secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus that causes a tonically increased secretion of LH instead of the normal pulsatile pattern with a surge during ovulation. It has been proposed that LH levels
may rise further because of hyperandrogenism: after androstenedione is converted in the peripheral fat to estrone by aromatase, estrone enhances LH secretion by increasing LH-producing gonadotroph sensitivity to GnRH. In response to increased LH, ovarian thecal cells undergo hypertrophy and their androgen secretion is further increased, thus establishing a vicious cycle. On the contrary, follicle stimulating hormone (FSH) secretion is normal or decreased due to negative feedback from increased estrogen levels produced through aromatization of androgens. Thus, the LH:FSH ratio is often increased.

The ovarian theory attributes primary pathogenic role in the development of PCOS to the ovary, where the production of androgens is increased. According to this theory, dysregulation of the enzyme cytochrome P450c17-alpha, which comprises 17-hydroxylase and 17/20 lyase activities, results in increased amount of androgens. Increased levels of androstenedione and estrone could also be secondary to reduced levels of the enzyme 17-ketosteroid reductase, which converts androstenedione to testosterone and estrone to estradiol.

When ovarian theca cells from women with PCOS were propagated in vitro, it was shown that the activity of 17α-hydroxylase/C17,20 lyase and 3β-hydroxysteroid dehydrogenase levels were elevated. This results in increased production of testosterone precursors, and, ultimately, causes increased testosterone production. Thus, thecal cells from PCOS patients, when cultured in vitro, possess intrinsic ability to produce increased amounts of testosterone.

In summary, main hormonal abnormalities in PCOS include elevated androgen and estrogen levels and commonly, although not always, an elevated LH:FSH ratio. Hyperinsulinemia, commonly observed in patients with PCOS, contributes to the development of these hormonal abnormalities.

**Insulin Resistance in PCOS**

In 1921, Archard and Thiers described “the diabetes of bearded women,” the first reference to an association between abnormal carbohydrate metabolism and hyperandrogenism. Since then, several syndromes of extreme insulin resistance have been described in patients with distinctive phenotypes which include acanthosis nigricans, hyperandrogenism, polycystic ovaries, or ovarian hyperthecosis and, sometimes, diabetes mellitus. These syndromes (described in detail in Chapter 17) are rare and include leprechaunism, type A and B syndromes of insulin resistance, lipoatrophic diabetes and, Rabson–Mendenhall syndrome. Severe insulin resistance observed in these rare syndromes can be due to a mutation of the insulin receptor gene or other genetic defects in insulin action. In the type B syndrome of insulin resistance, anti-insulin receptor autoantibodies have been identified as a cause of severe insulin resistance.

Euglycemic hyperinsulinemic glucose/insulin clamp studies are used to quantify insulin resistance. After a priming dose of insulin, euglycemia is maintained by a constant dose of insulin infusion and simultaneous glucose infusion, the rate of which is adjusted to achieve normal circulating glucose levels. When stable glucose levels are achieved, the rate of peripheral glucose utilization, measured in grams glucose/m² of body surface area, is equal to the rate of glucose infusion. Insulin clamp studies in PCOS subjects have demonstrated significant reduction in insulin-mediated glucose disposal similar to that seen in type 2 diabetes mellitus, thus proving that many patients with PCOS are insulin resistant.

Insulin sensitivity is affected by several independent parameters, including obesity, muscle mass, and the site of body fat deposition (central versus peripheral obesity). When insulin clamp studies are performed in PCOS women who are matched to non-PCOS controls for body mass index and body composition, insulin resistance is demonstrated in PCOS women independent of these parameters. Thus, lean PCOS women are more insulin resistant than lean controls. However, body fat does have a synergistically negative effect on insulin sensitivity in PCOS, so that lean PCOS women are usually less insulin resistant than the obese PCOS subjects. Central obesity is the characteristic form of obesity in PCOS and it magnifies insulin resistance and hyperinsulinemia in PCOS patients. The etiology of insulin resistance in polycystic ovary syndrome is unknown, although abnormalities of insulin receptor signaling have been reported in some patients.

Two theories of the pathogenesis of insulin resistance, one involving free fatty acids (FFAs) and another involving tumor necrosis factor-α (TNF-α) have been proposed. First, increased FFA flux into the liver decreases
hepatic insulin extraction, increases gluconeogenesis, produces hyperinsulinemia, and reduces glucose uptake by the skeletal muscle. Second, TNF-α, produced by adipose tissue, leads to insulin resistance by stimulating phosphorylation of serine residues of the insulin receptor substrate-1 (IRS-1), which leads to the inhibition of insulin receptor cascade. Elevated circulating levels of FFA and TNF-α have been reported in PCOS patients.

It has been hypothesized that elevated serum insulin levels in patients with PCOS result in excessive ovarian androgen production, as well as ovarian growth and cyst formation. Several in vitro studies have demonstrated the presence of insulin receptors in the ovary and the stimulation of androgen production in ovarian cells by insulin. Continuous stimulation of the ovary by hyperinsulinemia in synergism with LH over a prolonged period of time may produce morphological changes in the ovary, such as ovarian growth and cyst formation. The effects of insulin on the ovary can be mediated by the binding of insulin to its own receptor or to the type 1 IGF receptor in what is known as the “specificity spillover” phenomenon. The latter could be an important mechanism in cases of extreme insulin resistance with severe hyperinsulinemia.

Role of Insulin in Ovarian Function

Despite Joslin’s early observations of abnormal ovarian function in women with type 1 diabetes mellitus, insulin was not thought to play a significant role in ovarian function until the late 1970s, when patients with extreme forms of insulin resistance were described. Manifestations of ovarian hypofunction (primary amenorrhea, late menarche, anovulation, and premature ovarian failure) in untreated type 1 diabetes mellitus can be understood if it is accepted that insulin is necessary for the ovary to reach its full steroidogenic and ovulatory potential. Thus, patients with insulin deficiency commonly exhibit hypothalamic-pituitary and ovulatory defects, but not hyperandrogenism. On the other end of the clinical spectrum, women with syndromes of severe insulin resistance and consequent hyperinsulinemia exhibit anovulation associated with hyperandrogenism, as discussed above.

If insulin is capable of stimulating ovarian androgen production in insulin resistant patients, one has to postulate that ovarian sensitivity to insulin in these patients is preserved, even in the presence of severe insulin resistance in the classical target organs, such as liver, muscle, and fat. To explain this paradox, we will briefly review cellular mechanisms of insulin action in the ovary and the relationships between insulin, insulin-like growth factors (IGFs), and their receptors.

The term “insulin-related ovarian regulatory system” has been proposed to describe a complex system of ovarian regulation by insulin and IGFs. The components of this system include insulin, insulin receptors, insulin-like growth factor I (IGF-I), insulin-like growth factor II (IGF-II), type 1 IGF receptors, type 2 IGF receptors, IGF binding proteins (IGFBPs) 1-6, and IGFBP proteases. The relationships among the various components of this system are illustrated in Fig. 33.1 and are discussed in detail in Poretsky et al.

Insulin receptors are widely distributed in the ovaries. These ovarian insulin receptors are structurally and functionally similar to insulin receptors found in other organs (see Chapter 5). Regulation of insulin receptor expression, however, may be somewhat different in the ovaries compared to other target tissues. While in classical target tissues insulin receptors are down-regulated by hyperinsulinemia, there is evidence that circulating factors other than insulin may regulate insulin receptor expression in the ovaries of premenopausal women. These factors may include sex steroids, gonadotropins, IGFs, and IGFBPs. The phenomenon of differential regulation of ovarian insulin receptors, with their preservation on cell membrane in spite of hyperinsulinemia, may provide one explanation for the ovarian responsiveness to insulin in premenopausal women with insulin resistance in peripheral target organs.

The ovarian insulin receptors have heterotetrameric α₂β₂ structure, possess tyrosine kinase activity, and may stimulate the generation of inositolglycans. After insulin binds to the α-subunits of the insulin receptor, the β-subunits are activated via phosphorylation of the tyrosine residues and acquire tyrosine kinase activity, e.g., the ability to promote phosphorylation of other intracellular proteins. The intracellular proteins phosphorylated
Fig. 33.1 The relationships among the various components of the insulin-related ovarian regulatory system. Insulin, IGF-I, and IGF-II, acting through insulin receptors or type I IGF receptors, increase pituitary responsiveness to GnRH; stimulate gonadotropin secretion directly; stimulate ovarian steroidogenesis; inhibit IGFBP-1 and SHBG production; and act synergistically with gonadotropins to promote ovarian growth and cyst formation. (Adapted, with permission, from L. Poretsky et al. ©The Endocrine Society)

under the influence of the insulin receptor tyrosine kinase are the insulin receptor substrates (IRS) (see Chapter 5).

The insulin receptor activation and IRS phosphorylation result in the activation of phosphatidylinositol-3 kinase (PI-3-kinase). This activation is necessary for transmembrane glucose transport. Mitogen-activated protein kinase (MAPK), responsible for DNA synthesis and gene expression, is also activated by insulin; MAPK activation does not require activation of PI-3-kinase.

Tyrosine kinase activation is the earliest postbinding event and is necessary for many of the effects of insulin. Although it is believed to be the main signaling mechanism of the insulin receptor, an alternative-signaling pathway involving the generation of inositolglycan second messengers has been described (see Fig. 33.2). This alternative pathway has been found to mediate several of the effects of insulin, including, possibly, ovarian steroid production. Thus, activation of MAP-kinase and inositolglycan signaling cascades follows pathways that are distinct from those involved in glucose transport. This phenomenon of postreceptor divergence of insulin signaling pathways helps explain how some of the effects of insulin may be normally preserved, or even over-expressed, in the presence of hyperinsulinemia observed in insulin resistant states. In fact, it has been demonstrated that some of the ovarian effects of insulin are PI-3-kinase independent.

Finally, the ovaries may remain sensitive to the actions of insulin in the presence of insulin resistance because, as mentioned above, insulin, when present in high concentration, can activate type 1 IGF receptors. This pathway of insulin action may be operative in patients with syndromes of extreme insulin resistance whose insulin receptors are rendered inactive by a mutation or by anti-insulin receptor antibodies. There is evidence that type 1 IGF receptors may be up-regulated in the presence of hyperinsulinemia both in animal models and in women with PCOS.

Recent studies suggested yet another pathway which explains preserved insulin sensitivity in the ovary by invoking insulin-induced activation of PPAR-γ gene. This activation was shown to have direct and indirect effects in the ovary (Table 33.2). Activation of PPAR-γ by PPAR-γ agonists, thiazolidinediones (TZD) (rosiglitazone or pioglitazone), has been shown to produce direct effects in the ovary, which can be both insulin-independent and
Fig. 33.2 Insulin receptor, its signaling pathways for glucose transport, and hypothetical mechanisms of stimulation or inhibition of steroidogenesis. The main pathways for the propagation of the insulin signal include the following events: after insulin binds to the insulin receptor α-subunits, the β-subunit tyrosine kinase is activated; IRS-1 and -2 are phosphorylated; PI-3 kinase is activated; GLUT glucose transporters are translocated to the cell membrane, and glucose uptake is stimulated. An alternative-signaling system may involve generation of inositolglycans at the cell membrane after insulin binding to its receptor. This inositolglycan signaling system may mediate insulin modulation of steroidogenic enzymes. (Adapted, with permission, from L. Poretsky et al.15 ©The Endocrine Society)

Table 33.2 Effects of TZDs related to ovarian function (adapted with permission from Seto-Young et al.53)

<table>
<thead>
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<th>1. Direct</th>
<th>2. Indirect</th>
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<tr>
<td></td>
<td>Can be observed in vitro, may be present in vivo</td>
<td>Observed in vivo; are due to systemic insulin-sensitizing action and reduction of hyperinsulinemia</td>
</tr>
<tr>
<td>A. Insulin-independent</td>
<td>▲ Progesterone production&lt;br&gt;▼ Testosterone production&lt;br&gt;▼ Estradiol production&lt;br&gt;▲ IGFBP-1 production in the absence of insulin</td>
<td>▼ Testosterone production&lt;br&gt;▼ Estradiol production&lt;br&gt;▲ IGFBP-1 production&lt;br&gt;▼ SHBG ▼ free T</td>
</tr>
<tr>
<td>B. Insulin sensitizing (enhanced insulin effect)</td>
<td>▼ IGFBP-1 production&lt;br&gt;▲ Estradiol production (in vivo, in a setting of high-dose insulin infusion)</td>
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insulin sensitizing.53 Another study demonstrated an interaction between PPAR-γ and insulin signaling pathways with steroidogenic acute regulatory (StAR) protein, thus, suggesting that PPAR-γ may represent a novel human ovarian regulatory system.54

In summary, the paradox of preserved ovarian sensitivity to insulin in insulin resistant states can be explained by differential regulation of insulin receptors in the ovaries of premenopausal women; by activation of signaling pathways distinct from those involved in glucose transport (inositolglycan and MAP-kinase pathways, rather than tyrosine kinase and PI-3 kinase pathways); by the activation of type 1 IGF receptors which may be up-regulated in the presence of hyperinsulinemia; and by activation of PPAR-γ gene leading to improvement in insulin sensitivity.
Table 33.3  Possible mechanisms of preserved ovarian sensitivity to insulin in insulin resistant states

<table>
<thead>
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<th>Mechanism</th>
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<tr>
<td>1. Differential regulation of ovarian insulin receptors in premenopausal women</td>
</tr>
<tr>
<td>2. Activation of alternative insulin signaling pathways (MAP-kinase and inositolglycan), rather than PI-3 kinase pathway of glucose transport</td>
</tr>
<tr>
<td>3. Activation of type 1 IGF receptors which may be up-regulated by hyperinsulinemia</td>
</tr>
<tr>
<td>4. Activation of PPAR-γ</td>
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</table>

either by direct or indirect effects in the ovary (Table 33.3). In conclusion, in PCOS patients, ovarian sensitivity to insulin appears to be preserved and the insulin signaling pathways do not exhibit hypersensitivity.55

**Insulin Effects Related to Ovarian Function**

Potential mechanisms underlying the gonadotropic activity of insulin include direct effects on steroidogenic enzymes, synergism with FSH and LH, enhancement of pituitary responsiveness to GnRH, and effects on SHBG and on the IGF/IGFBP systems (see Table 33.4). Investigations focused on these mechanisms have provided insights not only into normal ovarian physiology, but also into the pathogenesis of ovarian dysfunction in a wide spectrum of clinical entities, such as obesity, diabetes mellitus, PCOS, and syndromes of extreme insulin resistance.

Table 33.4  Insulin effects related to ovarian function

<table>
<thead>
<tr>
<th>Effect</th>
<th>Organ</th>
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<tbody>
<tr>
<td>Directly stimulates steroidogenesis</td>
<td>Ovary</td>
</tr>
<tr>
<td>Acts synergistically with LH and FSH to stimulate steroidogenesis</td>
<td>Ovary</td>
</tr>
<tr>
<td>Stimulates 17 α-hydroxylase</td>
<td>Ovary</td>
</tr>
<tr>
<td>Stimulates or inhibits aromatase</td>
<td>Ovary, adipose tissue</td>
</tr>
<tr>
<td>Up-regulates LH receptors</td>
<td>Ovary</td>
</tr>
<tr>
<td>Promotes ovarian growth and cyst formation synergistically with LH/hCG</td>
<td>Ovary</td>
</tr>
<tr>
<td>Down-regulates insulin receptors</td>
<td>Ovary</td>
</tr>
<tr>
<td>Up-regulates type I IGF receptors or hybrid insulin/type I IGF receptors</td>
<td>Ovary</td>
</tr>
<tr>
<td>Inhibits IGFBP-I production</td>
<td>Ovary, liver</td>
</tr>
<tr>
<td>Potentiates the effect of GnRH on LH and FSH</td>
<td>Pituitary</td>
</tr>
<tr>
<td>Inhibits SHBG production</td>
<td>Liver</td>
</tr>
<tr>
<td>Up-regulates PPAR-γ</td>
<td>Ovary</td>
</tr>
<tr>
<td>Activates StAR protein</td>
<td>Ovary</td>
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Adapted, with permission, from L. Poretsky et al.15 ©The Endocrine Society

**Effects on steroidogenesis.** In vitro, insulin acts on the granulosa and thecal cells to increase production of androgens, estrogens, and progesterone. This action is likely mediated by the interaction of insulin with its receptors. Several in vitro studies, however, have demonstrated that supraphysiologic concentrations of insulin are needed to achieve this steroidogenic effect on the ovary, suggesting that, under some circumstances, insulin action may be mediated via the type 1 IGF receptor.20,42

Studies that attempted to determine whether insulin stimulates or inhibits aromatase or 17-α-hydroxylase have resulted in contradictory conclusions. For example, Nestler et al. reported that 17-α-hydroxylase activity appears to be stimulated by insulin,56 but Sahin et al. in a later study found no relation between insulin levels and 17-hydroxyprogesterone (17-OHP) after treatment with GnRH agonist.57 One study showed that, after gonadotropin infusion, hyperinsulinemic women with PCOS had an increased estradiol/androstenedione ratio compared with women with PCOS and normal insulin levels,58 thus suggesting insulin’s stimulatory effect on
aromatase. However, in other studies increased circulating levels of androstenedione were found during insulin infusions, suggesting that insulin inhibits aromatase.\textsuperscript{59,60}

Ovarian androgen production in response to insulin has also been extensively studied in vivo both directly, in the course of insulin infusions, and indirectly, after a reduction of insulin levels by insulin sensitizers or other agents, such as diazoxide. While insulin infusion studies did not produce consistent evidence of increased androgen production, reduction of insulin levels has consistently resulted in decreased androgen levels.\textsuperscript{15}

Synergism with LH and FSH on the stimulation of steroidogenesis. At the ovarian level, insulin has been demonstrated to potentiate the steroidogenic response to gonadotropins.\textsuperscript{20,52} This effect is possibly caused by an increase in the number of LH receptors that occurs under the influence of hyperinsulinemia.\textsuperscript{20,61}

Enhancement of pituitary responsiveness to GnRH. Another area of uncertainty is whether insulin enhances the sensitivity of gonadotropes to GnRH in the pituitary. Several investigators have demonstrated increased responsiveness of gonadotropes to GnRH in the presence of insulin in cultured pituitary cells.\textsuperscript{62,63} Nestler and Jakubowicz showed decreased circulating levels of LH in patients treated with insulin sensitizers.\textsuperscript{64} But in another study, gonadotropin responsiveness to GnRH did not change after insulin infusion.\textsuperscript{65} Similarly, in rats with experimentally produced hyperinsulinemia, response of gonadotropins to GnRH does not appear to be altered.\textsuperscript{50}

The effect on SHBG. Insulin has been shown to suppress hepatic production of sex hormone-binding globulin (SHBG).\textsuperscript{66–69} Lower levels of SHBG result in increased serum levels of unbound steroid hormones, such as free testosterone. In PCOS and other hyperinsulinemic insulin resistant states, insulin may increase circulating levels of free testosterone by inhibiting SHBG production. When insulin sensitizers are used, SHBG levels rise, thereby decreasing free steroid hormone levels.\textsuperscript{64}

The effect on IGFBP-1. Insulin has been found to regulate insulin-like growth factor-binding protein-1 (IGFBP-1) levels. In both liver and ovarian granulosa cells, insulin inhibits IGFBP-1 production.\textsuperscript{41,70,71} Lower circulating and intraovarian IGFBP-1 concentrations result in higher circulating and intraovarian levels of free IGFs that may contribute to increased ovarian and adrenal steroid secretion.\textsuperscript{15,72}

Type 1 IGF receptor. Insulin increases ovarian IGF-I binding in rats, suggesting an increase in the expression of ovarian type 1 IGF receptors or hybrid insulin/type 1 IGF receptors.\textsuperscript{57} In these studies, ovarian type 1 IGF receptors are up-regulated even though insulin receptors are either down-regulated or preserved. Studies in women with PCOS appear to confirm this phenomenon.\textsuperscript{51,73}

PPAR-\(\gamma\). Insulin increases expression of PPAR-\(\gamma\) in vitro in human ovarian cells. Activation of PPAR-\(\gamma\) enhances steroidogenesis via activation of StAR protein (Fig. 33.3).\textsuperscript{54}

StAR protein. In addition to being activated through PPAR-\(\gamma\), StAR protein can be also activated by insulin directly via insulin signaling pathway (Fig. 33.3).\textsuperscript{54}

Ovarian growth and cyst formation. It has been shown that insulin enhances theca-interstitial cell proliferation in both human and rat ovaries.\textsuperscript{74–78} In a report of a patient with the type B syndrome of insulin resistance, infusion of insulin resulted in a significant increase of ovarian volume with sonogram demonstrating that the ovaries doubled in size.\textsuperscript{79} Experimental hyperinsulinemia in synergism with hCG produces significant increase in ovarian size and development of polycystic ovaries in rats (Fig. 33.4).

In summary, in a number of in vitro animal and human ovarian cell systems and in vivo experiments in animals and in women a variety of insulin effects related to ovarian function have been demonstrated. These effects can account for many features of PCOS in hyperinsulinemic insulin resistant women.\textsuperscript{15} Insulin effects related to ovarian function are summarized in Table 33.4.

Risk of Diabetes Mellitus; Prevention of Diabetes

A major risk factor for the development of type 2 diabetes mellitus in PCOS is insulin resistance. However, a defect in pancreatic \(\beta\)-cell function resulting in deficient insulin secretion has also been reported in PCOS patients.\textsuperscript{80}
Fig. 33.3 Proposed interactions among PPAR-γ, insulin receptor (IR), IRS-1, and StAR protein in human ovarian cells. Both insulin (by activating primarily insulin receptor) and TZDs (by activating primarily PPAR-γ) lead to stimulation of StAR protein expression. In addition, TZDs activate insulin receptor expression while insulin activates expression of PPAR-γ, thus, further enhancing StAR protein expression and stimulating steroidogenesis. Both insulin and TZDs activate a downstream component of insulin signaling pathway, IRS-1. This effect of TZDs may be mediated with or without activation of the insulin receptor (adapted with permission from Seto-Young et al.54)

![Diagram of proposed interactions among PPAR-γ, insulin receptor (IR), IRS-1, and StAR protein in human ovarian cells.]

Fig. 33.4 The effects of 23 days of daily injections of normal saline (control), hCG, insulin, or insulin plus hCG and GnRHant on gross ovarian morphology in rats. Female Sprague-Dawley rats were randomized into the following treatment groups: vehicle; high-fat diet (to control for the effects of weight gain); insulin; hCG; GnRH antagonist (to control for possible central effects of insulin vs. direct effects on the ovary); GnRHant and hCG; insulin and GnRHant; insulin and hCG; insulin, hCG, and GnRHant. Ovarian morphology in the group treated with insulin and hCG (not shown) did not differ from that seen in the group treated with insulin, hCG, and GnRHant (shown above). [Reproduced with permission from L. Poretsky et al.40 ©W.B. Saunders Co.]

The prevalence and predictors of risk for type 2 diabetes mellitus have been studied in PCOS women. In prospective studies of glucose tolerance in women with hyperandrogenism and chronic anovulation, the prevalence of undiagnosed diabetes mellitus was 7.5% and that of impaired glucose tolerance (IGT) was 31.1%. Further analysis of the non-obese subgroup demonstrated that the risk for diabetes decreased to 1.5% and for IGT to 10.3%. However, these rates were still significantly increased compared to a population-based study of age-matched women in the United States in whom the prevalence rate of undiagnosed diabetes mellitus was 1.0% and that of IGT was 7.8%.81
A study of women with previous history of gestational diabetes revealed a greater prevalence of polycystic ovaries (PCO) compared to controls (39.4% versus 16.7%), higher serum levels of adrenal androgens, and significantly impaired glucose tolerance. Oral glucose tolerance testing in these women uncovered a decreased early phase insulin response while euglycemic clamp studies demonstrated impaired insulin sensitivity. The investigators theorized that a dual component of insulin resistance plus impaired pancreatic insulin secretion could explain the vulnerability of PCOS patients to diabetes.82

PCOS, and not PCO (in which the polycystic ovarian morphology is not associated with hyperandrogenism or anovulation), has been found to be a substantially more significant risk factor for diabetes mellitus than race or ethnicity.81 Factoring in obesity, age, family history of diabetes, and waist/hip ratios, the prevalence of glucose intolerance increases. This suggests that the pathogenesis of diabetes mellitus in PCOS is a result of underlying genetic defects, resulting in insulin resistance and pancreatic $\beta$-cell dysfunction, and an interplay of various environmental factors.

Primary prevention of type 2 diabetes mellitus was the focus of the Diabetes Prevention Program (DPP). The DPP, a National Institutes of Health-sponsored clinical study, targeted preventive measures at specific individuals or groups at high risk for the future development of type 2 diabetes (see Chapter 50). The study interventions included intensive lifestyle modification or pharmacological intervention versus placebo. The primary outcome was the development of diabetes mellitus in these high-risk groups. The results of this study showed that both lifestyle modification and treatment with metformin prevented or delayed the onset of type 2 diabetes in individuals with impaired glucose tolerance (IGT).83,84 Thus, specific interventions may be implemented at an early enough time period to prevent the development of diabetes mellitus and its accompanying complications in high-risk individuals. PCOS, with its dual defect of insulin resistance and $\beta$-cell dysfunction, is a significant risk factor for diabetes mellitus. When effective protocols for prevention of diabetes mellitus are established, PCOS patients may become one target group for such measures.

Role of Insulin Sensitizers

There are numerous treatment modalities for signs and symptoms of PCOS. However, traditional approaches, although often successful, do not address insulin resistance.

Hyperandrogenism and its consequences, such as hirsutism and acne, have many treatment modalities. Hirsutism can be treated with depilatories, shaving, waxing, electrolysis, or laser therapy. Oral contraceptives and anti-androgen medications, such as spironolactone85 or cyproterone acetate, 86 may be used to reduce androgen levels and manifestations of hyperandrogenism.

Oral contraceptive pills may also be used to treat menstrual irregularities. This treatment leads to a reduction in LH and an increase in SHBG. The increased SHBG binds the excess androgens, thereby decreasing the amount of free circulating androgens. 87 Progesterins may be used to regulate the menstrual cycle, however they do not affect the hair growth or metabolic abnormalities.

Weight loss, when successful, is a very effective measure which addresses insulin-related abnormalities of PCOS by decreasing insulin resistance and circulating insulin levels. One report studied 18 obese women who were hyperandrogenic and insulin resistant. A weight reduction diet resulted in a decrease in plasma androstenedione and testosterone levels.88 Pasquali et al. found decreased concentrations of LH, fasting insulin, and testosterone levels after weight loss in 20 obese women with hyperandrogenism and oligo-ovulation.89 In another study, 67 obese anovulatory women were treated with weight reduction. Sixty of these women ovulated and 18 became pregnant.90

When weight loss is not achieved, insulin resistance can be reduced with the help of insulin sensitizers, such as biguanides or thiazolidinediones. The goal of these approaches is to decrease the amount of circulating insulin, thereby decreasing insulin’s stimulatory effect on androgen production and gonadotropin secretion. Circulating levels of SHBG and IGFBP-1 are increased, leading to clinical improvement via mechanisms described above.91 Metformin decreases hepatic gluconeogenesis and increases fat and muscle sensitivity to insulin. There are many reports showing meformin’s efficacy in PCOS, however, most of the studies have been short-term only.
One long-term study followed women with PCOS treated with metformin (500 mg tid) for 6–26 months. These women not only had a reduction in insulin and androgen levels, independent of any change in weight, but also a sustained increase in menstrual regularity.

Nestler and coworkers showed that when insulin secretion is decreased by metformin administration either alone or in combination with clomiphene in obese women with PCOS, the ovulatory response is increased. In an analysis of 14 studies of metformin treatment of PCOS, 57% of women had ovulatory improvement with metformin. The improvement in ovulation may have been only due to weight loss. However, lean women with PCOS, who had increased P450c17-alpha activity and whose circulating insulin levels were reduced while on metformin, experienced a decline in P450c17-alpha activity and improvement in hyperandrogenism. In another study, women with PCOS who were given metformin demonstrated decreased circulating levels of LH, free testosterone, and a decreased LH/FSH ratio, as well as a reduced body mass index (BMI).

In one study of women with PCOS given metformin, improved endometrial function and intrauterine environment were found. This observation suggests that metformin can be used to improve implantation and pregnancy maintenance in women with PCOS. Treatment of infertility using either metformin or clomiphene citrate in anovulatory PCOS women has been successful. In the study by Legro et al. clomiphene was shown to be superior to metformin in achieving live births. Later in a smaller study by Palomba et al., both agents have been found to be equally effective.

A thiazolidinedione (TZD) troglitazone, an insulin-sensitizing agent, was the first in its class to improve insulin action in patients with PCOS. Studies with troglitazone in patients with PCOS showed improvements in ovulation, insulin resistance, hyperandrogenemia, and hirsutism. However, troglitazone was taken off the market because of hepatotoxicity. Since other members of TZD family (rosiglitazone and pioglitazone) became available, multiple studies evaluating their efficacy in PCOS patients have been published. Studies of overweight and non-obese females treated with rosiglitazone showed an improvement in ovulation, glucose tolerance, insulin sensitivity, hirsutism, and a decrease in hyperinsulinemia and androgen levels, as well as a small increase in BMI. Pioglitazone in PCOS patients showed similar effects (increased insulin sensitivity, ovulation rate, and SHBG levels and decreased insulin secretion and free androgen index) but BMI remained unchanged. While assessing the effects of TZDs in such studies, it is important to remember that TZDs exhibit both systemic insulin-sensitizing action and direct insulin-independent effects in the ovary (Table 33.2).

Some of the medications were evaluated in a head-to-head comparison to determine the best therapy of PCOS. When metformin was compared with spironolactone, both medications increased frequency of menstrual cycles and decreased testosterone, DHEA-S, and hirsutism score. Spironolactone produced more significant changes, but metformin improved glucose tolerance and insulin sensitivity. In another study, metformin was compared with rosiglitazone in obese and lean women with PCOS. Women taking these agents exhibited decrease in insulin resistance and increase in insulin sensitivity but only rosiglitazone group showed significant reduction in androgen levels as well as small but significant increase in BMI (metformin had significant decrease in BMI). Pioglitazone was compared with metformin in yet another study. Both medications were equally effective in improving insulin sensitivity and hyperandrogenism (hirsutism and androgen levels) despite an increase in BMI in pioglitazone group.

Single medication therapy (monotherapy) sometimes is not sufficient to ameliorate the symptoms of PCOS. Various studies have explored the effects of combination therapies. One study involved combination therapy of metformin and oral contraceptive pills (OCPs). When a combination of metformin and OCP (ethinyl estradiol-cyproterone acetate) was compared to OCP alone, the group using combination therapy had more dramatic reduction in androstenedione and increase in SHBG. This group, unlike OCP group, also had significant decrease in BMI, waist-to-hip ratio, and fasting insulin level; however, these differences between the groups did not reach statistical significance. There was significant increase in total cholesterol in OCP group, while the rest of the lipid panel remained unchanged in both groups. Elter et al. suggested that insulin sensitivity (glucose-to-insulin ratio) improved in combination therapy group but these results were not supported by the study of Cibula et al. which used more definitive test (euglycaemic hyperinsulinaemic clamp). Another combination therapy that has been studied involved rosiglitazone with OCP. In the study by Lemay et al. overweight women with PCOS and insulin resistance were divided into two groups to receive either rosiglitazone or ethinyl estradiol/cyproterone acetate for the first 6 months and then a combination therapy for an additional 6 months. Women receiving
combination therapy had greater reduction in androgens and increase in SHBG and HDL than either agent alone. Improved insulin sensitivity and increased triglycerides were found in only one of the two combination groups. In summary, combination therapies of oral contraceptives and insulin sensitizers have small but beneficial effect on androgen levels.

Patients and physicians should be aware that at this time there is no medical therapy which is approved by the Food and Drug Administration for the treatment of PCOS. Women with PCOS who think that they are infertile and therefore do not use contraception may become pregnant while on these medications. Thus, it is important to discuss contraception before prescribing any of these medications.

Conclusions

PCOS is a compilation of multiple endocrine and metabolic abnormalities. The main features of PCOS include chronic anovulation, hyperandrogenemia, and polycystic ovaries. Many patients have insulin resistance and hyperinsulinemia of unknown etiology, although often related to obesity. Besides the hirsutism, acne, and infertility, these women are at an increased risk for diabetes.

New therapeutic strategies addressing insulin resistance in PCOS are developing. As research elucidates specific ovarian effects of insulin and specific pathways of insulin signaling in the ovary, new targets will be identified for emerging therapies.

References


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