Polycystic ovary syndrome (PCOS) is characterized by varying degrees of hyperandrogenism, oligoanovulation, and insulin resistance. It is the most common endocrine disorder in women, affecting 5% to 10% of reproductive-aged women [1]. Approximately 3.5 to 5 million women in the United States may have PCOS. The most common cause of female infertility, PCOS also has serious metabolic consequences, such as insulin resistance, type 2 diabetes, and possibly cardiovascular disease [2,3]. According to the 1990 National Institutes of Health (NIH) criteria, the diagnosis of PCOS requires the presence of oligo- or anovulation and clinical or laboratory evidence of hyperandrogenism [4]. Polycystic ovarian morphology on ultrasound was not included in the NIH criteria for the diagnosis of PCOS, because 20% to 30% of women in the general population have polycystic ovaries on ultrasound. Most women with polycystic ovaries on ultrasound have normal androgen levels and regular menstrual cycles, and therefore do not have an endocrinopathy [5]. Recently, however, an international consensus conference recommended adding ultrasound criteria to the diagnostic schema (Table 1) [6]. Expert opinion recommended identifying polycystic ovaries based on follicle counts (> 12 in a plane) (Figure 1) or an increased ovarian volume (> 10 cm² in the absence of a developing or dominant follicle or corpus luteum cyst) [7]. Before making the diagnosis of PCOS, other potential etiologies must be excluded, including androgen-secreting ovarian or adrenal tumors and nonclassical congenital adrenal hyperplasia (21-hydroxylase deficiency), hyperprolactinemia, and Cushing’s syndrome.

CASE STUDY
Initial Presentation and History
A 24-year-old woman complains of excessive hair growth on her face, chin, and neck since the onset of puberty. Her menstrual cycles have been irregular since menarche, which occurred at age 11. She reports having had only 2 menstrual periods in the past year. She also complains of an inability to lose weight and a gradual increase in her weight since puberty. She also has acne. Family history is significant for type 2 diabetes in her mother and maternal grandfather.

Physical Examination
On physical examination, the patient is 5 ft 7 in tall and weighs 180 lb (body mass index [BMI], 28). The majority of
her weight is distributed centrally. She has a thickening of her skin at the nape of her neck consistent with acanthosis nigricans. Her blood pressure is 130/85 mm Hg. The rest of her physical examination, including a pelvic examination, is unremarkable. There is no evidence of virilization. Because of her history of oligomenorrhea, acne, and hirsutism, the physician suspects PCOS.

- Which laboratory studies should be obtained when there is a clinical suspicion of PCOS?

There is no consensus on which clinical tests should be ordered in a woman being evaluated for PCOS, although a suggested evaluation is shown in Table 2. Some form of androgen excess, either clinical or biochemical, is required as one of the diagnostic criteria. The case patient has clinical evidence of androgen excess based on her hirsutism. If a tumor is suspected or if there are no clinical signs of androgen excess, total and/or bioavailable testosterone levels should be measured. These are commonly elevated in PCOS, well below levels associated with virilization (< 200 ng/dL) and contribute to hirsutism, acne, and female pattern androgenic alopecia. Testosterone levels are also useful in women without clinical signs of hyperandrogenism. Elevated levels of circulating androgens through inappropriate feedback at the hypothalamic pituitary axis contribute to disordered and excess luteinizing hormone (LH) secretion. This in turn leads to a feedback loop inhibiting the growth and development of a dominant ovarian follicle and subsequent ovulation. Most thin women with PCOS have elevated LH or LH/follicle-stimulating hormone (FSH) ratio. Between 60% and 70% of women with PCOS will have an LH/FSH ratio over 2 [8]. Currently, however, an elevated LH/FSH ratio is less common in women with PCOS because of newer assays, although some have suggested that bioactive LH levels may be more accurate than immunoactive levels [9]. Furthermore, obesity tends to blunt LH levels [9]. Therefore, gonadotropins are not part of the current diagnostic criteria for PCOS.

Congenital adrenal hyperplasia, most commonly due to mutations in the 21-hydroxylase gene, should be excluded by measuring the morning 17-OH progesterone level, or, if borderline or elevated, performing an adrenocorticotropic hormone stimulation test. If the woman is ovulatory, the 17-OH progesterone level should be checked in the follicular phase of her menstrual cycle. Dehydroepiandrosterone should be measured to exclude adrenal tumors. Prolactin and thyroid-stimulating hormone levels should also be checked to exclude other potentially confounding causes of oligomenorrhea. In addition, if the patient has a Cushingoid appearance, such as facial and supraclavicular fat pads, purple abdominal striae, proximal muscle weakness, easy bruising, or mental status changes, one could measure 24-hour urine free cortisol to screen for the presence of Cushing’s syndrome. It may be difficult to distinguish between the 2 since many of the common features (eg, centripetal obesity, glucose intolerance, oligomenorrhea, androgen excess) overlap. Fortunately, Cushing’s is an extremely rare disorder.

In the case patient, the presence of acanthosis nigricans and central distribution of body weight suggests insulin resistance. Insulin resistance, a common finding in PCOS, may exacerbate hyperandrogenemia by stimulating adrenal and ovarian androgen secretion. Insulin resistance is even more important because it is associated with increased risk of type 2 diabetes and possibly long-term increased cardiovascular risk. Risk of type 2 diabetes is further increased in PCOS if the woman has a family history of diabetes or a personal history of gestational diabetes, obesity, sedentary behavior, and minority ethnicity [10]. For these reasons, the American College of Obstetricians and Gynecologists recommends screening women with PCOS for glucose intolerance by obtaining a 2-hour glucose tolerance test [11].

Women with PCOS, especially those that are obese, may make up the largest group of young women at risk for type 2 diabetes. Women with PCOS have a 7-fold increased risk of type 2 diabetes compared with non-PCOS women [2]. In one study of 254 women with PCOS, about 40% had glucose intolerance, including 31% with impaired glucose tolerance.
and 7.5% with type 2 diabetes, detectable even among non-obese women [2]. Studies have shown that fasting glucose is not an effective screening tool for diabetes in women with PCOS (Figure 2) [10]. Most of PCOS women with glucose intolerance have normal fasting glucose levels. The use of fasting glucose alone would have missed 58% of diabetes in these women with PCOS [2]. The oral glucose tolerance test is especially important in high-risk PCOS women, such as those who are obese or have a family history of type 2 diabetes. Dyslipidemia is also commonly associated with insulin resistant states, such as PCOS; therefore, PCOS women should be periodically screened for dyslipidemia with a fasting lipid profile [12].

**Laboratory Testing**

This patient has an elevated total testosterone level of 82 ng/dL (normal < 60 ng/dL). The thyroid-stimulating hormone, prolactin, and 17-OH progesterone are normal. The thyroid-stimulating hormone (thyroid dysfunction) and 17-hydroxyprogesterone (nonclassical congenital adrenal hyperplasia due to 21 hydroxylase deficiency): random normal < 4 ng/mL or fasting morning < 2 ng/mL Consider screening for Cushing’s syndrome: DHEAS (adrenal tumor) Evaluation for metabolic abnormalities: 2-hour oral glucose tolerance test (fasting glucose < 110 mg/dL, normal; 110–125 mg/dL, impaired fasting glucose; > 126 mg/dL, type 2 diabetes) followed by 75 g oral glucose ingestion and then 2-hour glucose level (< 140 mg/dL, normal glucose tolerance; 140–199 mg/dL, impaired glucose tolerance; > 200 mg/dL, type 2 diabetes) Fasting lipid and lipoprotein level (total cholesterol, HDL-C, triglycerides [LDL usually calculated by Friedewald equation]) Radiologic Consider ultrasound examination of ovaries for baseline evaluation/morphology prior to ovulation induction or in cases of virilization or rapid conversion to an androgen excess state

**What is the etiology of PCOS?**

The etiology of PCOS is unknown. Because PCOS is a highly prevalent heterogeneous syndrome, there are likely several causes of PCOS. Most would agree that PCOS includes a group of disorders with several different etiologies that produce a common phenotype of oligo- or anovulation, hyperandrogenism, and insulin resistance. One hypothesis is that PCOS is caused by primary central hypothalamic-pituitary axis (HPA) abnormalities of gonadotropin-releasing hormone and LH dysfunction. Another hypothesis is that the HPA abnormalities in PCOS are due to a primary enzymatic defect of ovarian or both ovarian and androgen steroidogenesis. In recent years, insulin resistance has been found to play an integral role in the pathophysiology of PCOS. Insulin resistance and hyperandrogenism appear to be
present early on in PCOS, perhaps as early as in utero or even manifesting clinically before puberty [13]. Therefore, PCOS may indeed be a primary metabolic disorder of insulin resistance and compensatory hyperinsulinemia, which adversely affects the hypothalamus, pituitary, ovaries, and possibly adrenal glands. All women with insulin resistance do not have PCOS; this may be due to genetic differences in the ovary and pancreas. Also, only about 50% of women with PCOS have biochemical evidence of insulin resistance on dynamic testing. Insulin binding in PCOS is normal. Insulin receptor mutations can cause severe insulin resistance and often a wasting appearance due to the inability to respond to insulin’s anabolic effects; however, no mutations in the insulin receptor gene have been detected in PCOS. Some evidence suggests that the primary defect in PCOS is a postreceptor signaling defect, which is extrinsic to the insulin receptor [14]. There is little agreement on the underlying molecular mechanisms behind PCOS. PCOS does cluster in families, suggesting a genetic etiology to some forms. The mode of inheritance is unclear, but many studies suggest an autosomal dominant pattern that is modified by environmental factors. One or several genes may be linked to PCOS susceptibility, although no clear causative gene has yet been identified [14].

**Diagnosis and Initial Management**

Given the patient’s history of oligomenorrhea and androgen excess, both biochemical with elevated total testosterone levels and clinical with hirsutism and acne, and with other diagnoses excluded, the physician diagnoses the patient with PCOS. She is currently single and not sexually active. She is not interested in becoming pregnant any time soon. She is started on an oral contraceptive pill (OCP) and she begins to have regular menstrual bleeding every month; in addition, her acne begins to improve. After 6 months of treatment, the patient has noticed very little reduction in the hirsutism. She returns to the clinic for further management of her PCOS. Her BMI is unchanged.

**What is the first line of treatment for PCOS in a young woman?**

Lifestyle modification through diet and exercise should be the first line of treatment for all overweight women with PCOS, especially those who are obese. Even in slightly overweight women with PCOS, weight loss may decrease insulin resistance and restore normal ovulatory menstrual cycles [15,16]. Metformin may also be used in PCOS to decrease insulin resistance and in some women may result in weight loss [17]. The effects of combination therapy are still being studied. In one study, metformin plus a low-calorie diet was better than diet alone in producing weight loss in both PCOS and obese non-PCOS women [18]. It is important to note that without diet or exercise, metformin is not associated with significant weight loss even though it may decrease hunger in some patients [19].

Other than lifestyle modification and metformin, the treatment of PCOS is mainly based on symptoms. In women who are not seeking pregnancy, OCPs are commonly used to regulate menstrual bleeding and prevent endometrial hyperplasia and decrease the risk of endometrial carcinoma. OCPs also significantly improve acne and may reduce hirsutism slightly. There are many unanswered questions about the best OCP and method of administration in women with hyperandrogenism. Theoretical evidence suggests that an OCP containing a progestin that also has antiandrogenic effects (eg, drospirenone or cyproterone acetate) may offer a better clinical response [20]. Other means to increase OCP efficacy may be continuous administration of the pill to avoid the pill-free week, using what is referred to as extended-cycle treatment. At least one such medication, Seasonale, is now approved in the United States for 91-day use (84 days of active pill followed by 1 week of placebo).

A topical cream of efloinithine hydrochloride is FDA-approved for the treatment of female facial hirsutism. For more severe cases of acne, hirsutism, or male pattern baldness, antiandrogens, such as spironolactone (usually 100 mg daily) or flutamide, may be used. Antiandrogens should not be used in women desiring pregnancy or at risk for pregnancy because androgen receptor antagonists have teratogenic effects in a male fetus; therefore, these agents are commonly used with OCPs or in women not at risk for pregnancy. Hirsutism may also be managed by physical removal such as by waxing, tweezing, electrolysis, or laser hair removal.

**Further Management**

The patient is prescribed Vaniqa cream for her facial hirsutism. Eventually, spironolactone 50 mg twice daily is added to the OCP, and she achieves satisfactory control of her symptoms over the next 6 to 12 months. Because spironolactone is a diuretic, it is prudent to ensure normal renal function and the absence of hyperkalemia at baseline and periodically in women with PCOS.

A few years later the patient returns to the office. Now 29 years old and married, she wants to become pregnant and has tried for over a year without success. As part of an infertility evaluation (with the suspected etiology of anovulation), the physician evaluates possible other contributing factors. Her hysterosalpingogram is normal, suggesting normal tubal patency and function. Her partner’s semen analysis is normal, suggesting no evidence of a male factor.

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What is the treatment of infertility in PCOS?

Lifestyle modification through diet and exercise should be the first line of treatment for infertility in obese PCOS women. In obese PCOS women, weight loss decreases insulin levels and increases ovulation [21]. In one study, lifestyle modifications that increased insulin sensitivity, measured by insulin-glucose clamp, also increased ovulation and fertility in obese PCOS women [21]. Even without weight loss, increased insulin sensitivity improves ovulation [22]. Thus, insulin sensitivity may be as important as absolute weight in determining fertility in PCOS. However, often obese PCOS women are unsuccessful in lifestyle changes. Also, they often wish to achieve pregnancy right away, accepting the increased risks of pregnancy in overweight women, including higher rates of gestational diabetes and hypertension. Therefore, the concomitant use of insulin-sensitizing medications with lifestyle changes may be an alternate treatment strategy in these patients.

Insulin resistance and its associated hyperinsulinemia are important factors in the pathogenesis of infertility in PCOS. Insulin resistance is more severe in anovulatory women with PCOS compared with hyperandrogenic women with normal menstrual cycles, suggesting that insulin resistance contributes to anovulation [23]. Possible mechanisms by which insulin resistance and its associated hyperinsulinemia inhibit ovulation include increased ovarian androgen secretion or abnormal gonadotropin secretion. Improving insulin sensitivity through diet, exercise, or with the use of insulin-sensitizing medications has been shown to improve both the reproductive and metabolic abnormalities of PCOS. In both lean and obese women with PCOS, improved insulin sensitivity results in more frequent ovulation, more regular menstrual cycles, increased success with inducing ovulation with clomiphene citrate, decreased ovarian production of androgens, some reduction in hyperandrogenic symptoms, such as acne and hirsutism, and reduction of acanthosis nigricans secondary to reduction in hyperinsulinism.

A meta-analysis of studies of women with PCOS has shown that insulin-sensitizing pharmacotherapy increases spontaneous ovulation, improves ovulation induction with clomiphene citrate, and in conjunction with clomiphene citrate increases rates of pregnancy [19]. Metformin is the most extensively studied insulin sensitizer in PCOS. It is not FDA-approved for PCOS, but the evidence supporting its usefulness is strong; therefore, it is widely accepted as a beneficial treatment for PCOS. Several small clinical studies suggest that metformin treatment in PCOS restores normal ovulatory cycles in 25% of women by 3 months and in 50% to 95% of women within 6 months [22,24]. Metformin also reduces plasma insulin, improves insulin sensitivity, decreases or maintains BMI, and may or may not improve androgen levels or the lipid profile [19].

It is not known why metformin induces normal ovulatory cycles in some women with PCOS but not in others, although the more mild phenotypes tend to have a better response. Since we do not really know which PCOS women will respond to metformin, it is reasonable to consider metformin as an ovulation induction adjuvant in all women with PCOS, whether or not they are obese or whether or not they have demonstrated insulin resistance. In most PCOS studies, metformin 500 mg 3 times per day improves menstrual cyclicity, spontaneous ovulation, and fertility. Higher doses of metformin such as 1000 mg twice daily have been shown to be optimal for glucose control in type 2 diabetes. This higher dose may also be more beneficial in PCOS [25]. Unfortunately the best dose and the adequate duration of treatment (? 3–6 months) with metformin for ovulation induction in women with PCOS remains a matter of speculation.

Prior to initiating metformin therapy, normal hepatic and renal function should be documented. Metformin is excreted by the kidney; therefore, the use of metformin is contraindicated in a woman with a serum creatinine of 1.4 mg/dL or greater, as this may increase the risk of lactic acidosis. Metformin is also contraindicated when other conditions that may increase the risk of lactic acidosis are present, including congestive heart failure, sepsis, active liver disease, and a history of lactic acidosis. Metformin should be held before any major surgery when fluid intake will be limited. Metformin should also be held before any procedure involving intravenous contrast dye. Metformin therapy can then be resumed once fluid intake is reinstituted and normal renal function is confirmed. A more common side effect of metformin is nausea and diarrhea. Gastrointestinal side effects may be minimized by taking the metformin with meals and also by starting it at a low dose and slowly titrating the dose upwards as tolerated. An extended-release version is also available.

Traditionally, clomiphene has been the first-line therapy for infertility in PCOS. Emerging evidence suggests that insulin sensitizers, metformin in particular, may be the agent of choice for primary treatment of infertility in PCOS. It is not yet known which of the 2, clomiphene or metformin, is superior in the treatment of infertility in PCOS. Whether metformin is more efficacious than clomiphene is an important issue because clomiphene is associated with a small but significant risk of multiple gestation. However, some women with PCOS do not respond to metformin. In such women, perhaps combination metformin plus clomiphene may be more effective. An ongoing randomized controlled trial of clomiphene versus metformin versus combination clomiphene and metformin for the initial treatment of infertility in PCOS may clarify this issue.
When ovulation induction with clomiphene fails, the emerging standard of practice is to try combination clomiphene and metformin therapy before proceeding to more expensive treatments, such as gonadotropin injections. In one study, women who failed to respond to clomiphene were treated with clomiphene plus metformin or gonadotropin therapy. Both treatment groups had similar pregnancy rates, but the cost of gonadotropin therapy was 4 times greater than that of combination metformin plus clomiphene [26]. In vitro fertilization is an expensive treatment and, as with gonadotropin therapy, has a substantial risk of multiple gestations; therefore, it is often an end of the line treatment.

It is important to note that women with PCOS are considered to be at high risk for gestational diabetes. According to the American Diabetes Association (2005 clinical practice recommendations), women at high risk for gestational diabetes should be screened with an oral glucose tolerance test early in their pregnancy [27]. If this initial screening is negative, the woman should be retested between 24 and 28 weeks of gestation.

**Treatments of Infertility**

The patient is started on metformin 500 mg daily with dinner, to be increased over a few weeks to a target dose of 1000 mg twice daily. The patient is monitored on a monthly basis with a midluteal progesterone level to document ovulation, and she responds with monthly ovulations. Three months later, the patient ovulates and becomes pregnant.

**Should metformin be continued during pregnancy in women with PCOS?**

This is a controversial area of treatment with an uncertain risk-benefit ratio. PCOS has been associated with a 30% to 40% risk of first trimester pregnancy loss (acknowledging that early pregnancy loss is high even in normal women, approaching 25%), but this may be because pregnancies are more closely monitored in PCOS than in normal women. However, there is no clear evidence that women with PCOS are even at increased risk for early pregnancy loss compared with the general population. There have been several retrospective PCOS studies that recommended continuing metformin therapy throughout pregnancy as its use was associated with decreased early pregnancy loss [28,29]. There are no adequate randomized controlled trials using metformin during early pregnancy to prevent pregnancy loss to support these observational case series, so the prophylactic use of metformin to prevent pregnancy loss appears to be a leap of faith at this point.

**Additional Follow-up**

The physician discusses the risks and benefits of continuing metformin therapy during pregnancy, and the patient decides to discontinue metformin. She has a normal spontaneous vaginal delivery at term without complications.

The patient returns to the office many years later. She is now 44 years old. Over the years, she has gradually gained weight, and now her BMI is 32. She has been off of all medications for many years. She is now menstruating regularly and hirsutism is no longer a significant problem for her. She has 2 healthy children and is finished with childbearing. Her only complaint is her weight gain. She has a strong family history of diabetes. Her fasting blood glucose is 105 mg/dL and her HDL-C is now lower at 38 mg/dL.

**What are the long-term consequences of PCOS?**

PCOS usually presents at menarche with oligoanovulation and hyperandrogenism. But when women with PCOS approach their 40s, the hyperandrogenism and menstrual irregularities tend to improve [30,31]. At this point, long-term metabolic consequences of insulin resistance and PCOS may become the predominant concern. Women with PCOS tend to exhibit features of the metabolic syndrome, such as obesity, high blood pressure, glucose intolerance, diabetes, and dyslipidemia, and therefore may be at greater risk for endometrial cancer and cardiovascular disease. The risk factor profile for endometrial cancer, including centripetal obesity, chronic anovulation with unopposed estrogen exposure, and diabetes, overlaps closely with the PCOS phenotype, but other than risk factor profiling there are few epidemiologic studies to support increased event rates in women with PCOS [32]. Currently, there are no recommended screening tests for detecting endometrial cancer, although increasing endometrial thickness on ultrasound exam in anovulatory women with PCOS should elicit concern [33]. There are as of yet no clear cut-offs for further evaluation by biopsy. Persistent spotting or bleeding in a prior oligo- or amenorrheic woman is also a suspicious sign meriting further evaluation.

Similarly, there are no prospective longitudinal studies on adverse cardiovascular events in women diagnosed with PCOS, but the epidemiologic literature is richer. In data published from the Nurses’ Health Study, women with a history of oligomenorrhea were found to have an increased risk of fatal myocardial infarction compared with normally menstruating women. This risk increased with increasing menstrual irregularity even after controlling for BMI differences and was increased 67% in the most irregular group [34]. Many of these women likely had PCOS.

PCOS may have detrimental effects on the cardiovascular
system, even in young women asymptomatic for cardiac disease. Women with PCOS have increased coronary artery calcification, endothelial dysfunction, carotid intima-media wall thickness, and agonist-induced platelet aggregation compared to controls [35–37]. Even in the absence of overt cardiovascular disease, endothelial dysfunction and structural changes in the heart have been demonstrated in PCOS women as young as 26 years [38]. All this suggests that women with PCOS have lifelong exposure to adverse cardiovascular risks that may predispose them to premature atherosclerosis.

- How can progression to diabetes be prevented in PCOS?

The conversion rate of women with PCOS to glucose intolerance and type 2 diabetes has been shown to be high in small studies [39]. Chronic therapy in women with PCOS should include measures such as lifestyle modification and metformin to prevent diabetes in those at highest risk, such as those with glucose intolerance. The Diabetes Prevention Program, a large randomized trial in subjects with impaired glucose tolerance, showed that lifestyle modification or metformin therapy in patients with impaired fasting glucose prevents progression to diabetes. Lifestyle intervention was more effective than metformin and decreased the risk of diabetes by 58% compared with placebo, whereas metformin decreased the risk of diabetes by 31% compared with placebo [40]. The goals used in the lifestyle intervention group of this study, weight loss of 7% of body weight and at least 150 minutes of exercise weekly, may also be appropriate goals for obese PCOS women. The Finnish Diabetes Prevention Program found a similar magnitude of benefit to lifestyle interventions in high-risk individuals [41]. If lifestyle interventions are unsuccessful, metformin may be added.

- Should all women with PCOS receive chronic metformin therapy?

The use of chronic insulin-sensitizing pharmacotherapy in PCOS is controversial. In recent years, insulin resistance has been found to play a major pathophysiologic role in PCOS. Lean woman with PCOS possess a form of insulin resistance intrinsic to PCOS. Obese women are even more insulin resistant because they have both insulin resistance intrinsic to PCOS and insulin resistance secondary to excess adiposity. Insulin resistance is associated with an increased risk of type 2 diabetes and subsequent cardiovascular disease. Therefore, insulin-sensitizing drugs may be potentially beneficial in the chronic treatment of PCOS. Many experts recommend chronic treatment with metformin, especially in those women with PCOS who are obese or have insulin resistance. Treating women at high risk for diabetes with insulin-sensitizing drugs has been shown to decrease the progression to diabetes [42]. Insulin-sensitizing medications may also improve surrogate markers of cardiovascular risk in women with PCOS [43,44].

Traditionally, the standard treatment for PCOS in women who are not seeking pregnancy has been OCPs. Long-term controlled studies documenting the metabolic effects of OCP treatment in PCOS are needed. For now, OCP treatment remains an important therapy in PCOS, as there is strong epidemiologic evidence showing that it protects against endometrial carcinoma, normalizes menses, and reduces hirsutism and acne. Until well-controlled studies on the long-term effects of OCP therapy or insulin-sensitizing therapy in PCOS become available, chronic treatment of women with PCOS should be determined on a case-by-case basis.

- Are thiazolidinediones superior to metformin in the treatment of PCOS?

Troglitazone, a thiazolidinedione (TZD), has been shown to improve ovulation in a dose-response fashion as well as to improve glycemic parameters [45]. However, it has been removed from the market due to severe liver toxicity. TZDs are primarily insulin sensitizers, whereas metformin primarily suppresses hepatic glucose production. With the exception of the troglitazone trial in PCOS, TZDs as a class have not been as well studied in PCOS as metformin. Furthermore, TZDs may not be ideal in PCOS because they can be associated with weight gain and edema and have uncertain fetal toxicity and/or teratogenicity. There have been few adequately powered head-to-head trials of metformin versus TZDs in women with PCOS. The best and largest to date randomized non-obese women with PCOS and normal insulin sensitivity to either metformin monotherapy, rosiglitazone monotherapy, or the combination of metformin and rosiglitazone. All treatments significantly increased the frequency of ovulation and decreased serum free testosterone levels compared with placebo. Metformin monotherapy was more effective than rosiglitazone monotherapy and comparable to combination metformin and rosiglitazone. This study is also important because it shows that insulin-sensitizing therapy increases ovulation and decreases hyperandrogenism, even in PCOS women with normal insulin sensitivity [46].

Further Management

The physician prescribes the patient metformin together with lifestyle modification, as he is concerned.
about her rising glucose level and her falling HDL-C level. She loses 20 lb over 6 months, has a fasting glucose level of 95 mg/dL, and her HDL-C rises to 48 mg/dL. She remains normotensive.

SUMMARY

PCOS is not just a disorder of oligoanovulation, infertility, and hirsutism. PCOS has serious medical consequences that may be reduced by early detection and treatment of PCOS and its associated metabolic and cardiovascular risk factors. The chronic treatment of women with PCOS includes reduction of insulin resistance through lifestyle modification with or without metformin. Improving insulin sensitivity in PCOS increases the frequency of ovulation and may decrease progression to type 2 diabetes and possibly cardiovascular disease. Some of the benefits of metformin therapy in PCOS include weight maintenance and sometimes weight loss, improved insulin sensitivity, and increased ovulation. In those symptomatic women who are not seeking pregnancy, OCPs and antiandrogens may be used to treat hyperandrogenic symptoms such as acne, hirsutism, and alopecia in PCOS. Oligoamenorrhea should be treated with OCPs to prevent endometrial hyperplasia, and subsequent endometrial carcinoma. As for women with PCOS who are seeking pregnancy, available treatments include metformin and clomiphene citrate in addition to lifestyle modification. Metformin alone may induce ovulation in some women with PCOS. If metformin or clomiphene monotherapy fail to induce ovulation, the other agent may be added. Further studies are needed to investigate the long-term effects of metformin therapy on cardiovascular disease and diabetes in PCOS.

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References

POLYCYSTIC OVARY SYNDROME

Diagnosis and Management of Polycystic Ovary Syndrome

DIRECTIONS: Each of the questions below is followed by 5 possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. Which of the following are characteristics of polycystic ovary syndrome (PCOS)?
   (A) Hyperandrogenism
   (B) Absolute insulin deficiency
   (C) Oligo-/anovulation
   (D) A and C only
   (E) All of the above

2. Which of the following laboratory test results is consistent with PCOS?
   (A) Oral glucose tolerance test: 2-hour glucose elevated > 140 mg/dL
   (B) 17-OH progesterone level elevated > 4 ng/mL
   (C) Testosterone elevated > 200 ng/dL
   (D) A and C only
   (E) All of the above

3. Which of the following statements is true?
   (A) The American College of Obstetricians and Gynecologists recommends screening women with PCOS for glucose intolerance by obtaining a fasting glucose level
   (B) Women with PCOS have a 7-fold increased risk of type 1 diabetes compared with non-PCOS women
   (C) The risk of diabetes is increased in PCOS if the woman has a family history of diabetes
   (D) A and C only
   (E) All of the above statements are true

4. The first line of treatment for all women with PCOS is
   (A) Metformin
   (B) Spironolactone
   (C) Oral contraceptive pills
   (D) Lifestyle modifications
   (E) None of the above

5. Which of the following statements regarding metformin is true?
   (A) Metformin induces ovulation in all women with PCOS
   (B) Metformin has been shown to prevent type 2 diabetes in women with PCOS
   (C) Metformin is commonly associated with gastrointestinal side effects
   (D) A and C only
   (E) All of the above statements are true
EVALUATION FORM: Diagnosis and Management of Polycystic Ovary Syndrome

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   _ Yes _ No

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