

Mini-Reviews

Polycystic Ovary Syndrome in Adolescents

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Introduction

Polycystic ovary syndrome (PCOS) is a common disorder, affecting 5–10% of women,¹ with multiple etiologies and a variable clinical presentation. Symptoms and signs include menstrual dysfunction, acne, hirsutism, obesity, infertility, insulin resistance, and polycystic ovaries by ultrasonography. Onset of the menstrual disorder begins peripubertally and has been associated with childhood antecedents of low birth weight and premature pubarche.^{2,3} Adolescent girls with PCOS, similar to adult women with the condition, are at increased risk for the development of type 2 diabetes mellitus and the metabolic syndrome (glucose intolerance, dyslipidemia, hypertension and central obesity) as compared to the general adolescent population. This is particularly true for those with obesity; however, hyperandrogenemia is a risk factor for metabolic syndrome independent of obesity and insulin resistance.⁴ It is important to recognize girls and young women at risk for PCOS as early intervention may prevent long term sequelae and improve quality of life.⁵ This review will address the current definition, clinical features, pathophysiology, and diagnostic and treatment considerations of polycystic ovary syndrome in adolescent and young adult women.

Definition

Difficulties in the diagnosis of PCOS and controversies in definition^{6,7} arise from the heterogeneous nature of the disorder. Even in the classic 1935 report by Stein and Leventhal describing their case series of seven women with amenorrhea associated with bilateral polycystic ovaries treated with wedge resection of the ovaries, only three of these women were obese,

only four were hirsute (one obese), and one had acne.⁸ The 2003 revised diagnostic criteria for PCOS reached at a consensus conference held in Rotterdam jointly by the European Society for Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) are compared to the earlier definition reached at the 1990 National Institute of Health (NIH) international workshop in Table 1. In the 1990 NIH criteria, definite criteria for PCOS were hyperandrogenism and/or hyperandrogenemia, oligoanovulation, and exclusion of other etiologies such as Cushing's syndrome, hyperprolactinemia, and congenital adrenal hyperplasia (CAH). Probable criteria included insulin resistance, perimenarcheal onset, elevated luteinizing hormone:follicle stimulating hormone (LH:FSH) ratio, and polycystic ovaries by ultrasound.⁹ The key features were thus defined as menstrual irregularity and clinical or biochemical androgen excess, deemphasizing ovarian morphology.

As the availability of high definition pelvic ultrasound with use of a vaginal probe has become more widespread, use of ultrasound criteria to define the polycystic ovary (PCO) emerged at the 2003 Rotterdam ESHRE/ASRM consensus conference. A PCO is defined as having at least one of the following: either 12 or more follicles measuring 2–9 mm in diameter, or increased ovarian volume (>10 cm³). If a single follicle is present over 10 mm in diameter the scan should be repeated at a time of ovarian quiescence in order to calculate volume and area. A single PCO is sufficient for diagnosis. Although the distribution of the tiny cysts in a peripheral pattern, the "string of pearls" configuration, or ovarian stromal hyperechogenicity or increased stromal volume are specific to PCO, the consensus guideline did not require this description, and ovarian volume or area was recommended as an adequate surrogate marker.¹⁰ The revised 2003 Rotterdam definition of PCOS requires 2 of 3 criteria to be met: (1) oligoanovulation or anovulation, (2) hyperandrogenemia (elevated levels of circulating androgens) or hyperandrogenism

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Table 1. Diagnostic Criteria for PCOS According to the 1990 NIH Conference,⁹ the Revised Criteria from the ESHRE/ASRM-sponsored Consensus Meeting,¹¹ and the Androgen Excess Society²⁰

NIH 1990	Rotterdam 2003	Androgen Excess Society 2006
(1) Chronic anovulation	(1) Oligo- and/or anovulation	(1) Ovarian dysfunction: oligo-anovulation and/or polycystic ovaries
(2) Clinical and/or biochemical signs of hyperandrogenism	(2) Clinical and/or biochemical signs of hyperandrogenism (3) Polycystic ovaries	(2) Hyperandrogenism: Hirsutism and/or hyperandrogenemia

All three criteria assume exclusion of other diagnoses that may replicate symptoms of PCOS such as nonclassical congenital adrenal hyperplasia. The NIH and the AES definitions require both criteria to make the diagnosis; the ESHRE/ASRM Rotterdam requires two of three.

(clinical evidence of androgen excess) or (3) polycystic ovaries by ultrasound as described above. Similar to the earlier 1990 NIH consensus criteria, other medical conditions that cause irregular menstrual cycles and hyperandrogenism need to be excluded.¹¹ (See Table 2 for conditions to be excluded in the diagnosis of PCOS and distinguishing features.)

The 2003 Rotterdam criteria will include more phenotypes of PCOS. The most controversial group to be included as having a diagnosis of PCOS are those women with oligo- or anovulation and polycystic ovaries by ultrasound who lack clinical or laboratory evidence of androgen excess; several researchers have argued that such criteria may be nonspecific.^{6,7,12} The group of ovulatory women with androgen excess

and polycystic ovaries by ultrasound may be less controversial as several studies have documented the entity of hyperandrogenism (clinically as hirsutism or biochemical) with regular menstrual cycles and polycystic ovaries on ultrasound as possibly representing a mild form of PCOS.^{13–16}

A recent study of 290 consecutive hyperandrogenic young women compared those with classic PCOS (hyperandrogenism and chronic anovulation) with so-called “ovulatory” PCOS (hyperandrogenism and polycystic ovaries but with ovulatory cycles) who would be diagnosed with the new 2003 Rotterdam criteria and those with idiopathic hyperandrogenism (ovulatory cycles and normal ovaries) to age-matched normal weight ovulatory controls and body mass

Table 2. Conditions for Exclusion in the Diagnosis of Polycystic Ovary Syndrome

Condition	Hyperandrogenemia, Hyperandrogenism or Both	Oligomenorrhea or Amenorrhea	Distinguishing Features	
			Clinical	Hormonal or biochemical
Nonclassical congenital adrenal hyperplasia due to deficiency of 21-hydroxylase	Yes	Variable	Family history of infertility, hirsutism or both; common in Ashkenazi Jews	Elevated (basal) level of 17-hydroxyprogesterone in the morning or on stimulation with ACTH
Cushing's syndrome	Yes	Yes	Hypertension, striae, easy bruising	Elevated 24 hr urinary free cortisol level
Hyperprolactinemia or prolactinoma	None or mild, variable	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 may also be increased
Acromegaly	None or mild	Often	Acral enlargement, coarse features, prognathism	Increased plasma insulin-like growth factor 1
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	Clitoromegaly, extreme hirsutism, or male-pattern alopecia	Extremely elevated plasma androgen level
Drug-related condition ^a	Often	Variably	Evidence provided by history	None

^aA drug-related condition is a condition due to the use of androgens, valproic acid, cyclosporine, or other drugs. Adapted from Ehrmann DA: Polycystic Ovary Syndrome. *N Engl J Med* 2005; 352:1225, with permission.

index-matched controls on markers of elevated cardiovascular risk including obesity, insulin resistance, dyslipidemia, C-reactive protein, and homocysteine. The prevalence of at least one elevated cardiovascular risk marker was 45% among those with classic PCOS, 38% in ovulatory PCOS, and not increased in those with idiopathic hyperandrogenism (6%). Obesity was present in 29% of the classic PCOS group and was uncommon in the other two groups. The ovulatory PCOS group and idiopathic hyperandrogenism group had similar ages, body-mass index (BMI), gonadotropins, and androgen levels, yet the ovulatory PCOS group had more insulin resistance and higher cardiovascular risk, suggesting polycystic ovaries might be a significant factor.¹⁶ However it is unclear whether ovulatory women with polycystic ovaries and hyperandrogenism will ultimately develop metabolic complications including type 2 diabetes mellitus (DM).⁶

Diagnosing PCOS in adolescents by these new (2003) criteria poses several challenges. During puberty adolescent menstrual cycles are frequently anovulatory, acne and mild hirsutism are common, and the prevalence of obesity and its consequences of insulin resistance and metabolic syndrome are increasing.¹² Limited normative data of androgen levels by BMI and pubertal stage in adolescents exists¹¹ and in some normal girls transient hyperandrogenism in early puberty is documented with later normal ovulatory cycles.¹⁷ Adult polycystic ovary ultrasound criteria in asymptomatic adolescents may not be as helpful, because polycystic-type ovaries can occur in healthy asymptomatic adolescents¹⁸ and fewer adolescents with PCOS will demonstrate polycystic ovaries (55%) than adults (75%), in part because virginal adolescents may be less likely to have a vaginal probe placed during the study.¹⁹

In 2006, the Androgen Excess Society (AES) Task Force on the Phenotype of PCOS²⁰ narrowed the Rotterdam criteria to exclude women who did not have androgen excess. The criteria include (1) hyperandrogenism (hirsutism and/or hyperandrogenemia); (2) ovarian dysfunction (oligo-anovulation and/or polycystic ovarian morphology on ultrasound); and (3) exclusion of other disorders (see Table 1). In the authors' opinion, these criteria are the most useful for diagnosis of PCOS in adolescence.

Pathogenesis

For some adolescents with PCOS, there appears to be an abnormal and exaggerated transition to puberty in four key physiologic processes: (1) increase in LH secretion, (2) increase in adrenal androgen production, (3) increase in body mass and (4) onset of adult patterns of insulin resistance.²¹ However, research over the past two decades has documented a spectrum of

abnormalities within the hypothalamic-pituitary-ovarian axis. As discussed below in more detail, dysregulation of steroidogenesis within the ovary or adrenal gland leads to excess androgen production. Insulin-resistant hyperinsulinemia is seen as an important contributing factor to the dysregulation.¹² No single etiologic factor appears to explain the full spectrum of clinical disorders seen with PCOS.¹

Hypothalamic-Pituitary-Gonadal Alterations

Studies have shown that women with PCOS have an exaggerated increase in LH pulse frequency although whether this is due to an intrinsic abnormality of the GnRH pulse generator or related to the abnormal feedback of low levels of progesterin from anovulation is unclear.¹ Most, but not all, women with PCOS have chronically elevated levels of LH and the LH:FSH ratio may be elevated, particularly in women with a BMI <30. LH stimulates the ovarian thecal cell to produce androgens (Fig. 1) mediated by cytochrome P-450c17 α , a single enzyme with both 17 α -hydroxylase and 17,20-lyase activity which enhances production of androstenedione. Androstenedione is converted to testosterone by 17 β -hydroxysteroid dehydrogenase or aromatized by the aromatase enzyme in the granulosa cell to form estrone which can be converted to estradiol by 17 β -hydroxysteroid dehydrogenase. Insulin and insulin-like growth factor (IGF-1) act in synergy with LH to stimulate ovarian androgen production via cytochrome P-450c17 α and act to inhibit sex hormone binding globulin (SHBG) production in the liver. This allows more testosterone to circulate in the "free" or active state. Free testosterone stimulates androgen receptors of the pilosebaceous unit which can lead to the clinical findings of hirsutism and acne.^{1,23}

Dysregulation of Androgen Production

PCOS can be seen in the absence of LH excess and research supports a theory of intraovarian androgen excess caused by dysregulation of steroidogenesis, in particular the expression of the cytochrome P450c17(CYP17) enzyme system as discussed above, as an important event causing anovulation in this disorder. Support for this theory includes in vitro evidence that theca cells from women with PCOS have elevated CYP17 gene expression of 17 α -hydroxylase/17,20-lyase activity and increased 3 β -hydroxysteroid dehydrogenase leading to increased production of androgen precursors to testosterone. 17 β -hydroxysteroid dehydrogenase activity was not increased.²⁴⁻²⁶ This dysregulation may explain why women with PCOS have hyperresponsiveness to GnRH agonist with excessive production 17-hydroxyprogesterone.¹²

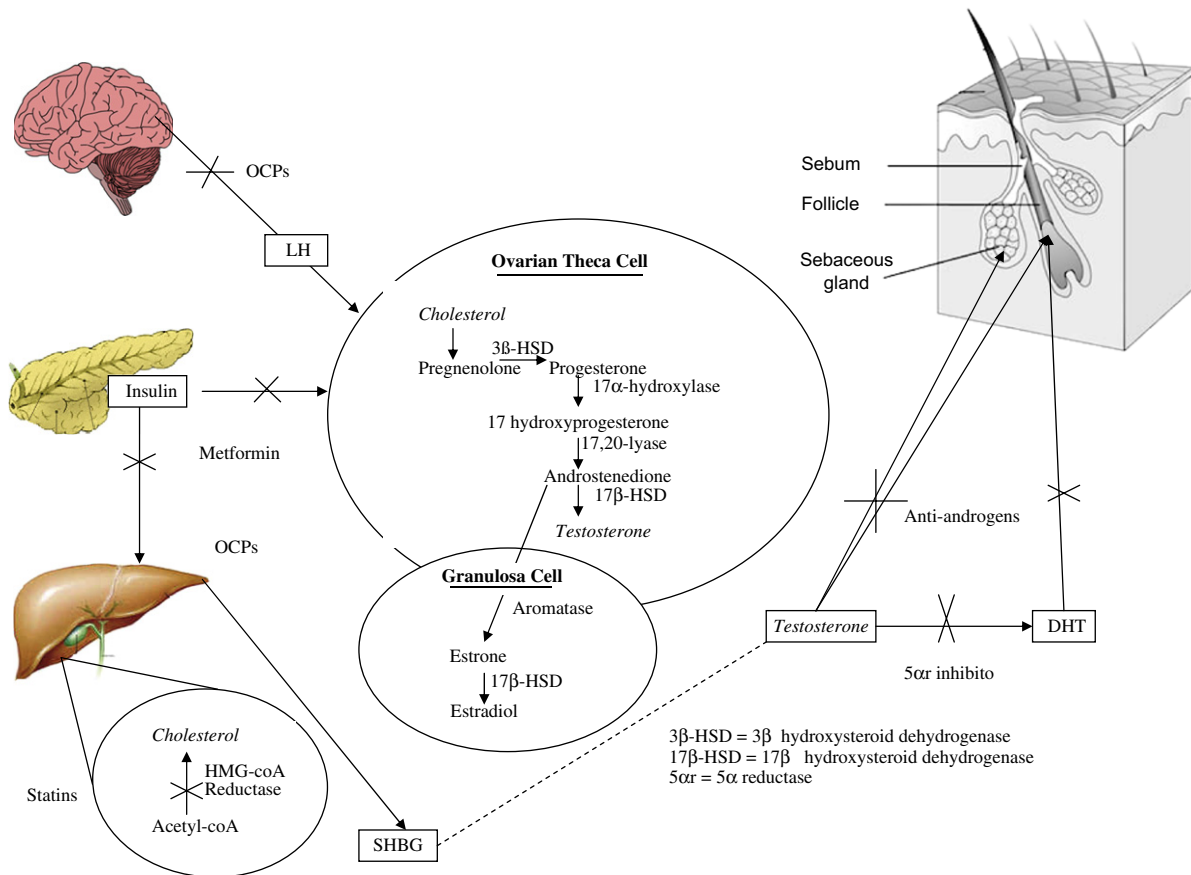


Fig. 1. Schematic of pathophysiology of polycystic ovary syndrome and mechanism of therapeutic drugs. DHT=dihydrotestosterone; LH=Leutenizing hormone; SHBG=sex hormone binding globulin; OCPs=oral contraceptive pills. Adapted from Hassan A, Gordon. Polycystic ovary syndrome in adolescence. *Curr Opin Pediatr* 2007; 19(4): 389 with permission.

The anovulation seen in PCOS can be explained on the basis of increased intraovarian androgen biosynthesis within the ovarian theca cell as the primary event.^{12,27} This intraovarian androgen excess causes excessive growth of small follicles and lack of development of a dominant follicle.²⁸ The granulosa cells of the ovary likewise display dysregulation by being overly responsive to FSH.^{27,29}

Insulin Resistance/Metabolic Disorder

The importance of insulin resistance in women with PCOS and its role in the pathogenesis of anovulation and hyperandrogenemia has become increasingly recognized.³⁰ Research suggests that the hyperinsulinemia seen in PCOS causes hyperandrogenemia by its effect on steroidogenesis, stimulating 17,20 lyase activity and decreasing SHBG production in the liver. In PCOS it appears to be a selective defect in insulin action with the ovaries and adrenal glands maintaining sensitivity to the excess insulin action while insulin resistance is seen in the glucose-metabolic effects of insulin^{30,31} (see Fig. 1). Clinical findings of

hyperinsulinism may be seen as the epidermal hyperplasia of acanthosis nigricans. Adolescent and adult women with PCOS demonstrate increased incidence of glucose intolerance, metabolic syndrome (MBS), and type 2 diabetes. An increased incidence of insulin resistance is found in women with PCOS even when controlling for effects of obesity.³² A recent study in adolescent girls with PCOS found 37% had MBS as compared to a 5% in a control population of similar age and ethnicity. After adjusting for BMI, girls with PCOS were 4.5 times as likely to have MBS and risk was related to level of bioavailable testosterone, the relative odds increasing approximately 5 times with each quartile increase in free testosterone.⁴

Etiology

The genetic etiology of PCOS remains to be fully elucidated despite strong familial incidence. A number of candidate genes involved in the secretion and action of insulin and those encoding steroidogenic enzymes have been studied. It appears to be a complex multigenic disorder in which genetic and

environmental factors lead to the heterogeneous phenotypes observed.^{1,33} Legro and colleagues studied 115 sisters of 80 probands with PCOS and found that 46% had evidence of hyperandrogenemia with 22% fulfilling criteria for PCOS and 24% with hyperandrogenemia but regular menstrual cycles.³⁴ This group also studied brothers of women with PCOS and found that these brothers had elevated dehydroepiandrosterone (DHEAS) levels compared to control men, suggesting a genetic trait with a biochemical phenotype in men in PCOS families.³⁵ A recent study of parents of 36 adolescent girls with PCOS found that the 19 fathers studied had a high incidence of adiposity (94%) and metabolic syndrome (79%) and the probands' PCOS status was completely concordant with fathers' MBS status, but not their mother's MBS status, in families where the premenopausal mothers lacked PCOS. The majority of the 35 mothers studied were obese (54.4%) or overweight (11.4%) and 34% had MBS, but only 14% had PCOS.³⁶

While PCOS manifests clinically in adolescence, recent evidence is accumulating that an intrauterine environment of prenatal androgen excess is associated with the development of PCOS later in life. Female primates exposed in utero to androgen excess develop PCOS in adult life. Women who were prenatally androgenized due to congenital adrenal hyperplasia or congenital adrenalizing tumors, even when treated after birth to normalize androgen levels, have an increased risk of developing PCOS in adolescence.³⁷ Other clinical observations that may provide clues to the etiology include the association with premature pubarche and increased risk for development of PCOS.³⁸ Girls with premature pubarche appear to have adrenal hyperresponsiveness, elevated insulin and IGF-1 levels, and decreased binding proteins SHBG and IGF-BP1.^{39,40}

Clinical Presentation and Patient Evaluation

The consensus diagnostic criteria for PCOS discussed above were established for adult women and may not reflect the challenges of diagnosis and variable clinical features seen in adolescent girls. *Menstrual dysfunction* is seen in two thirds of adolescents with PCOS and includes a spectrum of anovulatory symptoms including primary or secondary amenorrhea, oligomenorrhea, dysfunctional uterine bleeding or anovulatory regular menses. History should include age of menarche, regularity of cycles, presence of menstrual cramps, number of cycles per year, and if premature pubarche occurred.

Hyperandrogenism is seen clinically as acne, hirsutism, male pattern baldness, diffuse alopecia, seborrhea, or hyperhidrosis.^{12,41} Hirsutism is present in two thirds of adolescents with PCOS⁴¹ and is defined as

the presence of sexual hair in a male pattern (terminal hair on the face, back, chest, abdomen, inner thighs) and often graded with the Ferriman and Gallwey scoring system with a score of 8 or more indicating hirsutism (a score of 6–8 is the 95th percentile for black and white women).⁴² The hirsutism of PCOS is often slowly progressive and adolescents may not have developed clinically significant symptoms. Rapidly progressive or abrupt onset of hirsutism or virilization raises concern for an androgen secreting tumor or intersex state. History should include the timing, location, and rate of progression and recent changes in the amount of hair.²¹ It is important to ask directly about methods employed to remove unwanted hair such as plucking, waxing, shaving, depilatories, electrolysis, laser hair removal, or bleaching, because the adolescent may not disclose these measures without prompting⁴³ and the degree of hirsutism may be underappreciated on clinical exam when such measures are used. Early or late onset of acne, persistence of acne, or severe acne requiring Accutane treatment should prompt an evaluation for hyperandrogenism. To assess for other cause of hyperandrogenism, history of medications or anabolic steroid use, changes in voice pitch or scalp hair distribution, symptoms of thyroid disorders, galactorrhea, stigmata of Cushing's syndrome should also be included in the evaluation. Family history of PCOS, hirsutism, ethnicity, adrenal enzyme deficiencies such as 21 hydroxylase deficiency (late onset congenital adrenal hyperplasia), seen at higher prevalence in those of Eastern European Jewish descent, diabetes, hyperinsulinism, or infertility should be obtained²¹ (see Table 2).

Insulin resistance appears to be the key etiologic feature in development of PCOS and is noted in the majority of women, although the severity varies between lean and obese women with PCOS. Using the criterion standard euglycemic clamp technique, Dunaf and colleagues^{31,32} demonstrated that both lean and obese women with PCOS have lower rates of insulin-mediated glucose uptake than weight-matched controls, thus indicating insulin resistance. Studies support the additive roles of obesity on the level of insulin resistance that is seen in PCOS.^{44,45} Acanthosis nigricans, a velvety rash, on the back of the neck, axilla, and groin is a cutaneous manifestation of insulin resistance.

Glucose intolerance was studied in 254 women with PCOS by 2 hour oral glucose tolerance test (OGTT). This study found that 31% of obese patients had evidence of impaired glucose tolerance (IGT) and 7.5% had diabetes, while in the non-obese women only 10.3% had IGT and 1.5% diabetes. In patients with PCOS the fasting glucose was a poor predictor of IGT.⁴⁶ Similarly, Palmert et al studied 27 adolescents with PCOS, both lean and obese, and found that 33%

of the study population (8/27) had abnormal glucose tolerance and one had previously undiagnosed type 2 DM. Fasting plasma glucose did not reliably predict the impaired glucose tolerance or diabetes in these patients, suggesting the OGTT is a more reliable screening test for the presence of glucose intolerance.⁴⁷

Clinical practice guidelines suggest that PCOS is a diagnosis of exclusion, recognizing the inconsistent availability of reliable specialized hormone assays, particularly for androgens, and the need for cost effective evaluation strategies. Laboratory screening aims to rule out other causes of androgen excess and irregular menses such as late onset CAH, thyroid disorders, prolactinoma, and ovarian failure (see table 2). It should be noted that only the androgen levels (testosterone, free testosterone, and DHEAS) are part of the criteria for making a diagnosis of PCOS. At the time of the clinic visit, typical blood tests include FSH, LH, prolactin, thyroid stimulating hormone (TSH), total and free testosterone, sex hormone binding globulin, DHEAS, cholesterol, high density lipoprotein (HDL-C), and random blood glucose. If the adolescent girl with PCOS is obese and/or has acanthosis nigricans (some test all girls with PCOS), a fasting glucose and insulin and 2 hour glucose (and insulin) level after 75 g oral glucose are obtained. If the clinician is suspicious for late onset CAH (high DHEAS, clitoromegaly, premature pubarche, early onset, or family history), a serum 17 hydroxyprogesterone in the follicular phase between 7 and 8 AM is obtained; in some centers, all patients are screened. A pelvic ultrasound can be helpful in defining ovarian morphology for the Rotterdam or AES criteria and is of particular importance with high testosterone levels or rapidly progressive hirsutism or virilization. If there is a high suspicion for an adrenal tumor, a CT scan or MRI should be performed. In the girl with regular menses, hirsutism, and apparently normal androgen levels, the menses may or may not be ovulatory (idiopathic hirsutism) or anovulatory (PCOS). The presence of premenstrual symptoms may suggest ovulatory cycles but the preferable approach is to obtain a serum progesterone on day 22–24.

Treatment

Treatment is aimed at the underlying pathophysiology and the presenting symptoms of the patient. Goals of therapy include management of irregular menses, protection of the endometrium from unopposed estrogen stimulation (and later development of endometrial cancer), decrease in hirsutism and acne, lessened risk of diabetes mellitus, improved quality of life, and a discussion of fertility. A previous study of adolescents with PCOS has shown a significant impact of this disorder on quality of life.⁵ Management

strategies include lifestyle modification and medications including oral contraceptive agents, anti-androgens, insulin sensitizing agents, and statins. A combination of therapies is often employed.

Lifestyle Modifications

For the overweight or obese adolescent with PCOS first line treatment is a serious attempt at weight loss. The impact of lifestyle changes to affect the underlying pathophysiology of insulin resistance cannot be overemphasized. In the large Diabetes Prevention Program study of nondiabetic adults with elevated fasting glucose, lifestyle modification with a goal of 7% weight loss and at least 150 minutes of exercise resulted in a 58% reduced incidence of diabetes versus placebo and this reduction was greater than that achieved with metformin therapy (31%).⁴⁸ A recent review of the evidence supports lifestyle modification with reduction of weight to reduce elevated androgens and improve reproductive function in obese women with PCOS. Studies among adolescent women are limited, but weight loss has been associated with a decrease in serum testosterone, increase in sex hormone binding globulin, and decrease in free androgen index. Further research is needed in this population because there is limited data on the impact of lifestyle modification on the clinical manifestations of PCOS or on the progression of PCOS in adolescence.⁴⁹

Oral Contraceptive Agents

Hirsutism, acne and irregular menstrual cycles in adolescents are improved with combined oral contraceptives (OCs). The estrogen component suppresses LH and thus ovarian androgen production as well as increasing hepatic production of sex hormone binding globulin, SHBG, resulting in less free testosterone to stimulate the androgen receptor. Combination OCs also inhibit 5-alpha-reductase in the skin lowering levels of dihydrotestosterone.^{1,43} Generally a combined OC that provides 30 to 35 mcg of ethinyl estradiol is given cyclically or continuously. There do not appear to be meaningful clinical differences among the androgenicity of different progestins in combination with estrogen and all of the current preparations suppress gonadotropins and thus ovarian androgen production.⁴³ One newer combined OC containing the progestin drospirenone, a derivative of spiroinolactone (equivalent to about 25 mg of spiroinolactone), has been suggested as the ideal choice for women with PCOS. One study of combined metformin, flutamide and OC therapy for adolescents with PCOS found a decrease in total and abdominal fat when drospirenone was substituted for a third generation progestin in the oral contraceptive agent.⁵⁰

In the majority of adolescents with mildly elevated androgens and a clinical response to therapy with OCs, androgens do not need to be repeated. In those who had high initial levels of testosterone or a poor clinical response, rechecking the total and free testosterone in the second or third week of the cycle can assure adequate suppression and compliance.²¹ In those with incomplete response, changing to continuous OCs for better suppression and/or adding an anti-androgen are often beneficial.

Progestins

Cyclic progestins such as medroxyprogesterone, norethindrone acetate, and prometrium can be used to provide regular menses every one to three months but do not treat the insulin resistance or the androgen excess effectively. Continuous norethindrone can be used for patients who have a contraindication to estrogen and need suppression of androgens.

Anti-androgens

Anti-androgens are used to control hair growth and are often used in combination with OCs. It may take 9 to 18 months to appreciate the effects of anti-androgens to reverse the androgen-induced transformation of vellus to terminal hairs.¹² In the United States, spironolactone is most commonly used. It acts both as an aldosterone antagonist and it has anti-androgenic effects by its action as a competitive androgen receptor antagonist and inhibition of 5 alpha reductase. In a recent Cochrane review, spironolactone 100 mg/day compared with placebo was associated with subjective improvement and decrease in Ferriman-Gallwey scores.⁵¹ Spironolactone is usually given as 50 mg twice daily, although some authors have used 100 mg twice daily (200 mg/day) initially for maximal effect.¹² This drug is typically used in combination with OCs to decrease irregular bleeding and to decrease the risk of exposure to a male fetus if pregnancy occurs. Side effects such as polyuria, polydipsia, dizziness, lethargy, nausea, hyperkalemia, breast pain, and headache are usually transient.²¹ Although not available in the United States, cyproterone acetate is an anti-androgen with potent progestational action and is used in combination with ethinyl estradiol. It inhibits 5 alpha reductase activity in the skin, increases SHBG levels, and has anti-gonadotropin (contraceptive) efficacy. It appears to have similar beneficial effects as other anti-androgenic agents.⁵²

Flutamide is an anti-androgen with efficacy similar to cyproterone acetate and spironolactone although the potential for hepatocellular toxicity and expense have limited its use. Finasteride is a 5 alpha reductase inhibitor that appears to be less effective than spironolactone.⁵¹

Insulin Sensitizing Agents

While a trend toward the use of insulin sensitizing agents has been advocated, because they target the underlying pathophysiologic understanding of insulin resistance in causing the disorder, their use in adolescent women without a diagnosis of type 2 diabetes or documented glucose intolerance or insulin resistance remains understudied. It is not known if insulin sensitizing agents in such women will alter the course of the disease and prevent development of long-term metabolic, cardiovascular, or infertility complications. Treatment with insulin sensitizing agents in adolescent and adult women improves ovulatory dysfunction, hyperandrogenemia, insulin resistance, and possibly hirsutism.⁵³ A recent Cochrane review of studies that directly compared insulin sensitizing drugs to combined OCs to treat polycystic ovary syndrome found that there was limited data yet available (only 104 participants comparing metformin versus OCs and 70 participants comparing metformin plus OC versus OC alone). There were no differences in effect on hirsutism and acne and insufficient evidence or no data on prevention of diabetes, cardiovascular disease, or endometrial cancer. Menstrual pattern and suppression of androgens was more effective with OCs while metformin more effectively reduced fasting insulin and triglycerides.⁵⁴ The thiazolidiones, troglitazone, rosiglitazone, and pioglitazone also improve ovulation and reduce androgens in adult women; however, troglitazone was associated with hepatotoxicity and the newer drugs need further studies in adolescents.¹

Metformin has been studied in several small series of adolescent girls with PCOS⁵⁵ as summarized in Table 3. In general, metformin appears to improve insulin levels, reduce androgens, and lead to more regular menstrual cycles. Many of the studies were short term, Ibanez and colleagues had the longest follow-up at 12 months in their randomized trial of 24 postpubertal adolescents (mean age 12.4) with history of precocious puberty, hyperinsulinemia, and hyperandrogenism treated with 850 mg of metformin. The untreated group all showed increases in the endocrine-metabolic and body composition abnormalities and the treated group showed improvements with normalization of insulin sensitivity, decreased androgen levels, decreased fat mass and abdominal fat mass, and improved lipid profiles. When treatment was discontinued these improvements reversed in this study.³ In another small study, metformin treatment for 6 months in overweight adolescent girls (BMI 25.5–27) found improved menstrual cyclicality, decreased androgen levels, and reduced weight to the normal range with results that persisted 6 months after discontinuation of metformin.⁶²

Table 3. Metformin in Adolescents with PCOS

Reference	Design	Method for Measuring		Age	BMI	Dose (mg/day)	Duration (months)	Insulin Sensitivity	Androgens	Lipids	Menses or Ovulation
		Insulin Sensitivity	n								
Ibanez, 2004 ³	RT	OGTT	24	12.4	21	850	12	Improved	Reduced	Reduced	
Arslanian, 2002 ⁵⁶	O	OGTT	15	14	38	1700	3	Improved	Reduced	Reduced	Improved
Glueck, 2001 ⁵⁷	O	Fasting hyperglycemia	11	16.2	33.6	1500–2550	4.5–26.5	Improved	Not changed	Reduced	Improved
Ibanez, 2001 ⁵⁸	O	OGTT	18	16	21.4	1275	6	Improved	Reduced	Reduced	Improved
Freemark, 2001 ⁵⁹	RT	IGTT	29	12–19	>30	1500	6	Improved	Reduced		
Kay, 2001 ⁶⁰	RT	OGTT	24	15.7	>30	1700	2	Improved	Reduced		
Bridger, 2006 ⁶¹	RT	OGTT	22	16	>30	750 plus lifestyle	3	Improved (NS)	Improved	Improved HDL	Improved
DeLeo, 2006 ⁶²	O	OGTT	18	15–18	25.5–27	1700	6	Improved	Reduced		Improved

Adapted with permission from La Marca A. Metformin treatment of PCOs during adolescence. *European J Obstetrics Gynecol Reprod Biol* 2005; 121:3-7. RT = randomized trial; O = observational; OGTT = Oral glucose tolerance test; HDL = High density lipoprotein

Drawbacks to the use of metformin in adolescence include gastrointestinal side effects and thus compliance problems. It appears that those with documented insulin resistance may have the most benefit from metformin therapy over traditional therapy. These agents are most commonly prescribed to adolescents with impaired glucose tolerance, insulin resistance not responsive to lifestyle modification, family history of type 2 diabetes mellitus, obesity, and acanthosis nigricans. Further research is needed to understand whether early treatment with insulin sensitizing agents will prevent development of long term metabolic and cardiovascular sequelae in adolescents.

Combination Therapies

Several approaches to treatment of PCOS have combined oral contraceptive agents with GnRH antagonists or with anti-androgens and with metformin.⁶³ Use of OCs with anti-androgen spironolactone is discussed above. A recent review of flutamide-metformin therapy for hyperinsulinemic hyperandrogenism in non-obese adolescents and women demonstrates this combination of therapy, with and without the addition of OCs, can normalize the PCOS spectrum more than an oral contraceptive agent alone. Using flutamide-metformin therapy alone may induce ovulation and with concern for postconception embryotoxicity it would be most useful in combination with a contraceptive. The authors conclude that this therapy should not be used in widespread clinical practice until further research has been conducted and risks for hepatotoxicity better understood.⁶⁴

Summary

Polycystic ovary syndrome is a common disorder among adolescent women and its association with risk of long-term metabolic and cardiovascular sequelae is increasingly recognized over and above the cosmetic and fertility concerns. PCOS may be overlooked in early adolescence because during puberty adolescent menstrual cycles are frequently anovulatory, acne and mild hirsutism are common, and the prevalence of obesity and its consequences of insulin resistance and metabolic syndrome are increasing. Research over the past two decades has documented a spectrum of abnormalities within the hypothalamic-pituitary-ovarian axis, excess androgen production within the ovary or adrenal gland, and insulin-resistant hyperinsulinemia seen as an important contributing factor to the dysregulation of steroidogenesis seen in PCOS. No single etiologic factor appears to explain the full spectrum of PCOS. Therapies are increasingly combined to target the variety of symptoms and our increasing understanding of the pathophysiology of

PCOS. Lifestyle modification with weight reduction through diet and exercise is the first and best therapy for women with PCOS. Depending on the patient's symptoms, this approach can be combined with oral contraceptive agents, metformin, and/or antiandrogens to maximize clinical response and improve quality of life. Long term, prospective studies to assess the effects of these interventions on the adverse metabolic and cardiovascular outcomes are needed.

Resource materials for patients may be found at Children's Hospital Boston's Center for Young Women's Health website <http://www.youngwomen-health.org/pcosinfo.html> and the Androgen Excess Society website: <http://www.ae-society.org>.

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