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Adolescent Polycystic Ovary Syndrome

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INTRODUCTION

Once a diagnosis made primarily in fertility clinics, polycystic ovary syndrome (PCOS) was considered to be a condition of the adult female. Now, however, PCOS is recognized as a diagnosis that begins prenatally and manifests itself through early childhood, puberty, and adolescence.[1] Both ovarian and adrenal hyperandrogenism have roles in the signs and symptoms of the syndrome. Ovarian hyperandrogenism can be elucidated by administration of a gonadotropin releasing hormone agonist, with subsequent exaggerated 17-hydroxyprogesterone production with incomplete suppression of testosterone secretion when glucocorticoid-mediated adrenal suppression is performed. Adrenal hyperandrogenism has been documented by 17-hydroxypregnenlone and dehydroepiandrosterone sulfate (DHEAS) surges with adrenocorticopin hormone (ACTH) stimulation.[2,3] How to define PCOS and when the diagnosis of PCOS can be made in adolescence remain topics of controversy; however, associated risk factors can now be recognized in infancy and childhood, and 11–26% of adolescent girls may be affected.[4] Although obesity is commonly associated with adolescent PCOS, some adolescent PCOS patients are lean; both lean and obese PCOS patients, however, may begin to manifest signs of insulin resistance in childhood.[5] As the field of molecular genetics has advanced, our understanding of the heritability of adrenal and ovarian androgen synthesis and insulin metabolism has elucidated the relationship of adolescent PCOS to familial inheritance of type 2 diabetes mellitus and metabolic syndrome. Many questions remain regarding what prenatal or early postnatal interventions might change the pathway leading to adolescent PCOS, and for adolescents with PCOS, many other questions remain regarding appropriate treatment and follow-up.

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Girls and women with PCOS share a commonality of varying degrees and presentations of menstrual irregularity, clinical and/or biochemical hyperandrogenism, ovarian morphology, increased body mass index (BMI), metabolic syndrome, and insulin resistance. Among adolescents referred to one multidisciplinary clinic, 64% had oligomenorrhea or secondary amenorrhea, 63% had a glucose/insulin ratio less than 4.5, 84% were overweight (BMI > 85th percentile), and 70% were obese.[6] Seventy percent of that same group had acne, 60% were hirsute, and 52% had elevated free testosterone. In another study of adolescents with PCOS, 37% were noted to have metabolic syndrome, with hyperandrogenism being an independent risk factor.[7] Yet another study by Hickey in 2009 identified that girls who had BMIs above average were 10-fold more likely to have adolescent PCOS (using National Institutes of Health [NIH] criteria).[8] Adult surveys have found menstrual abnormalities in 80–100% of patients, polycystic ovarian morphology in 70–95% of some series, obesity in 30–60%, and insulin resistance or hyperinsulinism in 50–70%.[9] Menstrual abnormalities increase the risk of endometrial hyperplasia and uterine cancer. Dyslipidemia is seen in up to 70% of adult PCOS patients[10] and often begins with hypertriglyceridemia and low high density lipoprotein (HDL) in both adolescent and adult patients.

IN THE BEGINNING

Both genetics and environment are involved in the development of adolescent PCOS. Among the factors pointing toward genetics are patterns of disease variability that track through families affected by PCOS, the high penetrance of PCOS among sisters of women with PCOS, and the observation of PCOS in daughters of fathers with type 2 diabetes mellitus. In one study of 93 women with PCOS, 40% of sisters were also affected, as were 35% of mothers.[11] Brothers of women with PCOS have been observed to have elevated levels of DHEAS, and a study of men whose sisters had PCOS documented insulin resistance in those men.[12] Many genes are under scrutiny as candidates in the genetic milieu that predisposes a female to PCOS. These can be broadly classified into (1) genes affecting the synthesis and action of steroids; (2) genes affecting gonadotropic action; (3) metabolism genes that regulate weight and energy use; (4) genes that are a part of the pathway of insulin action; and (5) other genes with unknown function.[13-16]

Environmental influences occur both prenatally and postnatally. Among the prenatal associations are the relationship of adolescent PCOS with high birth weight and mothers with gestational diabetes or metabolic syndrome.[17] The development of PCOS after prenatal hyperandrogenism has been described in other primates. Rhesus monkeys exposed in utero to hyperandrogenism develop a PCOS phenotype of hyperinsulinism, hyperandrogenism, oligo-ovulation, and dyslipidemia, particularly if allowed to become overweight.[18] Another relationship that has been demonstrated is that of intrauterine growth retardation (IUGR) with subsequent premature adrenarche and lean adolescent PCOS.[19] In the latter example, the IUGR state would appear to be a result of in utero insulin resistance

because fetal growth is determined by insulin. Interestingly, puberty would seem to be a critical time for intervention if a metabolic syndrome is to be avoided in the IUGR female destined for PCOS. Ibanez has reported the successful use of metformin at puberty to decrease adiposity in key body regions known to have interplay in the development of metabolic syndrome and insulin resistance.[20]

DEFINING ADOLESCENT POLYCYSTIC OVARY SYNDROME

The criteria used to diagnose PCOS have been reviewed and refined through several permutations of consensus groups (Table 1). The 1990 NIH criteria focused on the presence of oligo/anovulation and clinical or biochemical evidence of hyperandrogenism to establish a diagnosis.[21] The 2003 Rotterdam criteria, developed jointly by the European Society for Human Reproduction and Embryology with the American Society for Reproductive Medicine, defined PCOS as being present if 2 of 3 criteria were present: clinical or biochemical hyperandrogenism, oligo/anovulation, and/or radiographic evidence of polycystic ovaries. The Rotterdam criteria introduced some heterogeneity into the population of PCOS patients, as it was now possible to have the diagnosis without having any hyperandrogenism.[22] Considerable disagreement exists in the medical community regarding whether this heterogeneity is helpful in following the evolution of PCOS in some patients or simply muddies the waters in trying to evaluate the efficacy of therapies in patients identified as having PCOS. Certainly, the Rotterdam criteria may actually identify several genetically distinct groups, including some with fewer tendencies toward metabolic syndrome and insulin resistance. Androgen Excess-PCOS (AE-PCOS) Society criteria attempted in 2009 to define PCOS with more attention to hyperandrogenism by defining PCOS as hyperandrogenism plus either oligo/anovulation or radiographic evidence of polycystic ovaries.[23,24] A polycystic ovary was defined in both the Rotterdam criteria and the AE-PCOS criteria as one which contains at least 12 or more follicles (2–9 mm) in a peripheral pattern, or an ovary with a volume greater than 10 mL[22] (Figure 1).

The use of any of the previously described criteria is difficult in the evaluation of a young adolescent patient. Puberty is known to be a state of physiologic insulin

Table 1. Comparison of Diagnostic Criteria for Polycystic Ovary Syndrome

Criteria	Hyperandrogenism	Anovulation	Polycystic ovaries	Lack of other diagnoses
NIH Criteria	Required	Required	Not required	+
Rotterdam Criteria (2 of first 3 required)	+/−	+/−	+/−	+
AE-PCOS Society Criteria (1st and either 2nd or 3rd findings required)	Required	+/−	+/−	+

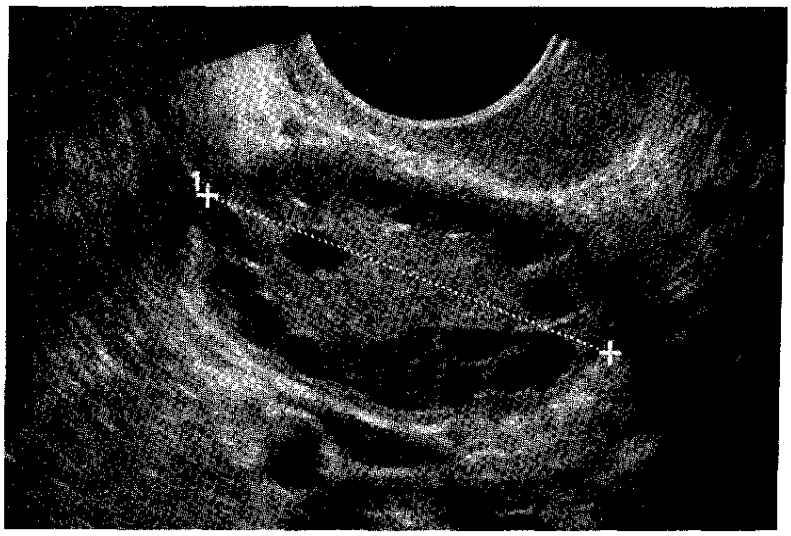

Figure 1. Ultrasonography of Polycystic Ovary with "String of Pearls" Appearance of Follicles

resistance, and insulin is known to have roles in ovarian and adrenal metabolism, as well as hepatic sex hormone binding globulin (SHBG) production. Specifically, insulin decreases hepatic SHBG production, leading to increased free testosterone in the serum. Oligo-ovulation with subsequent menstrual irregularity is a common finding in the first 18 months following menarche. Furthermore, recent studies have found considerable overlap between polycystic ovaries and normal ovaries in both adolescents and adults. Chinese adolescents who had PCOS were found to have a mean ovarian volume of 6.7 mL, rather than the 10 mL traditionally used in the definition of polycystic ovarian volume in adult women.[25] Further complicating the evaluation of PCOS in puberty is the fact that ovarian volume continues to increase for 2–3 years following menarche, and although measurements are more accurate with transvaginal rather than transabdominal ovarian ultrasound, most sonographic data obtained on adolescents are transabdominal. Hyperandrogenism diagnosed clinically by acne may actually reflect increased free androgen production in puberty rather than a pathologic state. With these unique aspects of adolescence in mind, Carmina et al has recommended that adolescent PCOS be defined much more stringently, requiring all components of the Rotterdam criteria for absolute diagnosis, waiting at least 2 years postmenarche to evaluate for the diagnosis, and considering girls with hyperandrogenism and oligomenorrhea as having "probable but unconfirmed PCOS."[26] The advantage of these criteria is prevention of inclusion of girls who do not have PCOS from temporarily having a stigmatizing or pessimistic diagnosis that is ultimately disproved after a transient period of irregular menses or androgen excess. The disadvantage of the use of Carmina's criteria could be a delay in definitive treatment of girls who have hirsutism or oligomenorrhea due to PCOS but do not yet have polycystic ovaries and delayed evaluation of these

girls for the insulin resistance of PCOS, known to be a significant risk factor for metabolic system and cardiovascular disease.

The diagnosis of PCOS at any age must be made only after absolute exclusion of the diagnoses of Cushing syndrome, hypothyroidism, prolactinoma, an androgen-secreting tumor, congenital adrenal hyperplasia, and exogenous androgen exposure. In adolescent girls, the diagnosis of Cushing syndrome is best excluded by obtaining 11 PM salivary cortisol measurements, as the normal diurnal variation of cortisol results in extremely low late night salivary cortisol levels in patients without Cushing syndrome. Urinary free cortisol measurements are second best, but are difficult to obtain in adolescent girls who find the collections cumbersome, unpleasant, and intrusive. Thyroid abnormalities should be ruled out with a third generation thyroid-stimulating hormone (TSH) assay, and serum prolactin rules out hyperprolactinemia. Some patients with PCOS will have prolactin levels in the 20s or 30s but not in the greater than 100 ng/mL range typical of a pituitary tumor. Total testosterone levels greater than 200 ng/dL may indicate an androgen-secreting tumor, but the variability of both total and free testosterone assays in women and children requires consideration in interpretation.[27] Testosterone secreting tumors do not always lead to clitoromegaly, so the assay should always be obtained regardless of physical findings. Congenital adrenal hyperplasia screening should be carried out by assessing 17 OH progesterone, DHEAS, and androstenedione between 8 AM and 9 AM, taking advantage of the ACTH secretion peak. Elevated follicle stimulating hormone (FSH) levels should alert the clinician to the differential diagnosis of premature ovarian failure. Lastly, pregnancy should always be considered as a cause of amenorrhea, even in an adolescent with acne or hirsutism.

Some laboratory measurements are suggestive but not absolutely diagnostic of PCOS. An LH/FSH ratio greater than 2 suggests PCOS, as the luteinizing hormone (LH) increases in response to both hyperinsulinemia and hyperandrogenism, as well as to elevated estrogen. However, a woman may meet diagnostic criteria for PCOS without having such a ratio. Similarly, low sex hormone binding globulin production by the liver may be seen as a result of hyperinsulinism. Low sex hormone binding globulin can produce an elevated free testosterone level. Some patients with PCOS, however, exhibit signs consistent with hyperandrogenism without having biochemical hyperandrogenism, probably as a result of receptor responsiveness. Thus, the laboratory evaluation is essential for excluding other diagnoses but not necessarily diagnostic of PCOS.

If an adolescent is diagnosed with PCOS by Rotterdam criteria, AE-PCOS criteria, or the more stringent criteria proposed by Carmina et al, subsequent laboratory studies should include assessment of metabolic syndrome risk factors, including hyperinsulinism/insulin resistance, glucose tolerance, and hyperlipidemia. Fasting glucose values are of less value in assessing the stage of glucose tolerance than are values of an oral glucose tolerance test, carried out with ingestion of 75 g of a glu-

cose drink after a 12 hour fast; impaired glucose tolerance as evidenced by a 2 hour glucose greater than 140 mg/dL is present before impaired fasting glucose. Obtaining an insulin value with the fasting glucose allows calculation of the glucose/insulin ratio, another surrogate marker of insulin resistance. Although some studies have used a glucose/insulin ratio less than 7 in nondiabetic subjects as indicative of insulin resistance, such a cutoff will include some normal adolescents with physiologic resistance of puberty; therefore, a cutoff of less than 4.5 in a nondiabetic subject is preferable.[28,29] The fasting lipid profile of an insulin resistant patient with PCOS may reveal an elevated triglyceride level and low high density lipoprotein (HDL), with relatively mild increases in total or low density lipoprotein (LDL) cholesterol, reflecting the initial changes due to insulin resistance.

THERAPEUTIC CONSIDERATIONS

The approach to the adolescent with PCOS must address each of the following concerns[30]:

1. Menstrual dysfunction, risk of endometrial cancer, and future fertility
2. Hyperandrogenism, including acne, hirsutism, and alopecia
3. Metabolic syndrome risks
4. Psychological concerns impeding or influencing the patient's perception of therapy, quality of life, and likelihood of success with recommended treatments
5. Risk of other comorbidities

Menstrual Dysfunction and Future Fertility

Adolescent PCOS may present with secondary amenorrhea, menorrhagia, metrorrhagia, or menometrorrhagia. Excessive bleeding may result in missed schooldays and extracurricular activities, anemia, or even a need for transfusion. Primary amenorrhea has been described as a historical feature in some women eventually diagnosed with PCOS. Dysmenorrhea and oligomenorrhea (fewer than 6 menstrual cycles per year) are common findings in adolescent PCOS. In the patient with excessive bleeding, a careful family history of bleeding diatheses should be sought, and evaluation for clotting deficiencies considered. Patients with amenorrhea, oligomenorrhea, and menorrhagia may benefit from menstrual regulation with a combined estrogen and progesterone tablet in the form of an oral contraceptive pill (OCP), unless the patient has a personal or family history of clotting disorders. Individual OCP selection should begin with a low to moderate estrogen component (usually 20–35 mcg estradiol) and less androgenic progesterone. Dysmenorrhea may also respond well to these therapeutic choices, and the more favorable progesterone component OCPs can be useful in the management of hirsutism and acne. Some patients may opt for the vaginal contraceptive ring, particularly those who have difficulty remembering to take daily oral medications. Patients with oligomenorrhea who have a clotting disorder history

in themselves or in their families can regulate menses with progesterone-only therapies, including monthly, bimonthly, or trimonthly use of 5–10 days of medroxyprogesterone 10 mg, norethindrone 5 mg, or prometrium 200 mg. Some girls may opt for protection from endometrial cancer risk with the levonorgestrel intrauterine system (IUS); this option may be particularly favorable to those who are sexually active. Girls choosing to use an IUS should be advised of the frequent development of secondary amenorrhea with this method. Advantages of the use of OCP therapy in those patients without contraindications include improvements in both the menstrual and hyperandrogenism symptoms. A combined OCP decreases pituitary LH production, which subsequently decreases ovarian theca cell stimulation and ovarian hyperandrogenism.

Some controversy has arisen regarding newer contraceptives containing the fourth generation progestin drospirenone. These OCPs have seen a sharp rise in prescriptions filled due to the popularity both of the low dose estrogenic component and of the androgen receptor blockade action, similar to about 25 mg of spironolactone. Some increase in serum potassium is possible, but more concern has been expressed about a possible increase in the incidence of thromboembolic events in users of pills containing drospirenone as opposed to levonorgestrel.[31] A recent *British Medical Journal* editorial made the observation that, although the studies have been small, have not been prospective controlled studies, and have not controlled for obesity and the inclusion of new contraceptive users, no study has demonstrated a lower incidence of thromboembolism with drospirenone than levonorgestrel.[32] The use of an OCP that does not contain drospirenone would seem advisable in girls with PCOS presenting for institution of OCP therapy.

Care should be taken when prescribing OCPs to the adolescent with PCOS to discuss the risk of thromboembolic events with OCP use, and OCPs should not be prescribed if there is a known history of clots in the patient and should be used with caution if the history is in family members. Girls should also be counseled that the risk of thromboembolic events increases with obesity, a sedentary lifestyle, and cigarette use.

Patients and parents often have numerous questions about future fertility. Girls must be counseled that a diagnosis of PCOS is not a guarantee of protection from pregnancy if they have unprotected sex. At the same time, if a young woman does have difficulty conceiving when pregnancy is desired, numerous methods of improving the likelihood of conception do exist. Patients with a diagnosis of PCOS should also be counseled that having a healthy BMI improves the likelihood of achieving a successful pregnancy.

Hyperandrogenism

Hyperandrogenism can manifest differently in each girl with PCOS, even in the same family. A history of early, severe, scarring acne may be described in some

patients. Thus, dermatologists considering isotretinoin use in adolescent girls should screen clinically and biochemically for PCOS. Other girls may have little or no acne but may have hirsutism beginning in the peripubertal or postpubertal periods. Hirsutism must be distinguished from hypertrichosis, which is fine, vellus hair in nonandrogen-dependent regions. By contrast, hirsutism is androgen dependent and is characterized by terminal hairs, often described as being "central" in location: The face, chin, center of the breasts, periareolar area, lower abdomen, central thighs, and lower back areas are often involved. The Ferriman-Gallwey score (FGS) is often utilized in studies assessing hirsutism, although interpretation should consider ethnicity and the fact that many of the regions considered are areas of potential hypertrichosis.[33] Eight or higher on the FGS is considered hirsute in Caucasians, yet some ethnic groups with less body hair may be hirsute with a lower score, and some ethnicities known for hypertrichosis should have their FGS interpreted cautiously.

Antiandrogen therapy for acne and hirsutism may begin with OCPs that have low androgenic potential. A gradual decrease in new hair growth and acne can be seen in some patients with OCPs alone over the first year of therapy. Hair that is already present must be removed by conventional methods. For patients not responding to OCPs alone, and those in whom OCPs are not an option, spironolactone can be used as an effective antiandrogen that blocks the androgen receptors. An initial dose of 50 mg twice daily may gradually be increased to 100 mg twice daily as needed. Use of the drug requires attention to hydration status, avoidance of dehydration, and avoidance of high potassium containing foods. Serum potassium should be checked at least annually. Spironolactone's effect may not be fully seen for 6 months. Girls must be counseled regarding the teratogenicity of spironolactone. (As an antiandrogen, spironolactone causes ambiguity of the genitalia of male infants.) Therefore, contraception must be used at all times by a patient taking spironolactone, and spironolactone must be discontinued before conception if pregnancy is planned or immediately if an unplanned pregnancy occurs.

During the initial period of use of spironolactone, other acne treatments and methods of hair removal should be continued. One topical treatment for hirsutism is eflornithine, which blocks the enzyme ornithine decarboxylase in hair follicles; it must be applied twice daily and is generally not covered by medical insurance policies.[34]

Successful treatment for hirsutism stops or significantly slows terminal hair production. Treatment does not change hypertrichosis, which has a familial inheritance and is more noticeable in girls with dark hair. Furthermore, treatment does not remove hair already present. Terminal hairs can be removed by waxing, shaving, sugaring, depilatory use, laser treatments, electrolysis, or threading. If laser therapy is chosen, a girl should have a test treatment in a small area of hair not readily visible to be certain skin color changes do not occur.

Metabolic Syndrome

PCOS is associated with an increased incidence of metabolic syndrome, and metabolic syndrome significantly increases a woman's risk for future cardiovascular disease through increased insulin resistance, glucose intolerance/diabetes mellitus, hypertension, and dyslipidemia. Independent from BMI, adiponectin levels are lower in adolescent girls with PCOS than in age-matched controls.[35] Adiponectin is well-recognized as an "anti-inflammatory marker" in adolescents and adults, and low adiponectin levels are predictive of metabolic syndrome risk.

The diagnosis of PCOS mandates an evaluation of BMI, resting blood pressure, a fasting lipid panel, HgbA1c, glucose tolerance, and the glucose/insulin ratio. For adolescent girls, blood pressure and BMI should be assessed using sex and age-related normative data. A BMI percentile greater than or equal to the 85th percentile (overweight) or greater than or equal to the 95th percentile (obese) requires immediate lifestyle interventions; these should include recommendations for 150 minutes per week of aerobic activity and dietary modifications. Dietary modifications include elimination of juice, regular soda, and high carbohydrate energy drinks; use of skim milk; avoidance of intake of large amounts of high fructose corn syrup; and the implementation of a meal plan in which roughly 50% of the solid meal consists of fruits and vegetables with the remaining 50% composed of equal amounts of protein and whole grain carbohydrates.

Specific weight loss goals should be discussed specifically with each adolescent with PCOS, as even a modest weight loss of 5–10% can be associated with significant improvements in multiple components of PCOS, including ovulatory function, menstrual patterns, lipid profiles, testosterone levels, and insulin sensitivity.[36,37] Weight loss of 6.5% in one study was associated with improvement of menstrual function in an adolescent cohort, with those who achieved weight loss being 3.4 times more likely to have improved menstrual function than those who did not.[38]

Metformin has been frequently prescribed in an off-label use for PCOS among adult women and adolescents to address the role of insulin resistance in the syndrome and to attempt to decrease the risk of metabolic syndrome and the development of further abnormalities in glucose metabolism. Studies in adolescents with PCOS have documented safety and some variable efficacy in improving menstruation, reducing hyperandrogenism, and improving insulin sensitivity at metformin doses of 1500 to 2000 mg per day.[39]

The most common side effects of metformin are gastrointestinal in the form of loose stools, flatulence, loss of appetite, and/or abdominal pain; these can be minimized by beginning therapy with a single 500 mg daily dose with food, which is increased over 2–4 weeks to doses of 500–1000 mg twice daily. Some patients tolerate the extended release form of the tablet better than the conven-

tional form. All patients should be advised to avoid taking metformin if consuming alcoholic beverages and to omit metformin therapy if receiving radiologic contrast or if there is vomiting. To date, although the risk of lactic acidosis was considered a concern when metformin first entered the market, it has been an extremely rare event. Patients receiving metformin should have annual laboratory studies for serum creatinine and B12 levels. Liver enzymes should be evaluated before initiation of therapy and then every 4–6 months thereafter.

Psychological Concerns

The physical stigma of disfiguring acne or worsening hirsutism can be associated with significant social distress for adolescents and can result in school phobia or avoidance. Obesity and acanthosis nigricans pose similar problems, and some girls are reluctant to exercise in public for fear of taunting. Worries about future fertility can be significant for older adolescent girls and for the parents of girls with PCOS. PCOS and obesity often affect many family members, and families may approach diagnostic evaluation and prescribed therapies with some trepidation, shame, or guilt. Furthermore, depression, anxiety, and other psychiatric diagnoses including attention deficit disorder (ADD) may complicate a girl's adherence to or her family's support of recommended therapies. Recognition of all of these psychological concerns and provision of referrals to appropriate psychological or psychiatric services can improve outcomes for adolescent girls with PCOS.

Goals of therapy should be discussed at the initial visit with each girl. In having such discussions, the practitioner may learn that the goals and desires of the adolescent are very different than that of the practitioner or the parents. For example, the pediatrician may want to address hypertriglyceridemia, the risks associated with long-standing secondary amenorrhea, and the long-term risk of metabolic syndrome with dietary modification, an exercise prescription, and a trial of oral medroxyprogesterone or an OCP, whereas the 16-year-old's goals might involve rapid weight loss before the prom and elimination of mild hirsutism (which she views as disfiguring) but avoidance of any menses.[40] Validation of the patient's and parent's concerns, education regarding PCOS and metabolic syndrome, and use of motivational interviewing to identify and set realistic goals can be a turning point in improving the adolescent girl's health.

Other Associated Comorbidities

A number of comorbidities may accompany PCOS in an obese adolescent and worsen insulin resistance and the risk for metabolic syndrome and subsequent cardiovascular complications.[41] Among these comorbidities are obstructive sleep apnea, steatohepatitis, renal insufficiency, and orthopedic complications.

Obstructive sleep apnea (OSA) is seen in a significant number of girls with PCOS. Neuroendocrine responses to hypoxia and hypercapnia from OSA may

worsen insulin resistance, hypertension, and hyperinsulinism,[42] and OSA is a risk factor for type 2 diabetes mellitus. Treatment of OSA has been associated with improvements in insulin sensitivity, norepinephrine release, and diastolic blood pressure in young obese women with PCOS.[42,43,44]

Nonalcoholic fatty liver disease (NAFLD), or steatohepatitis, is common in PCOS and is a marker of insulin resistance and inflammation in girls and women with PCOS.[45,46] NAFLD-induced cirrhosis is expected to become the leading diagnosis in patients awaiting hepatic transplantation. Current gold standard methods of detecting NAFLD are quantitative liver enzyme measurements and hepatic biopsy, both of which can miss the heterogeneous early stages of the disease. Better accuracy is possible with quick hepatic MRI techniques that measure total hepatic triglyceride content.[47,48] Diagnosing NAFLD sooner may prevent the progression of NAFLD to a need for hepatic transplantation.

Renal insufficiency can occur with obesity[49] and is a significant problem for the adolescent with PCOS, particularly because of the use of medications for the components of PCOS. Many of these medications require renal clearance or affect volume delivery to the kidney. Metformin, which may be desirable for type 2 diabetes or insulin resistance, cannot be used in adolescents with renal insufficiency. The presence of hirsutism may require the use of spironolactone, which would not be acceptable in the patient with renal insufficiency. Hypertension accompanying the metabolic syndrome in an adolescent patient with PCOS is often treated with angiotensin converting enzyme (ACE) inhibitor therapy; again, this would not be recommended for the patient with renal insufficiency. Thus, careful monitoring of serum creatinine, as well as urine protein to creatinine ratios, would seem prudent in the obese adolescent with PCOS.

CONCLUSIONS

The management of the adolescent with PCOS must address multiple health care issues, both short-term and long-term. The practitioner must navigate the current social climate of health care coverage to advocate for the services the adolescent with PCOS needs. Judicious use of a multidisciplinary team or "medical PCOS home" to address the menstrual dysfunction, hyperandrogenism, long-term psychological concerns, metabolic syndrome, insulin resistance, and other comorbidities of adolescent PCOS is indicated. Such a team may include a primary care provider, pediatric gynecologist, dietician, psychologist, social worker, pediatric endocrinologist, radiologist, and/or dermatologist in meeting the needs of the girl with PCOS. Addressing insulin sensitivity and dyslipidemia without improving hirsutism and its perceived stigma does not achieve the quality of life the adolescent is seeking. Regulating menses without achieving weight loss in the girl with a BMI above the 99th percentile does not prevent metabolic syndrome sequelae. Addressing adolescent PCOS and its comorbidities requires a multitasking approach by the clinician, the patient, and the parents.

References

1. Rosenfield R. Clinical review: identifying children at risk for polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2007;92:787–796
2. Ehrmann DA, Barnes RB, Rosenfield RL. Polycystic ovary syndrome as a form of functional ovarian hyperandrogenism due to dysregulation of androgen secretion. *Endocr Rev.* 1995;16:322–353
3. Rosenfield RL. Ovarian and adrenal function in polycystic ovary syndrome. *Endocrinol Metab Clin North Am.* 1999;28:265–293
4. Driscoll DA. Polycystic ovary syndrome in adolescence. *Ann NY Acad Sci.* 2003;997:49–55
5. Lewy VD, Danadian K, Witchel SF, et al. Early metabolic abnormalities in adolescent girls with polycystic ovary syndrome. *J Pediatr.* 2001;138:38
6. Bekx MT, Connor EL, Allen DB. Characteristics of adolescents presenting to a multidisciplinary clinic for polycystic ovarian syndrome. *J Pediatr Adolesc Gynecol.* 2010;23:7–10
7. Coviello AD, Legro RS, Dunaif A. Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels independent of obesity and insulin resistance. *J Clin Endocrinol Metab.* 2006;91:492–497
8. Hickey M, Sloboda DM, Atkinson HC, et al. The relationship between maternal and umbilical cord androgen levels and ovarian function in adolescence: a prospective cohort study. *J Clin Endocrinol Metab.* 2009;94:3714–3720
9. Goodarzi MO, Azziz R. Diagnosis, epidemiology, and genetics of the polycystic ovary syndrome. *Best Pract Res Clin Endocrinol Metab.* 2006;20(2):193–205
10. Diamanti-Kandarakis E, Papavassiliou AT, Kandarakis SA, et al. Pathophysiology and types of dyslipidemia in PCOS. *Trends Endocrinol Metab.* 2007;18:280
11. Azziz R, Kashar-Miller MD. Family history as a risk factor for the polycystic ovary syndrome. *J Pediatr Endocrinol Metab.* 2000;13(Suppl 5):1303–1306
12. Yildiz BO, Yarali H, Oguz H, Bayraktar M. Glucose intolerance, insulin resistance, and hyperandrogenemia in first degree relatives of women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2003;88:2031–2036
13. Escobar-Morreale HF, Luque-Ramirez M, San Millan JL. The molecular genetic basis of functional hyperandrogenism and the polycystic ovary syndrome. *Endocr Rev.* 2005;26:251–282
14. Rosenratz MA, Coffler MS, Haggan A, et al. Clinical evidence for predominance of delta-5 steroid production in women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2011;96:1106–1113
15. Urbanek M, Sam S, Legro RS, Dunaif A. Identification of a polycystic ovary syndrome susceptibility variant in fibrillin-3 and association with a metabolic phenotype. *J Clin Endocrinol Metab.* 2007;92:4191–4198
16. Ewens KG, Stewart DR, Ankener W, et al. Family-based analysis of candidate genes for polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2010;95:2306–2315
17. Leibel NI, Baumann EE, Kocherginsky M, Rosenfield RL. Relationship of adolescent polycystic ovary syndrome to parental metabolic syndrome. *J Clin Endocrinol Metab.* 2006;91:1275–1283
18. Abbott DH, Tarantal AF, Dumesic DA. Fetal, infant, adolescent, and adult phenotypes of polycystic ovary syndrome in prenatally androgenized female rhesus monkeys. *Am J Primatol.* 2009;71:776–784
19. Ibanez L, Potau N, Francois I, de Zegher F. Precocious pubarche, hyperinsulinism, and ovarian hyperandrogenism in girls: relation to reduced fetal growth. *J Clin Endocrinol Metab.* 1998;83:3558–3662
20. Ibanez L, Valls C, Potau N, Marcos MV, de Zegher F. Sensitization to insulin in adolescent girls to normalize hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism after precocious pubarche. *J Clin Endocrinol Metab.* 2000;85(10):3526–3530
21. Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: toward a rational approach. In: Dunaif A, Givens JR, Haseltine FP, Merriam GR, eds. *Polycystic Ovary Syndrome.* Boston, MA: Blackwell Science Publications; 1992:377–384
22. The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and longterm health risks related to polycystic ovary syndrome (PCOS). *Human Reprod.* 2004;19:41–47

23. Azziz R, Carmina E, Dewailly D, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab.* 2006;91:4237–4245
24. Azziz R, Carmina E, Dewailly D, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertil Steril.* 2009;91(2):456–488
25. Chen Y, Yang D, Li L, Chen X. The role of ovarian volume as a diagnostic criterion for Chinese adolescents with polycystic ovary syndrome. *J Pediatr Adolesc Gynecol.* 2008;21(6):347–350
26. Carmina E. The diagnosis of polycystic ovary syndrome in adolescents. *Am J Obstet Gynecol.* 2010;203(3):201.e1-5
27. Vieira JG. The importance of methodology in serum testosterone measurement: comparison between a direct immunoassay and a method based on a high performance liquid chromatography and tandem mass spectroscopy. *Arq Brs Endocrinol Metab.* 2008;52(6):1050–1055
28. Legro RS, Finegood D, Dunaif A. A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 1998;83:2694–2698
29. Vuguin P, Saenger P, diMartino-Nardi J. Fasting glucose insulin ratio: a useful measure of insulin resistance in girls with premature adrenarche. *J Clin Endocrinol Metab.* 2001;86:4618–4621
30. Berlan ED, Emans SJ. Managing polycystic ovarian syndrome in adolescent patients. *J Pediatr Adolesc Gynecol.* 2009;22:137–140
31. Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested, case-control study based on UK General Practice Research Database. *Br Med J.* 2011;342:d2139
32. Dunn N. The risk of deep venous thrombosis with oral contraceptives containing drospirenone. *BMJ.* 2011;342:d2519
33. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab.* 1961;21:1440
34. Malhotra B, Noveck R, Behr D, Palmisano M. Percutaneous absorption and pharmacokinetics of Eflornithine Hcl 13.9% cream in women with unwanted facial hair. *J Clin Pharmacol.* 2001;41:972–978
35. Yasar L, Ekin M, Gedikbasi A, Erturk AD, Savan K, Ozdemir A, Temur M. Serum adiponectin levels in high school girls with polycystic ovary syndrome and hyperandrogenism. *J Pediatr Adolesc Gynecol.* 2011;24:85–89
36. Hoeger KM. Role of lifestyle modification in the management of polycystic ovary syndrome. *Best Pract Res Clin Endocrinol Metab.* 2006;20:293
37. Wabitsch M, Hauner H, Heinze E, et al. Body fat distribution and steroid hormone concentrations in obese adolescent girls before and after weight reduction. *J Clin Endocrinol Metab.* 1995;80:3469
38. Ornstein RM, Copperman NM, Jacobson MS. Effect of weight loss on menstrual function in adolescents with polycystic ovary syndrome. *J Pediatr Adolesc Gynecol.* 2011;24:161–165
39. Allen HF. Randomized controlled trial evaluating response to metformin versus standard therapy in the treatment of adolescents with polycystic ovary syndrome. *J Pediatr Endocrinol Metab.* 2005;18(8):761–768
40. Trent ME, Rich M, Austin SB, et al. Quality of life in adolescent girls with polycystic ovary syndrome. *Arch Pediatr Adolesc Med.* 2002;156:556
41. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *J Am Coll Cardiol.* 2008;52:686–717
42. Tasali E, Ip MS. Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. *Proc Am Thorac Soc.* 2008;5:207–217
43. Fogel RB, Malhotra A, Pillar G, Pittman SD, Dunaif A, White DP. Increased prevalence of obstructive sleep apnea in obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2001;86:1175–1180

44. Tasali E, Chapotot F, Leproult R, Whitmore H, Ehrmann DA. Treatment of obstructive sleep apnea improves cardiometabolic function in young obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2011;96(2):365–374
45. Ma RCW, Liu KH, Lam PM et al. Sonographic measurement of mesenteric fat predicts presence of fatty liver among subjects with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2011;96(3):799–807
46. Setji TL, Holland ND, Sanders LL, et al. Nonalcoholic steatohepatitis and nonalcoholic fatty liver disease in young women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2006;91:1741
47. Reeder SB, Robson PM, Yu H, et al. Quantification of hepatic steatosis with MRI: the effects of accurate fat spectral modeling. *Mag Reson Imaging.* 2009;29(6):1332–1339
48. Rehm JL, Connor EL, Reeder SB. Nonalcoholic fatty liver disease in an adolescent with polycystic ovarian syndrome. *J Pediatr Adolesc Gynecol.* 2011;24(2):e61 [Abstract]
49. Reisen E. Obesity and hypertension: mechanisms, cardio-renal consequences, and therapeutic approaches. *Med Clin North Am.* 2009;93(3):733–751