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Interventional studies for polycystic ovarian syndrome in children and adolescents

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Abstract

Polycystic ovarian syndrome (PCOS) is characterized by chronic anovulation, clinical and/or biochemical hyperandrogenism, which can be associated with altered insulin action. Symptoms usually begin around menarche, but onset after puberty may also occur as a result of environmental modifiers such as weight gain. The consequences of PCOS extend beyond the reproductive axis; there is a substantial risk for development of metabolic and cardiovascular abnormalities similar to the metabolic syndrome. Currently, the treatment is targeted to the patient's primary complaint such as hirsutism, restoration of regular menses or pregnancy. Pharmacological agents available for the treatment of hirsutism include androgen suppressors and peripheral androgen blockers. Recently, our understanding of the role of insulin resistance has led to the use of insulin-sensitizing medications as first-choice therapy. In conjunction with weight reduction and exercise, a pharmacologic reduction in insulin levels by either metformin or thiazolidinediones ameliorates both hyperinsulinemia and hyperandrogenism.

Keywords

adolescent; hirsutism; hyperandrogenism; infertility; irregular period; metabolic syndrome; ovarian dysfunction; polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) is a syndrome of ovarian dysfunction [1–3]. It is one of the most common endocrinopathies in reproductive-age women with an estimated prevalence of 4–12% [4]. Having PCOS implies an increased risk of infertility, dysfunctional bleeding, endometrial carcinoma, obesity, Type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, and possibly cardiovascular disease [5]. Over the years, the definition has remained a point of controversy [5]. Initially, the diagnosis was based on the 1990 NIH/NICHD consensus that stated that you need three out of three features to be diagnosed with PCOS.

NIH 1990 criteria (three out of three) [6]:

- Signs of androgen excess (clinical or biochemical);

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- Oligoovulation;
- All other entities are excluded that would cause polycystic ovaries.

Since then it has become apparent that women with regular cycles and hyperandrogenism, and/or PCOS morphology on ovarian ultrasound may be part of the syndrome, or will display ovarian dysfunction without clinical evidence of androgen excess [7,8]. Recognizing that the diagnosis may be broader than these two features, the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine jointly sponsored a PCOS consensus workshop in 2003, which essentially created the revised 2003 consensus on diagnostic criteria, better known as the Rotterdam criteria.

Revised 2003 criteria (two out of three) [1,5]:

- Oligo- and/or anovulation;
- Clinical and/or biochemical androgen excess (hyperandrogenism);
- Polycystic ovaries;
- Exclusion of other etiologies (congenital adrenal hyperplasias, androgen-secreting tumors and Cushing's syndrome).

In 2005, the Androgen Excess Society (AES) commissioned a seven-member task force to look into the controversy surrounding PCOS [9]. They published a highly recommended paper that defines PCOS based on a review of published evidence. A principal conclusion was that PCOS should be first considered a disorder of androgen excess:

- Hyperandrogenism (HA): hirsutism and/or hyperandrogenemia;
- Ovarian dysfunction: oligo–anovulation and/or polycystic ovaries;
- Exclusion of other androgen excess or related disorders.

In Table 1, presence (+) or absence (−) of different features will determine the potential phenotypes (√) that would establish the diagnosis.

Definition of polycystic ovarian syndrome in adolescents

During adolescence, some features that define PCOS in women may overlap with normal puberty [10–13]. Anovulatory, and or irregular periods may occur following menarche, and clinical evidence suggesting androgen excess (e.g., acne) is common during pubertal development.

It has been proposed that at least four of the following five criteria are needed to define adolescent PCOS [14]:

- Oligomenorrhea or amenorrhea, 2 years after menarche;
- Clinical hyperandrogenism: persistent acne or severe hirsutism;
- Biologic hyperandrogenism: elevated plasma testosterone or increased LH:FSH ratio;
- Insulin resistance/hyperinsulinemia: acanthosis nigricans, abdominal obesity or glucose intolerance;
- Polycystic ovaries on ultrasound: enlarged ovaries, peripheral microcysts or increased stroma.

Polycystic ovarian syndrome in adolescents should be considered if persistence of ovulatory dysfunction extends beyond 2 years, and if either onset or augmentation of HA occurs at the

time of menarche. Other factors that may increase the risk of PCOS in adolescents include obesity, medical history of intrauterine growth retardation, premature adrenarche, and a family history of T2DM or PCOS [1,3,10,15–23]. It has been proposed that a significant proportion of the daughters of a PCOS woman may be at risk for developing PCOS [24]. Daughters of a PCOS woman exhibit hyperinsulinemia and an increased ovarian volume before the onset of puberty, followed by hyperandrogenia at the end of the pubertal development [25]. Thus, identifying girls at risk for PCOS may offer the potential of eventually preventing some of the long-term complications associated with this syndrome.

Pathogenesis

The precise cause of PCOS is unknown; however, it is considered to be a complex multi-genetic disorder characterized by disordered gonadotropin release and dysregulation of steroidogenesis [26]. Hyperinsulinism has also been shown to play a role in the pathogenesis of PCOS and its metabolic component [3].

Abnormal pituitary function

Under normal circumstances, the hypothalamic gonadotropin-releasing hormone (GnRH) pulses cause luteneizing hormone (LH) and follicle-stimulating hormone (FSH) release. LH stimulates ovarian theca cells to produce androgens (mainly androstenedione) and FSH stimulates granulosa cells to convert the androstenedione to estrone and estradiol [27]. Estrogen and progesterone provide negative feedback to GnRH-secreting neurons as well as the pituitary. Adolescents with PCOS have increased LH levels above average follicular phase levels as well as increased pulse secretion [28,29]. This pattern is exaggerated in adolescents with increased adiposity [30]. Higher LH levels increase thecal production of androgens, which in turn will counteract the LH-suppressive role of female hormones as well as regulation of GnRH neurons by progesterone [31–34].

Abnormal steroidogenesis

High levels of androstenedione and testosterone can also be attributed to intraovarian androgen excess, which arises from functional ovarian hyperandrogenism (FOH) [8,35]. In polycystic ovaries, the ovarian theca cells, the site of *de novo* androgen biosynthesis, are increased in number and have an increased steroidogenic capacity. FOH is caused by increased LH levels, as well as in some women, elevated insulin concentrations secondary to insulin resistance. Insulin has a direct synergistic effect with LH on theca cells further enhancing androgen production [36,37]. The granulosa cells in arrested follicles fail to increase the expression of aromatase, causing markedly decreased estrogen secretion. In contrast, an increase in 5α-reductase enzyme concentration in granulose cells leads to the production of 5α-androstane-3,17-dione, a competitive inhibitor of aromatase activity further increasing androgen levels. The granulosa cells are also over-responsive to LH and produce increased amounts of progesterone [38]. Excess androgen production (dehydroepiandrosterone sulfate [DHEAS]) in PCOS can also be attributed to a primary functional defect of adrenal steroidogenesis (functional adrenal hyperandrogenism [FAH]) [39,40]. Increased androgen production by the ovaries and or the adrenals decreases the liver production of sex hormone-binding globulin (SHBG), the major circulating protein that binds testosterone, thus increasing free circulating testosterone levels (biologically active). A further decrease in the hepatic production of SHBG can be observed in insulin-resistant states such as obesity, further elevating free testosterone levels [41].

Diagnosis

Symptoms usually begin around menarche, but onset after puberty may also occur as a result of environmental modifiers such as weight gain. PCOS may be a lifelong disorder where

certain precursors are present well before the full onset of disease. Indeed, polycystic-appearing ovaries have been found in girls as young as 6 years [42]. Furthermore, an altered intrauterine milieu has been implicated, particularly its metabolic component [20]. However, diagnosing the disorder before puberty is difficult because patients with PCOS are generally diagnosed only after seeking help for irregular menses or skin changes that do not take place until puberty [43].

Results from a questionnaire-survey sent to members of the Lawson Wilkins Pediatric Endocrine Society (LWPES) demonstrated that the majority of participants would consider initiating diagnostic tests in teenagers with oligomenorrhea or secondary amenorrhea 12–24 months after menarche. At baseline, 50% of the participants would measure LH and FSH, total and free testosterone, prolactin, 17-OH progesterone and DHEAS. Most pediatric endocrinologists surveyed in this study suggested using glucose/insulin measurements, which may in part reflect the physiologic insulin resistance of puberty and are not well standardized tests; by contrast, a very small percentage recommended performing an oral glucose tolerance test (OGTT) [44].

Menstrual & ovulatory dysfunction

Ovulatory dysfunction may present with disruption of the menstrual flow pattern such as oligo-amenorrhea (vaginal bleeding episodes at 35-day intervals or <10 bleeds per year), polymenorrhea (<25 days between bleeds), amenorrhea (lack of menstrual bleeding for more than 3–6 months) or abnormal uterine bleeding. Ovulatory dysfunction can also present subclinically, with no obvious disruption in the regularity of vaginal bleeding. Anovulation may be determined by measuring serum progesterone level at day 20–24 of the cycle. If the progesterone level is below 3–4 ng/ml, depending on the laboratory, then the cycle is deemed to be oligo–anovulatory. Between 75 and 85% of women have clinical evidence of menstrual dysfunction. It is generally characterized by infrequent or absent menstrual bleeding. Between 20 and 30% of women with PCOS will present with a history of eumenorrhea, despite evidence of oligo–anovulation; the remainder will present with overt oligoamenorrhea, and less than 2% of the patients will present with polymenorrhea. Primary amenorrhea is an uncommon manifestation of PCOS ranging from 1.4 to 14% according to the different cohorts [12,45–47]. Recently, Rachmiel *et al*. suggested that adolescents with primary amenorrhea secondary to PCOS may represent a more severe end of the PCOS spectrum and exhibit a greater degree of hyperandrogenemia and metabolic disturbances [47]. Menstrual irregularity may start at menarche and may change with age decreasing as the patient approaches menopause [48]. Some patients may give a history of regular cycles for a short period of time following menarche, followed by the onset of oligomenorrhea [5].

Clinical hyperandrogenemia

Clinical features of hyperandrogenism frequently observed in PCOS include hirsutism, acne and androgenic alopecia. The prevalence of hirsutism, acne and alopecia will vary according to race and ethnicity [49,50].

Hirsutism—Hirsutism in females is defined as the presence of terminal hairs on the face and/or body in a male-type pattern, and it affects 65–75% of the population with PCOS [9]. Hirsutism is determined by using a visual score system (Ferriman and Gallwey [51,52]) that evaluates nine body areas, including: the upper lip; chin; chest; upper back; lower back; upper and lower abdomen; upper arm and thigh. The areas are assigned a score of 0–4 based on the density of terminal hairs. A score of 0 represented the absence of terminal hairs, a score of 1 minimally evident terminal hair growth, and a score of 4 extensive terminal hair growth.

Acne—Acne affects approximately 15–25% of PCOS patients [9]. Approximately 20% of individuals in their midteens and 15% of those in their early 20s complain of acne [53]. Even though acne clearly affects a subset of PCOS patients, it is unclear whether the prevalence of acne is significantly increased in PCOS compared with the general population, thus, acne is not one of the major criteria for the diagnosis of PCOS [9].

Androgenic alopecia—The pattern of hair loss in PCOS generally involves thinning of the crown with preservation of the anterior hairline and may be the sole dermatologic sign of PCOS. The prevalence of alopecia in women with PCOS varies widely, from 5 to 50% [9]. The prevalence in adolescents is not clear, thus further studies are needed [5]. Other potential etiologies of alopecia or diffuse scalp hair loss in woman are: genetic, nutritional (poor protein intake, zinc deficiency, biotin deficiency and iron-deficient anemia) and environmental (damage following the use or abuse of hair cosmetics).

Biochemical hyperandrogenemia

Elevated free testosterone levels are observed in approximately 70% of adult and 25% of adolescent PCOS patients [5,11]. Estimating the prevalence of HA in adolescents is complicated by the lack of normative data available. HA refers to the finding of supranormal levels or estimates of circulating endogenous androgens. The most frequent androgen measured is testosterone (total, unbound or free). The vast majority of the abnormal values are in the form of free testosterone, with the sole measurement of total testosterone adding little to the diagnosis [5]. The present recommendation is to measure free testosterone concentration either directly by equilibrium dialysis, or to calculate free testosterone based on the total testosterone measured accurately (e.g., by radio-immunoassay using column chromatography, or by LC-MS or GC-MS) and SHBG (e.g., measured using competitive binding or a high-quality immune-based assay). As with any other analytical procedure, it is highly recommended that each laboratory establishes its own analytical performance and normal ranges [5]. Other possible androgens that may help in identifying adolescents with PCOS are androstenedione, dehydroepiandrosterone (DHEA and DHEA with sulfate ester [DHEAS]). The value of measuring androstendione, which is synthesized in the adrenal cortex and in ovarian theca cells, is unclear, but it may increase the number of subjects identified with HA by 9% [4]. Androgen production (DHEA and DHEAS) is also found to be exaggerated in a fraction of patients with PCOS [54–56]. DHEA is secreted by the adrenocortical zona reticularis and sulfated by sulfotransferase in the adrenal to DHEAS. The measurement of DHEA for the diagnosis of PCOS has limited diagnostic valve owing to its relatively low concentration, diurnal and inter-subject variation, and its stress response can result in false increases in circulating levels. In contrast, DHEAS is stable during the day and during the menstrual cycle, is the most abundant adrenal androgen found in the serum, and its long half-life makes it an interesting candidate for the diagnosis of adrenal hyperandrogenemia [57].

Polycystic ovaries

The presence of cysts on ultrasound does not indicate the presence of PCOS [58–60]. There is currently no agreement on the need for obtaining a pelvic ultrasound on all patients unless a tumor is suspected. A vaginal ultrasound is more appropriate for ovarian imaging [61]. Three features are generally assessed to define polycystic ovaries, including ovarian size and volume, stromal volume and follicle size and number. Rotterdam criteria defines polycystic ovaries as the presence of 12 or more follicles throughout the ovary measuring 2–9 mm in diameter and/or increased ovarian volume higher than 10 ml in at least one ovary [3,5]. It has been shown that woman with polycystic ovaries on ultrasound may represent a heterogeneous group with respect to endocrine function. Mortensen *et al*., has demonstrated that 25% of asymptomatic women with polycystic ovaries on ultrasound are

hyperandrogenemic, thus meeting Rotterdam criteria for PCOS [62]. A total of 22% have an abnormal 17-OH-progesterone response to gonadotropin-releasing hormone analog (GnRHag), but lacked a HA condition, known as 'dysregulated PCO', and the rest have normal endocrine function [62]. It is not clear whether the adult criteria for a polycystic ovary described above apply to adolescents because the number of large antral follicles reaches its maximum around the time of menarche [63,64]. Polycystic ovaries on ultrasound are only found in 55% of adolescents and 10% of regularly menstruating girls. Furthermore, the functional significance of these arrested follicles is unclear. Their prevalence increased significantly with the irregularity of the menstrual cycle, and 40% of girls with arrested follicles demonstrated a subclinical PCOS-like phenotype with abnormal 17-hydroxyprogesterone responses to GnRHag [65].

Gonadotropic abnormalities

More than 75% of PCOS patients present with a dysregulation in gonadotropic function [29,66–68]. Increased secretion of LH and an increase in the ratio of serum LH to FSH during the follicular phase of the menstrual cycle has been considered as a marker of PCOS [67]. However, the cut-off value for the LH:FSH ratio depends on the assay used. Obesity in PCOS may confound the measurement, explaining the normal LH:FSH ratio found in many patients, particularly if the assessment is based on a single LH and FSH determination [69].

Metabolic screen

Polycystic ovary syndrome is associated with metabolic abnormalities, such as dyslipidemia, obesity and glucose intolerance, which are also components of the metabolic syndrome (MetSyn) (Table 2) [70–73]. Between 50 and 70% of women with PCOS have features of MetSyn [5,74]. The prevalence of adolescent females with MetSyn in the USA is 12–44% [71], and adolescents with PCOS were found to be at higher risk for MetSyn in comparison with controls [75–77]. In a group of obese adolescents with and without PCOS, obesity was a stronger predictor of MetSyn [78]. By contrast, PCOS was associated with an increase in glucose abnormalities, suggesting that obese PCOS adolescent are at increased risk for developing glucose intolerance (IGT) and T2DM compared with their non-PCOS counterparts [3,74,78]. The prevalence of IGT (fasting blood glucose levels of 100–125 mg/dl, and/or 2 h posprandial glucose level after a 75 g oral glucose challenge between 140–200 mg/dl) is not clear. Bridger *et al*., showed that in a study of 22 obese adolescents with PCOS, only one participant had IGT (4.5%) [79]. Others studies involving obese adolescents with PCOS report rates of IGT as high as 33 [80] to 52% [81]. By contrast, nonobese adolescents with evidence of PCOS or ovarian hyperandrogenism do not seem to have an increased risk of IGT as shown in studies carried out by Ibanez *et al*. [82] and Silfen *et al*. [83]. As adults, the most reliable screening test for IGT in PCOS adolescents is the 2-h OGTT after a 75-g glucose load, interpreted using ADA guidelines [74]. This is an interesting paper that reviews ADA guidelines. Although the most appropriate screening interval is not clearly defined, the conversion from IGT to T2DM can occur in as little as 5 years [84], most likely because of the strong correlation of PCOS and insulin resistance and β-cell failure.

Dyslipidemia

The prevalence of at least one abnormal lipid level by National Cholesterol Education Program guidelines approaches 70% [85]. In adolescents, PCOS [86] and HA are major risk factors for dyslipidemia [87].

Obesity

Approximately 50% of women with PCOS are obese [88]. Obesity exacerbates the PCOS phenotype [78,89–91], and weight gain may unmask the syndrome in previously asymptomatic, susceptible individuals. In adolescents as well as adults there is a positive association between BMI and androgen levels, and weight reduction leads to improvements in free androgen levels, insulin sensitivity and ovulatory function [1,92,93].

Obstructive sleep apnea

The prevalence of obstructive sleep apnea (OSA) in adult women with polycystic ovary syndrome is higher than expected and cannot be explained by obesity alone [35]. A study carried out by De Sousa *et al*. has demonstrated that OSA does not appear to be more prevalent in obese adolescents with PCOS, suggesting that OSA may develop as the disease progresses [94].

Other disorders

Although PCOS has specific diagnostic criteria, other disorders associated with androgen excess and/or menstrual irregularities and/or ovulatory dysfunction should be excluded, such as adrenal hyperplasias, syndromes of severe insulin resistance and HA, idiopathic hirsutism, hirsutism secondary to medical treatments (anabolic or androgenic steroids or valproic acid), androgen-secreting neoplasms, Cushing disease or syndrome, hyperprolactinemia and thyroid abnormalities (Box 1) [5].

Treatment

The course of treatment for women with PCOS largely depends on the severity of the symptoms (Table 3). Adolescents with PCOS tend to be troubled by the cosmetic effects, such as acne, hirsutism and/or acanthosis nigricans. These symptoms are disturbing to them as they occur during a particularly vulnerable stage of their psychological development. Thus, treatment of the PCOS adolescent must address these issues as well as take into account the metabolic consequences such as the risk for development of T2DM and other metabolic abnormalities.

Lifestyle modification

Lifestyle modification is effective, cheap and has no side effects. The preferred and effective method of treatment for obese adolescents with PCOS is lifestyle modification; however, it is also the hardest for patients to comply with and achieve [95]. Minimal weight loss of 2–7% of bodyweight reduces androgen levels and improves ovulatory function in many patients with PCOS [96]. In adolescents, lifestyle modification alone can result in a 59% reduction in free androgen index with a 122% increase in sex hormone-binding globulin (SHBG) [97]. While a low fat/high carbohydrate diet is traditionally thought to improve metabolic and reproductive function due to weight loss, a high-protein/low-carbohydrate diet increases weight loss due to the increased satiating power and improved insulin action [98]. Similarly, meal replacements followed by a moderate fat or carbohydrate restriction are equally effective in maintaining weight reduction and improving reproductive and metabolic function [99]. Carbohydrate restriction versus fat restriction is generally considered advantageous; however, several recent studies did not demonstrate a distinct benefit from calorie-restricted diets that limit carbohydrates rather than fat [100,101]. However, improvements of clinical parameters occur maximally in energy restriction and are maintained or reversed during weight maintenance. Although enhanced reproductive function may be induced by caloric deficit and relatively small weight loss, the maintenance of weight is critical for reduced complications. Interestingly, the addition of aerobic or aerobic-resistance exercise to an energy-restricted diet improved body composition but had

no additional effect on improvements in cardiometabolic, hormonal and reproductive outcomes relative to diet alone [102].

Box 1. Differential diagnosis

- Cushing syndrome
- Late-onset congenital adrenal hyperplasia
- Obesity
- Ovarian failure
- Androgen-secreting tumors (ovarian, adrenal)
- Metabolic syndrome
- Prolactinoma
- Idiopathic hirsutism
- Acromegaly
- Thyroid dysfunction
- Drugs: testosterone, danazol, androgenic progestins, valproic acid, acetazolamide, minoxidil and high-dose glucocorticosteroids

Cosmetic treatment

Cosmetic and dermatologic treatments for the treatment of hirsutism include depilation, epilation or destruction of the dermal papilla with electrolysis or laser [103–106]. The last-mentioned technique is painful and expensive, and thus practical only for the treatment of limited areas. Recently, intense pulsed light (IPL) has proved to be an effective and safe hair removal method for patients affected by facial hirsutism and an endocrine abnormality (PCOS, CAH and obesity). Hair removal by IPL has demonstrated long-lasting results, and at the 2-year follow-up, 70% of patients reported that the technique was satisfactory [107]. The newest addition to the topical treatment is eflornithine hydrochloride 13.9% (Vaniqua®), which has been recently approved for the treatment of hirsutism [108]. Vaniqua takes 6–9 months to work and the hair will grow back after discontinuation of this treatment.

Hormonal treatment

Estrogen–progestin therapy remains the predominant treatment for hirsutism and acne (Table 3 & Table 4). The estrogenic component suppresses LH levels and thus androgen production, and enhances hepatic production of SHBG thereby reducing free testosterone. Various progestins are utilized in oral contraceptive pills (OCPs), with some progestins having more androgenic activity than others (Table 4). Norgestimate, desogestrel and gestodene are considered to have low androgenic potential whereas levonorgestrel and norgestrel have high androgenic activity. Most pediatric endocrinologists still prefer to use OCPs with low androgenic potential, such as Demulen 1/50® (useful in obese patients who need higher doses of estrogen), Ortho-Tri-Cyclen® (US FDA approved for treatment of acne in women) or Yasmin®, which contains drospirenone 3 mg dose (a spironolactone-related, antimineralocorticoid with antiandrogenic activity) in combination with ethinyl estradiol (EE) 30 μg (for an interesting review in the use of Yasmin in PCOS women see [109]). A new formulation of Yasmin has been developed combining drospirenone 3 mg with EE 20 μg or YAZ (Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ, USA), and has the same

metabolic benefit with a lower estrogen dose [110]. Yasmin has been found to be effective in the treatment of mild-to-moderate acne [111].

At this time, clinical studies have not demonstrated that a lower androgenic progestin is more effective for the treatment of hirsutism. OCP therapy is recommended for 1–2 years and studies have demonstrated that suppression of serum androgens can continue for up to 2 years after discontinuation of OCPs [112] (however, another study caused controversy by demonstrating that serum androgens returned to baseline results after 3 months of discontinued therapy [113]). Potential side effects include alterations in insulin action, vascular reactivity and hypercoagulativity. OCPs should be used with caution and in the lowest estrogen dose possible in patients with a history of migraine headaches [114]. Contrary to popular opinion, OCPs do not cause weight gain or increase of body fat in teenagers [115]. OCP treatment of adolescent girls with PCOS is associated with a significant decrease in total testosterone, and free androgen index, but also results in an increase in C-reactive protein and cholesterol, suggesting that OCPs may increase the risk of inflammation and dyslipemia [95]. The use of combined oral contraceptive formulations containing either cyproterone acetate or desogestrel are equally effective at normalizing menstrual cycles, reducing hirsutism scores, and increasing insulin resistance [116], total cholesterol, LDL and HDL-cholesterol levels [117]. Despite similar changes in lipid values, treatment with cyproterone acetate is associated with higher triglycerides and cholesterol levels [117], and with an increase in insulin secretion and hyperinsulinemia [116]. Thus, potential adverse cardiometabolic effects of OCPs represent a major concern [118], and it should be kept in mind that OCP use might increase the risk of diabetes, particularly in obese patients with severe insulin resistance (Box 2).

Antiandrogens

Antiandrogens effectively treat hirsutism and acne. They act as competitive antagonists of steroid binding to the androgen receptor and reverse the androgen-induced transformation of vellus to terminal hairs. Cyproterone acetate is not available in the USA. Spironolactone, an antiandrogen and aldosterone antagonist, in large doses (200 mg/day), possesses moderate antiandrogenic effects and occasionally may cause vaginal bleeding. Spironolactone has multiple antiandrogenic effects, including inhibition of ovarian and adrenal androgen production; blockade of dihydrotestosterone (DHT) binding to skin androgen receptors, elevation of SHBG levels, and increased testosterone clearance from the body and decreased 5α-reductase activity. The effectiveness of spironolactone in hirsute women is related to the utilized dose. An initial dose of 100 mg/day is considered appropriate for the lean hirsute woman but higher daily doses of 200 or 300 mg might be necessary for successful treatment of a woman who is severely hirsute or obese. Spironolactone appears better than metformin in the treatment of hirsutism, menstrual cycle frequency, and hormonal derangements and is associated with fewer adverse events [119]. Side-effects include polydypsia, polyuria, nausea, headaches, fatigue, gastritis and ovulatory dysfunction resulting in polymenorrhea. Because of its action as an aldosterone antagonist, spironolactone is also a diuretic and has the potential to cause hyperkalemia. For the healthy young PCOS patient, hyperkalemia remains a theoretical concern because this complication has only been reported in patients who are elderly, diabetic, on drugs that can raise potassium levels or who have impaired renal function. To minimize side-effects, a starting dose of 25 mg/day should be increased over several weeks. Spironolactone should be given for at least 6 months to gain maximum improvement in hirsutism. The maintenance dose can then be dropped to 25–100 mg daily, with overweight women requiring a higher dose [120]. Spironolactone has also been shown to decrease sebum production and improve acne. The therapeutic dose range for acne therapy is 50–100 mg a day, with some women having positive benefits with only 25 mg daily. Dermatologists have recommended the addition of spironolactone to OCP treatment

for a resistant adult because it will result in an increased therapeutic benefit to the skin. The addition of an OCP to spironolactone therapy is also recommended for contraceptive purposes as feminization of a male fetus can occur while on this medication.

Flutamide (potent nonsteroidal antiandrogen) has minimal indications because of its 'potential hepatotoxicity'. Recently, Ibanez *et al*. has shown that nonobese young women with hyperinsulinemic androgen excess that received metformin and OCPs, a low-dose pioglitazone and flutamide, improved their cardiovascular status (visceral fat, lean mass, insulin sensitivity and ratio of LDL/HDL cholesterol) without any complications or side effects for 2 years after discontinuation of therapy [121]. For a full review on the effect of flutamide treatment in PCOS please refer to Ibanez *et al*. 2006 [122].

Finasteride, an inhibitor of type 2 5α–reductase, and eflornithine hydrochloride have been approved for the treatment of hirsutism, but clinical data are too limited to recommend its use [123].

Insulin sensitizers

Insulin sensitizers are an adjuvant to general lifestyle improvements and not a replacement for exercise and diet [124]. Recently, our understanding of the role of insulin resistance has led to the use of insulin-sensitizing medications as first-choice therapy. In conjunction with weight reduction, a pharmacologic reduction in insulin levels by either metformin or thiazolidinediones ameliorates both hyperinsulinemia and hyperandrogenism [124]. As beneficial as metformin can be for adults with PCOS [125] (2009 Cochrane review in the use of insulin sensitizer in PCOS), it appears even more effective in adolescents with PCOS [126,127]. In addition, metformin has been shown to delay the progression to PCOS in a group of postmenarchal females with premature adrenarche who were born small for gestational age [128].

A summary of metformin treatments and outcomes in adolescents is given in Table 5. Metformin administration significantly improved insulin levels, regularizing menstrual cycles in oligo-amenorrheic teenagers with PCOS. In a small randomized, double-blind, placebo-controlled trial of metformin in obese adolescents showed significant changes in BMI [129] and in fasting blood glucose and insulin levels. Furthermore, treatment for 6–12 months has demonstrated a significant decrease androgen levels, serum lipid levels and hirsutism [129–132]. Metformin, lifestyle modification and OCP treatment reduced central adiposity, total testosterone and increased HDL [95]. Recently, an important study by Hoeger *et al*. demonstrated that lifestyle modification alone resulted in a significant reduction in free androgen index with an increase in SHBG [97]. OCP alone resulted in a significant decrease in total testosterone and free androgen index but increased C-reactive protein and cholesterol, causing an increase in the risk for the development of inflammatory and metabolic disturbances. The combination of lifestyle modification, OCP and metformin resulted in a significant decrease in total testosterone, waist circumference, and a significant increase in HDL, but did not increase overall weight reduction [97]. Metformin use in adolescents with PCOS might be a permanent treatment. It has been demonstrated that all the improvements are lost 3 months after cessation of metformin treatment [132]. Recent data have shown that the use of these agents is associated with spontaneous ovulation [133]. Thus, the risk of pregnancy can increase, and if pregnancy occurs, the continuous use of metformin during pregnancy should be re-evaluated, as metformin can cross the placenta [134].

Thiazolidinediones (troglitazone, rosiglitazone or pioglitazone) [125,135] are another class of insulin-sensitizing medications that are potentially effective in the treatment of PCOS [124,136]. Pioglitazone and rosiglitazone are the only currently available TZDs.

Troglitazone has been withdrawn secondary to hepatotoxicity. Pioglitazone and rosiglitazone possess mainly the same properties, except that pioglitazone has a positive effect on lipid profile [137]. They improve insulin action and glucose utilization at the level of the liver, skeletal muscle and adipose tissue. Pioglitazone has been shown to improve androgen and lipid profiles as well as insulin secretion and sensitivity in obese PCOS women [136]. Nonetheless, before using it in the adolescent population, more studies are necessary to estimate the potential risk of these compounds.

Insulin sensitizers should always be used as an adjuvant to general lifestyle improvements and not as a replacement for increased exercise and better diet.

Box 2. General contraindication to the use of low-dose (35 mg of ethinyl estradiol) combined oral contraceptive pills

Absolute contraindications (i.e., unacceptable health risk)

- Less than 6 weeks postpartum if breastfeeding
- Smoker over 35 years of age (>15 cigarettes per day)
- Hypertension (systolic blood pressure >160 or diastolic >100 mm Hg)
- History of, or current deep venous thrombosis/pulmonary embolism
- Major surgery with prolonged immobilization
- Current and history of ischemic heart disease
- Known thrombogenic mutations (e.g., factor V Leiden; prothrombin mutation; protein S; protein C; and antithrombin deficiencies). Routine screening is not recommended because of the rarity of the conditions and the high cost of the screening
- Stroke (history of cerebrovascular accident)
- Complicated valvular heart disease
- Migraine headache with focal neurologic symptoms
- Current breast cancer
- Diabetes with nephropathy/retinopathy/neuropathy
- Active viral hepatitis, severe cirrhosis or liver tumors

Selected relative contraindications (risks generally outweigh benefits)

- Smoker over 35 years of age (<15 cigarettes/day)
- Adequately controlled hypertension
- Hypertension (systolic blood pressure 140–159 or diastolic 90–99 mmHg)
- Migraine headache over 35 years of age
- Current gallbladder disease
- Past oral contraceptive pill-related history of cholestasis
- Mild (compensated) cirrhosis
- Use of drugs that affect liver enzymes

Adapted from [201].

Alternative treatments

Adolescents girls with PCOS require a long-term committed treatment that can have serious side effects. Therefore, alternative treatments may be possible options for a subset of PCOS adolescent females. Acupuncture has been shown to improve ovulation as well as the metabolic and endocrine function in PCOS by modulating the sympathetic, endocrine and neuroendocrine system [138]. The chinese herbal formula 'Tiangui Fang' has also been shown to reduce insulin levels and induce ovulation in women with PCOS [139]. The essential mineral chromium has demonstrated a beneficial role in the regulation of insulin action and lipid metabolism [140,141]. Myoinositol, a component of the vitamin B complex and insulin desensitizer, has been shown to improve insulin signaling, thereby restoring normal ovulatory function in PCOS women [125,142]. Last, surgical therapy with laparoscopic ovarian 'drilling' has demonstrated controversial results regarding spontaneous ovulation and conception after the procedure [143].

Conclusion

Polycystic ovary syndrome is one of the most common hormonal disorders affecting adolescents and adult women. PCOS affects the reproductive, metabolic, and cardiovascular system. Early diagnosis and treatment is essential in restoring self-esteem and preventing adult disease. Treatments for an adolescent with PCOS include diet and exercise, metformin, spironolactone and OCPs. Current dietetic and medical advice should continue to focus on weight loss as an important treatment goal in overweight adolescents with PCOS with regard to reducing long-term risk. The use of OCP should be recommended, especially if the adolescent is interested in birth control, spironolactone for the treatment of hirsutism and the highly effective metformin if there is evidence of insulin resistance, always stressing that healthy diet and regular exercise are the most beneficial in treating PCOS symptoms and preventing further health dilemmas.

Future perspective

Long-term cohort studies are particularly needed in young women with PCOS. Large-scale clinical outcome trials that start during childhood should be designed. These studies should investigate the roles of pertinent genes associated with the syndrome, the prevalence of dyslipidemia among other possible cardiovascular risks and the molecular defect associated with the development of the MetSyn. Additional diagnostic criteria for PCOS should be defined, especially during late childhood and early adolescent years to identify at-risk subtypes, particularly those at risk of cardiovascular disease later on. It should also be determined whether all adolescents with PCOS, irrespective of their body weight, should be screened for glucose intolerance, insulin resistance or both, and how often that should be done. Short-term trials of pertinent interventions, for example lipid regulators, antioxidants and insulin sensitizers, on surrogate cardiovascular outcomes are necessary to generate new hypotheses that can explain the relationship between HA and insulin resistance. The high incidence of PCOS in women of reproductive age and its implications for cardiovascular health make future research in this area a priority.

Executive summary

- Polycystic ovarian syndrome is a hyperandrogenic disorder.
- Ovulatory dysfunction is a prominent, but not universal feature of polycystic ovarian syndrome.

- Eumenorrhea in the presence of dermatologic features suggestive of hyperandrogenism could not reliably be used to establish the presence of normal ovulation.
- Ovarian morphology should be considered when establishing the diagnosis.
- Other well-defined disorders that could result in ovulatory dysfunction should be ruled out.
- Associated metabolic abnormalities must be recognized.

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Table 1

Potential phenotypes according to each criteria.

NIH 1990 Criteria	√	√	√	√	√	√				
Rotterdam 2003 Criteria	√	√	√	√	√	√	√	√	√	√
AES 2006 Criteria	√	√	√	√	√	√	√	√	√	
Biochemical hyperandrogenemia	+	+	+	+	−	−	+	−	+	−
Clinical hyperandrogenemia hirsutism	+	+	−	−	+	+	+	+	−	−
Oligo−anovulation	+	+	+	+	+	+	−	−	−	+
Polycystic ovaries on ultrasound	+	−	+	−	+	−	+	+	+	+

Data taken from [9].

Table 2

Definition of metabolic syndrome.

Criteria	Adult (70)	Adolescent (71)	Adolescent (72–73) by the IDF
Triglycerides	>150 mg/dl or drug treatment for elevated triglycerides	>110 mg/dl	>1.7 mmol/l
High-density lipoprotein cholesterol	<50 mg/dl or drug treatment for low high-density lipoprotein cholesterol	<40 mg/dl	<1.03 mmol/l
Fasting glucose	>100 mg/dl or drug treatment for high glucose	>110 mg/dl	>5.6 mmol/l or known Type 2 diabetes mellitus
Waist circumference	>88 cm (women)	>90th percentile/age and sex	>90th percentile (this element + two others required for IDF definition)
Systolic or diastolic blood pressure	>135 mmHg systolic or >85 mmHg diastolic, or drug treatment for hypertension	>90th percentile/age, sex, and height, or use of antihypertensive drugs	>130 mmHg systolic or >85 mmHg diastolic

For all definitions, the presence of three or more criteria resulted in the diagnosis of metabolic syndrome, with the IDF definition requiring an increased waist circumference in addition to two other features.

HDL: High-density lipoprotein; IDF: International Diabetes Institute.

Table 3

Hormone treatment for hirsutism and acne.

Treament	Mechanism (s) of action	Uses(s)
Estrogen–progestins	Increase SHBG; suppress LH and FSH; suppress with a progestin that acts as an antiandrogen	Hirsutism/acne
Antiandrogens	Inhibit androgens from binding to the androgen receptor	Hirsutism
Glucocorticoids	Suppress ACTH and thus adrenal androgen production	Hirsutism/acne/ovulation
5α-reductase inhibitors	Inhibition of 5α-reductase	Hirsutism
Ornithine decarboxylase inhibitors	Inhibition of ornithine decarboxylase	Hirsutism
Metformin	Reduce hepatic glucose production, secondarily lowering insulin levels; and direct effects on ovarian steroidogenesis	Hirsutism/acne/ovulation/ insulin-lowering Rx
Thiazolidinediones	Enhance insulin action at target tissue level (adipocyte and muscle); some evidence for direct effects upon ovarian steroidogenesis	Hirsutism/acne/ovulation/ insulin-lowering Rx

ACTH: Adrenocorticotropic hormone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; Rx: Treatment-Rx; SHBG: Sex-hormone binding globulin.

Table 4

Androgenic activity of progestins.

Progestin	Progestogenic	Antiandrogenic	Antimineralo-corticoid	Androgenic
Progesterone	+	+	+	−
Drospirenone	+	+	+	−
Norgestimate	+	−	−	+
Levonorgestrel	+	−	−	+
Desogestrel	+	−	−	+
Norethindrone	+	−	−	+
Cyproterone acetate	+	+	−	−

Table 5

Summary of metformin treatments and outcomes in adolescents with polycystic ovary syndrome.

Author (year)	Design	Age (year)	Duration (months)	Dose (mg/day)	Insulin sensitivity	Lipids	Androgens	Menstruation ovulation	Ref.
Ibanez *et al.* (2000)	10 nonobese PA	16	6	1275	Improved	Reduced	Reduced	Improved	[132]
Glueck *et al.* (2001)	11 obese	16	4–26	1500 rising to 2550	Improved	Reduced (cholesterol)	Not changed	Improved	[130]
Ibanez *et al.* (2001)	18 PA/lean	16	6	1275	Improved	Reduced	Reduced	Improved	[131]
Arslanian *et al.* (2002)	15	14	3	1700	Improved	–	Reduced	–	[126]
Ibanez *et al.* (2004)	RT (24) LBW/PA/lean	12	12	850	Improved	Reduced	Reduced	–	[122]
Bridger *et al.* (2006)	RT (22) obese	12–18	12	1500	Improved	Increased HDL	Reduced	Improved	[79]
De Leo *et al.* (2006)	18 obese	15–18	6	1700	–	–	Reduced	Improved	[129]
Hoeger *et al.* (2008)	RT (79) obese	16	6	1700	Reduced Fasting Blood glucose	Reduced triglyceride	Not changed	Improved	[97]

HDL: High-density lipoprotein; LBW: Low birth weight; PA: Premature adrenarche; RT: Randomized trial.