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METABOLISM (M DALAMAGA, SECTION EDITOR)

Polycystic ovary Syndrome in Adolescents: Pitfalls in Diagnosis and Management

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Abstract

Purpose of Review Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder during a woman's reproductive lifespan, with well-documented diagnostic criteria and therapeutic strategies in adults; the same is not necessarily true for adolescents. The purpose of this review was to identify frequent pitfalls in PCOS diagnosis and management during adolescence.

Recent Findings Although there is no global consensus on the definition, most experts converge to the presence of both oligo/amenorrhea and (clinical and/or biochemical) hyperandrogenism, as a prerequisite for diagnosis in adolescents. The former criterion includes: (a) consecutive menstrual intervals > 90 days even in the first year after menarche; (b) menstrual intervals persistently < 21 or > 45 days for ≥ 2 years after menarche; or (c) lack of menses by the age of 15 or 2–3 years after pubarche. However, these menstrual irregularity patterns may overlap with other common entities in adolescents, such as frequent or infrequent uterine bleeding or anovulation due to immaturity of the hypothalamic-pituitary-ovarian axis. Clinical signs of hyperandrogenism are obscure, without well-validated criteria. Finally, the criterion of polycystic morphology cannot be safely used in adolescents, mostly due to technical limitations of the transabdominal ultrasound. Except for the efficacy of lifestyle intervention in overweight and obese adolescents with PCOS, limited and low-quality data exist regarding the available medications, such as oral contraceptives, metformin, and anti-androgens.

Summary Individualized management, guided by clinical experience and research data and close monitoring appear the most effective approach in this PCOS population for optimal control of its reproductive and metabolic outcomes. Research focusing on PCOS genetic and molecular mechanisms may elucidate what diagnostic and therapeutic strategies will be most appropriate in adolescents with PCOS in the future.

Keywords Oligomenorrhea · Hyperandrogenism · Adolescence · Adolescents · Diagnosis

Introduction

Polycystic ovary syndrome (PCOS) constitutes the most common endocrine disorder in females of reproductive age [1], accounting for 70–80% of all cases with hyperandrogenism [2]. Its prevalence is estimated to 6–8% of the general premenopausal population [2], depending on the criteria used, it may reach up to 20% [3, 4]. PCOS is considered a multifactorial syndrome of unknown cause. Disordered gonadotropin secretion with elevated luteinizing hormone (LH), ovarian hyperandrogenism, and insulin resistance are key components of the syndrome [5]. Its etiopathogenesis involves an interaction between genetic and environmental factors. Studies have focused on mutations in genes that participate in androgen biosynthesis and action, glucose metabolism, such as the insulin and insulin receptor genes, and systemic inflammation, such as the *CYP11A1*, *CYP17A*, *CYP19*, *CYP21*, *HSD17B5*,

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HSD17B6, *INS*, *INSR*, *IRS-1*, *IRS-2*, *IGF*, *PPAR-γ*, the tumor necrosis factor-alpha (*TNF-α*), and interleukin-6 (*IL-6*) genes [6]. Besides the strong genetic component, an epigenetic component seems to play a significant role [2]. With regard to the environmental component, it has been hypothesized that intrauterine growth restriction (IUGR) or exposure to androgens in utero may result in the development of PCOS in adult women [5, 7].

In general, there is heterogeneity in the clinical presentation of PCOS, which varies with age, body weight, ethnicity, and the influence of environmental factors, such as medications [8]. The diagnosis of the syndrome, which is the result of the exclusion of other causes of menstrual irregularity and androgen excess, becomes challenging after taking into consideration that the evolution of its features may occur any time throughout a woman's lifespan [9]. Based on the American Society for Reproductive Medicine (ASRM)/European Society of Human Reproduction and Embryology (ESHRE) ("Rotterdam") criteria, which are the most widely applied, the presence of at least two of the following three criteria are needed to confirm the diagnosis of PCOS: ovulatory dysfunction, hyperandrogenism (clinical or biochemical), and polycystic ovarian morphology (PCOM) on ultrasound [3, 4]. However, the clinical presentation is more obscure in adolescents compared with the adults, complicating the diagnostic and therapeutic approach.

The purpose of this narrative review is to focus on PCOS in adolescence, in an attempt to identify frequent pitfalls in its diagnosis and management.

Diagnostic Features of PCOS in Adults

Menstrual Irregularity and Ovulatory Dysfunction

Menstrual irregularity is present in > 75% of adult women with PCOS. Oligomenorrhea is defined as intervals of > 6–8 weeks between menses. Adrenal (non-classical congenital adrenal hyperplasia (NCCAH)), thyroid (hypothyroidism, hyperthyroidism), and pituitary disorders (hyperprolactinemia) should be excluded [10].

Androgen Excess

Androgen excess may be either biochemical or clinical. Biochemical hyperandrogenemia is present in 60–80% of adults with PCOS, mainly attributed to excess androgen production by the ovaries, whereas the adrenal glands and peripheral adipose tissue contribute to a small degree [10]. Androgen excess may clinically manifest as hirsutism (i.e., excess facial and body hair), acne, or alopecia (male-pattern baldness) [11]. Nonetheless, clinical assessment of hyperandrogenism (hirsutism, acne, alopecia) has limitations, as it is often subjective, poorly specific, or standardized and varies among ethnic groups. Moreover, > 90% of 18-year-old women have some form of acne [12].

In addition, biochemical hyperandrogenemia is not clearly defined, depending on which androgen is measured, its upper normal serum concentrations and the method of assessment. The usefulness of serum total testosterone as a surrogate marker of female hyperandrogenism is low due to the poor accuracy and sensitivity of traditional immunoassays in the female range [13, 14]. Furthermore, total testosterone concentrations exhibit a high intra- and inter-individual variability and are subject to variations of the binding proteins, such as albumin and sex hormone-binding globulin (SHBG); therefore, precise reference values cannot be determined [1]. In contrast, serum-free testosterone (fT) is a more sensitive marker of hyperandrogenism compared with total testosterone [15, 16]; albeit the method of choice for its measurement, equilibrium dialysis, is time consuming, and not available worldwide. Therefore, an indirect measurement of fT, the free androgen index (FAI), calculated as the quotient 100 × total testosterone/SHBG (both expressed in nmol/l), has been proposed [16]. Of note, it has been reported that only 50% of women with PCOS and hyperandrogenic phenotype have total testosterone concentrations > 95th percentile of the reference values, whereas nearly 90% of them have fT concentrations > 95th percentile [17]. The diagnostic utility of other less-potent androgens, such as dehydroepiandrosterone sulfate (DHEAS) and Δ_4-androstenedione in PCOS, is limited due to their almost exclusive adrenal production [10].

However, many patients with PCOS present with clinical signs of hyperandrogenism but without biochemical hyperandrogenism. This may be attributed to increased peripheral androgen metabolism of androgens or increased conversion of testosterone to the potent dihydrotestosterone (DHT) at the hair follicles and sebaceous glands, through the action of the enzyme 5α-reductase. Peripherally produced androgens act in an intracrine way that is not reflected in blood concentrations [2]. Moreover, androgen excess may affect the menstrual cycle and fertility, through ovarian dysregulation and impaired follicular maturation that result in anovulation and subfertility [2].

Polycystic Ovarian Morphology

PCOM, defined as the presence of ≥ 12 follicles (2–9 mm in diameter in each ovary) or increased ovarian volume (> 10 ml), has been introduced as one of the Rotterdam diagnostic criteria for PCOS and has received criticism for broadening the definition of PCOS. PCOM has been associated with both irregular menses and hyperandrogenism [18].

Controversy persists with regard to the recommended criteria for an accurate diagnosis of PCOS, since the criteria proposed by the National Institutes of Health (NIH) consensus

in 1990 for PCOS in adult women require menstrual irregularity and androgen excess [19]. The NIH criteria proposed in 2012 are in agreement with the Rotterdam criteria [20]. By contrast, the Androgen Excess and PCOS Society (AEPCOS) requires the presence of hyperandrogenism in combination with either menstrual irregularity or PCOM for the diagnosis of PCOS [10].

Diagnostic Challenges in Adolescence

Diagnostic Criteria

Although there is no consensus on the definition of PCOS in adolescents, according to the aforementioned international scientific groups, the same diagnostic criteria can be extrapolated in the adolescent population [3, 4]. However, the main shortcoming in these cases is the fact that many adolescents exhibit physiologic menstrual irregularity and signs of androgen excess peripubertal [2, 21]. Furthermore, adolescent ovarian morphology overlaps with that of women with PCOS [22, 23]. Although there is no global consensus on the exact PCOS definition in adolescents, the diagnosis is suggested to be based on the concomitant presence of clinical and/or biochemical hyperandrogenism with persistent oligomenorrhea [4, 24, 25]. The following criteria have been proposed for the latter: (a) consecutive menstrual intervals > 90 days, even from the first year after menarche; (b) menstrual intervals persistently < 21 or > 45 days for ≥ 2 years after menarche; or (c) lack of menses by the age of 15 or 2–3 years after pubarche (development of breast budding) [25]. With regard to PCOS prevalence in adolescents, a recent meta-analysis reported rates of 11.0% (95% confidence interval (CI), 6.8–16.1), 3.4% (95% CI, 0.3–9.5), and 8.0% (95% CI, 6.2–10.0), according to the Rotterdam, NIH, or AEPCOS criteria [26•].

Menstrual Irregularity and Ovulatory Dysfunction in Adolescence

Menstrual irregularity is often the earliest clinical manifestation of PCOS in adolescence [27]. It may manifest as oligomenorrhea or excessive uterine bleeding [25], which usually resolve within 2 years post-menarche. In some cases, however, regular menses might be established later on, without any pathological cause [28]. Oligomenorrhea at the age of 15 years persists for 3 years more in 51% of the cases; on the other hand, only 2% of adolescents with regular menstrual cycles develop oligomenorrhea later on [29]. Thus, oligomenorrhea at 15 years of age may be a good predictor of oligomenorrhea in 3 years. Moreover, PCOS has been reported as the predominant diagnosis in hospitalized adolescents with excessive uterine bleeding, accounting for 33% of the cases [30].

Anovulation is also common at the beginning of puberty due to the immaturity of the hypothalamic-pituitary-ovarian axis and involves approximately 40–50% of adolescent girls [31]. Therefore, differentiation between physiological anovulation during adolescence and ovulatory dysfunction is challenging.

Androgen Excess in Adolescence

Although acne may be associated with underlying hyperandrogenism, it cannot be used as the sole criterion for clinical hyperandrogenism, due to its high prevalence (up to 90%) in adolescence [32]. Hirsutism is considered a more reliable marker of hyperandrogenism in adolescents compared with acne. It becomes more prominent in adulthood as the duration of exposure to androgens is increasing [33]. According to the international consensus of 2003 [34], moderate-to-severe hirsutism is considered a clinical feature of androgen excess, as well as persistent acne. In contrast, mild hirsutism is considered to be normal soon after menarche [25]. The Ferriman-Gallwey scoring system is applied for the quantification of hirsutism (a score of 8–15 indicates mild hirsutism and a score of > 15 indicates moderate or severe hirsutism, although the same thresholds are used in adults and adolescents). There is a paucity of data concerning androgenic alopecia in adolescents.

Since clinical signs of hyperandrogenism are not reliable in adolescence, biochemical hyperandrogenemia remains a defining feature of PCOS in this population [17], despite the physiological increase in androgen concentrations during adolescence. Increased calculated fT is the most prevalent biochemical finding, although total testosterone and DHEAS may also be increased [17]. To date, there are no well-defined thresholds for androgen concentrations adjusted for adolescence. As in adults, a sensitive testosterone assay remains the *sine qua non* for accurate results. The AEPCOS Society recommends mass spectrometry as the optimal method for assessing total and free testosterone concentrations [35].

PCOM in Adolescence

The presence of multifollicular ovaries (≥ 6 cysts, 4–10 mm in diameter, and of normal or slightly increased size) is frequent in adolescents [34] and may reach 57.9% in adolescents with menstrual irregularities [36]; thus, the clinical significance and diagnostic reliability of this criterion in adolescence are questioned. PCOM and increased ovarian volume are features of physiologic puberty and may subsequently subside with the onset of regular menstrual cycles [37]. Hence, it is recommended that the ultrasonographic picture should not be included in the diagnostic criteria of PCOS during adolescence, as it has not been validated for this age group [31].

There are several reports in the literature with regard to PCOM in adolescents. It has been estimated that 10–48% of adolescents without PCOS may have a polycystic appearance of their ovaries, suggesting an overlap in ovarian morphology between adolescents with PCOS and control adolescents [21, 38, 39]. It has also been reported that one third of normal weight or overweight girls may have PCOM without ovulatory dysfunction within 2–4 years after menarche [23, 40].

On the same concept, PCOM may exist in one third of adolescents with hyperandrogenism [41], as well as in 9 and 28% of those with regular and irregular menses (average cycle length 22–41 days), respectively, and in 45% of adolescents with oligomenorrhea and increased androgen concentrations [42]. However, the early menstrual pattern is predictive of the late one [29]; therefore, oligomenorrhea that persists 2 years beyond menarche should be evaluated as an early clinical sign of PCOS. Another shortcoming of PCOM in adolescents is that transabdominal ultrasound, which is the primary imaging tool used in this population (instead of transvaginal ultrasound), may limit the diagnostic accuracy and usefulness of this imaging modality in overweight or obese adolescents. Magnetic resonance imaging (MRI) has been suggested as a more accurate approach, but it is not routinely used [43].

Further studies in larger populations during the second decade of life are needed for safe conclusions to be drawn. With these limitations, the diagnosis of PCOS hinges on the evidence of androgen excess and ovulatory dysfunction, rather than ovarian imaging [25].

Diagnostic Approach of PCOS in Adolescence

A thorough medical history has to be obtained, including information on exogenous medication intake, such as androgenic steroids and anti-epileptics. Of note, PCOS features may be covered by medications used to treat acne [44]. Furthermore, obtaining a family history is required, since a genetic component may be present. A detailed physical examination is also important. Acanthosis nigricans and truncal obesity may be detected as clinical signs of insulin resistance. The degree of hirsutism can be assessed by the Ferriman-Gallwey score [45], and the severity of acne can be graded based on lesion type and count [8].

Biochemical workup in PCOS should mainly include fasting plasma glucose, lipid profile [46], and total or calculated fT concentrations (or FAI), preferably in the morning [3]. If treatment has been initiated in the interim, androgen concentrations may be altered, and this should be taken into consideration by the clinicians [10, 11, 46, 3]. To discriminate between different causes of hyperandrogenemia or menstrual irregularity, additional testing may include DHEAS, Δ_4-androstenedione, 17-hydroxyprogesterone [17(OH)P], thyroid-stimulating hormone (TSH), prolactin, LH, FSH, and estradiol from the 3rd to 5th day of the menstrual cycle. In adolescents with baseline morning 17(OH)P > 200 mg/dl, a cosyntropin stimulation test should be performed to exclude NCCAH [47]. A pregnancy test is essential.

Although pelvic ultrasonography is not universally recommended for setting the diagnosis of PCOS in adolescents [25], a pelvic ultrasound may be useful for excluding other underlying pathology, particularly androgen-secreting tumors in cases of hyperandrogenemia and anovulation [48, 49].

Complications of PCOS

Cumulative evidence supports that PCOS is associated with long-term consequences, including impaired reproductive health, psychological dysfunction, dysregulation of glucose homeostasis (impaired glucose tolerance (IGT) or type 2 diabetes mellitus (T2DM)), non-alcoholic fatty liver disease (NAFLD), dyslipidemia, metabolic syndrome (MetS), cardiovascular disease, and increased endometrial, breast, and ovarian cancer risk [50–52]. Obesity exacerbates PCOS-associated metabolic dysregulation [53, 54]. Furthermore, insulin stimulates ovarian androgen synthesis [55] and inhibits the production of SHBG in the liver [56]. As a result, circulating free androgen concentrations are increased. Although this metabolic dysregulation is a core defect in PCOS, these "physiologic" metabolic changes are also prominent during puberty. Indeed, reduced insulin sensitivity and hyperinsulinemia are quite common in healthy adolescents [57]. It has been reported that insulin sensitivity decreases by 50% during puberty, compensated by doubling of insulin secretion [56].

However, adolescents diagnosed with PCOS should be screened for metabolic disorders, as approximately one third of them meet the criteria for MetS, such as central obesity, arterial hypertension, atherogenic dyslipidemia, and glucose intolerance, as opposed to only 5% of those without PCOS [58, 59]. Of note, the diagnostic criteria for MetS differ in the adolescent population. In particular, three of the following five are required for setting the diagnosis: (i) fasting blood glucose concentrations > 100 mg/dl; (ii) high-density lipoprotein cholesterol (HDL-C) < 40 mg/dl; (iii) triglycerides ≥ 110 mg/dl; (iv) waist circumference ≥ 90th percentile for age and sex; and (v) blood pressure ≥ 90th percentile for age and sex [60].

These abnormalities may present early in the course of the PCOS [61]. Obesity has shown to exacerbate these metabolic abnormalities in adolescents with PCOS [62•]. Although PCOS poses a heightened risk for MetS, independently of body mass index (BMI), the prevalence of MetS is higher in the presence of obesity [59], especially abdominal obesity [63]. Interestingly, although obesity is considered a better predictor of MetS compared with androgen excess [64, 65], the latter may conversely increase the risk of obesity independently of BMI [59, 66].

PCOS may be a sign of systemic inflammation, since increased concentrations of IL-6 and reduced adiponectin concentrations have been found in lean adolescents with hyperandrogenism compared with adolescents without hyperandrogenism [67]. Low adiponectin concentrations have been correlated with insulin resistance and visceral adiposity [68]. With respect to dyslipidemia, increased triglyceride and low-density lipoprotein- cholesterol (LDL-C) concentrations have been reported in adolescents with PCOS and androgen excess [66]. Another complication of PCOS in adolescence that should be taken into account is its effect on the quality of life (QoL). Indeed, a meta-analysis has shown that QoL, mostly referring to a psychological profile, is impaired in adolescent patients with PCOS, with obesity strongly mediating this effect [69•].

Follow-up of PCOS in Adolescence

Regular follow-up is of utmost importance to record the severity and progression of hirsutism, acne, and menstrual disturbances. Additionally, monitoring for PCOS-associated comorbidities, such as the presence of metabolic disturbances, as described above, is also crucial [25, 59, 70].

A 2-h oral glucose tolerance test (OGTT) is the gold-standard screening test for diagnosing impaired glucose regulation and periodic screening using this test has been suggested [49]. The increased prevalence of MetS at such a young age underscores the importance of regular screening of this population to decrease the future risk of diabetes and coronary artery disease.

The psychological impact of PCOS in adolescent patients should also be addressed at regular intervals. Depression and anxiety are seen in this population at an increased prevalence, and expert guidance may be needed in specific cases [71, 72]. Eating disorders are prevalent in adolescents with PCOS, and physicians should be aware [73].

Management of PCOS in Adolescence

Goals and Principles of Management

The goals of PCOS treatment are to improve QoL and reduce the risk of long-term health outcomes [11]. Individualized treatment based on the clinical presentation, needs and preferences of each patient is imperative. The initiation of treatment for PCOS does not require a definitive diagnosis of the syndrome, as it may decrease the risk for future comorbidities [25].

Lifestyle Modifications

Lifestyle modifications to avoid weight gain in non-obese patients or to reduce body weight in cases of excess body fat remain the mainstay of treatment [3, 4]. Weight loss is beneficial for PCOS-associated menstrual irregularity, androgen excess, and cardiometabolic risk. Interestingly, it seems to be of no benefit in normal-weight women with PCOS [3, 4]. It is the calorie restriction itself rather than the type of diet (i.e., protein content) that has an impact on reproductive and metabolic profile [3, 4, 74]. Lifestyle intervention may also ameliorate the lipid profile in adolescents with PCOS [75].

Although 40–70% of adolescents with PCOS are overweight or obese, adherence to lifestyle intervention is suboptimal and drugs used for weight loss in adults have not been approved in this population. Furthermore, the optimal diet has not been defined [76].

Few data exist regarding the effect of lifestyle modification on the metabolic and reproductive profile in adolescents. In a prospective study (59 obese PCOS girls, aged 12–18 years), lifestyle intervention (diet modification plus regular exercise), leading to a mean BMI reduction of 3.9 kg/m^2 after 1 year, ameliorated lipid profile (increased HDL-C and reduced triglyceride concentrations), and reduced insulin resistance index and blood pressure. It also reduced the prevalence of oligo- and amenorrhea, by 42 and 19%, respectively. Interestingly, carotid-intima media thickness (cIMT) decreased, as well as testosterone concentrations [77]. On the same note, a randomized-controlled trial (RCT) in obese adolescents with PCOS (n = 60) showed that intensive dietary program with conventional calorie restriction led to an improvement in menstrual pattern and hirsutism score, compared with a healthy diet, without energy restriction [78]. In this study, lifestyle modification in adolescents with PCOS resulted in a decrease in waist circumference, denoting a decrease in insulin resistance [78].

Oral Contraceptives

Combined oral contraceptives (COCs) are recommended as a first-line medical treatment for the management of menstrual irregularity and clinical signs of androgen excess in women with PCOS [3, 4]. The combination of estrogen and progesterone has a suppressive effect on the hypothalamus-pituitary-ovarian (HPO) axis, by blocking the ovarian androgen production. Furthermore, COCs increase SHBG concentrations, thereby further reducing androgen excess [79]. The progesterone component of the COC prevents estrogen action and decreases the risk of endometrial hyperplasia [11]. COCs are indicated for all forms of menstrual irregularity, including amenorrhea, oligomenorrhea, menorrhagia, and abnormal uterine bleeding [4, 45]. The positive effect of COCs in menstruation is evident 2–3 months after initiation of treatment.

Although the duration of treatment with COCs is not well defined, one or more years is the suggested period for HPO axis recovery and potential resolution of menstrual irregularity [11]. COCs may also be efficacious for the management of acne and hirsutism [11].

Common adverse effects associated with COC use include nausea, breast tenderness, headaches, and mood changes, which are mitigated after the first months of administration [80]. Studies in adults with PCOS indicate that COCs may have either negative or neutral impact on lipid profile and glucose metabolism, mostly dependent on the dose of estrogen and type of progestin; data are derived from studies of small sample size and short duration [80]. According to a Cochrane meta-analysis, there is no effect of COCs on body weight in women with PCOS [81]. Recent meta-analyses have shown that potential cardiometabolic COC-related adverse effects may be blunted when COCs are combined with metformin or lifestyle modification [82, 83].

Regarding adolescents, the evidence is not robust for safe conclusions. A Greek study has shown that 30 μg/day of ethinyl-estradiol combined with 150 mg/day of desogestrel, for 21 days per cycle of 28 days, may reduce androgen concentrations without worsening the lipid profile, weight, or waist-to-hip ratio [79]. However, some data suggest an increase in systemic inflammation, as assessed by high-sensitivity C-reactive protein concentrations and cIMT, with the use of COCs [84, 85]. Contra-indications, such as a history of deep vein thrombosis (DVT) or migraine, should be strongly taken into consideration before the initiation of COCs [80].

Metformin

In general, metformin, as an insulin sensitizer, is recommended as a second-line therapeutic modality in patients with PCOS and disordered glucose metabolism (IGT or T2DM) in whom lifestyle intervention was ineffective or who have contra-indications or are intolerant to COCs [3, 4]. The use of other insulin sensitizers, such as inositols or thiazolidinediones, is not recommended for the treatment of PCOS [3, 4]. Metformin may improve the cardiometabolic profile and menstrual irregularity in women with PCOS, although with a negligible effect on clinical hyperandrogenism [3, 4]. Interestingly, it may ameliorate the reproductive function regardless of insulin resistance and IGT [86].

A few non-RCTs, of small sample size and short duration studies exist on metformin use in adolescents with PCOS. In one prospective study in non-obese adolescents with PCOS (n = 18, mean BMI 21.4 kg/m^2) with hyperinsulinemic hyperandrogenism and persistent anovulation, metformin 1275 mg/day for 6 months, restored menstrual irregularity in all patients [87]. Ovulation induction was achieved in almost 80% of patients in 6 months. In the same study, metformin improved clinical and biochemical hyperandrogenemia and resulted in a less atherogenic profile, characterized by a reduction in total cholesterol, triglyceride, and LDL-C concentrations [87]. This was also the case in another study in adolescents with PCOS and IGT, in which metformin (850 mg, twice daily), improved insulin sensitivity and biochemical hyperandrogenemia and mitigated the adrenal steroidogenic response to adrenocorticotropic hormone [88]. In these studies, the effect of metformin on BMI was either beneficial [88] or neutral [87].

Additional studies have shown that the combination of metformin with a low-carbohydrate diet resulted in normalization of menstrual cycles and restoration of ovulation in adolescents with PCOS within a few months [89, 90]. A few months of metformin therapy has also led to normalization of glucose tolerance, reduction in total and free testosterone concentrations, and improvement of BMI, body composition, and insulin sensitivity in adolescents [88].

A few comparative data exist with regard to metformin use vs. COCs in adolescents. A meta-analysis of four RCTs (n = 170), published in 2016, showed that COC use induced a modest amelioration in menstrual pattern and acne scores. In contrast, metformin led to greater BMI reduction and improvement in glucose dysregulation, total cholesterol, and LDL-C concentrations in adolescents with PCOS. No difference in hirsutism and HDL-C or triglyceride concentrations were observed between groups [91]. However, available data were of poor quality. Additional studies are needed regarding the management of PCOS in adolescents. Gastrointestinal adverse effects (nausea, stomach upset, diarrhea) constitute the most common shortcoming with metformin use, which may occur in up to 30% of adolescents with PCOS [92].

Anti-androgens

These medications are suggested in cases with severe clinical hyperandrogenemia, not successfully managed with COCs or, in which, COCs are contra-indicated. Prerequisite of their use is the application of effective contraception in sexually active adolescents, due to their potential teratogenic action. In general, anti-androgens are effective in improving clinical signs of androgen excess, psychological profile, and QoL in women with PCOS [3, 4].

Data in adolescents are limited. Spironolactone, an aldosterone- and androgen-receptor antagonist, may improve menstrual disturbances and cutaneous manifestations of hyperandrogenism but not metabolic disorders [93]. It can be used as an adjunct to treatment with COCs or metformin, at doses of 50–200 mg/day [93, 94]. With respect to the adolescent population with PCOS, low dose of the triple combination spironolactone (50 mg/day)/pioglitazone (7.5 mg/day)/metformin (850 mg/day) (SPIOMET) exerted comparable effect with COCs on the reduction in biochemical hyperandrogenemia and body fat distribution. Furthermore,

SPIOMET reduced insulin and increased adiponectin concentrations and ovulation rates up to threefold during the post-treatment period (after 12 months) compared with COCs [95].

Flutamide is another anti-androgen, acting at the level of the androgen receptor [96]. In addition to its anti-androgenic action in adults with PCOS, it has proven efficacy in clinical and biochemical hyperandrogenism in non-obese adolescents with PCOS, at the dose of 250 mg/day. However, the medication had no effect on the menstrual regularity and insulin resistance [97]. Also, clinicians should be mindful of its potential liver toxicity [3, 4].

Cyproterone acetate (CPA) is another anti-androgen most commonly used in a contraceptive pill, at the dose of 2 mg in combination with 35 mg ethinyl-estradiol or at doses of 50–100 mg/day as adjuvant therapy to COC [3, 4]. In adult women with PCOS, CPA reduced hirsutism score in more than 50% of them and improved acne [98, 99]. However, it may increase triglyceride concentrations [79] and DVT risk [100]. Furthermore, finasteride, an inhibitor of 5α-reductase isoenzyme, at low doses (2.5 mg every 3 days), has been trialed in a pilot study and was found to be effective for the treatment of hirsutism in adolescents [101].

Local Treatment/Cosmetic Treatment

Treatment of hirsutism includes local application of eflornithine cream; the duration of treatment is not clearly defined, as data in adolescents are limited. Non-pharmaceutical treatment approaches, offering immediate results, are also available, including mechanical hair removal by laser or electrolysis [11]. The combination of eflornithine with laser therapy is more efficacious compared with each approach alone; again, more data are needed [102, 103].

Conclusions

The diagnosis of PCOS in adolescents is not straightforward, due to the high degree of phenotypical variability in its presentation. The impaired menstruation in adolescents, manifested as frequent or infrequent uterine bleeding, as well as the high prevalence of clinical signs of hyperandrogenism and PCOM, overlap with symptoms and signs of PCOS, further complicating the process of establishing a firm diagnosis. Menstrual irregularity as a clinical expression of PCOS is difficult to be distinguished from anovulation due to the immaturity of the HPO axis. Furthermore, the clinical value of signs of hyperandrogenism is low; therefore, increased serum androgen concentrations represent the best marker of androgen excess. In addition, the value of PCOM, a key criterion for setting the diagnosis in adult women, is low in adolescents, due to the changes in ovarian appearance and the technical limitations of the transabdominal ultrasound. As a result, a high index of suspicion and close follow-up are necessary for establishing the diagnosis of PCOS.

Concerning treatment, individualized management is required to change the natural history of the reproductive and metabolic outcomes of this complex condition. Lifestyle intervention in overweight and obese adolescents may reduce PCOS-associated long-term complications, such as T2DM and cardiovascular disease. The efficacy and safety of the pharmaceutical approach are well-documented in adults with PCOS but limited in adolescents. Therefore, more data from RCTs are needed to establish a therapeutic strategy. Close monitoring for metabolic derangements, evaluation of the process of the disease and exclusion of other PCOS-mimicking diseases is crucial in this population.

Compliance with Ethical Standards

Conflict of Interest The authors have no conflict of interest to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril. 2012;97(1):28–38e25. https://doi.org/10.1016/j.fertnstert.2011.09.024.
2. Fanelli F, Gambineri A, Mezzullo M, Vicennati V, Pelusi C, Pasquali R, et al. Revisiting hyper- and hypo-androgenism by tandem mass spectrometry. Rev Endocr Metab Disord. 2013;14(2):185–205. https://doi.org/10.1007/s11154-013-9243-y.
3. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, et al. The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. Eur J Endocrinol. 2014;171(4):P1–29. https://doi.org/10.1530/EJE-14-0253.
4. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013;98(12):4565–92. https://doi.org/10.1210/jc.2013-2350.
5. Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific Statement on the Diagnostic Criteria, Epidemiology, Pathophysiology, and Molecular Genetics of Polycystic Ovary Syndrome. Endocr Rev. 2015;36(5):487–525. https://doi.org/10.1210/er.2015-1018.
6. Zhao H, Lv Y, Li L, Chen ZJ. Genetic Studies on Polycystic Ovary Syndrome. Best Pract Res Clin Obstet Gynaecol. 2016;37:56–65. https://doi.org/10.1016/j.bpobgyn.2016.04.002.

7. Sir-Petermann T, Hitchsfeld C, Maliqueo M, Codner E, Echiburu B, Gazitua R, et al. Birth weight in offspring of mothers with polycystic ovarian syndrome. Hum Reprod. 2005;20(8):2122–6. https://doi.org/10.1093/humrep/dei009.
8. Rosenfield RL. The diagnosis of polycystic ovary syndrome in adolescents. Pediatrics. 2015;136(6):1154–65. https://doi.org/10.1542/peds.2015-1430.
9. Pasquali R, Gambineri A. Polycystic ovary syndrome: a multifaceted disease from adolescence to adult age. Ann N Y Acad Sci. 2006;1092:158–74. https://doi.org/10.1196/annals.1365.014.
10. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, 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(11):4237–45. https://doi.org/10.1210/jc.2006-0178.
11. Kamboj MK, Bonny AE. Polycystic ovary syndrome in adolescence: diagnostic and therapeutic strategies. Transl Pediatr. 2017;6(4):248–55. https://doi.org/10.21037/tp.2017.09.11.
12. Cunliffe WJ, Gould DJ. Prevalence of facial acne vulgaris in late adolescence and in adults. Br Med J. 1979;1(6171):1109–10. https://doi.org/10.1136/bmj.1.6171.1109.
13. Herold DA, Fitzgerald RL. Immunoassays for testosterone in women: better than a guess? Clin Chem. 2003;49(8):1250–1. https://doi.org/10.1373/49.8.1250.
14. Taieb J, Mathian B, Millot F, Patricot MC, Mathieu E, Queyrel N, et al. Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children. Clin Chem. 2003;49(8):1381–95. https://doi.org/10.1373/49.8.1381.
15. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19(1):41–7. https://doi.org/10.1093/humrep/deh098.
16. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab. 1999;84(10):3666–72. https://doi.org/10.1210/jcem.84.10.6079.
17. Chang WY, Knochenhauer ES, Bartolucci AA, Azziz R. Phenotypic spectrum of polycystic ovary syndrome: clinical and biochemical characterization of the three major clinical subgroups. Fertil Steril. 2005;83(6):1717–23. https://doi.org/10.1016/j.fertnstert.2005.01.096.
18. Fernandes AR. de Sa Rosa e Silva AC, Romao GS, Pata MC, dos Reis RM. Insulin resistance in adolescents with menstrual irregularities. J Pediatr Adolesc Gynecol. 2005;18(4):269–74. https://doi.org/10.1016/j.jpag.2005.05.006.
19. Zawadzki JKDA. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine F, et al., editors. Polycystic ovary syndrome 1992. Boston: Blackwell Scientific Publications. p. 377–84.
20. Terry NL, Ryan ME. Polycystic Ovary Syndrome (PCOS). Bethesda, Md: National Institutes of Health Library. 2012. Available at: http://prevention.nih.gov/workshops/2012/pcos/docs/PCOS_Bibliography.pdf. Accessed 27 Mar 2013.
21. Blank SK, Helm KD, McCartney CR, Marshall JC. Polycystic ovary syndrome in adolescence. Ann N Y Acad Sci. 2008;1135:76–84. https://doi.org/10.1196/annals.1429.005.
22. Villarroel C, Merino PM, Lopez P, Eyzaguirre FC, Van Velzen A, Iniguez G, et al. Polycystic ovarian morphology in adolescents with regular menstrual cycles is associated with elevated anti-Mullerian hormone. Hum Reprod. 2011;26(10):2861–8. https://doi.org/10.1093/humrep/der223.
23. Codner E, Villarroel C, Eyzaguirre FC, Lopez P, Merino PM, Perez-Bravo F, et al. Polycystic ovarian morphology in postmenarchal adolescents. Fertil Steril. 2011;95(2):702–6e1–2. https://doi.org/10.1016/j.fertnstert.2010.06.015.
24. Pena AS, Witchel SF, Hoeger KM, Oberfield SE, Vogiatzi MG, Misso M, et al. Adolescent polycystic ovary syndrome according to the international evidence-based guideline. BMC Med. 2020;18(1):72. https://doi.org/10.1186/s12916-020-01516-x.
25. Witchel SF, Oberfield S, Rosenfield RL, Codner E, Bonny A, Ibanez L, et al. The diagnosis of polycystic ovary syndrome during adolescence. Horm Res Paediatr. 2015;83:376–89. https://doi.org/10.1159/000375530.
26.• Naz MSG, Tehrani FR, Majd HA, Ahmadi F, Ozgoli G, Fakari FR, et al. The prevalence of polycystic ovary syndrome in adolescents: a systematic review and meta-analysis. Int J Reprod Biomed (Yazd). 2019;17(8):533–42. https://doi.org/10.18502/ijrm.v17i8.4818. **This meta-analysis recorded a wide variation (3.4% to 11%) in the prevalence of PCOS in adolescents, depending on the diagnostic criteria used.**
27. Avvad CK, Holeuwerger R, Silva VC, Bordallo MA, Breitenbach MM. Menstrual irregularity in the first postmenarchal years: an early clinical sign of polycystic ovary syndrome in adolescence. Gynecol Endocrinol. 2001;15(3):170–7.
28. Gardner J. Adolescent menstrual characteristics as predictors of gynaecological health. Ann Hum Biol. 1983;10(1):31–40. https://doi.org/10.1080/03014468300006161.
29. van Hooff MH, Voorhorst FJ, Kaptein MB, Hirasing RA, Koppenaal C, Schoemaker J. Predictive value of menstrual cycle pattern, body mass index, hormone levels and polycystic ovaries at age 15 years for oligo-amenorrhoea at age 18 years. Hum Reprod. 2004;19(2):383–92. https://doi.org/10.1093/humrep/deh079.
30. Maslyanskaya S, Talib HJ, Northridge JL, Jacobs AM, Coble C, Coupey SM. Polycystic ovary syndrome: an under-recognized cause of abnormal uterine bleeding in adolescents admitted to a children's hospital. J Pediatr Adolesc Gynecol. 2017;30(3):349–55. https://doi.org/10.1016/j.jpag.2016.11.009.
31. Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. Am J Obstet Gynecol. 2010;203(3):201.e1–5. https://doi.org/10.1016/j.ajog.2010.03.008.
32. Slayden SM, Moran C, Sams WM Jr, Boots LR, Azziz R. Hyperandrogenemia in patients presenting with acne. Fertil Steril. 2001;75(5):889–92. https://doi.org/10.1016/s0015-0282(01)01701-0.
33. Pfeifer SM, Kives S. Polycystic ovary syndrome in the adolescent. Obstet Gynecol Clin N Am. 2009;36(1):129–52. https://doi.org/10.1016/j.ogc.2008.12.004.
34. Balen AH, Laven JS, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: international consensus definitions. Hum Reprod Update. 2003;9(6):505–14. https://doi.org/10.1093/humupd/dmg044.
35. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91(2):456–88. https://doi.org/10.1016/j.fertnstert.2008.06.035.
36. Adams J, Franks S, Polson DW, Mason HD, Abdulwahid N, Tucker M, et al. Multifollicular ovaries: clinical and endocrine features and response to pulsatile gonadotropin releasing hormone. Lancet. 1985;2(8469–70):1375–9. https://doi.org/10.1016/s0140-6736(85)92552-8.
37. Venturoli S, Porcu E, Fabbri R, Pluchinotta V, Ruggeri S, Macrelli S, et al. Longitudinal change of sonographic ovarian aspects and endocrine parameters in irregular cycles of adolescence. Pediatr Res. 1995;38(6):974–80. https://doi.org/10.1203/00006450-199512000-00024.

38. Bridges NA, Cooke A, Healy MJ, Hindmarsh PC, Brook CG. Standards for ovarian volume in childhood and puberty. Fertil Steril. 1993;60(3):456–60.
39. Mortensen M, Rosenfield RL, Littlejohn E. Functional significance of polycystic-size ovaries in healthy adolescents. J Clin Endocrinol Metab. 2006;91(10):3786–90. https://doi.org/10.1210/jc.2006-0835.
40. Hart R, Doherty DA, Norman RJ, Franks S, Dickinson JE, Hickey M, et al. Serum antimullerian hormone (AMH) levels are elevated in adolescent girls with polycystic ovaries and the polycystic ovarian syndrome (PCOS). Fertil Steril. 2010;94(3):1118–21. https://doi.org/10.1016/j.fertnstert.2009.11.002.
41. Ibanez L, Lopez-Bermejo A, Callejo J, Torres A, Cabre S, Dunger D, et al. Polycystic ovaries in nonobese adolescents and young women with ovarian androgen excess: relation to prenatal growth. J Clin Endocrinol Metab. 2008;93(1):196–9. https://doi.org/10.1210/jc.2007-1800.
42. van Hooff MH, Voorhorst FJ, Kaptein MB, Hirasing RA, Koppenaal C, Schoemaker J. Polycystic ovaries in adolescents and the relationship with menstrual cycle patterns, luteinizing hormone, androgens, and insulin. Fertil Steril. 2000;74(1):49–58. https://doi.org/10.1016/s0015-0282(00)00584-7.
43. Yoo RY, Sirlin CB, Gottschalk M, Chang RJ. Ovarian imaging by magnetic resonance in obese adolescent girls with polycystic ovary syndrome: a pilot study. Fertil Steril. 2005;84(4):985–95. https://doi.org/10.1016/j.fertnstert.2005.04.039.
44. Eichenfield LF, Krakowski AC, Piggott C, Del Rosso J, Baldwin H, Friedlander SF, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Pediatrics. 2013;131(Suppl 3):S163–86. https://doi.org/10.1542/peds.2013-0490B.
45. Martin KA, Chang RJ, Ehrmann DA, Ibanez L, Lobo RA, Rosenfield RL, et al. Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2008;93(4):1105–20. https://doi.org/10.1210/jc.2007-2437.
46. Salley KE, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. Glucose intolerance in polycystic ovary syndrome–a position statement of the Androgen Excess Society. J Clin Endocrinol Metab. 2007;92(12):4546–56. https://doi.org/10.1210/jc.2007-1549.
47. Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(9):4133–60. https://doi.org/10.1210/jc.2009-2631.
48. Bremer AA. Polycystic ovary syndrome in the pediatric population. Metab Syndr Relat Disord. 2010;8(5):375–94. https://doi.org/10.1089/met.2010.0039.
49. Buggs C, Rosenfield RL. Polycystic ovary syndrome in adolescence. Endocrinol Metab Clin N Am. 2005;34(3):677–705, x. https://doi.org/10.1016/j.ecl.2005.04.005.
50. Hart R, Doherty DA. The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage. J Clin Endocrinol Metab. 2015;100(3):911–9. https://doi.org/10.1210/jc.2014-3886.
51. Anagnostis P, Tarlatzis BC, Kauffman RP. Polycystic ovarian syndrome (PCOS): Long-term metabolic consequences. Metabolism. 2018;86:33–43. https://doi.org/10.1016/j.metabol.2017.09.016.
52. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nat Rev Endocrinol. 2011;7(4):219–31. https://doi.org/10.1038/nrendo.2010.217.
53. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab. 1999;84(1):165–9. https://doi.org/10.1210/jcem.84.1.5393.
54. Sam S. Obesity and polycystic ovary syndrome. Obes Manag. 2007;3(2):69–73. https://doi.org/10.1089/obe.2007.0019.
55. Nestler JE, Jakubowicz DJ, de Vargas AF, Brik C, Quintero N, Medina F. Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. J Clin Endocrinol Metab. 1998;83(6):2001–5. https://doi.org/10.1210/jcem.83.6.4886.
56. Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, et al. A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. J Clin Endocrinol Metab. 1991;72(1):83–9. https://doi.org/10.1210/jcem-72-1-83.
57. Hannon TS, Janosky J, Arslanian SA. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. Pediatr Res. 2006;60(6):759–63. https://doi.org/10.1203/01.pdr.0000246097.73031.27.
58. Alemzadeh R, Kichler J, Calhoun M. Spectrum of metabolic dysfunction in relationship with hyperandrogenemia in obese adolescent girls with polycystic ovary syndrome. Eur J Endocrinol. 2010;162(6):1093–9. https://doi.org/10.1530/EJE-10-0205.
59. 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(2):492–7. https://doi.org/10.1210/jc.2005-1666.
60. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. Arch Pediatr Adolesc Med. 2003;157(8):821–7. https://doi.org/10.1001/archpedi.157.8.821.
61. Roe AH, Dokras A. The diagnosis of polycystic ovary syndrome in adolescents. Rev Obstet Gynecol. 2011;4(2):45–51.
62.• Li L, Feng Q, Ye M, He Y, Yao A, Shi K. Metabolic effect of obesity on polycystic ovary syndrome in adolescents: a meta-analysis. J Obstet Gynaecol. 2017;37(8):1036–47. https://doi.org/10.1080/01443615.2017.1318840. **This meta-analysis highlighted the importance of preventing/treating obesity for the management of PCOS in adolescents.**
63. Bruni V, Dei M, Nannini S, Balzi D, Nuvolone D. Polycystic ovary syndrome in adolescence. Ann N Y Acad Sci. 2010;1205:175–84. https://doi.org/10.1111/j.1749-6632.2010.05648.x.
64. Fulghesu A, Magnini R, Portoghese E, Angioni S, Minerba L, Melis GB. Obesity-related lipid profile and altered insulin incretion in adolescents with polycystic ovary syndrome. J Adolesc Health. 2010;46(5):474–81. https://doi.org/10.1016/j.jadohealth.2009.10.008.
65. Rossi B, Sukalich S, Droz J, Griffin A, Cook S, Blumkin A, et al. Prevalence of metabolic syndrome and related characteristics in obese adolescents with and without polycystic ovary syndrome. J Clin Endocrinol Metab. 2008;93(12):4780–6. https://doi.org/10.1210/jc.2008-1198.
66. Fruzzetti F, Perini D, Lazzarini V, Parrini D, Genazzani AR. Adolescent girls with polycystic ovary syndrome showing different phenotypes have a different metabolic profile associated with increasing androgen levels. Fertil Steril. 2009;92(2):626–34. https://doi.org/10.1016/j.fertnstert.2008.06.004.
67. Ibanez L, Valls C, Marcos MV, Ong K, Dunger DB, De Zegher F. Insulin sensitization for girls with precocious pubarche and with risk for polycystic ovary syndrome: effects of prepubertal initiation and postpubertal discontinuation of metformin treatment. J

Clin Endocrinol Metab. 2004;89(9):4331–7. https://doi.org/10.1210/jc.2004-0463.

68. Athyros VG, Tziomalos K, Karagiannis A, Anagnostis P, Mikhailidis DP. Should adipokines be considered in the choice of the treatment of obesity-related health problems? Curr Drug Targets. 2010;11(1):122–35. https://doi.org/10.2174/138945010790030992.
69.• Kaczmarek C, Haller DM, Yaron M. Health-related quality of kife in adolescents and young Adults with Polycystic Ovary Syndrome: A Systematic Review. J Pediatr Adolesc Gynecol. 2016;29(6):551–7. https://doi.org/10.1016/j.jpag.2016.05.006. **This meta-analysis showed a significant impairment in the quality of life of adolescent girls with PCOS. Body weight and BMI mediated this association.**
70. Glueck CJ, Morrison JA, Friedman LA, Goldenberg N, Stroop DM, Wang P. Obesity, free testosterone, and cardiovascular risk factors in adolescents with polycystic ovary syndrome and regularly cycling adolescents. Metabolism. 2006;55(4):508–14. https://doi.org/10.1016/j.metabol.2005.11.003.
71. Dokras A, Clifton S, Futterweit W, Wild R. Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis. Obstet Gynecol. 2011;117(1):145–52. https://doi.org/10.1097/AOG.0b013e318202b0a4.
72. Dokras A, Clifton S, Futterweit W, Wild R. Increased prevalence of anxiety symptoms in women with polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril. 2012;97(1):225–30 e2. https://doi.org/10.1016/j.fertnstert.2011.10.022.
73. Bernadett M, Szeman NA. Prevalence of eating disorders among women with polycystic ovary syndrome. Psychiatr Hung. 2016;31(2):136–45.
74. Toscani MK, Mario FM, Radavelli-Bagatini S, Wiltgen D, Matos MC, Spritzer PM. Effect of high-protein or normal-protein diet on weight loss, body composition, hormone, and metabolic profile in southern Brazilian women with polycystic ovary syndrome: a randomized study. Gynecol Endocrinol. 2011;27(11):925–30. https://doi.org/10.3109/09513590.2011.564686.
75. Salmi DJ, Zisser HC, Jovanovic L. Screening for and treatment of polycystic ovary syndrome in teenagers. Exp Biol Med (Maywood). 2004;229(5):369–77. https://doi.org/10.1177/153537020422900504.
76. Vatopoulou A, Tziomalos K. Management of obesity in adolescents with polycystic ovary syndrome. Expert Opin Pharmacother. 2020;21(2):207–11. https://doi.org/10.1080/14656566.2019.1701655.
77. Lass N, Kleber M, Winkel K, Wunsch R, Reinehr T. Effect of lifestyle intervention on features of polycystic ovarian syndrome, metabolic syndrome, and intima-media thickness in obese adolescent girls. J Clin Endocrinol Metab. 2011;96(11):3533–40. https://doi.org/10.1210/jc.2011-1609.
78. Marzouk TM, Sayed Ahmed WA. Effect of Dietary Weight Loss on Menstrual Regularity in Obese Young Adult Women with Polycystic Ovary Syndrome. J Pediatr Adolesc Gynecol. 2015;28(6):457–61. https://doi.org/10.1016/j.jpag.2015.01.002.
79. Mastorakos G, Koliopoulos C, Creatsas G. Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. Fertil Steril. 2002;77(5):919–27. https://doi.org/10.1016/s0015-0282(02)02993-x.
80. Yildiz BO. Approach to the patient: contraception in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2015;100(3):794–802. https://doi.org/10.1210/jc.2014-3196.
81. Gallo MF, Lopez LM, Grimes DA, Carayon F, Schulz KF, Helmerhorst FM. Combination contraceptives: effects on weight. Cochrane Database Syst Rev. 2014;1:CD003987. https://doi.org/10.1002/14651858.CD003987.pub5.
82. Wang A, Mo T, Li Q, Shen C, Liu M. The effectiveness of metformin, oral contraceptives, and lifestyle modification in improving the metabolism of overweight women with polycystic ovary syndrome: a network meta-analysis. Endocrine. 2019;64(2):220–32. https://doi.org/10.1007/s12020-019-01860-w.
83. Luque-Ramirez M, Nattero-Chavez L, Ortiz Flores AE, Escobar-Morreale HF. Combined oral contraceptives and/or antiandrogens versus insulin sensitizers for polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2018;24(2):225–41. https://doi.org/10.1093/humupd/dmx039.
84. Harmanci A, Cinar N, Bayraktar M, Yildiz BO. Oral contraceptive plus antiandrogen therapy and cardiometabolic risk in polycystic ovary syndrome. Clin Endocrinol. 2013;78(1):120–5. https://doi.org/10.1111/j.1365-2265.2012.04466.x.
85. Ibanez L, Diaz M, Sebastiani G, Marcos MV, Lopez-Bermejo A, de Zegher F. Oral contraception vs insulin sensitization for 18 months in nonobese adolescents with androgen excess: posttreatment differences in C-reactive protein, intima-media thickness, visceral adiposity, insulin sensitivity, and menstrual regularity. J Clin Endocrinol Metab. 2013;98(5):E902–7. https://doi.org/10.1210/jc.2013-1041.
86. Pasquali R, Gambineri A. Glucose intolerance states in women with the polycystic ovary syndrome. J Endocrinol Investig. 2013;36(8):648–53. https://doi.org/10.1007/BF03346757.
87. Ibanez L, Valls C, Ferrer A, Marcos MV, Rodriguez-Hierro F, de Zegher F. Sensitization to insulin induces ovulation in nonobese adolescents with anovulatory hyperandrogenism. J Clin Endocrinol Metab. 2001;86(8):3595–8. https://doi.org/10.1210/jcem.86.8.7756.
88. Arslanian SA, Lewy V, Danadian K, Saad R. Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. J Clin Endocrinol Metab. 2002;87(4):1555–9. https://doi.org/10.1210/jcem.87.4.8398.
89. Glueck CJ, Aregawi D, Winiarska M, Agloria M, Luo G, Sieve L, et al. Metformin-diet ameliorates coronary heart disease risk factors and facilitates resumption of regular menses in adolescents with polycystic ovary syndrome. J Pediatr Endocrinol Metab. 2006;19(6):831–42. https://doi.org/10.1515/jpem.2006.19.6.831.
90. Glueck CJ, Wang P, Fontaine R, Tracy T, Sieve-Smith L. Metformin to restore normal menses in oligo-amenorrheic teenage girls with polycystic ovary syndrome (PCOS). J Adolesc Health. 2001;29(3):160–9. https://doi.org/10.1016/s1054-139x(01)00202-6.
91. Al Khalifah RA, Florez ID, Dennis B, Thabane L, Bassilious E. Metformin or oral contraceptives for adolescents with polycystic ovarian syndrome: a meta-analysis. Pediatrics. 2016;137(5). https://doi.org/10.1542/peds.2015-4089.
92. Al-Zubeidi H, Klein KO. Randomized clinical trial evaluating metformin versus oral contraceptive pills in the treatment of adolescents with polycystic ovarian syndrome. J Pediatr Endocrinol Metab. 2015;28(7–8):853–8. https://doi.org/10.1515/jpem-2014-0283.
93. Ganie MA, Khurana ML, Eunice M, Gupta N, Gulati M, Dwivedi SN, et al. Comparison of efficacy of spironolactone with metformin in the management of polycystic ovary syndrome: an open-labeled study. J Clin Endocrinol Metab. 2004;89(6):2756–62. https://doi.org/10.1210/jc.2003-031780.
94. Zulian E, Sartorato P, Benedini S, Baro G, Armanini D, Mantero F, et al. Spironolactone in the treatment of polycystic ovary syndrome: effects on clinical features, insulin sensitivity and lipid profile. J Endocrinol Investig. 2005;28(1):49–53. https://doi.org/10.1007/bf03345529.
95. Ibanez L, Diaz M, Garcia-Beltran C, Malpique R, Garde E, Lopez-Bermejo A, et al. Toward a Treatment Normalizing Ovulation

Rate in Adolescent Girls With Polycystic Ovary Syndrome. J Endocr Soc. 2020;4(5):bvaa032. https://doi.org/10.1210/jendso/bvaa032.

96. Simard J, Luthy I, Guay J, Belanger A, Labrie F. Characteristics of interaction of the antiandrogen flutamide with the androgen receptor in various target tissues. Mol Cell Endocrinol. 1986;44(3):261–70. https://doi.org/10.1016/0303-7207(86)90132-2.
97. Ibanez L, Potau N, Marcos MV, de Zegher F. Treatment of hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism in nonobese, adolescent girls: effect of flutamide. J Clin Endocrinol Metab. 2000;85(9):3251–5. https://doi.org/10.1210/jcem.85.9.6814.
98. Golland IM, Elstein ME. Results of an open one-year study with Diane-35 in women with polycystic ovarian syndrome. Ann N Y Acad Sci. 1993;687:263–71. https://doi.org/10.1111/j.1749-6632.1993.tb43875.x.
99. Sahin Y, Dilber S, Kelestimur F. Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism. Fertil Steril. 2001;75(3):496–500. https://doi.org/10.1016/s0015-0282(00)01764-7.
100. Seaman HE, de Vries CS, Farmer RD. Venous thromboembolism associated with cyproterone acetate in combination with ethinyloestradiol (Dianette): observational studies using the UK General Practice Research Database. Pharmacoepidemiol Drug Saf. 2004;13(7):427–36. https://doi.org/10.1002/pds.896.
101. Tartagni MV, Alrasheed H, Damiani GR, Montagnani M, De Salvia MA, De Pergola G, et al. Intermittent low-dose finasteride administration is effective for treatment of hirsutism in adolescent girls: a pilot study. J Pediatr Adolesc Gynecol. 2014;27(3):161–5. https://doi.org/10.1016/j.jpag.2013.09.010.
102. Hamzavi I, Tan E, Shapiro J, Lui H. A randomized bilateral vehicle-controlled study of eflornithine cream combined with laser treatment versus laser treatment alone for facial hirsutism in women. J Am Acad Dermatol. 2007;57(1):54–9. https://doi.org/10.1016/j.jaad.2006.09.025.
103. Smith SR, Piacquadio DJ, Beger B, Littler C. Eflornithine cream combined with laser therapy in the management of unwanted facial hair growth in women: a randomized trial. Dermatol Surg. 2006;32(10):1237–43. https://doi.org/10.1111/j.1524-4725.2006.32282.x.