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Adolescence and Polycystic Ovary Syndrome: current concepts on diagnosis and treatment

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ABSTRACT

Background: Adolescence is a time characterized by changes in reproductive hormones and menstrual patterns, which makes it difficult to diagnose Polycystic Ovary Syndrome (PCOS) in this population. The diagnosis of PCOS has great physical and psychosocial impact in the young person. Despite the importance of a diagnosis of PCOS at adolescence, data available are limited. **Aims:** This review focuses on analyzing markers of PCOS diagnosis and possible treatments in adolescence. **Results:** Although during adolescence diagnosis criteria of PCOS overlap with physiological changes including clinical manifestations of hyperandrogenism (acne and hirsutism,), oligo/amenorrhea, anovulation and ovarian microcysts, there is agreement that irregular menses and hyperandrogenemia should be used to diagnose PCOS in this population. Moreover, considering that PCOS phenotype could change through the reproductive age and that adolescents display heterogeneous ovarian morphology, it has been proposed that diagnosis of PCOS should be confirmed after the age of 18. The first-line treatment for menstrual irregularity and hirsutism are oral contraceptive pills and for obesity and metabolic abnormalities are lifestyle changes. Insulin-sensitizer drugs, such as metformin, may be added to the treatment in the presence of metabolic alterations. Antiandrogen drugs may also be associated for treating moderate to severe hirsutism. **Conclusions:** During adolescence, physiological changes overlap with signs and symptoms of PCOS; thus the diagnosis criteria should be carefully considered. Regarding the treatment of adolescents with PCOS, non-pharmacological interventions include lifestyle changes. Pharmacological treatments comprise oral contraceptive pills, antiandrogens and metformin, used isolated or combined.

Keywords: Polycystic Ovary Syndrome; adolescence; oligo/amenorrhea; anovulation; cardiovascular risk; metformin; oral contraceptive pills

Review criteria

• PubMed searches were used to classify diagnosis criteria and treatments for adolescents with PCOS.

• Relevant articles were identified using search terms including adolescence and PCOS, prevalence of PCOS in adolescence, obesity and PCOS, cardiovascular risk and PCOS adolescent, treatments of adolescence with PCOS, for articles published in English before February 2015.

• Search results were evaluated to identify diagnosis criteria and adequate treatment of adolescents with PCOS.

Message for the clinic

• Physiological changes in adolescence overlap with signs and symptoms of PCOS; thus the diagnosis criteria should be carefully considered.

• Clinical presentation may be subtler than in adults with PCOS; therefore PCOS diagnosis in adolescence should include the three criteria: oligo/anovulation, biochemical hyperandrogenism, and polycystic ovaries on ultrasound.

• Early and continuous follow-up of adolescents with suspected or confirmed PCOS is relevant in order to prevent that more severe PCOS phenotypes develop during the adult life.

• The first line treatment for adolescents with PCOS is lifestyle changes. Pharmacological treatments comprise oral contraceptive pills, antiadrogens and metformin, used isolated or combined.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in reproductive-aged women with a prevalence of 8%–18% (1), however; the prevalence changes when comparing different ethnicities (2-5). PCOS is regarded as more than a pathology focused on the ovary since this syndrome is associated with a wide range of reproductive and metabolic disorders including obesity, type 2 diabetes mellitus, dyslipidemia, hypertension, and risk factors for cardiovascular disease (6, 7).

The classic criteria, developed at a US National Institutes of Health (NIH) consensus conference (8), require chronic anovulation and clinical or biochemical signs of hyperandrogenism and the absence of other metabolic/endocrine causes for the diagnosis of PCOS. The Rotterdam criteria (9) introduce the clinical picture of polycystic ovarian morphology on ultrasound as additional criteria, and require two of the following features: a history of ovulatory disorders with menstrual irregularity, and clinical/biochemical signs of hyperandrogenism and the polycystic ovary appearance on ultrasound. Later, the Androgen Excess and Polycystic Ovary Syndrome Society (AEPCOS Society) criteria (10) and their subsequent revisions stress hyperandrogenemia as the primary pathophysiologic feature (11, 12).

Adolescence is a time characterized by changes in reproductive hormones and menstrual patterns making difficult the diagnosis of PCOS in this population. The

present review aims to discuss the possible markers in the diagnosis and treatment of PCOS during adolescence.

Review methods

In this review, the diagnosis criteria for adolescents with PCOS are considered and possible early markers are discussed. According the different signs and symptoms (menstrual irregularity, hirsutism and obesity and metabolic disorders) each corresponding treatment is discussed. Relevant articles were identified by a literature search in PubMed and analyzed by each author.

Markers of Polycystic Ovary Syndrome and diagnosis during adolescence

Adolescence is a period of life when signs and symptoms that characterize PCOS overlap with physiological changes (13). However, while an early diagnosis of PCOS is relevant, the management of adolescents with PCOS depends on pediatric specialties. In fact, among 181 adolescents with PCOS from the Cincinnati Children´s Hospital, Auble *et al* (14) assessed for differences in the diagnosis of PCOS across 3 pediatric specialties. They found that failure in the diagnostic PCOS occurred in 38% of Pediatric Endocrinology clinic and in 20% of Adolescent Medicine and Pediatric and Adolescent Gynecology clinics. These data reveal a high prevalence of failure in the early detection of a potential population of young PCOS patients.

During puberty and adolescence, the three criteria for the diagnosis of PCOS: oligo/amenorrhea/anovulation, clinical or biochemical hyperandrogenism, and/or polycystic ovaries on ultrasound (15) have common characteristics with physiological features found in adolescence. Firstly, analyzing the pattern of menstrual cycles, after menarche, oligo/amenorrhea and anovulation are highly prevalent (85% in the first year post-menarche to 59% in the third year) (16), menstrual irregularity is present in a 14% of adolescents (<22 or > 41 days for two or more in previous year), and oligomenorrhea in 47% of adolescents (17). A relevant study carried out by West *et al.* (18) reveals that menstrual irregularity and/or elevated androgen levels at 16 years are associated with symptoms of PCOS at 26 years. Second, regarding clinical evidence of hyperandrogenism, hyperinsulinemic-related androgen excess is the most common cause of hirsutism, acne and menstrual irregularity in adolescent girls (19). Third, considering ovarian volume, 30% of adolescents have ovarian volume larger than adults (> 10 cm^3) (19). A recent study (20) reported that adolescent women display increased ovarian size (11.5 cm3) during first 2 years from menarche. The authors also found that ovarian size decreased with age (20). These data point out the importance of avoiding

ovarian size as marker of diagnosis of PCOS during the first 2 years after menarche. In addition, during puberty and adolescence, polycystic ovaries are determined by pelvic ultrasound instead of trans-vaginally, thus, conducting to less accurate examination and no uniform data (19). Taking together, these data suggest that the most reliable diagnostic criteria for PCOS during adolescence are the presence of the three signs and symptoms of PCOS: hyperandrogenemia, irregular menses persisting 2 years after menarche and polycystic ovarian morphology as suggested by increased ovarian volume (Figure 1). In agreement with previous suggestions (21), we consider that, if the vaginal ultrasound is not available, the diagnosis of PCOS during adolescence may be suggested by using irregular menses in association with hyperandrogenemia. A recent Task Force (22) recommends to use follicle number per ovary (FNPO) for the definition of polycystic ovary morphology setting the threshold at ≥25, but only when using newer technology that affords maximal resolution of ovarian follicles (i.e. transducer frequency ≥8 MHz). The authors recommend the use of ovarian volume rather than FNPO for the diagnosis of polycystic ovary morphology when such technology is not available. In addition, other markers should be considered for an early diagnosis of PCOS, some of them are discussed in the following paragraphs.

Premature pubarche (PP) is defined as the development of pubic and axillary hair before age of 8 years (23). Most cases of PP occur because of an early and isolated maturation of the zona reticularis of the adrenal gland and idiopathic PP has been considered an early sign of PCOS (24). Although the relationship between low-birth weight (LBW) and PP remains controversial (25- 28), evidence indicates that LBW and PP are associated with endocrine-metabolic abnormalities during adolescence including hyperinsulinemia and dyslipidemia of pubertal onset, and functional ovarian hyperandrogenism and ovulatory dysfunction at adolescence (26, 27, 29). Moreover, genetic and environmental factors acting in complex multifactorial pathways underlie this sequence (26, 30). The current hypothesis proposed to explain the development of these long-term alterations involves the adaptive response to in-uterus malnutrition and modifications thereof, called “Fetal Origins” with the risk to conduce to obesity (31, 32). Menarche represents the end of maximal skeletal growth and the beginning of reproductive life. The duration of puberty in girls depends on the timing of its onset; the earlier the onset of puberty the longer its duration. (33). The less prepubertal height gain is usually compensated by more pubertal growth, however; in girls who have experienced LBW followed by rapid catch-up growth in infancy, this compensatory

mechanism fails and there is a higher secretion of suprarenal androgens (34). As it was concluded in the First Latin-American Consensus of PCOS (32), among the factors contributing to PP, it has been reported: 1.- altered androgen receptor gene CAG repeat polymorphism (34); 2.- increased methylation of androgen receptor (36); 3.- increased levels of insulin and insulin growth factors (37, 38); 4.- decreased insulin sensitivity during prepubertal and pubertal stages (35); 5.- reduced aromatase activity as a consequence of the CYP19 gene variation (39); and 6.- alterations in other gene involved is steroidogenesis, such as 21-hydroxylase, 3-beta-hydroxysteroid dehydrogenase type 2, 5-alpha reductase and 11-beta-hydroxysteroid dehydrogenase (24).

In summary, considering that PP is associated with ovarian hyperandrogenism, decreased insulin sensitivity and LBW (23, 27), PP is taken as an early marker of future pathologies during adolescence and adult life and thus, girls with PP should be continuously monitored until at least two years of menarche (23, 27, 32, 40). While genes related to steroidogenesis may be altered in girls with PP, it appears that obesity – as compensatory mechanism of LBW during the first years of life- represents a more determinant factor which could favor the onset of PCOS in genetically predisposed girls. In view of girls and adolescents show a heterogeneous ovarian morphology overlapping with PCOS and that PCOS phenotype could change through the reproductive age, it appears that the diagnosis of PCOS should be confirmed after the age of 18 years. However, we suggest that girls given the diagnosis of LBW and PP should have periodical follow ups.

Menarche in girls with PCOS exhibits a wider age range than control subjects, ranging between 9 to 16 years old (41) and it is difficult to define predictors for age at menarche in these girls (42- 46). Based on several factors that have opposing influence, the age of menarche in girls with PCOS may be earlier or later than controls. In that context, disturbed gonadotropin secretion and arrest on follicle growth that are frequent characteristics of PCOS, results in a later age at menarche (47, 48) whereas girls who develop PCOS and were born small for gestational age (SGA) (49) as well as those with higher weight have an earlier age at menarche (50, 51). In addition to overweight and arrested follicle development, genetic variants may also be involved in normal menarche. In fact, the chromosome 6 rs7759938-T variant has recently been reported to be associated with earlier age at menarche in women with PCOS (42).

In summary, environmental and genetic factors influence age at menarche and also the development of PCOS during adolescence. In addition, all these findings suggest that those factors involved in the fetal development may be implicated in the generation of PCOS. In this sense, although the origin of disturbances on insulin-like growth factor (IGF)-1 system in adulthood needs to be elucidated, its potential contribution to metabolic complication associated with fetal growth restriction is accepted (51). Moreover, under-nutrition is related to decreased IGF-1 levels (52), and SGA newborns have lower levels of IGF-1 and IGF-binding protein-3 (IGFBP-3) than appropriate weight for gestational age newborns (53). Alterations on the IGF-IGBP-3 axis have been reported to persist in the adult life and seem to contribute to the long-term metabolic and cardiovascular complications associated with fetal growth restriction (32, 54).

It is well known that pulse frequency of gonadotropin-releasing hormone (GnRH) is increased in women with PCOS which results in high levels of luteinizing hormone (LH) and increased LH to follicle stimulating hormone (FSH) ratio (55). Increased pulse frequency of GnRH and altered diurnal pulse pattern may occur even before menarche, and this is a major feature in adolescent girls with PCOS (16). Moreover, in these adolescents with PCOS the increased GnRH pulse frequency is associated with hyperandrogenism and increased ovarian volume (16) and is resistant to suppression by progesterone (56). These data denote that the reproductive axis is altered in adolescents with PCOS; in addition, studies have shown that anti-mullerian hormone (AMH) levels are higher in PCOS girls as compared with controls (57- 60).

It is important to point out that metabolic features of PCOS are already present in daughters of PCOS women before the onset of hyperandrogenism. In this sense, evidence suggests that both pre-pubertal and pubertal daughter of PCOS women (PCOSd) show increased insulin levels after oral glucose tolerance test, triglycerides and serum testosterone levels and lower adiponectin and sex hormone binding globulin (SHBG) levels when compared with pre-pubertal and pubertal daughters of controls (61).

In summary, clinical history, LBW, PP, timing of menarche and SGA may be the first alerts to the development of PCOS during adolescence; additional markers may also be considered, such as IGF-1 related to SGA newborns, LH/FSH ratio, and AMH (Figure 2).

Prevalence of Polycystic Ovary Syndrome in Adolescence

The prevalence of PCOS was early reported between 6.5-6.7% in adult women (62, 63). Later studies are given as approximately 8%-18% depending on the diagnosis criteria and ethnic population (64). However, because of the diversity among the diagnostic criteria and the fact that, as it was already cited in the previous paragraphs, many symptoms and signs of PCOS may overlap with normal puberty (65, 66) estimating the prevalence of PCOS in adolescents is not a simple issue. In consequence, only few reports have been published evaluating the prevalence of PCOS at adolescence. A cross-sectional community-based study was undertaken in a sampled census block of Mumbai, India to assess the prevalence of PCOS among 778 adolescents and young women aged 15-24 years (67) that was estimated to be 22.5% by Rotterdam and 10.7% by Androgen Excess Society criteria. Non-obese comprised 71.8% of PCOS diagnosed by Rotterdam criteria and mild PCOS (oligomenorrhea and polycystic ovaries on ultrasonography) reached the 52.6% (67). In other cross-sectional study from the Columbia University Medical Center, including Caucasian, Hispanic and African American girls, 24.2% of girls showed to present PCOS as defined by NIH criteria (68). However, authors did not correlate the prevalence of PCOS in adolescents with ethnicity. Other cross-sectional study conducted in 1549 high school student girls aged 16-20 years from Iran reported a prevalence of 8.3% PCOS (69). Limitations on interpreting these data are mostly related to different ethnics and the lack of prevalence studies based on specific diagnostic criteria for adolescent populations, in which distinguish PCOS features and physiological changes is a challenge to overpass.

Treatment of Polycystic Ovary Syndrome in Adolescence

The most frequent concerns about the treatment of adolescents with PCOS include those related to menstrual irregularity, symptoms of androgen excess, obesity and its consequences, and the impact of self-esteem and self-image at this crucial developmental stage (Table 1).

Menstrual irregularity

The 3rd PCOS Consensus carried out in Amsterdam (70) determined that menstrual irregularity in adolescents with PCOS is secondary to chronic anovulation and may present as persistent oligomenorrhea, secondary amenorrhea, or primary amenorrhea. In addition, during adolescence, oligomenorrhea may also be accompanied by menorrhagia (70, 71).

Obesity worsens metabolic and reproductive features of PCOS and the rising prevalence of peripubertal obesity may heighten the severity of PCOS during adolescence. In addition, recent findings have revealed a high prevalence of hyperandrogenemia among obese peripubertal adolescents indicating that those girls are at risk for progressing toward PCOS (72). Obesity affects the severity of PCOS by worsening insulin resistance and compensatory hyperinsulinemia, which augments the production of androgens by ovaries and adrenals and suppresses sex hormone-binding globulin (SHBG), thereby increasing androgen bioavailability. Moreover, altered luteinizing hormone (LH) secretion plays an important role in the pathophysiology of PCOS, and although obesity is generally associated with relative reductions of circulating LH, higher LH appears to be the best predictor of increased free testosterone among peripubertal girls with obesity (72).

Obesity in adolescents may also impact on androgen production in the expanded adipose tissue and disturbing adipokine/cytokine secretion (72, 73). Therefore, adolescents with PCOS present higher risk for developing metabolic comorbidities such as metabolic syndrome, dysglicemia and dyslipidemia (72). All these data point out the relevance of weight loss as a key goal on the management of adolescents with PCOS (71, 72).

It has been reported that the loss of 5 to 10% of body weight in obese women with PCOS restores regular menstrual cycles (74, 75). Similar findings have been found in adolescents. Mean weight loss of 6.5% in adolescents with PCOS following two different dietary intervention (low carbohydrate or low fat) improved menstrual irregularity after 12-week of treatment (76). Weight loss and resumption of menses were similar between low carbohydrate and low flow fat (76). In other study with obese adolescents with PCOS, oligomenorrhea and/or amenorrhea decreased by 58% after 1-year trial of intensive lifestyle intervention, including nutrition education, exercise training, and behavior therapy, achieving weight loss around 3.9 kg/m^2 (77). Indeed, Mediterranean diet, low in fat and high in fruits and vegetables, along with moderate-intensity exercise and smoking cessation have also been reported as the recommended interventions especially for obese adolescents with PCOS (78).

There is still no consensus whether the insulin-sensitizer drug, metformin, offers any additional benefit in weight loss when it is administrated as an adjuvant for dietary and lifestyle interventions in obese adolescents with PCOS (79- 81). In fact, some authors argue that metformin monotherapy is not recommended for restoration of

menstrual regularity in adolescents (82), but others agree that metformin may be the treatment of choice when lifestyle modifications are ineffective (79- 81). A recent study reports that metformin shows limited or no benefit in treating hirsutism and acne in adolescents with PCOS but is recommended to treat metabolic abnormalities (21).

Hormonal contraceptives are considered as the first-line pharmacological treatment for adult PCOS women with menstrual irregularities and not been managed for infertility. Regarding adolescents with PCOS, oral contraceptive pills (OCPs) may be also employed to manage menstrual irregularity in lean or overweight PCOS girls not presenting metabolic comorbities. For obese PCOS girls, who fail to lose weight through diet or lifestyle intervention, metformin, could be added as an adjuvant of the lifestyle changes (71). Metformin could act on decreasing ovarian androgen secretion and contributing to improvement of menstrual cyclicity in those patients (83). In a recent meeting to design clinical practice guideline for the diagnosis and treatment of women with PCOS, the Endocrine Society and the European Society of Endocrinology concluded that OCPs are an important treatment option to adolescents with PCOS (20). Moreover, it has been established that combined OCPs are preferred in adolescents with menstrual irregularity and hirsutism since cyclic progestin is no effective in treating androgenic symptoms (71). In view of OCPs are a common treatment for menstrual irregularity and hirsutism, in the following section this treatment is widely discussed.

Hirsutism

Hirsutism is a relatively common condition in women, characterized by excessive growth of terminal hair in a male pattern distribution. Androgen excess is the most common cause of hirsutism, acne and menstrual irregularity in adolescent girls (19). Hyperinsulinemia secondary to insulin resistance may aggravate androgen excess because insulin act as a co-gonadotropin activating the enzymatic cytochrome C450 complex in the ovary, leading to an increased ovarian androgen release (19). Furthermore, androgens play a fundamental role in the conversion of fine, non-pigmented vellus hair into course, pigmented terminal hair in androgen-sensitive areas (84). Not only circulating but also local androgens contribute to terminal hair development (71). In this sense, the enzyme 5α reductase, responsible for converting testosterone to the potent androgen dihydrotestosterone, is essential in the local androgen environment (71). In contrast, circulating androgen levels are not entirely

associated with local androgen concentration and for this reason the severity of hirsutism may not closely correlate with measurable androgens (71).

PCOS remains the most common cause of hirsutism (69, 85, 86). The treatment of hirsutism consists of management of expectations, destruction of terminal hair growth through cosmetic actions, and prevention of terminal hair growth (71). As we previously discussed, obese adolescents with PCOS who achieved a modest weight loss through a lifestyle intervention (diet, exercise and behavior modifications) restores menstrual cycles with the reductions in free androgen index levels and increases in sex hormone-binding globulin (SHBG) concentrations (76- 81, 87). Besides non-pharmacological therapy (weight loss through dietary or lifestyle modification and mechanical/physical hair removal), OCPs remain the first-line treatment for hirsutism (88). Combined OCPs, containing ethinyl estradiol (EE_2) and a progestin, reduce androgen excess and hirsutism in adolescents with PCOS (89). The treatment with OCPs increased SHBG levels after 3 months of treatment and reduced hirsutism after 6 month (89). Vitek and Hoeger (71) point out the needing to consider that progestins can exert both antiandrogenic and androgenic effects by competitively binding 5α reductase and androgen receptor when selecting a combined OCP for the treatment of hirsutism. However, despite cyproterone acetate is a progestin that exhibits significant antiandrogenic properties whereas drospirenone (DRSP), analogue of spironolactone, exhibits weak antiandrogenic and antialdosterone effects (71, 90, 91) evidence indicates that any OCP increases SHBG levels, decreases testosterone concentrations, and decreases Ferriman-Gallwey scores in women with PCOS (89). Another variable to consider for selecting a combined OCP is the dose of EE_2. OCPs containing 30 or 35 µg of EE_2 reduce hirsutism (90, 91) but only few studies with lower doses have been studied suggesting OCPs containing 20 µg of EE_2 may be effective for treating mild hirsutism (92, 93). It is important to consider that higher dose of EE2 than 35 µg are less favorable in metabolic and cardiovascular aspects (94).

Antiandrogen agents may be needed in addition to OCPs in adolescents with moderate to severe hirsutism (95). It is important to consider that to prevent feminization of a male fetus the use of antiandrogen drugs requires concurrent use of an effective contraception method (96) in sexually active women. Antiandrogen drugs include spironolactone and cyproterone acetate. The androgen receptor antagonist, flutamide shows liver toxicity depending on the dose and for this reason, whereas some authors suggest a limited role in managing hirsutism (97), others reported that the use of

low doses of flutamide (62.5-250 mg/day), in girls and young women, is associated with complete hepatic tolerability even after long-term use (98- 100). Given the absence of hepatoxicity with low flutamide dose and the relevance of flutamide in modulating lipid profile (101) and insulin sensitivity (102) reported in PCOS women these additional benefits should be considered in girls and adolescents with PCOS.

Data supports the use of non-pharmacological treatments such as electrolysis for removing permanent hair in localized areas and lasers (particularly alexandrite and diode lasers) for long-term to permanent hair reduction (88, 103, 104). Topical eflornithine is used as monotherapy for mild hirsutism, mainly facial, and also as an adjuvant therapy with lasers or pharmacotherapy in more severe cases (88, 105).

While insulin sensitizers improve important metabolic and endocrine disturbances in PCOS (73, 78, 82, 106), they are not recommended when hirsutism is the sole indication for use. Thus, monotherapy with an insulin sensitizer does not significantly improve hirsutism (68, 81).

In a comparison study, Ibañez *et al* (107) found that both ethinylestradiol-cyproterone acetate (EE_2-CA) and a low-dose association of pioglitazone (7.5 mg/d), flutamide (62.5 mg/d), and metformin (850 mg/d) (PioFluMet) treatments for 18 months attenuated androgen excess (107). Summarizing, the first line of treatment for hirsutism is combined OCP. Evidence indicates that combined OCP indirectly reduce hirsutism by decreasing androgen levels and increasing SHBG production. In the presence of moderate to severe hirsutism, it will be often needed to add an antiandrogen agent to therapy with OCPs.

Obesity and metabolic disorders

Obesity, defined as body mass index (BMI) > 95 th percentile, is present in a significant proportion of adolescents with PCOS (71) and is associated with lower quality of life (108). As previously mentioned, intensive lifestyle interventions (weight loss and physical exercise) reduces androgen excess, restores menstrual regularity, and improves insulin resistance and dyslipidemia (76, 77, 87). In turn, there are limiting data regarding the most effective dietary intervention or physical exercise for obese adolescents with PCOS (71, 109). Caloric reduction of 500-1,000 kcal per day lead to weight loss but it is unclear if low carbohydrate or low fat diets are preferred for achieving and maintaining long term weight loss (71, 109). Regarding physical exercise, 3 h per week for 12 weeks reduces insulin resistance, triglycerides, and visceral fat in women with PCOS (71, 110). Considering that continued weight gain is

common in adult women with PCOS, prevention of weight gain during adolescence should be one of the most important goals in the management of this population (71, 111).

Currently it is well established that adolescents with PCOS should be screened for metabolic disturbances (112). However, there are some controversial points about the definition of metabolic syndrome (MetS) in adolescents by the International Diabetes Federation (113, 114). In this context, while the prevalence of MetS in adolescents with PCOS is higher than in BMI-paired control girls, MetS is associated to the presence of obesity (115). In addition, it has been recently reported that adolescents with PCOS show significantly increased insulin resistance but without clinical features of MetS or obesity (116).

Regarding treatments of metabolic disorders in adolescents with PCOS, Ibañez et al (117) demonstrated that metformin alone (1,275 mg per day) and associated with low-dose flutamide (metformin 1,275 mg + flutamide 250 mg per day) improved lipid profiles in lean hyperinsulinemic adolescents with PCOS. In a recent clinical review, Palomba *et al* (118) discussed the management of oligo-amenorrhea in adolescents with PCOS. The authors suggest that metformin and OCPs are both effective drugs for treating oligo-amenorrhea in adolescents with PCOS. In contrast, other studies have reported that diet and lifestyle changes may improve metabolic parameters in obese individuals and there is no evidence that metformin alone improve metabolic parameters in adolescent with PCOS in the absence of glucose intolerance or diabetes (71, 87). In summary, evidence indicates that diet and lifestyle changes are the first line of obesity treatment in adolescents with PCOS and metformin is useful in the presence of insulin resistance and metabolic alterations.

Anxiety, cognitive, and depressive assessment

Adult women with PCOS suffer from minor psychiatric disorders, such as depression and anxiety and they are more likely to be depressed compared to healthy women but little is known whether rates of depression or anxiety are increased in adolescent with PCOS. Teens with PCOS have serious health issues that impact them on multiple levels - hormonal concerns affecting female health and fertility, disfiguring body changes causing self-image problems, and lifelong health consequences related to metabolic disorders (119). A recent review on articles published during the period from 1985 to 2009 to deal with the association between psychological morbidity, and clinical and biochemical changes affecting the quality of life in adolescents with PCOS found

high risks for depression and affective disorders that impair their quality of life (120). On the other hand, in a small pilot study, Ghazeeri *et al* (121) assessed for cognitive, anxiety, and depressive states in Lebanese adolescent girls with and without PCOS, showing no major differences between both groups except in cognitive levels. In agreement with these data, no different rates of depression or anxiety have been described in a large community-based sample in New Zeland (122, 123). In summary, while an association between PCOS and depression assessments has not been established yet, improvements on hormonal and metabolic parameters may impact positively in self-image and esteem.

Conclusions

Adolescence is a time characterized by changes in reproductive hormones and menstrual patterns making difficult the diagnosis in this population and physiological changes overlap with signs and symptoms that characterize PCOS. There is a consensus that for the diagnosis of PCOS during adolescence all the three criteria for PCOS and not only two out of three - as recommended by the Rotterdam Consensus for adult women (oligo/amenorrhea/anovulation, biochemical hyperandrogenism, and polycystic ovaries on ultrasound) have to be present.

Unfortunately there is a failure on diagnosing PCOS during early ages and for this reason, early markers of the syndrome need to be better explored as predictor factors for PCOS in young girls. Some of these markers include LBW, PP, obesity, premature menarche and later higher AMH levels, increased androgen levels, menstrual irregularity and hirsutism. In view of PCOS phenotype could change through life and considering that adolescents show heterogeneous ovarian morphology and metabolic features that may overlap with PCOS, there is agreement that diagnosis should be confirmed after the age of 18 years. However, girls in the risk groups (LBW, PP, obesity, premature menarche and later, those presenting higher AMH levels, increased androgen levels, menstrual irregularity and hirsutism) should be continuously monitored.

Regarding the treatment of adolescents with PCOS, non-pharmacological interventions include lifestyle changes for obese girls or normal-weight girls with metabolic abnormalities and cosmetic treatments for hirsutism. The first line pharmacological treatment is represented by combined OCP. Combined OCP are effective in treating androgenic symptoms and menstrual irregularity. For moderate or severe hirsutism, the addition of an antiandrogen drug should be considered. Metformin

is beneficial for metabolic/glycemic abnormalities and is regarded as a second-line treatment for improving menstrual irregularities, but it has limited or no benefit in treating hirsutism. Risks and benefits of treatment must be carefully considered and discussed with the patient. A minimum of 6 months is required to see benefits from pharmacotherapy and lifelong treatment is often necessary for sustained effects. Non-pharmacological mechanical or physical treatments for hirsutism are additional, current options.

Further studies on prevalence, diagnosis accuracy and new treatment options are needed in this population of young girls with PCOS.

Author contributions

PMS: Concept/design, Data analysis/interpretation, Critical revision of article; ABM: Concept/design, Data analysis/interpretation, Data collection.

References

1. March WA, Moore VM, Willson KJ et al. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod* 2010; **25**: 544-51.
2. Asuncion M, Calvo RM, San Millan JL et al. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *J Clin Endocrinol Metab* 2000; **85**: 2434-8.
3. Azziz R, Sanchez LA, Knochenhauer ES et al. Androgen excess in women: experience with over 1000 consecutive patients. *J Clin Endocrinol Metab* 2004; **89**: 453-62.
4. Diamanti-Kandarakis E, Christakou C, Marinakis E. Phenotypes and enviromental factors: their influence in PCOS. *Curr Pharm Des* 2012; **18**: 270-82.
5. Knochenhauer ES, Key TJ, Kahsar-Miller M et al. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab* 1998; **83**: 3078-82.
6. Azziz R. Diagnostic criteria for polycystic ovary syndrome: a reappraisal. *Fertil Steril* 2005; **83**: 1343-6.
7. Goverde AJ, van Koert AJ, Eijkemans MJ et al. Indicators for metabolic disturbances in anovulatory women with polycystic ovary syndrome diagnosed according to the Rotterdam consensus criteria. *Hum Reprod* 2009; **24**: 710-7.

8. Zawadski J, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. *Polycystic ovary syndrome Boston: Blackwell Scientific* 1992; **377**.

9. Rotterdam EA-SPCWG. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004; **81**: 19-25.

10. Azziz R, Carmina E, Dewailly D et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab* 2006; **91**: 4237-45.

11. Fauser BC, Tarlatzis BC, Rebar RW 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**: 28-38 e25.

12. Geisthovel F, Rabe T. The ESHRE/ASRM consensus on polycystic ovary syndrome (PCOS)--an extended critical analysis. *Reprod Biomed Online* 2007; **14**: 522-35.

13. Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. *Am J Obstet Gynecol* 2010; **203**: 201 e1-5.

14. Auble B, Elder D, Gross A, Hillman JB. Differences in the management of adolescents with polycystic ovary syndrome across pediatric specialties. *J Pediatr Adolesc Gynecol* 2013; **26**: 234-8.

15. Azziz R, Carmina E, Dewailly D et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertil Steril* 2009; **91**: 456-88.

16. Apter D, Butzow T, Laughlin GA, Yen SS. Metabolic features of polycystic ovary syndrome are found in adolescent girls with hyperandrogenism. *J Clin Endocrinol Metab* 1995; **80**: 2966-73.

17. van Hooff MH, Voorhorst FJ, Kaptein MB et al. Polycystic ovaries in adolescents and the relationship with menstrual cycle patterns, luteinizing hormone, androgens, and insulin. *Fertil Steril* 2000; 74: 49-58.

18 West S, Lashen H, Bloigu A et al. Irregular menstruation and hyperandrogenaemia in adolescence are associated with polycystic ovary syndrome and infertility in later life: Northern Finland Birth Cohort 1986 study.

Hum Reprod 2014; 29:2339-51.

19. Hickey M, Doherty DA, Atkinson H et al. Clinical, ultrasound and biochemical features of polycystic ovary syndrome in adolescents: implications for diagnosis. *Hum Reprod* 2011; **26**: 1469-77.

20. Fruzzetti F, Campagna AM, Perini D et al. Ovarian volume in normal and hyperandrogenic adolescent women. *Fertil Steril* 2015; **28**. doi: 10.1016/j.fertnstert.2015.03.026.

21. Legro RS, Arslanian SA, Ehrmann DA et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2013; **98**: 4565-92.

22. Dewailly D, Lujan ME, Carmina E et al. Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society. *Hum Reprod Update* 2014; **20**: 334-52.

23. Ibanez L, Dimartino-Nardi J, Potau N, Saenger P. Premature adrenarche--normal variant or forerunner of adult disease? *Endocr Rev* 2000; **21**: 671-96.

24. Witchel SF. Puberty and polycystic ovary syndrome. *Mol Cell Endocrinol* 2006; **254-255**: 146-53.

25. Boonstra VH, Mulder PG, de Jong FH, Hokken-Koelega AC. Serum dehydroepiandrosterone sulfate levels and pubarche in short children born small for gestational age before and during growth hormone treatment. *J Clin Endocrinol Metab* 2004; **89**: 712-7.

26. Ibañez L, Valls C, Potau N et al. Polycystic ovary syndrome after precocious pubarche: omtogeny of the low birth-weight effect. *Clin Endocrinol* 2001; **55**: 667-72.

27. Ibanez L, Ferrer A, Ong K et al. Insulin sensitization early after menarche prevents progression from precocious pubarche to polycystic ovary syndrome. *J Pediatr* 2004; **144**: 23-9.

28. Meas T, Chevenne D, Thibaud E et al. Endocrine consequences of premature pubarche in post-pubertal Caucasian girls. *Clin Endocrinol (Oxf)* 2002; **57**: 101-6.

29. Neville KA, Walker JL. Precocious pubarche is associated with SGA, prematury,weight gain and obesity. *Arch Dis Child* 2005; **90**: 258-61.

30. Ibanez L, Ong K, Potau N et al. Insulin gene variable number of tandem repeat genotype and the low birth weight, precocious pubarche, and hyperinsulinism sequence. *J Clin Endocrinol Metab* 2001; **86**: 5788-93.

31. Mericq V. Low birth weight and endocrine dysfunction in postnatal life. *Pediatr Endocrinol Rev* 2006; **4**: 3-14.

32. Motta AB. Report of the international symposium: polycystic ovary syndrome: first Latin-American consensus. *Int J Clin Pract* 2010; **64**: 544-57.

33. Marti-Henneberg C, Vizmanos B. The duration of puberty in girls is related to the timing of its onset. *J Pediatr* 1997; **131**: 618-21.

34. Ong KK, Dunger DB. Birth weight, infant growth and insulin resistance. *Eur J Endocrinol* 2004; **151 Suppl 3**: U131-9.

35. Ibanez L, Ong KK, Mongan N et al. Androgen receptor gene CAG repeat polymorphism in the development of ovarian hyperandrogenism. *J Clin Endocrinol Metab* 2003; **88**: 3333-8.

36. Vottero A, Capelletti M, Giuliodori S et al. Decreased androgen receptor gene methylation in premature pubarche: a novel pathogenetic mechanism? *J Clin Endocrinol Metab* 2006; **91**: 968-72.

37. Mesiano S, Katz SL, Lee JY, Jaffe RB. Insulin-like growth factors augment steroid production and expression of steroidogenic enzymes in human fetal adrenal cortical cells: implications for adrenal androgen regulation. *J Clin Endocrinol Metab* 1997; **82**: 1390-6.

38. Silfen ME, Manibo A, Ferin M et al. Elevated free IGF-1 levels in prepubertal Hispanic girls with premature adrenarche relationship with hyperandrogenism and insulin sensitivity. *J Clin Endocrinol Metab* 2002; **87**: 398-403.

39. Petry CJ, Ong KK, Michelmore KF et al. Association of aromatase (CYP 19) gene variation with features of hyperandrogenism in two populations of young women. *Hum Reprod* 2005; **20**: 1837-43.

40. Oberfield SE, Sopher AB, Gerken AT. Approach to the girl with early onset of pubic hair. *J Clin Endocrinol Metab* 2011; **96**: 1610-22.

41. Corrine K, Welt CK, Carmina E. Lifecycle of Polycystic Ovary Sydrome (PCOS): from in utero to menopause. *J Clin Endocrinol Metab* 2013; **98**: 4629-38.

42. Carroll J, Saxena R, Welt CK. Environmental and genetic factors influence age at menarche in women with polycystic ovary syndrome. *J Pediatr Endocrinol Metab* 2012; **25**: 459-66.

43. Dahlgren E, Johansson S, Lindstedt G et al. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. *Fertil Steril* 1992; **57**: 505-13.

44. Dramusic V, Goh VH, Rajan U et al. Clinical, endocrinologic, and ultrasonographic features of polycystic ovary syndrome in Singaporean adolescents. *J Pediatr Adolesc Gynecol* 1997; **10**: 125-32.

45. Nduwayo L, Despert F, Lecomte C, Lecomte P. Primary amenorrhea revealing micropolycystic ovary syndrome. *Presse Med* 1992; **21**: 1060-3.

46. Rachimel M, Kives S, Atenafu E et al. Primary amenorrhea as a manifestation of polycystic ovarian syndrome in adolescents: a unique subgroup ? *Arch Pediatr Adolesc Med* 2008; **162**: 521-5.

47. Guzick D. Polycystic ovary syndrome: symptomatology, pathophysiology, and epidemiology. *Am J Obstet Gynecol* 1998; **179**: S89-S93.

48. Macklon NS, Fauser BC. Aspects of ovarian follicle development throughout life. *Horm Res* 1999; **52**: 161-70.

49. Ibañez L, Jimenez R , de Zegher F. Early puberty-menarche after precocious pubarche: relation to prenatal growth. *Pediatrics* 2006; **117**: 117-21.

50. Laitinen J, Taponen S, Martikainen H et al. Body size from birth to adulthood as a predictor of self-reported polycystic ovary syndrome symptoms. *Int J Obes Relat Metab Disord* 2003; **27**: 710-5.

51. Fall CH, Pandit AN, Law CM et al. Size at birth and plasma insulin-like growth factor-1 concentrations. *Arch Dis Child* 1995; **73**: 287-93.

52. Hay WW, Jr., Catz CS, Grave GD, Yaffe SJ. Workshop summary: fetal growth: its regulation and disorders. *Pediatrics* 1997; **99**: 585-91.

53. Leger J, Oury JF, Noel M et al. Growth factors and intrauterine growth retardation. I. Serum growth hormone, insulin-like growth factor (IGF)-I, IGF-II, and IGF binding protein 3 levels in normally grown and growth-retarded human fetuses during the second half of gestation. *Pediatr Res* 1996; **40**: 94-100.

54. Verkauskiene R, Jaquet D, Deghmoun S et al. Smallness for gestational age is associated with persistent change in insulin-like growth factor I (IGF-I) and the ratio of IGF-I/IGF-binding protein-3 in adulthood. *J Clin Endocrinol Metab* 2005; **90**: 5672-6.

55. Taylor AE, McCourt B, Martin KA et al. Determinants of abnormal gonadotropin secretion in clinically defined women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 1997; **82**: 2248-56.

56. Chhabra S, McCartney CR, Yoo RY et al. Progesterone inhibition of the hypothalamic gonadotropin-releasing hormone pulse generator: evidence for varied effects in hyperandrogenemic adolescent girls. *J Clin Endocrinol Metab* 2005; **90**: 2810-5.

57. Crisosto N, Codner E, Maliqueo M et al. Anti-Mullerian hormone levels in peripubertal daughters of women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2007; **92**: 2739-43.

58. Kent SC, Gnatuk CL, Kunselman AR et al. Hyperandrogenism and hyperinsulinism in children of women with polycystic ovary syndrome: a controlled study. *J Clin Endocrinol Metab* 2008; **93**: 1662-9.

59. Sir-Petermann T, Codner E, Maliqueo M et al. Increased anti-Mullerian hormone serum concentrations in prepubertal daughters of women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2006; **91**: 3105-9.

60. Sir-Petermann T, Ladron de Guevara A, Codner E et al. Relationship between anti-Mullerian hormone (AMH) and insulin levels during different tanner stages in daughters of women with polycystic ovary syndrome. *Reprod Sci* 2012; **19**: 383-90.

61. Sir-Petermann T, Maliqueo M, Codner E et al. Early metabolic derangements in daughters of women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2007; 92: 4637-42.

62. Diamanti-Kandarakis E, Kouli CR, Bergiele AT et al. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. *J Clin Endocrinol Metab* 1999; 84:4006-11.

63. Asunción M, Calvo RM, San Millán JL et al. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *J Clin Endocrinol Metab* 2000; 85:2434-8.

64. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet* 2007; **370**: 685-97.

65. Bonny AE, Appelbaum H, Connor EL et al. Clinical variability in approaches to polycystic ovary syndrome. *J Pediatr Adolesc Gynecol* 2012; **25**: 259-61.

66. Hardy TS, Norman RJ. Diagnosis of adolescent polycystic ovary syndrome. *Steroids* 2013; **78**: 751-4.

67. Joshi B, Mukherjee S, Patil A et al. A cross-sectional study of polycystic ovarian syndrome among adolescent and young girls in Mumbai, India. *Indian J Endocrinol Metab* 2014; **18**: 317-24.

68. Chin V, Censani M, Lerner S et al. Gonadal dysfunction in morbidly obese adolescent girls. *Fertil Steril* 2014; **101**: 1142-8.

69. Esmaeilzadeh S, Delavar MA, Amiri M et al. Polycystic ovary syndrome in Iranian adolescents. *Int J Adolesc Med Health* 2014; **26**: 559-65.

70. Amsterdam ESHRE/ASRM-Sponsored 3 rd PCOS Consensus Worshop Group Consensus on women´s health aspects of polycystic ovary syndrome (PCOS). *Hum Reprod* 2012; **27**: 14-24.

71. Vitek W, Hoeger KM. Treatment of polycystic ovary syndrome in adolescence. *Semin Reprod Med* 2014; **32**: 214-21.

72. Anderson AD, Solorzano CM, McCartney CR. Childhood obesity and its impact on the development of adolescent PCOS. *Semin Reprod Med* 2014; **32**: 202-13.

73. Spritzer PM. Polycystic ovary syndrome: reviewing diagnosis and management of metabolic disturbances. *Arq Bras Endocrinol Metabol* 2014; **58**: 182-7.

74. Kiddy DS, Hamilton-Fairley D, Bush A et al. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 1992; **36**: 105-11.

75. Toscani MK, Mario FM, Radavelli-Bagatini S et al. 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**: 925-30.

76. Ornstein RM, Copperman NM, Jacobson MS. Effect of weight loss on menstrual function in adolescents with polycystic ovary syndrome. *J Pediatr Adolesc Gynecol* 2011; **24**: 161-5.

77. Lass N, Kleber M, Winkel K et al. 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**: 3533-40.

78. Cirik DA, Dilbaz B. What do we know about metabolic syndrome in adolescents with PCOS? *J Turk Ger Gynecol Assoc* 2014; **15**: 49-55.

79. 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**: 1555-9.

80. Glueck CJ, Wang P, Fontaine R et al. Metformin to restore normal menses in oligo-amenorrheic teenage girls with polycystic ovary syndrome (PCOS). *J Adolesc Health* 2001; **29**: 160-9.

81. Glueck CJ, Aregawi D, Winiarska M 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**: 831-42.

82. Bhagavath B, Vitek W, Queenan J, Hoeger K. Metformin and other insulin sensitizers in polycystic ovary syndrome. *Semin Reprod Med* 2014; **32**: 323-30.

83. Geller DH, Pacaud D, Gordon CM, Misra M. State of the Art Review: Emerging Therapies: The Use of Insulin Sensitizers in the Treatment of Adolescents with Polycystic Ovary Syndrome (PCOS). *Int J Pediatr Endocrinol* 2011; **2011**: 9.

84. Escobar-Morreale HF, Carmina E, Dewailly D et al. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. *Hum Reprod Update* 2012; **18**: 146-70.

85. Kim JJ, Hwang KR, Choi YM et al. Complete phenotypic and metabolic profiles of a large consecutive cohort of untreated Korean women with polycystic ovary syndrome. *Fertil Steril* 2014; **101**: 1424-30.

86. Zreik RS, Nasrallah MP. The prevalence of endocrinopathies among Lebanese women presenting with hirsutism to an endocrine clinic. *J Med Liban* 2014; **62**: 27-32.

87. Hoeger K, Davidson K, Kochman L et al. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in

obese adolescent women in two randomized, placebo-controlled clinical trials. *J Clin Endocrinol Metab* 2008; **93**: 4299-306.

88. Somani N, Turvy D. Hirsutism: an evidence-based treatment update. *Am J Clin Dermatol* 2014; **15**: 247-66.
89. Mathur R, Levin O, Azziz R. Use of ethinylestradiol/drospirenone combination in patients with the polycystic ovary syndrome. *Ther Clin Risk Manag* 2008; **4**: 487-92.
90. Guido M, Romualdi D, Giuliani M et al. Drospirenone for the treatment of hirsute women with polycystic ovary syndrome: a clinical, endocrinological, metabolic pilot study. *J Clin Endocrinol Metab* 2004; **89**: 2817-23.
91. Pehlivanov B, Mitkov M. Efficacy of an oral contraceptive containing drospirenone in the treatment of women with polycystic ovary syndrome. *Eur J Contracept Reprod Health Care* 2007; **12**: 30-5.
92. Gallo MF, Nanda K, Grimes DA et al. 20 microg versus >20 microg estrogen combined oral contraceptives for contraception. *Cochrane Database Syst Rev* 2013; **8**: CD003989.
93. Maier PS, Spritzer PM. Aromatase gene polymorphism does not influence clinical phenotype and response to oral contraceptive pills in polycystic ovary syndrome women. *Gynecol Obstet Invest* 2012; 74: 136-42.
94. Nader S, Diamanti-Kandarakis E. Polycystic ovary syndrome, oral contraceptives and metabolic issues: new perspectives and a unifying hypothesis. *Hum Reprod* 2007; 22:317-22.
95. Moghetti P, Tosi F, Tosti A et al. Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2000; **85**: 89-94.
96. Krunic A, Ciurea A, Scheman A. Efficacy and tolerance of acne treatment using both spironolactone and a combined contraceptive containing drospirenone. *J Am Acad Dermatol* 2008; **58**: 60-2.
97. Castelo-Branco C, Del Pino M. Hepatotoxicity during low-dose flutamide treatment for hirsutism. *Gynecol Endocrinol* 2009; 25: 419-22.
98. Ibáñez L, Jaramillo A, Ferrer A et al. Absence of hepatotoxicity after long-term, low-dose flutamide in hyperandrogenic girls and young women. *Hum Reprod* 2005; 20:1833-6.

99. Paradisi R, Porcu E, Fabbri R et al. Prospective cohort study on the effects and tolerability of flutamide in patients with female patternhair loss. *Ann Pharmacother* 2011; 45:469-75.

100. Dikensoy E, Balat O, Pence S et al. The risk of hepatotoxicity during long-term and low-dose flutamide treatment in hirsutism. *Arch Gynecol Obstet* 2009; 279: 321-7.

101. Diamanti-Kandarakis E, Mitrakou A, Raptis S et al. The effect of a pure antiandrogen receptor blocker, flutamide, on the lipid profile in the polycystic ovary syndrome. J Clin Endocrinol Metab 1998; 83: 2699-705.

102. Diamanti-Kandarakis E, Mitrakou A, Hennes MM et al. Insulin sensitivity and antiandrogenic therapy in women with polycystic ovary syndrome. Metabolism 1995; 44: 525-31.

103. Fernandez AA, Franca K, Chacon AH et al. From flint razors to lasers: a timeline of hair removal methods. *J Cosmet Dermatol* 2013; **12**: 153-62.

104. Harris K, Ferguson J, Hills S. A comparative study of hair removal at an NHS hospital: Luminette intense pulsed light versus electrolysis. *J Dermatolog Treat* 2014; **25**: 169-73.

105. Franks S. The investigation and management of hirsutism. *J Fam Plann Reprod Health Care* 2012; **38**: 182-6.

106. Leanza V, Coco L, Grasso F et al. Ovulation induction with clomiphene citrate and metformin in women with polycystic ovary syndrome. *Minerva Ginecol* 2014; **66**: 299-301.

107. Ibanez L, Diaz M, Sebastiani G et al. 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**: E902-7.

108. Trent M, Austin SB, Rich M, Gordon CM. Overweight status of adolescent girls with polycystic ovary syndrome: body mass index as mediator of quality of life. *Ambul Pediatr* 2005; **5**: 107-11.

109. Moran LJ, Pasquali R, Teede HJ et al. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. *Fertil Steril* 2009; **92**: 1966-82.

110. Hutchison SK, Stepto NK, Harrison CL et al. Effects of exercise on insulin resistance and body composition in overweight and obese women with and without polycystic ovary syndrome. *J Clin Endocrinol Metab* 2011; **96**: E48-56.

111. Teede HJ, Joham AE, Paul E et al. Longitudinal weight gain in women identified with polycystic ovary syndrome: results of an observational study in young women. *Obesity (Silver Spring)* 2013; **21**: 1526-32.

112. Nicandri KF, Hoeger K. Diagnosis and treatment of polycystic ovarian syndrome in adolescents. *Curr Opin Endocrinol Diabetes Obes* 2012; **19**: 497-504.

113. Marcovecchio ML, Chiarelli F. Metabolic syndrome in youth: chimera or useful concept? *Curr Diab Rep* 2013; **13**: 56-62.

114. Steinberger J, Daniels SR, Eckel RH et al. Progress and challenges in metabolic syndrome in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2009; **119**: 628-47.

115. Coviello AD, Legro RS, Dunaif A. Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels independent of obesity and insulin resistance. *J Clin Endocrinol Metab* 2006; **91**: 492-7.

116. Cankaya S, Demir B, Aksakal SE et al. Insulin resistance and its relationship with high molecular weight adiponectin in adolescents with polycystic ovary syndrome and a maternal history of polycystic ovary syndrome. *Fertil Steril* 2014; **102**: 826-30.

117. Ibanez L, Valls C, Ferrer A et al. Additive effects of insulin-sensitizing and anti-androgen treatment in young, nonobese women with hyperinsulinism, hyperandrogenism, dyslipidemia, and anovulation. *J Clin Endocrinol Metab* 2002; **87**: 2870-4.

118. Palomba S, Materazzo C, Falbo A et al. Metformin, oral contraceptives or both to manage oligo-amenorrhea in adolescents with polycystic ovary syndrome? A clinical review. *Gynecol Endocrinol* 2014; **30**: 335-40.

119. Dowdy D. Emotional needs of teens with polycystic ovary syndrome. *J Pediatr Nurs* 2012; **27**: 55-64.

120. Bishop SC, Basch S, Futterweit W. Polycystic ovary syndrome, depression, and affective disorders. *Endocr Pract* 2009; **15**: 475-82.

121. Ghazeeri G, Fakih A, Abbas HA et al. Anxiety, cognitive, and depressive assessment in adolescents with polycystic ovarian syndrome: a pilot study. *J Pediatr Adolesc Gynecol* 2013; **26**: 269-73.

122. Harris-Glocker M, Davidson K, Kochman L et al. Improvement in quality-of-life questionnaire measures in obese adolescent females with polycystic ovary syndrome treated with lifestyle changes and oral contraceptives, with or without metformin. *Fertil Steril* 2010; **93**: 1016-9.

123. Milsom SR, Nair SM, Ogilvie CM et al. Polycystic ovary syndrome and depression in New Zealand adolescents. *J Pediatr Adolesc Gynecol* 2013; **26**: 142-7.

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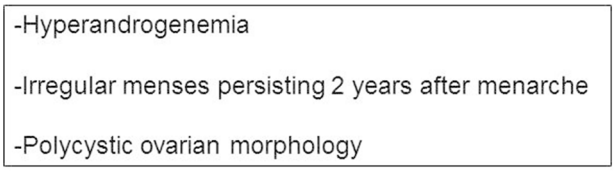
Legends of figures

Figure 1. Criteria to diagnose the Polycystic Ovary Syndrome (PCOS) in adolescents.

Figure 2. Clinical assessments for Polycystic Ovary Syndrome (PCOS) in adolescents.

Table 1. Main treatment options for adolescents with Polycystic Ovary Syndrome



Criteria to diagnose the Polycystic Ovary Syndrome (PCOS) in adolescents.
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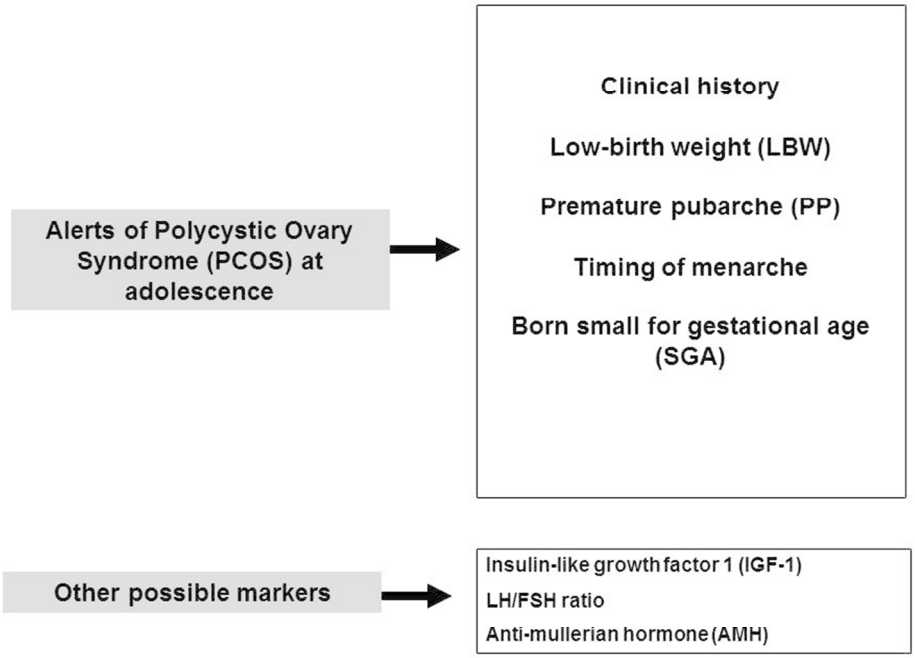

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Table 1. Main treatment options for adolescents with Polycystic Ovary Syndrome

Treatment	Mechanism of action	Reproductive and Metabolic effects
Weight loss	Increases insulin sensitivity Increases SHBG May decrease ovarian androgen secretion	Improves lipid and glucose profile and blood pressure control May improve/restore regular menses
Insulin-sensitizer drugs	Decreases glucose levels and Increases insulin action May decrease ovarian androgen secretion	Additional benefits in weight loss as adjuvant for dietary and lifestyle interventions May improve/restore regular menses May induce ovulatory cycles
E+P pills	Decreases GnRH pulses and gonadotropin secretion Decreases ovarian androgen secretion Increases SHBG At long-term may decrease 5alpha-reductase activity Decreases non-opposed estrogen action on endometrium	Reduces hirsutism Decreases total and free circulating androgens Promotes menstrual cyclicity Protect against endometrial hyperplasia
Antiandrogens	Compete with circulating androgens for binding with androgen receptors Decreases 5alpha-reductase activity	Decreases acne and hirsutism

SHBG= sex hormone binding globulin; E+P pills= combined estrogen plus progestin contraceptive pills; GnRH= gonadotropin-releasing hormone;