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Polycystic Ovary Syndrome in Adolescents

Adolesan Polikistik Over Sendromu

Recai PABUÇCU,[a] Ayça TÖREL ERGÜR,[b] Arzu BOSTANCI DURMUŞ,[a] Emre Göksan PABUÇCU[a]

[a]Department of Gynecology and Obstetrics, Ufuk University Faculty of Medicine,
[b]Department of Pediatric Endocrinology, Ufuk University Faculty of Medicine, Ankara

ABSTRACT

Objective: Polycystic ovary syndrome (PCOS) is the most common cause of hyperandrogenism in adolescent age group. PCOS is a syndrome that affects both the body and the soul negatively, especially in the adolescent age group. Body perception in this age group, impulse to behave, visual and mental state occupy an important place in the life of the person. In this study, we aimed to discuss all aspects of adolescent PCOS. **Material and Methods:** Pathogenesis, clinical symptoms, diagnostic criteria and different treatment modalities of PCOS are discussed. The effects of lifestyle changes, hormonal therapies, insulin agents and hirsutism treatment on adolescent PCOS are described. **Results:** PCOS is a complicated syndrome and its diagnostic criteria have been changed over a period of time since it was first described in the year 1935. Different theories have been identified to describe the pathogenesis of PCOS in adolescents but yet no certain mechanism is clear enough to explain the physiologic process of the disease. **Conclusion:** Identification of PCOS during adolescent period is important in order to prevent long term sequelae. It is beneficial to set a behavior pattern in this age group with regard to appropriate diet and exercise. In this review we aimed to discuss pathogenesis of PCOS, diagnostic criteria of the disease, to define the risk factors and to overview the treatment alternatives for this age group.

Keywords: Polycystic ovary syndrome; adolescents

ÖZET

Amaç: Adolesan yaş grubunda hiperandrojenizmin en sık nedeni polikistik over sendromudur (PKOS). PKOS özellikle adölesan yaş grubunda olan kişiyi hem bedenen hem de ruhen olumsuz etkileyen bir sendromdur. Bu yaş grubundaki beden algısı, beğenilme dürtüsü, görsellik ve ruhsal durumdaki dengesizlik kişinin hayatında önemli bir yer işgal etmektedir. Biz bu çalışmada adölesan PKOS'u tüm yönleri ile tartışmayı amaçladık. **Gereç ve Yöntemler:** PKOS'un patogenezi, klinik semptomları, tanı kriterleri ve farklı tedavi şekilleri ele alınmıştır. Yaşam şekli değişikliğinin, hormonal tedavilerin, insülin ajanlarının ve hirsutizmin tedavisinin adölensan PKOS üzerine olan etkileri anlatılmıştır. **Bulgular:** PKOS komplike bir sendromdur ve ilk tanımlanmış olduğu 1935 yılından bu yana zaman içinde tanı kriterleri değişmiştir. Adolesan PKOS patogenezini açıklamak için bir çok teori öne sürülmüş olsa da günümüzde halen hastalığın fizyolojik gelişim sürecini tam olarak açıklayan bir mekanizma bulunmamaktadır. **Sonuç:** Adölesanda PKOS tanısının konulması uzun dönem sekellerinin engellenmesi açısından önem taşımaktadır. Bu yaş grubunda uygun diyet ve egzersiz alışkanlıklarının oluşturulması faydalı olacaktır. Bu derlemede PKOS patogenezi ve tanı kriterlerini tartışmayı, risk faktörlerini tanımlamayı ve bu yaş grubu için tedavi seçeneklerini kısaca gözden geçirmeyi amaçladık.

Anahtar Kelimeler: Polikistik over sendromu; adölesanlar

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Yazışma Adresi/*Correspondence:*
Arzu BOSTANCI DURMUŞ
Ufuk University Faculty of Medicine, Department of Gynecology and Obstetrics,
Ankara, TÜRKİYE/TURKEY
drarzubostanci@gmail.com

Polycystic ovary syndrome (PCOS) is the most important cause of an anovulation, hirsutism and infertility in women. It is a heterogeneous syndrome the etiology of which is not known clearly yet. This multifactorial syndrome starts at puberty and its cardiovascular and metabolic sequelaes are observed during menopause. Adolescent patients pose particular diagnostic problems as characteristics of normal puberty often overlap with signs and symptoms of PCOS. However, identification of PCOS during adolescent period is important in order to prevent long term sequelae. It is beneficial to set a behavior pattern in this age group with regard to appropriate diet and exercise. On the other hand, whether to treat PCOS in adolescents in order to prevent long term sequelae is still controversial.

Stein and Leventhal published a series of seven cases of amenorrhea, hirsutism, and bilateral polycystic ovary, which are known as polycystic over syndrome (PCOS) in the future in 1935.[1] Modified diagnostic criteria determined by Rotterdam and the National Institutes of Health published by Buggs and colleagues in 1995.[2] According to this;

NIH CRITERIA

1. Presence of clinical and/or biochemical findings of hyperandrogenism

2. Anovulatory symptoms

ROTTERDAM CRITERIA

1. Presence of clinical and/or biochemical findings of hyperandrogenism

2. Anovulatory symptoms

3. Presence of ultrasonographic findings of PCOS (two of the three criteria are needed)

Definition of polycystic ovaries with ultrasound was based on the presence of 12 or more subcapsular follicles less than 10 mm in diameter and/or increased ovarian volume (>12 cm^3). But it is known that polycystic ovarian morphology is observed in up to 30% of healthy adolescents by transabdominal ultrasound when the Rotterdam definition is used.[3]

In the year 2012 a new consensus on PCOS was published. ASRM consensus on PCOS points out that criteria for diagnosis of PCOS in adolescents differ from adult PCOS cases and all the three elements of Rotterdam criteria must be present to diagnose PCOS in an adolesance. These are: presence of oligomenorrhea or amenorrhea at least two years after menarche or presence of amenorrhea at age 16 year, determination of the increment of the volumes of the ovaries >10 cm^3 and documented hyperandrogenism.[4]

In the year 2013, Endocrine Society declared a new consensus for diagnosis of PCOS in adolescent. According to this consensus; presence of persistent oligomenorrhea with presence of clinical and/or biochemical evidence of hyperandrogenism (after exclusion of other pathologies) were sufficient for diagnosis. It was stated that, since anovulatory symptoms and polycystic ovary morphology may be evident in normal stages of pubertal maturation; they were not sufficient to make a diagnosis.[5]

Androgen Excess Society defined PCOS as hyperandrogenism with ovarian dysfunction or polycystic ovaries.[6] Thus the Androgen Excess Society (AES) considered that androgen excess is a central event in the development and pathogenesis of polycystic ovary syndrome and established that androgen excess should be present and accompanied by oligomenorrhea or PCOM or both them.[6]

Some of the adolescents with PCOS do not show the symptoms of classical Stein-Leventhal form, and some of them do not have polycystic appearance in ultrasound despite of the anovulatory symptoms, and these cases are called as ***atypical and/or non-classical PCOS***.

Adolescents with PCOS are clinically, hormonally, and ultrasonographically similar to adult women with PCOS. But another issue to be clarified is that six or more cysts greater than four mm can be seen in ovaries during the normal pubertal development. This condition is believed to be the response of the ovaries to the nocturnal pulsatile gonadotropin secretion.[7] Because, this cysts are temporary and reversible, and they are not seen even after the menstruations are ameliorated. For

this reason, cystic ovaries in the childhood period are confused with the polycystic definition. Some authors call PCOS of adolescents as ***"exacerbated puberty"*** because of the similarities between the normal puberty and the PCOS. Furthermore, puberty is thought to trigger the PCOS in predisposed individuals. Studies about this issue are focused on the potential role of increased insulin and IGF 1 (insulin like growth factor-1) concentrations in puberty. IGF 1 and insulin increases steroidogenesis in ovaries and potentiates the effects of gonadotropins.[8] Hyperinsulinism caused by a temporary growth hormone production at puberty causes ***physiologic adolescent anovulation (PAA)***.[9] Hyperandrogenism was also determined in half of these anovulatuary cases. The important point here is that PAA does not exceed more than the first two years of puberty. The cases in which anovulation persist more than the first two years of puberty has to be considered as PCOS instead of PAA.[10] Anatomy and histology of ovaries in the PAA is similar to the anatomy and histology of ovaries in PCOS. Because of this, ovaries of a normal adolescence look like ovaries of a patient with PCOS.[11]

Exclusion of other androgen excess disorders should be excluded such as non-classical congenital adrenal hyperplasia, drug-induced androgen excess, thyroid disease, Cushing's syndrome, hyperprolactinemia, androgen secreting tumors, as well as other causes of oligomenorrhea or anovulation.[12]

Prevalence of syndrome varies according to diagnostic consensus used, with estimates ranging from %9 according to National Institutes of Health consensus up to %18 with the Rotterdam consensus.[13]

It is obvious that early diagnosis in adolescent age group would allow us for earlier treatment and even prevention of PCO-associated morbidity, but it should be noticed that premature diagnosis carries risks of psychological distress and unnecessary treatment.[14]

PATHOGENESIS

Various theories have been mentioned in the pathophysiology of PCOS (Table 1). But the main point here is the excess androgen increase.

In of approximately 80% of PCOS cases, ovaries are the responsible source androgen increase (Figure 1).

An exacerbated 17-OH-progesterone response to the gonadotropin or hCG stimulation can be determined in functional ovarian hyperandrogenism (FOH). Functional adrenal hyperandrogenism (FAH) that can be suppressed by dexamethasone can also be determined in about 60% of the cases. A moderate increase in 17-OH-progesterone or DHEA may be observed in the cases with FAH.[15] FAH may be the single source for hyperandrogenism in cases with atypical or non-classical PCOS. The underlying defect in these cases is structural dysfunction of steroidogenic cells.[16]

One of the most important hypotheses in development of PCOS is dysregulation of ovarian hormone production due to the ***increase in LH se-***

TABLE 1: Factors that have a role in pathogenesis of adolescent PCOS.

Inherited abnormality of GnRH pulse generator
Neuroendocrine loss in control of GnRH secretion
Impairment of gonadotropin release (LH increase)
Hyperinsulinsm
Increased activity of P450c-17α
Premature pubarche
Presence of metabolic syndrome of paternal origin (Type 2 diabetes, dyslipidemia, cardiovascular illness)
Transition of paternal insulin gene VNTR class-III allele
Gestational factors (LBW, higher birth weight)

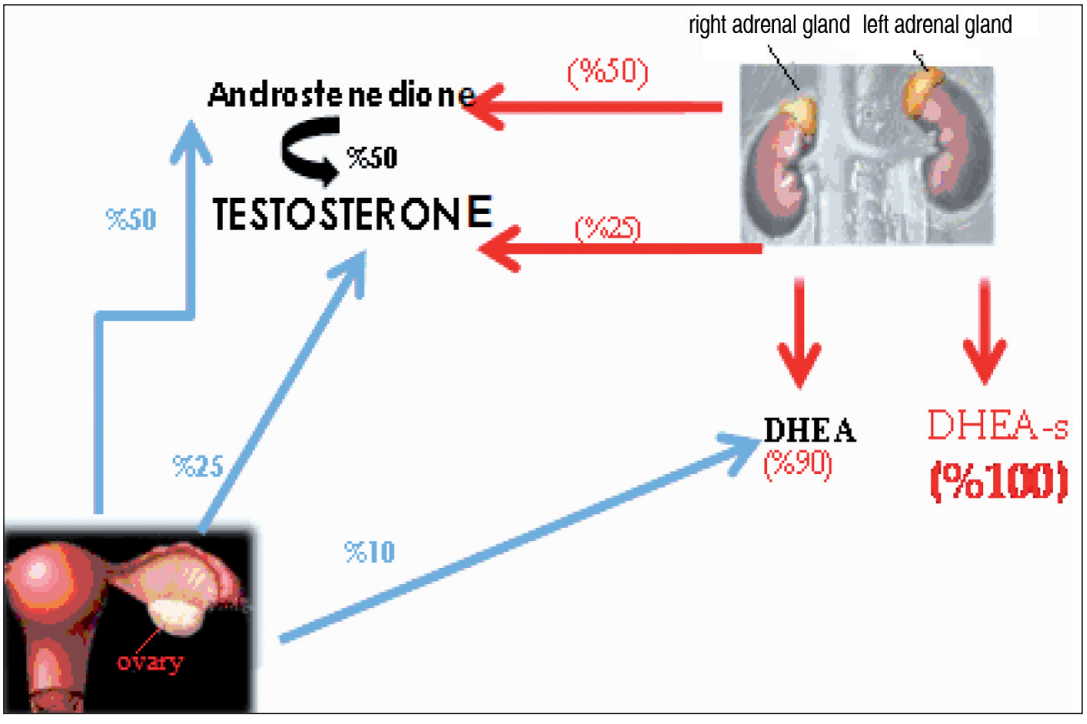

FIGURE 1: Androgen resources.

cretion/low FSH. In the PCOS cases, functions that control the secretion of androgens and estrogens is damaged and LH hypersensitivity occurs instead of the down regulation in response to LH stimulation. Intrinsic theca-cell defect causes over-expression of especially 17-hydroxylase and 17-20-lyase steroidogenic enzymes. Intra-ovarian excess androgen that occurred by LH stimulation stimulates growth of small follicles and thecal-stromal hyperplasia.[17,18] As known, LH stimulates androstenedione production in theca cells of the ovaries. FSH causes estradiol biosynthesis by aromatase stimulation. In a normal menstrual cycle FSH augments biosynthesis of estradiol by follicular growth and aromatase stimulation. When the increased concentrations of estradiol reach the threshold value, LH pikes and ovulation occurs. In the PCOS cases there is a dysregulation in gonadotrophin secretion and especially LH secretion increases.[17] This situation leads to an intense increase in androgens. In a study that compares the adolescent girls with hyperandrogenism and the girls with normal puberty, the number of LH pikes, LH/FSH ratio, and serum levels of 17-OH-progesterone were found to be increased.[19] Dysregulation of secretion in gonadotropins was thought to be caused by an inher-

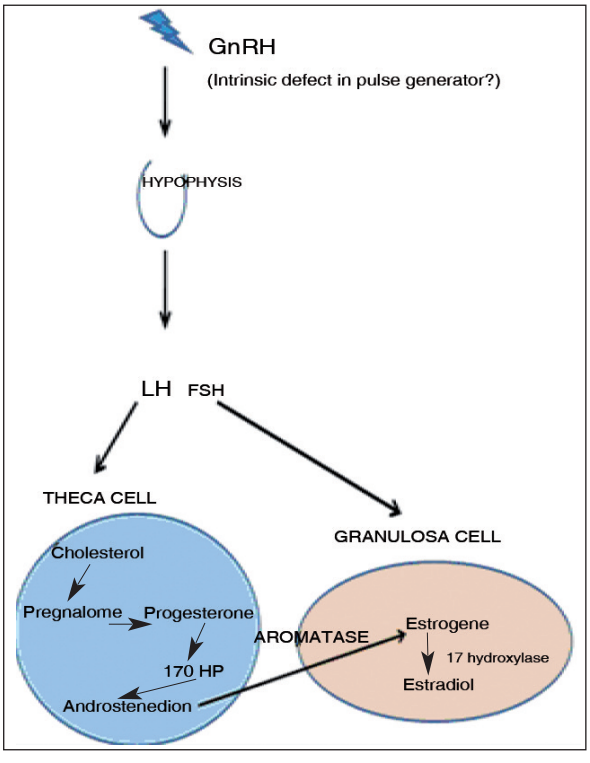

FIGURE 2: Abnormality of GnRH pulse generator.

ited abnormality of GnRH pulse generator, but there is still not an evidence for this hypothesis (Figure 2).

Another theory is the probable neuroendocrine control abnormality of GnRH secretion. But all of these theories are not clarified yet and they couldn't go further than speculations.[20]

Another recent hypothesis that gains popularity is that ***Hyperinsulinemia/insulin resistance*** causes abnormal production of androgens in ovaries and adrenals.[21] Hyperinsulinemia stimulates the activity of cytochrome P_{450c} 17-α. Cytochrome P_{450c} 17-α catalyzes the activities of both the 17-α-hydroxylase and the 17,20-lyase, and these enzymes have a key role in biosynthesis of ovarian androgens. Additionally they have a role in adrenal steroidogenesis. Because of this reason, damaged activity of cytochrome P_{450c} 17-α by hyperinsulinemia causes the FAH besides the FOH.[22] Recent studies demonstrated that insulin shows its effect in ovaries with PCOS by the cognate receptor pathway which normally modulates steroidogenesis. Under normal circumstances tyrosine in the receptor is phosphorylated after insulin binding to this receptor. In the presence of insulin resistance and/or hyperinsulinemia, serine is phosphorylated instead of tyrosine, and insulin cannot show its effect in the cell. Beta-cell dysfunction is seen in PCOS.[23] In 1980, Burgher and colleagues found a strong correlation between plasma concentrations of insulin, testosterone, and androstenedione in obese women with PCOS. This result made them to think that hyperinsulinemia may have a role in the etiology of PCOS.[24] In adult studies, prevalence of impaired glucose tolerance and type 2 DM is estimated to be 30-40%. In a study with adolescent A similar result of impaired glucose tolerance was found in a study of adolescent with PCOS.[25]

Hyperinsulinemia increases the presence and the availability of free hormones by decreasing the levels of IGFBP1 and SHBG (Sex Hormone Binding Globuline), and this increases the effect of free hormones on the target organ (Figure 3).

Insulin resistance and compensating hyperinsulinism are common phenomena seen during puberty and PCOS. Hyper-pulsatile release of gonadotrophins, hyperactive production of androgens in the ovaries and the adrenals, insulin resistance or hyperinsulinemia and the following IGFBP-1 and SHBG decrease are seen both in the normal puberty and in the PCOS. Because of the similarities in pathophysiology of PCOS and normal puberty, puberty is thought to be a trigger for PCOS.[26] In another study, higher responses of both fasting and first phase insulin were determined in adolescents with PCOS.[27]

Another important point in pathophysiology of PCOS is that, whether if the ***premature pub-***

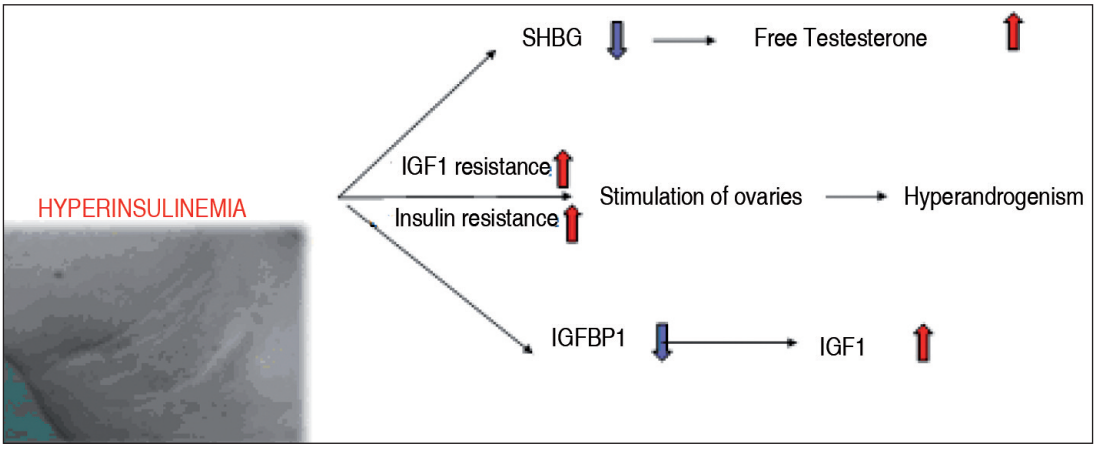

FIGURE 3: Effects of hyperinsulinemia.

arche is an early marker of the subsequent PCOS.[28] As known, premature pubarche is the appearance of the pubic hair before 8 years of age without the other signs of the puberty. Premature pubarche is associated with the early maturation of zona reticularis, and an increase in the adrenal androgens is seen in premature puberty period. This early activation is resulted with weight gain and hyperinsulinemia.[29] An increase in the androgens is seen after the activated kinase mutations that occurred for the activation of P_{450c} 17-α enzyme (serine/threonine phosphorylation of the enzyme).[30] In a study that conducted in girls with premature pubarche, FOH symptoms were increased during middle adolescence. In this study oligomenorrhea and increased levels of basal 17-OH-progesterone, androstenedione, and testosterone was determined in 45% of girls with premature pubarche.[31] In another study FOH was found in 40.7% of patients with premature pubarche.[32] Higher levels of insulin were seen during OGTT in adolescent girls with regular menstruation, premature pubarche, and FOH.[33] Also atypical central precocious puberty may pose a risk for PCOS.[34]

In a study of Andrea and colleagues, the prevalence of metabolic syndrome (Type II diabetes, dyslipidemia, cardiovascular illness) was found to be higher in adolescent girls with hyperinsulinemic PCOS compared to general adolescent population. Observations about the metabolic syndrome presence in adolescent girls with PCOS independent from obesity and insulin resistance showed that hyperandrogenism is a risk factor for metabolic syndrome.[33] Another study about the role of paternal metabolic syndrome in the pathogenesis in adolescent girls with PCOS is also interesting.[35] Transition of paternal insulin gene VNTR class-III allele in women with PCOS was found to be aggravating the severity clinical symptoms.[36] Familial inheritance pattern of PCOS is autosomal dominant.[15]

Risk factors for PCOS were evaluated in different studies and LGA (large for gestational (age) and SGA (small for gestational age) in prenatal age, congenital virilizing illness was found to be the most important risk factors. PCOS development in LGA babies of mothers that gain excess weight during pregnancy is thought to be a cause of fetal programming due to excess androgens.[37] Exposure to higher levels of androgens during early gestational period was shown to impair embryogenesis in animal models. In these cases ovarian/adrenal hyperandrogenism, oligomenorrhea, parafollicular ovaries and increased concentrations of LH can be observed. Additionally, development of abdominal obesity, impaired glucose tolerance, and dyslipidemia were shown. Similar views of LH and insulin distribution can be seen when the gestational androgen exposure becomes in later periods. These effected girl fetuses can be recovered by prenatal treatments. This treatment recovery not only the genital abnormality, also recovers the reproductive function in adult ages.[38] SGA is reported as a major risk factor for PCOS and premature pubarche. In some of the studies an association between the SGA and PCOS was shown but in some other studies this relation couldn't be proved.[39-41] Intrauterine growth retardation is a predisposing factor for postnatal insulin resistance. Premature pubarche and PCOS are results of insulin resistance associated with low birth weight.[39] Furthermore, cases that develop premature pubarche, obesity, acanthosis nigricans, and metabolic syndrome in childhood subsequently develops polycystic ovary syndrome in adolescence.[40] The evolutionary path of PCOS from fetal time to adult turnover is still complex and should be examined in more detail.

CLINICAL SYMPTOMS, DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

PCOS is a disease that often presents during adolescent but there is an overlap between features of PCO syndrome and physiological findings observed during the normal progression of puberty and this matter makes the diagnosis more complicated in this age group.[42] Different criteria that used for diagnosis of syndrome can result in different preva-

TABLE 2: Clinical and associated findings of PCOS.

Central obesity
Irregular menstruation
Hirsutismus
Acne, seborrhea
Alopecia
Cutaneous findings (hyperhidrosis/hidradenitis suppurativa)
Acanthosis nigricans

lence PCOS.[43] Absence of universally accepted criteria for PCOS diagnosis with certainly and the variable diagnosis of PCOS poses a vast range of challenges.

Clinical findings of PCOS in adolescents are associated mainly with hyperandrogenism (Table 2).

Acne vulgaris, seborrhea, alopecia pattern, hyperhidrosis, and hidradenitis supurativa are defined as "cutaneous hirsutism equivalents", and these are alternative findings of hyperandrogenism. Androgens not only enhance the production of sebum, but also cause the abnormal follicular epithelial cell desquamation, which causes the formation of comedones. Acne formation is related particularly with increased DHEA/DHEA-S levels.[43] Hirsutism must be distinguished from hypertrichosis. Hypertrichosis is vellus style (light-colored, thin form = fluff) pubescence in non-sexual areas of the body and it is unrelated to sex hormone imbalance. It may be due to the antiepileptic drugs used especially in childhood (such as valproic acid, phenytoin), hypercortisolism, hunger or hereditary factors. Hirsutism is defined as terminal style (dark-colored, thick) and androgenic hair growth in androgenic areas, which is a sign of hyperandrogenism. Hirsutism score is important for evaluation of hyperandrogenism since hair follicule contains an enzyme; 5-alpha reductase type 2; which converts androstenedione and testosterone to dihydrotestesterone (DHT). Testesterone and DHT convert vellus hair to terminal hair in androgen sensitive areas.[44] Ferriman-Gallwey scoring is being used in evaluation of hirsutism. Between 8 to 15 points is called as moderate, and more than 15 points is called as moderate severity (Figure 4).

No laboratory tests are needed if the adolescent girls have mild hirsutism and regular menstruation, but in moderate and/or severe hirsutism cases laboratory tests must be evaluated. Plasma testosterone is the single most important androgen that will be examined. The diurnal rhytm, stage of puberty, phase of menstrual cycle and SHBG concentrations are the factors that influence testosterone concentration. Free testosterone and SHBG are also need to be measured. Free androgen index (total testesteron/SHBG x100) greater than 5.63 is another marker used for biochemical hyperandrogenism.[45,46] These examinations must be made in

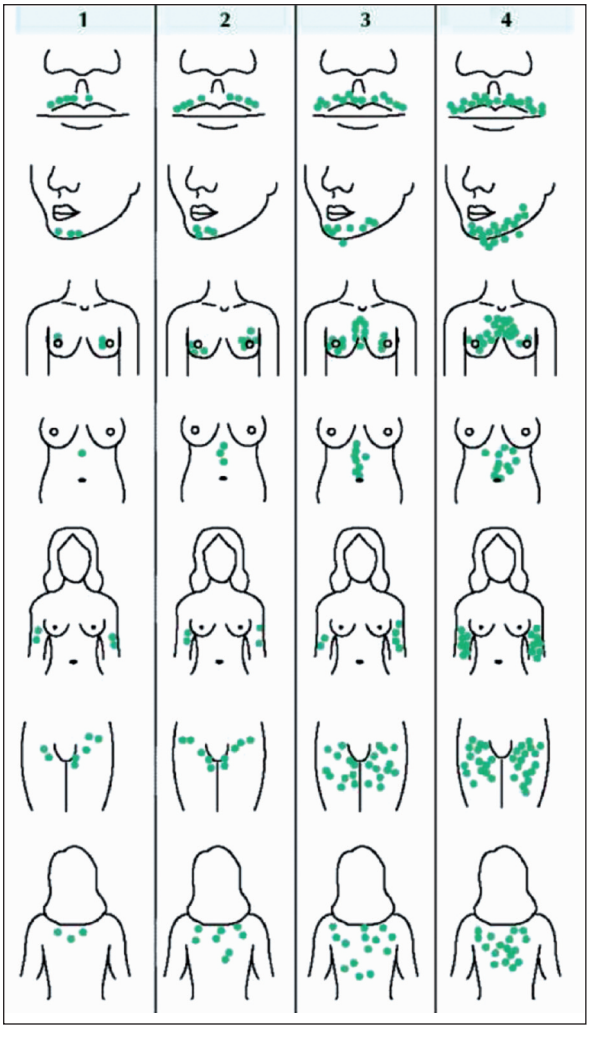

FIGURE 4: Ferriman-Gallwey scoring.

mid-follicular phase of menstrual cycle and early in the morning. The second step has to be the evaluation of ovaries by pelvic ultrasound. Ovaries have to be evaluated whether if they are greater than 10cm³ in volume, or if they have 12 or more subcapsular and peripherally localized follicles. Ovarian growth is the most exact criteria. Because, as it was stated before, multifollicular ovaries can also be found in normal puberty, normal findings on ultrasonography do not eliminate non-classical PCOS. DHEAS and 17-OH-progesterone measurements must be made in the evaluation of FAH and FOH. ACTH stimulation test must be performed if basal level of 17-OH-progesterone is above the 2 ng/ml and non classical CAH should be eliminated. An 17-OH-progesterone level > 12 ng/ml warrants the diagnosis of non classical CAH in ACTH stimulation test.[43] Increased 17-OHP responses after leuprolide acetate stimulation is also important for diagnosis of FOH (Figure 5).[47]

Testosterone >200 ng/dl and DHEA-S >700 ng/ml warrant consideration of neoplasms. Computerized tomography of adrenal gland and 17-OH-progesterone response to the acute gonadotrophin releasing hormone agonist must be evaluated for diagnosis of an adrenal tumor.[43]

A very common complaint is acne during adolescence but alopecia is one of the rare phenomena in girls and sometimes hirsutism is border line and aggravates slowly.[12] For these reasons it has been posited with various criticisms specifically for adolescents. Two groups have proposed different diagnostic criteria for adolescent PCOS. These;

1. Carmina et al. 2010 described the definition of PKOS as all three Rotterdam criteria (polycystic ovarian morphology, hyperandrogenism and choronic anovulation).

2. Sultan and Paris describe clinical hyperandrogenism as the presence of at least four of the criteria of oligomenorosis or amenorrhea, biological hyperandrogenism, insulin resistance, and policystic over morphology at least two years after menarche.

Clinical appearance may be in conjunction with PCOS in cases, which Cushing's syndrome is being suspected. Optimal screening test for these cases is measuring the free cortisol in 24 h urine. Three or four fold of normal levels is diagnosed as Cushing's syndrome.[43]

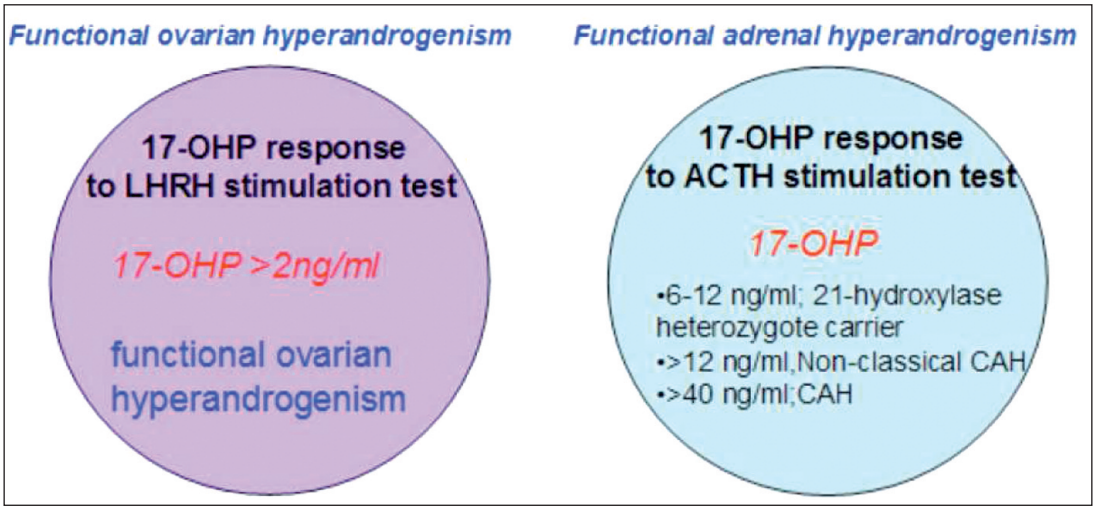

FIGURE 5: Diagnosis of functional ovarian hyperplasia and functional adrenal hyperplasia.

TREATMENT

The appropriate treatment approach for adolescents diagnosed with PCOS remains a major problem for clinicians and specialists in this area. PCOS management should include a multidisciplinary team and treatment of adolescents with PCOS should focus both on management of hyperandrogenism as well as PCOS related comorbidities (obesity, insulin resistance and dyslipidemia).[25,48]

LIFESTYLE MODIFICATION

In adult women with PCOS, lifestyle modification has been associated with improvements in endocrine and ovarian function.[49] Weight loss and the maintenance of normal weight seems to be the first step in treatment priority. First step of treatment in overweight or obese adolescents with PCOS must be weight reduction. Central obesity augments the insulin resistance and increases the vicious circle. In a study of adolescents 12-18 years old with BMI >95th% and PCOS, lifestyle modification alone resulted in a 59% reduction in the free androgen index with a 122% increase in SHBG.[50] According to the studies, 5-10% of weight reduction decreases hirsutismus by 40-55% in six months.[51] For this reason, diet is an important step in PCOS.

FERTILITY CONCERNS AND ADOLESCENT HEALTH

A common concern in adolescents with PCOS is fertility issue. 68% of adolescents express fertility concerns and adolescent with PCOS have more anger, anger management problems, anxiety and higher depression scores in Beck's scale compared to normal adolescent population.[52,53] Pediatricians should be prepared for questions and be able to orient parents and patient about management of the disease. Young adult patients who are interested in childbearing should be referred to a reproductive endocrinologist. There are many new reproductive technologies and pregnancy outcomes of women with PCOS are similar to normal population.[52] Because of these reasons, a multidisciplinary approach, including psychologists and dietician with parental involvement and readiness to change is necessary for optimal management of adolescents with PCOS.[24,53]

HORMONAL CONTRACEPTIVES AND ANTI-ANDROGENS

The purpose of medication is suppressing the androgen sources like ovary and adrenals, and blocking the effects of androgens on end-organ. Most frequent agents that used in the treatment of PCOS in adolescents are oral contraceptives (OC) and anti-androgens.[54] Oral contraceptives are effective on ovarian hyperandrogenism. They regulate irregular menstruations. They are recommended as first line treatment in sexually mature adolescents with PCOS and acne, hirsutism or anovulatory symptoms.[10] Major side effect of OC is increased risk of thromboembolism. A careful family history of thromboembolic events must be obtained and Factor V Leiden mutation should be ruled out in susceptible cases.[24]

Hormonal contraceptives should not be prescribed in patients with cardiovascular problems, venous thrombosis, liver disease, focal migraine, depression, extreme obesity, and untreated mass.

Anti-androgens are effective on hirsutismus. Anti-androgens that are being used in PCOS are: spironolactone, cyproterone acetate, drospirenone, flutamide. Sprinolactone is the most commonly used agent as an adjunct especially for hirsutism. Ganie et al showed that combination of sprinolactone and metformin for a period of 6 months was

TABLE 3: Drugs used in PCOS treatment of adolescents.

Oral contraceptives
Progestin
Anti-androgens
Cyproterone acetate (50-100 mg/day)
Spironolactone (200 mg/day)
Drospirenone
Flutamide
Finasteride
Insulin sensitizing agent
Metformin (500 mg/day)
GnRH agonist+estradiol

superior to either drug alone in improving menstrual irregularity, hirsutism, BMI, serum androgen levels and insulin resistance.[55] Cyproterone acetate, drospirenone are two progestirins with anti-androgenic activity, are usually used in combination with ethinyl estradoiol in OC. Finasterid, which is a 5 alpha reductase inhibitor, is also used for treatment.[56] Flutamide treatment reduces hirsutism score, decreases the androgen levels, but doesn't have much effect on menstrual cycles, therapeutic benefits can be maximized if flutamide is combined with metformin but it is not approved for use in pediatrics because of the concern about its hepatotoxicity (Table 3).[57,58]

INSULIN SENSITISERS

After the role of hyperinsulinism and insulin resistance in the pathogenesis is understood, insulin-sensitizing agent; metformin, has been another choice of treatment for PCOS. The oral biguanide, metformin, prevents the production of hepatic glucose and contributes to the reduction of insulin resistance by increasing the number of insulin receptors. Levels of androgen, LH, and SHBG decrease after the reduction of insulin levels.[59] Metformin also decreases the androgen production by its direct effect on the theca cells. Serious side effects have not been observed in adolescents.[60] Theoretically, when the hyperandrogenism decreases hirsutism, acne, and ovulatory dysfunction also reduces. In the long run, beta cell destruction and type 2 diabetes, and perhaps cardiovascular disease incidence will decrease due to elimination of hyperinsulinism. Since oral contraceptives and anti-androgens alone, are not effective on hyperinsulinemia; metformin is seen as an important part of the treatment.[61,66] In a study of adult patients, duration of menstural cycles were decreased in normoinsulinemic obese women, hirsutismus scores were decreased in the lean hyperinsulinemic women, DHEAS levels were decreased in lean hyperinsulinemic and normoinsulinemic women and siginificant effects on ovulation were observed only in lean hyperinsulinemic women.[62] In the study of Ibanez and collegues in which 30 adolescents were treated with with low dose flutamide and metformin combination, hirsutism and serum androgens levels were found to be decreased, insulin sensitivity was increased, improvements in lipid profile and ovulation, and reduction of abdominal fat have been observed.[60] Troglitazon which is a powerful insulin synthesizer in adults with PCOS, is very effective in reducing hyperandrogenemia shows its effect by inhibiting P-450c 17 and 3 beta OH steroid dehydrogenase type-2.[63] It was found to be associated with drug induced hepatitis and it is not an option for hirsutism treatment anymore.[64]

TREATMENT OF HIRSUTISM

One of the main concerns of adolescents with PCOS is hirsutism and it is usually annoying for an adolescent girl. Up to date, pharmological and non-pharmocological interventions for hirsutism are based on adult data. Therapeutic options can be divided in systemic, topical and cosmetic methods. OC and antiandrogens most commonly used systemic methods but due to long hair-growth cycle, effect of these therapeutic interventions slow and patients should be educated about this.[24] Prednisone treatment of 5 to 7.5 mg/day before going to bed at night may be tried in the patients with atypical obese hirsutismus with isolated form of CAH.[54] Endocrine therapy of cutaneous symptoms is indicated before application of the laser. Cosmetic prevention is an important part of treatment in hirsutismus control. Lighteninig color of hair and epilation are useful applications, but can lead to skin irritation. FDA has allowed the marketing of many laser tools and equivalents such as diode and flashlamp for permanent hair reduction. The criterion for permanent hair reduction is 30% or more permanent reduction of hair density in a region after 3-4 treatments. In the laser treatment hair follicle damage is created as a result of a combination of partial absorption of 694-1064 nm wavelength of the beam with a dark color hair and by penetration into the dermis. Burns, depigmentation, and scarring may occur. It has

to be applied in experienced and well-educated centers.[15] Eflornithine hydrochloride cream which inhibits ornithine decarboxylase enzyme may be beneficial with 2-6 months of the treatment of hirsutism in approximately 1/3 of the patients but its effect is reversable after cessation of treatment. It may also be used as a bridge treatment with combination of oral contraceptive treatment.[65]

In summary, adolescents who are candidates for pkos require more research on the atedal approach. Early evaluation and diagnostics can give us an opportunity to overcome the natural course of the syndrome.

Conflict of Interest

The authors declare that there is no financial support or conflict of interests regarding the publication of this paper..

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