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REVİEW ARTICLE

Polycystic Ovarian Syndrome: A Diagnostic and Therapeutic Challenge

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Abstract:
Polycystic ovarian syndrome (PCOS) is the commonest endocrinopathy in women with a multi-factorial etiology, and presents not just a diagnostic dilemma but also a therapeutic challenge as well. The clinical features of the syndrome in adolescents result from hyperandrogenemia and oligo/anovulation. Most women presenting with non-pregnancy related secondary amenorrhea, oligomenorrhoea, acne, hirsutism, and infertility have PCOS. Consensus diagnostic criteria have been developed by the United States National Institutes of Health (NIH), and the European Society of Human Reproduction and Embryology and American Society of Reproduction (Rotterdam criteria). PCOS needs to be suspected, recognized, and treated to prevent some long term complications. Treatment modalities need to be individualized to address the specific concerns of each female presenting with this entity. This article reviews the diagnosis and principles of management of PCOS.

Keywords: Polycystic ovarian syndrome, hyperandrogenism, insulin resistance, oral contraceptive pills (OCPs)
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Introduction

Polycystic ovarian syndrome (PCOS) is probably the most common endocrinopathy in females. Traditionally, it was recognized more as a disorder of the adult women in the reproductive age group, but in recent years PCOS is increasingly being recognized in the adolescents as a major concern. PCOS is a heterogenous disorder with protean clinical manifestations, therefore presenting not only a diagnostic but therapeutic challenge as well.

Definition

PCOS, as the name implies is a syndrome which portrays a heterogenous clinical presentation and may be caused by various underlying etiologies. The main components of the syndrome in adolescents result from hyperandrogenemia and oligoanovulation. However in young women, infertility may be an important presenting concern.

Etiology

The etiology of PCOS is believed to be multi-factorial, including the effects of multiple environmental factors on a genetically predisposed individual [1]. Factors in favor of a genetic predisposition include the observation that women/girls with PCOS are found in family clusters along with other members with PCOS, infertility, insulin resistance, type 2 diabetes mellitus, and metabolic syndrome [2]. This is further emphasized by twin studies showing increased predisposition of twins to PCOS [3]. Ongoing research continues to identify specific genetic mutations responsible. Multiple genes that have been implicated thus far may be grouped under: [1] genes related to androgen synthesis and action, [2] genes related to causation of insulin resistance, [3] genes encoding

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cytokines responsible for inflammation, and [4] other genes [4, 5]. Male relatives of females with PCOS are reported to express a 'male PCOS' phenotype characterized by early alopecia, generalized increased hair distribution, insulin resistance, and increased serum dehydroepiandrosterone sulfate (DHEAS) [5, 6]. *In utero* androgen excess seems to cause PCOS programming of the fetal ovaries leading to PCOS later in life [7].

Prevalence

PCOS affects about 5 to 10% of adolescents and women in the reproductive age group making it the most common endocrinopathy in females [8, 9]. A majority of adolescents and women presenting with non-pregnancy related secondary amenorrhea, oligomenorrhoea, acne, hirsutism, and infertility have PCOS [10].

Diagnostic Criteria

PCOS being an extremely heterogenous disorder becomes a diagnostic challenge. There exists a significant discrepancy and controversy about diagnostic criteria for PCOS. Consensus diagnostic criteria have been developed by the National Institute of Health (NIH), the European Society of Human Reproduction and Embryology and the American Society of Reproduction (Rotterdam criteria) (Table 1) [11, 12, 13]. These diagnostic criteria encompass some common features including evidence of hyperandrogenism (clinical or biochemical); menstrual irregularity usually with oligomenorhoea or amenorrhoea as a reflection of anovulation. The presence of polycystic ovaries is not an essential criterion for the diagnosis of PCOS. It is not one of the NIH criteria, but is one of the three Rotterdam criteria. Therefore the presence of polycystic ovaries are not essential even in the Rotterdam set of diagnostic criteria as only 2 of 3 criteria need to be fulfilled. However, the Rotterdam criteria encompass a group of patients who may not be diagnosed with PCOS using the NIH criteria, namely those women with polycystic ovaries but normal ovulation; and also those with polycystic ovaries and anovulation but no hyperandrogenemia [11, 12, 13]. The diagnostic controversy continues as it is felt by some clinicians that hyperandrogenemia should be an essential criterion for the diagnosis of PCOS [14].

There are no diagnostic criteria specific for PCOS in adolescents. Although the criteria developed for adult women are generally applied to adolescent females, there are some areas of concern that are unique to adolescents. These include: (1) In adult criteria, there is no consideration given to the period of normal physiologic anovulation in the first two years after menarche, (2) There are concerns about inadequate ovarian visualization on transabdominal ultrasonography versus transvaginal pelvic ultrasonography. Since adolescents who are not sexually active generally undergo only transabdominal ultrasonography, the presence of polycystic ovaries may be under-diagnosed, and (3) It is also known that multi-follicular ovaries may be found normally in adolescents without any underlying pathology [15, 16, 17].

Table I. Diagnostic Criteria for PCOS [11,12,13]

I. National Institute of Health (NIH) Criteria (1990):

- Menstrual irregularity
- Clinical or biochemical hyperandrogenism
  - Clinical
    - Hirsutism
    - Acne
    - Male pattern alopecia
  - Biochemical: high serum androgen levels
- Exclusion of other causes of menstrual irregularity and hyperandrogenemia

II. Rotterdam Criteria (European Society of Human Reproduction and Embryology, American Society of Reproduction, 2003):

1. Menstrual irregularity due to anovulation or oligo-ovulation
2. Hyperandrogenemia – clinical or biochemical
3. Polycystic ovaries (by ultrasound)

Pathogenesis

The basic underlying issue responsible for causing PCOS is believed to be high androgen levels in the ovary. This intraovarian hyperandrogenism is believed to be responsible for multiple ovarian cysts and anovulation. The cause of this hyperandrogenemia is still debatable. However, dysregulation in steroidogenesis, gonadotropin secretion, and insulin metabolism with evidence of hyperinsulinemia have been found in patients with PCOS [17]. A possible explanation for the insulin resistance (IR) and hyperandrogenism seems to be a defect in the underlying molecular mechanism affecting both these hormonal pathways [18]. IR and resultant hyperinsulinemia are believed to be important regulatory factors for ovarian androgen synthesis. IR and hyperinsulinemia have synergistic action with luteinizing hormone (LH). This results in increased androgen production and increased bioavailability of free androgen by reducing hepatic synthesis of sex hormone binding globulin (SHBG) [19]. Dysregulation of gonadotropin function includes increased pulsatility of hypothalamic gonadotropin releasing hormone (GnRH), causing increased LH secretion that results in increased androgen production by the ovarian theca cells [20].

The other mechanism of PCOS pathogenesis is believed to be dysregulation of steroidogenesis. In the ovary this is usually referred to as functional ovarian hyperandrogenesism (FOH), and in the adrenal gland usually referred to as functional adrenal hyperandrogenesism (FAH). This occurs at the level of the cytochrome P450C17 enzyme, which regulates the activity of two separate enzymes of steroidogenesis namely 17-hydroxylase and 17, 20 lyase [21]. This results in increased steroidogenesis. However, in PCOS, there is no block in the steroidogenenic pathway, such as that seen in congenital adrenal hyperplasia. The steroid pattern seen in FOH includes increased 17 hydroxy-progesterone (17-OHP) levels in response to GnRH stimulation test. 17-OHP is the most specific marker of FOH [21]. In FAH there is increased DHEA and 17 hydroxy-pregnenolone in response to adrenocorticotrophic hormone (ACTH) stimulation [21].

Clinical features

Since PCOS is a heterogenous syndrome the presenting clinical features may vary greatly. The main presenting features are generally a result of hyperandrogenemia or insulin resistance, both of which seem to have a cause and effect relationship in the underlying pathogenesis. Some clinical features may be attributed more to high androgen levels include hirsutism, acne, irregular menstrual periods, premature adrenarche, seborrhea, and male pattern alopecia. Obesity, acanthosis nigricans, glucose intolerance, pre-diabetes, and type 2 diabetes mellitus are attributed to the hyperinsulinemia and insulin resistance. Infertility is the presenting feature seen in most adult women. Adolescent females may present with any one or more of these features. A study looking at the presenting characteristics of adolescents in a primarily Caucasian population presenting to a PCOS clinic revealed 84% of patients with BMI above the 85th percentile, more than 50% had hyperinsulinemia, about 70% had some form of amenorrhoea or oligomenorrhoea, 50% with hirsutism, and 4% had type 2 diabetes [22].

Obesity: Obesity is not a diagnostic criterion in any of the presently accepted guidelines for PCOS, but it is seen quite frequently in PCOS. Although a large number of females with PCOS are obese, the thin PCOS phenotype is also well recognized. Obesity in women with PCOS is a risk factor for increased severity of metabolic complications [23, 24].

Acanthosis Nigricans (AN): AN is a clinical marker of insulin resistance and hyperinsulinemia. It is a common finding in obese adolescents with PCOS. AN is characterized by dark, velvety, thickened skin lesions most commonly distributed at the neck, axilla, groin, and in severe cases in the upper and mid chest, under the breast, and abdominal areas predominantly infraumbilical. Often the patients and families of adolescents mistake AN lesions for dirt in the dorsal neck area. Significant weight loss and normalization of insulin levels may reverse the AN in the early stages [25].

Hyperandrogenism: Clinical markers of hyperandrogenism include hirsutism, acne, androgenic alopecia, seborrhea, hyperhidrosis and hidradenitis suppurativa [26]. Hirsutism refers to the presence of excessive sexual hair in females, in the pattern of male distribution and therefore would include hair on the face (upper lip, chin, sideburns), around the nipple or areola, and infraumbilical area [27]. It is important to differentiate between hirsutism and hypertrichosis. Hypertrichosis refers to generalized increased body hair not limited to the sexual hair distribution. Hypertrichosis may be genetic or ethnic, or be caused due to side effects of some medications including diazoxide, glucocorticoids, and cyclosporine. The Ferriman-Gallwey score is generally used to grade hirsutism. Hair growth is graded using a scale from 0 to 4, with a maximum score of 36. A score of 8 and higher signifies hirsutism and possibly androgen excess [28, 29]. It is also important to remember that hirsutism may not always be caused by hyperandrogenism. Many females with hirsutism have idiopathic hirsutism with normal androgen levels and conversely some women with documented hyperandrogenemia may not have hirsutism possibly due to decreased sensitivity of the pilo-sebaceous unit [26, 30].

Premature adrenarche or pubarche: A positive history of premature adrenarche is seen in about 20% of adolescents with PCOS. This is believed to be an early manifestation of PCOS [31].

Anovulatory menstrual cycles: Signs of anovulation may be seen in as many as two thirds of all women with PCOS [30]. The presence of physiologic anovulatory periods for about two years after menarche makes this differentiation difficult in adolescents. A wide range of menstrual disturbances are seen in PCOS in adolescents [30]. These include primary amenorrhea (absence of menarche by 15 years of age), secondary amenorrhea (no menstrual period for 3 months), oligo-menorrhea (missing more than 4 periods a year), and dysfunctional uterine bleeding. Presence of persistent menstrual irregularities and hyperandrogenemia in adolescence will generally persist into adulthood [32].

Polycystic ovaries: The presence of polycystic ovaries on ultrasonogrphy is one of the three features in the Rotterdam Criteria for PCOS. However it is believed that in adolescents there is underestimation of the prevalence of polycystic ovaries because of the technical difficulty of

Table II. Testing for PCOS [30]

Which patients should be investigated for PCOS?
• Adolescent girls with a history of: ○ Irregular menstrual periods ○ Dysfunctional uterine bleeding ○ Obesity ○ Hirsutism ○ Signs of insulin resistance: • Acanthosis nigricans • Metabolic syndrome
What laboratory tests should be done?
• Tests to confirm hyperandrogenemia: ○ Free testosterone – best test! ○ Total testosterone – if free testosterone not available ○ DHEAS (dehydroepinandrosterone sulfate) • Test for ovarian morphology: Pelvic ultrasonography • Tests to evaluate for underlying causes of similar symptomatology: Endocrine laboratory tests to exclude other causes of hyperandrogenemia: ○ Serum prolactin ○ Serum cortisol ○ Free thyroxine (FT_4) and TSH (thyroid stimulating hormone) ○ 17 α hydroxyprogesterone (17αOHP) ○ Pregnancy test
• Other tests for hyperandrogenemia (if required): ○ Dexamethasone suppression test ○ ACTH stimulation test
• Laboratory investigation for other features: ○ 2 hour oral glucose tolerance test

visualizing ovarian morphology in transabdominal sonograms done in adolescents versus transvaginal sonograms [33] On the other hand, the presence of multi-cystic ovaries, which are a normal variant in adolescent girls, may be difficult to differentiate from polycystic ovaries. Therefore, the role of pelvic ultrasonography in adolescents who have evidence of anovulatory cycles and hyperandrogenemia remains debatable.

Laboratory tests

Various diagnostic and confirmatory tests and their indications are all listed in Table 2 [30].

Long-term Implications

Adolescents with PCOS may present later in life with some possible long term health implications resulting from unresolved PCOS which are listed in Table 3 [34].

Principles of management

The clinical manifestations of PCOS and their severity vary widely, therefore, treatment should be individualized as well. However, there are some common clinical manifestations seen in most cases that will need appropriate treatment. These include irregular menstrual periods, hirsutism, acne, obesity, hyperinsulinemia, and insulin resistance.

*Irregular menstrual periods***:** The menstrual irregularity resulting from chronic anovulation in adolescent females should be treated to prevent the development of endometrial hyperplasia, which is recognized as a predisposing factor for development of endometrial cancer. In adult women desirous of pregnancy, treatment of anovulatory cycles involves treatment for infertility to achieve ovulation. These options include treatment with

clomiphene citrate, exogenous gonadotropins, pulsatile GnRH (gonadotropin releasing hormone) or newer techniques such as laproscopic ovarian drilling.

For adolescent with menstrual irregularities, hormonal combination oral contraceptive pill (OCPs) offers a broad range of preparations and options for use. Most combination OCPs are a combination of an estrogen and a progestin. The aim of the treatment is to regularize menstrual cycles and normalize high androgen levels. These preparations therefore are ideal choices for girls presenting with hirsutism and resistant acne. The estrogen component functions not only to reduce the androgen production in the ovary but also to increase the production of sex hormone binding globulin (SHBG) thereby effectively lowers the levels of free androgen available. The progestin component prevents endometrial hyperplasia. Additionally in sexually active adolescents, OCPs serve as a reliable contraceptive agent. Various OCP preparations offer different combinations and options. Most of them have similar estrogen components (ethinyl estradiol of 30, 35 or 50 mcg) but the progestin components are more variable. The OCPs with low androgenic progestins are preferred in these cases. Newer progestin agents such as drospirenone, and norgestimate may be preferred in girls with hirsutism and acne respectively. Other options include OCPs with ethynodiol diacetate which is also a low androgenic progestin. OCPs with higher estrogen content may be preferred in patients with dysfunctional uterine bleeding [35, 36, 37, 38]. The androgen levels normalize within the first month of treatment. The duration of treatment is however less clear with suggestions varying from one to five years or even ongoing. Risks of venous thromboembolism especially with higher estrogenic preparations, and salt and water, retention causing difficulty with weight loss efforts need to be carefully considered. Progestin only preparations include micronized progesterone or medroxyprogesterone acetate. These agents may be used for 7 to 10 days each cycle every 6 weeks, thus allowing spontaneous menstrual cycles. Advantages of the progestin only preparations include elimination of the estrogen related side effects. However, the inability of this regimen to act as a contraceptive tool and the occurrence of bloating, breast tenderness and depression may be potential side effects [35].

Other options for the treatment of menstrual irregularities, including GnRH agonists such as depot leuprolide and glucocorticoid regimens, may be used in special circumstances where the above mentioned options are note feasible. These agents are not as effective and need close monitoring preferably by a pediatric endocrinologist.

Acne: For treatment of acne, options include the use of appropriate cleansing agents, topical creams and lotions with salicylic acid, antibiotics, benzoyl peroxide, and retinoids. Other adjunctive therapies such as laser treatments or chemical peels may be needed in some cases, which are best addressed by a dermatologist. In addition to topical skin care, oral agents are generally required for severe acne. These may include oral antibiotics, oral isotretinoin, and oral hormone therapy with OCPs. Combination OCPs of choice will be the ones with newer low androgenic progesterone preparations (such as norgestimate, desogestrel, gestodene), and antiandrogenic progestins (cyproterone acetate and drospirenone) [39, 40, 41, 42].

Hirsutism: Treatment of hirsutism essentially includes temporary or permanent methods of hair removal. Temporary methods of hair removal include shaving, hair removing creams or lotions, waxing, threading, or simple tweezing or plucking. These can often be done by adolescents themselves and are relatively cost-effective. However, depending on density of hair distribution and rate of hair growth these procedures may need to be repeated quite frequently and can often cause skin irritation and damage. Topical pharmacologic options for hirsutism include the relatively new agent eflornitine hydrochloride cream which has been FDA approved. It is useful for slowing the rate of facial hair growth but will

Table III. Long Term Complication of PCOS

- Concerns with insulin/glucose metabolism:
  - Hyperinsulinemia, insulin resistance
  - Pre-diabetes – impaired glucose tolerance
  - Type 2 diabetes mellitus
- Concerns with obesity:
  - Metabolic syndrome
  - Increased waist to hip ratio
- Concerns with cardiovascular heart disease:
  - Hypertension
  - Hyperlipidemia or dyslipidemia
  - Increased risk of premature atheroslerosis
    - Endothelial dysfunction
    - Increased vascular thickness
    - Chronic vascular inflammation
- Gynecologic complications:
  - Irregular menstrual periods
  - Endometrial cancer
  - Infertility

need to use on an ongoing basis for clinical effect. Other physical cosmetic procedures that may offer long term or somewhat permanent hair removal include electrolysis and laser (photoepilation) therapy. These procedures are undertaken by cosmetologists either on their own or under the supervision of dermatologists or plastic surgeons. Although these procedures offer somewhat permanent hair removal, they are generally quite expensive. Side effects of these procedures include scarring, pigmentation or slight burning. Electrolysis may be the preferred procedure in women with darker color skin.

The hormonal therapy for treatment of hirsutism has different targets for physiologic action. These include: (1) Reducing the production of ovarian androgens by inhibiting LH secretion and also indirectly reducing the adrenal androgen secretion as well, (2) Increasing the estrogen induced hepatic production of SHBG thus lowering the free testosterone or androgen levels, and (3) Blocking of androgen action at the level of the androgen receptors. The hormone therapy options for hirsutism may be divided into combination oral contraceptive pills and antiandrogenic agents. Combination OCPs of choice are again as mentioned in the hormone treatment of acne above. Hormonal treatment for hirsutism is useful in the setting of PCOS. The 2008 guidelines of the Endocrine Society (in the United States) suggest OCPs as first line of medical therapy for hirsutism [43].

Antiandrogens are added to the treatment regimen of patients on OCPs if there is an inadequate response to OCPs alone [43] Antiandrogens work by inhibiting binding of the androgen at the androgen receptor level and thus inhibit the androgen mediated change of vellus to terminal hair [44]. The antiandrogen agent should be generally prescribed along with an OCP to prevent teratogenic effects on the male fetus and also to prevent menstrual irregularities. Spironolactone is relatively safe, most effective, and the most commonly used antiandrogen agent. In women on sprironolactone, electrolytes need to be monitored for hyperkalemia, and complaints of fatigue maybe noted, but overall spironolactone is generally fairly well tolerated. Other antiandrogen agents available are cyproterone acetate, flutamide and finastride. These agents are not commonly used and may need evaluation for use on an individual basis. Use of flutamide is discouraged because of the risk of hepatoxicity. There is generally a lag of 9-12 months before clinical effects of antiandrogen agents can be appreciated. The antiandrogens need to be used on an ongoing basis for clinical effect. These treatment modalities are best addressed in conjunction with a pediatric endocrinologist.

Obesity: Treatment of obesity is challenging because of multiple factors including: (1)Poor understanding of the underlying mechanisms which if known could be used to address medical therapeutic options; (2) Well established social behaviors and dietary patterns resulting in excessive caloric intake in the form of excessive amount of processed, condensed, high caloric food intake; (3) Prevalence of an ever increasing sedentary lifestyle with the advent of cable televisions, video games, and computers, along with loss of safe neighborhoods and social interactions further restricting physical activity; (4) No successful or safe therapeutic options ("magic pills") to treat obesity in adolescents.

Successful weight control strategies need to address long term behavior changes and life style changes of not only individuals but families and society on the whole, incorporation of gym, recess activity, regular exercise and sports participation options for all children, adolescents and adults; nutrition behavior changes including healthy food options and elimination of caloric dense beverages and fast food choices; education and increased awareness of the public of complications of obesity; and healthy lifestyle awareness. Improvement in obesity is seen to result in some improvement in hyperandrogenemia, acanthosis nigricans, insulin resistance, and even ovulation [36, 37].

Hyperinsulinemia, insulin resistances, pre-diabetes, and type 2 diabetes mellitus: Metformin is recognized as a promising drug for hyperinsulinemia and insulin resistance. Metformin has some appetite suppressing effects which may contribute to modest weight loss, improve hyperandrogenemia, lower testosterone levels, and improve ovulation and menstrual cycling. It has no significant effect on hirsutism [45, 46, 47]. Metformin reduces the hepatic glucose output thus causing reduction in the hyperinsulinemia [48]. Metformin is generally started at a dose of 500 mg with dinner and gradually increased to 1000 mg to a maximum dose of 2000 mg daily. The long acting formulations are better tolerated with less gastrointestinal side effects.

Conclusion

PCOS continues to be a challenging clinical syndrome in young women. Heightened awareness and high index of suspicion in adolescents is important to diagnose PCOS early and institute appropriate management strategies in order to minimize long-term risks and complications. Ongoing work is needed to define this clinical entity more clearly, in addition to the development of improved therapeutic measures to fine-tune management strategies.

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