Polycystic Ovarian Syndrome (PCOS) in Adolescents: A Literature Review

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Abstract: Polycystic Ovarian Syndrome (PCOS) is one of complex familial disorders and mostly found endocrine disorder in women. The prevalence of PCOS ranges between 6-10% depending on the criteria used. Some attributes related to PCOS consist of ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology based on ultrasound finding. PCOS has been difficult to diagnose in adolescents since some changes in normal puberty with a phenotype similar to PCOS might appear. Early identification of PCOS may result in optimization of treatment regarding to metabolic problem and long-term reproduction. Individualized management is preferred and should be adjusted to the circumstances at which it is diagnosed in adolescents. The focus of the therapy should be based on multimodal approach with life style modification as the first line and pharmacological therapy as symptom relief.

Keywords: adolescents, endocrine, PCOS

1. Introduction

Adolescence is described as a dynamic developmental phase in one’s life. World Health Organization (WHO) defined adolescence as a period when an individual belongs to the 10-19-year age group and experiences several significant changes in physical growth and development. Polycystic ovarian syndrome is a type of endocrine disorders which is mostly found in women of reproductive age. [1]-[3]

A meta-analysis study reveals that PCOS accounts for 5-18% of cases in women of reproductive age. Research in India has shown a prevalence of 22, 6% in women between the age of 15-19 years based on the Rotterdam criteria for PCOS and 9, 8% on the criteria of the Androgen Excess and PCOS Society (AES-PCOS).3 Population-based studies regarding the prevalence of PCOS in adolescents are still extremely rare. The estimation of the prevalence of PCOS in adolescents is 0, 8% in the United States and 3% in Iran based on data provided. [4]

2. Adrenal and Ovarian Steroid Biosynthesis

Initial theca cells stimulation by luteinizing hormone (LH) leads to the transformation of cholesterol into androstenedione (Figure1). Testosterone is later synthesized within the theca cells from the latter by the enzyme 17β-hydroxysteroid dehydrogenase (17β-HSD) before eventually transformed into dihydrotestosterone. The diffusion of androstenedione into granulocytes results to the formation of estrone which is catalyzed by follicle stimulating hormone (FSH). The change from estrone into estradiol is assisted by the enzyme 17β-HSD. [5, 6] Coincidentally, adrenocorticotropic hormone (ACTH) stimulates the steroid biosynthesis in the adrenal cortex (Figure 2). [5, 6]

Prior to the formation of progesterone by 3β-hydroxysteroid dehydrogenase (3β-HSD), the formation of pregnenolone originally takes place in zona gromerulosa. Both pregnenolone and progesterone will be catalyzed by 17α-hydroxylase into 17-hydroxypregnenolone dan 17-hydroxyprogesterone (17-OHP) respectively inside the zona fasciculata. These intermediate forms will later be transformed into dehydroepiandrosterone (DHEA) and an-
drostenedione. In a lower concentration, DHEA might be transformed into androstenedione, which later be changed into testosterone and estrone. In addition, androgen is also produced in the liver, adipocytes and skin. [5, 6]

3. The Pathogenesis of PCOS in Adolescents

1) Potential Factors
An in-vitro study shows that excess expression of LH receptor and steroidogenic enzymes such as cytochrome P450c17, 3β-HSD and 17β-HSD. As a result, the production of steroids such as 17-OHP and testosterone was found to be increased compared to controls without PCOS. During puberty, there is maturation of the hypothalamus-pituitary-ovarian axis and a subsequent increase in circulating LH levels occurs. This increase will be excessive in women with a predisposition to experiencing PCOS and will further increase androgen production. Adolescents with PCOS show an increase in the frequency and amplitude of gonadotropin-releasing hormone (GnRH) and LH as well as an increase in the ratio of LH to FSH. [5, 7]

Theca cells produce androgens under the influence of LH and various intracrine factors. The activity of the P450c17 enzyme is a rate limiter of androgen synthesis. Increased expression of CYP17A1 or P450c17 activity was seen in theca cells obtained from women with PCOS. Hyperinsulinemia is commonly associated with PCOS, increasing the response of theca cells to circulating LH. Ovaries in PCOS also experience increased enzyme expression from an alternative signalling pathway for dihydrottestosterone production. Increased expression of CYP17A1 or P450c17 activity was seen in theca cells obtained from women with PCOS. Hyperinsulinemia is commonly associated with PCOS, increasing the response of theca cells to circulating LH. [8, 9]

2) The Role of Insulin and Obesity
There is an increase in insulin resistance along with the increase in serum fasting insulin concentrations during normal puberty and adolescence. As insulin levels increase, there is a corresponding decrease in sex-hormone bin-ding globulin (SHBG) due to inhibition of its production in the liver, which in turn increases the concentration of the free sex steroid. Insulin increases steroidogenesis in theca cells and ovarian granulosa cells due to stimulation of LH. The ovaries remain sensitive to insulin despite systemic insulin resistance in PCOS. Insulin enhances the effect of LH on granulosa cell steroidogenesis. Insulin resistance and hyperinsulinemia also have implications for the mechanisms underlying an ovulation through stopping follicular maturation. [10]

Insulin resistance and hyperinsulinemia have a central role in the pathogenesis of PCOS and a high prevalence is reported in adult women and adolescents with PCOS. Insulin resistance in PCOS occurs because of the complex interactions between genetic susceptibility, intrauterine factors, adaptation to excess energy, early puberty and adiposity. Insulin increases the effect of LH on theca cells, increases androgen synthesis and decreases the synthesis of sex hormone binding globulin (SHBG) in the liver, thereby increasing free androgen levels. Insulin resistance is caused by a post-receptor defect, in which serine phosphorylation occurs from tyrosine residues at insulin receptors and not on threonine residues. [10, 11]

Obesity is believed to play a role in the pathogenesis of PCOS by causing insulin resistance and exacerbating symptoms of hyperandrogenism in PCOS. The increase in androgen concentration is partially related to the decrease in SHBG in obesity. Excess adipose tissue contributes to an increase in androgens because it contains several steroidogenic enzymes that convert androstenedione into testosterone and testosterone to the more potent DHT. [5, 6]

3) Genetic Factors
Some of the key genes associated with steroidogenesis include CYP17A1, CYP19, CYP21, HSD17B5 and HSD17B6. Sex hormones and their receptors are also involved. Polycystic ovary syndrome is a metabolic disorder that is closely related to diabetes mellitus type 2, hyperlipidemia, obesity, and metabolic syndrome. Metabolic-related candidate genes include genes associated with insulin biosynthesis and function (INS), insulin receptor (INSR), insulin receptor substrate 1 (IRS1), IRS2, IGF, PPARG and CAPN10 and genes associated with obesity. (FTO). Genes associated with chronic inflammatory pro-cesses include several cytokines, namely tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-1A, IL-1B and plasminogen activator inhibitor (PAI). [5, 12]

Figure 3: Hypothesis model of the GWAS signaling cascade involved in the pathogenesis of PCOS [14]

Genome Wide Association Studies (GWAS) conducted on Han Chinese women identified 11 loci with a strong risk for PCOS (Figure 3). These results have also been validated in Caucasian populations. The gene Differentially Expressed in Normal and Neoplastic Development isoform A1 (DDEND1A) was identified as a strong marker of risk. Overexpression of DDEND1A. V2 in normal theca cells triggers increased CYP17A1 and CYP11A1 expression and androgen production whereas inhibition of their expression reverses this process. [13, 14]

4) Environmental Factors
The potential contribution of environmental and lifestyle factors adds to the complexity of the pathogenesis of PCOS. Endocrine disrupting chemical (EDC) is defined as
substances in the environment, food and consumption products that can affect the biosynthesis, metabolism, and work of hormones that cause deviations from the regulation of homeostasis or normal reproduction. Endocrine disrupting chemicals are a group of molecules that include plastic materials such as phthalates and bisphenol A (BPA) which are similar to advanced glycation end products (AGEs). Most humans are exposed through food packaging; however, these molecules are also used in medical equipment. Endocrine disrupting chemicals can cause a variety of disorders affecting the male and female reproductive systems, abnormal development and breast cancer, prostate cancer, neuroendocrine, thyroid, metabolism and obesity and cardiovascular. [5, 15]

4. Polycystic Ovary Syndrome Diagnosis Criteria in Adolescents

Clinical manifestations of PCOS include clinical hyperandrogenism (hirsutism, acne and alopecia) and menstrual disorders (primary or secondary amenorrhea, oligomenorrhea, irregular menstrual periods and heavy menstrual bleeding). Hyperandrogenemia in adolescents is likely a consequence of a lack of maturation of the hypothalamus-pituitary-ovarian axis during life, as well as prolonged anovulatory cycles that are typical of pubertal development are not an early manifestation of PCOS. Testing of total and / or free testosterone levels is recommended to assess hyperandrogenism. An elevated serum free testosterone level is the only sensitive indicator for hyperandrogenism (Figure 4). [16]

Importantly, it is unclear when persistent oligomenorrhea in adolescents is a significant clinical finding in PCOS. Insulin resistance and hyperinsulinemia are common in women with PCOS and can affect the development of PCOS in some patients. The current definition of PCOS in adolescents does not include obesity, insulin resistance and hyperinsulinemia as diagnostic criteria. [2], [17]-[19]

Endocrine Society clinical guidelines recommend the diagnosis of PCOS in adolescents using the criteria for hyperandrogenism and persistent anovulatory menstrual disorders that cannot be explained by the NIH. The evidence supporting this conclusion is so small that The Pediatric Endocrine Society invites representatives from pediatric, adult and reproductive endocrinologists, adolescent medicine and the subspecialty of adolescent gynecology to meet and discuss the appropriate criteria for establishing a diagnosis of PCOS in adolescents. [16]
5. Management of Polycystic Ovarian Syndrome in Adolescents

Management of PCOS in adolescents should be adjusted to the needs of each individual. The goal of treatment is to improve quality of life and obtain long-term health outcomes and balance the side effects of treatment. There is no specific treatment for the underlying causes and pathophysiology of PCOS. There are 2 components of therapy, first, controlling the symptoms of hyperandrogenism (hirsutism, acne, irregular menstrual cycles or infertility) and second, preventing long-term morbidity associated with PCOS (metabolic syndrome, type 2 diabetes, emotional health and self-confidence). Communication with adolescents themselves about their perceived concerns is key to engaging and maintaining adherence to the care plan. The various therapeutic options available are lifestyle intervention, local cosmetic therapy, pharmacological therapy and combined therapy. [5, 13, 17, 22]

Lifestyle modification is essential and considered as the first line of PCOS therapy in all patients. A small randomized clinical trial study in adolescents showed that a healthy lifestyle (dietary restriction with intense exercise) increased the number of menstrual cycles, decreased hirsutism score and decreased testosterone levels by increasing SHBG. One study showed that exercise compared to a low-calorie diet found that there was a greater increase in ovulation rate (65% vs 25%) and pregnancy rate (6.2% vs. 1.7%) in the exercise group than in the diet group. Both groups showed improvements in body weight, androgen levels, fasting glucose, and insulin resistance. The diet group showed a greater reduction in body weight (10% vs 5%) and a greater decrease in androgen levels than the exercise group. Furthermore, the exercise group showed greater increases in SHBG levels, decreased testosterone, free androgen index, and insulin resistance compared to the diet group (9% vs 41%). [23, 24]

Cosmetic hair removal methods for hirsutism symptoms can include bleaching, chemical epilation, plucking, waxing, shaving, electrolysis, and laser hair removal. Electro-lysis can result in permanent hair removal, but its efficacy and safety have not been advocated by several randomized controlled trials (RCTs). [17]

Combined oral contraceptive pills containing estrogen (specifically ethinylestradiol) and progestogen (progestin) can be considered as first-line drugs in adolescents diagnosed with PCOS to reduce symptoms of hyperandrogenism and/or to regulate the menstrual cycle. The estrogen component plays a role in increasing SHBG thereby reducing the bioavailability of testosterone by binding to free steroids, and ultimately reducing the symptoms of androgen excess. Progestins can lower LH levels, thereby reducing ovarian androgen production. The combined oral contraceptive pill also provides menstrual regulation and endometrial protection. [5, 17, 25, 26]

A meta-analysis of metformin with or without lifestyle changes on PCOS in 2014 showed a beneficial effect on changes in BMI and menstrual cycle. Observational studies and 6 clinical trials have found short-term beneficial effects of metformin use in adolescents with PCOS who are predominantly overweight or obese. A recent meta-analysis comparing metformin to the combined oral contraceptive pill including 4 RCTs and a total of 170 adolescents showed that metformin and the COCs have the same benefit on hirsutism, triglyceride levels and HDL cholesterol. [17, 25, 27, 28]

Antiandrogen therapy used for PCOS therapy consists of 2 types, namely androgen receptor blockers (spironolactone and flutamide) and third generation progestins (cyproterone acetate) and 5α-reductase inhibitors (finasteride). There are still no RCT studies that directly compare various antiandrogens in adolescents with PCOS. Spironolactone is a therapy that is often used because of its availability and safety with an initial dose of 25 mg/day and gradually increased to a maximum of 200 mg/day. Initial administration of spironolactone is associated with transient irregular menstruation or bleeding spots, breast pain and sometimes fatigue or orthostasis due to decreased blood volume. Treatment with antiandrogens significantly reduced hirsutism compared to placebo and normalized menstrual cycles and endocrine-metabolic variables were better than monotherapy using metformin. [17, 29]

6. Conclusion

Polycystic ovary syndrome is a long-recognized, complex familial disorder. The pathogenesis of PCOS involves a variety of biological systems. Changes in steroidogenesis, ovarian folliculogenesis, neuroendocrine function, metabolism, insulin secretion, insulin sensitivity, adipose cell function, inflammatory factors and sympathetic nerve function play a role in the pathogenesis of PCOS. Polycystic ovary syndrome is characterized by ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology based on ultrasonography.

Clinical manifestations of PCOS in adolescents include clinical hyperandrogenism, namely hirsutism, acne and alopecia. Menstrual disorders can include primary or secondary amenorrhea, oligomenorrhea, irregular menstrual periods and heavy menstrual bleeding. Testing of total and/or free testosterone levels is recommended to assess hyperandrogenism. Most laboratories use the upper limit for total testosterone is 55 ng/dL and free testosterone is 9 pg/dL. Polycystic ovary morphology in adult women according to consensus criteria was defined as an ovary with a volume> 10.0 mL or a small antral follicle 2-9 mm in diameter with a number of ≥ 12 pieces. MOPK criteria in adult women are found in one third to one half of normal adolescents.

The goal of treatment is to improve quality of life and obtain long-term health outcomes and balance the side effects of treatment. There are 2 components of therapy, first, controlling the symptoms of hyperandrogenism (hirsutism, acne, irregular menstrual cycles or infertility) and second, preventing long-term morbidity associated with PCOS (metabolic syndrome, type 2 diabetes, emotional health and self-confidence).
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