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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]

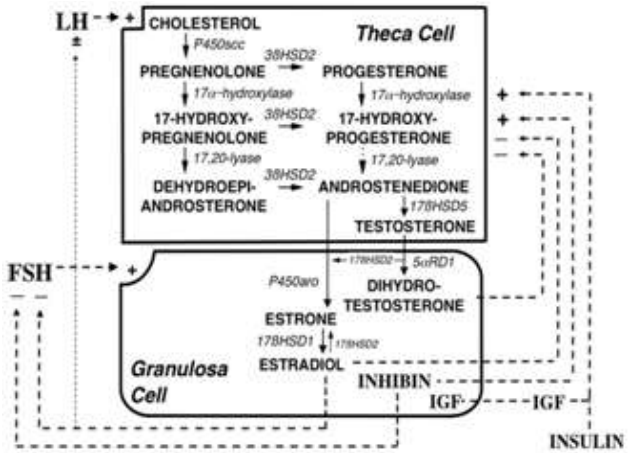

Figure 1: Formation and regulation of steroid biosynthesis in ovarian antral follicles [6]

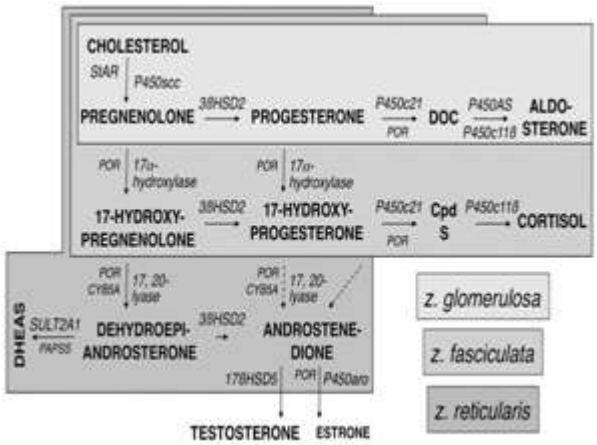

Figure 2: Formation and regulation of steroid biosynthesis in the adrenal cortex [6]

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-ova-rian 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 dihydrotestosterone 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, PPAR-g 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]

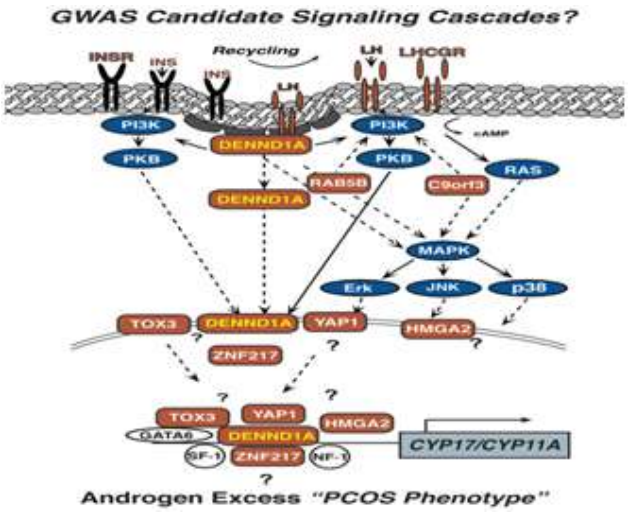

Figure 3: Hypothesis model of the GWAS signaling cascade involved in the pathogenesis of PCOS [14]

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 repro-duction. 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 me-dicine and the subspecialty of adolescent gynecology to meet and discuss the appropriate criteria for establishing a diagnosis of PCOS in adolescents. [16]

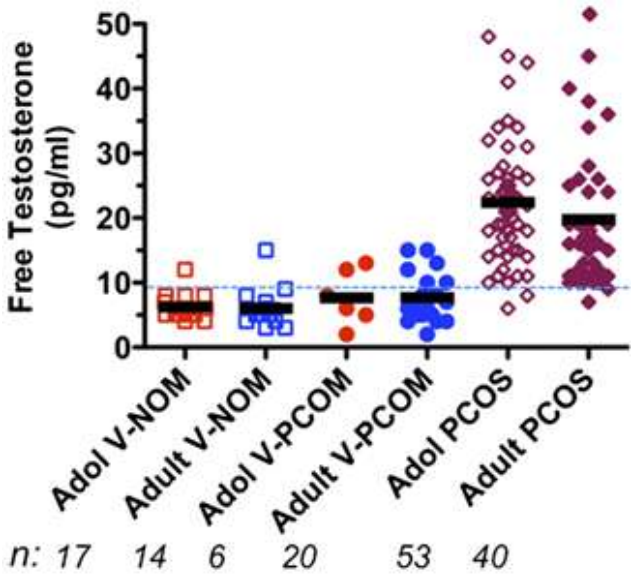

Figure 4. Serum testosterone levels in normal adolescent and adult women after menarche normal ovarian morphology (V-NOM) compared with polycystic ovary morphology (V-PCOM) and PCOS [16]

Imaging studies can be used to confirm the diagnosis of PCOS when clinical and laboratory evaluations are unclear (Figure 5). Transvaginal ultrasound examination is the modality of choice. In patients with uncertain clinical and laboratory findings, MRI can be used as an accurate diagnostic imaging modality (Figure 6). [20, 21]

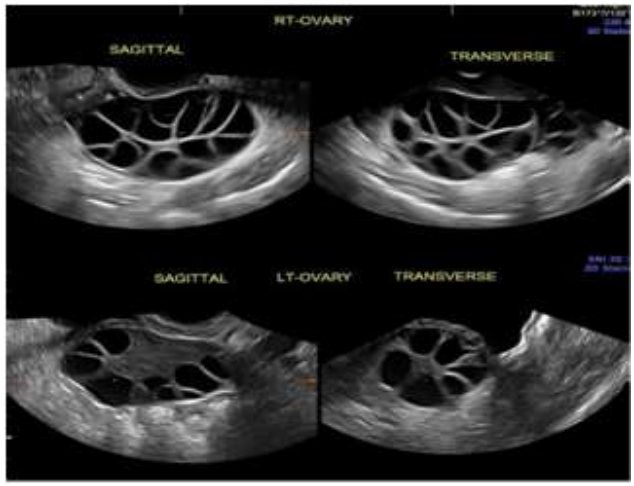

Figure 5: Display of TVS examination on PCOS [20]

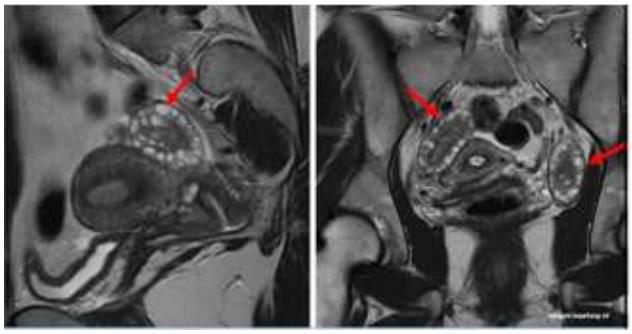

Figure 6: Display of MRI examination on PCOS [21]

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 de-creased 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 progesterone (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 func-tion, 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).

References

[1] Pardede N. Masa remaja. In: Narendra M, Sularyo T, Soetjiningsih, Suyitno H, Ranuh I, Wiradisuria S, editors. Tumbuh kembang anak dan remaja. Jakarta: Sagung Seto; 2002. p.138–70.
[2] Peña AS, Metz M. What is adolescent polycystic ovary syndrome? J Paediatr Child Health.2018 Apr; 54 (4): 351–5.
[3] Naz MSG, Tehrani FR, Majd HA, Ahmadi F, Ozgoli G, Fakari FR, et al. The prevalence of polycystic ovary syndrome in adolescents: A systematic review and meta-analysis. Int J Reprod Biomed (Yazd).2019 Aug; 17 (8): 533–42.
[4] Christensen SB, Black MH, Smith N, Martinez MM, Jacobsen SJ, Porter AH, et al. Prevalence of polycystic ovary syndrome in adolescents. Fertil Steril.2013 Aug; 100 (2): 470–7.
[5] Rothenberg SS, Beverley R, Barnard E, Baradaran-Shoraka M, Sanfilippo JS. Polycystic ovary syndrome in adolescents. Best Practice & Research Clinical Obstetrics & Gynaecology.2018 Apr; 48: 103–14.
[6] Rosenfield RL, Ehrmann DA. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyper-androgenism Revisited. Endocr Rev.2016; 37 (5): 467–520.
[7] Franks S. Polycystic ovary syndrome in adolescents. International Journal of Obesity.2008; 7.
[8] Marti N, Galván JA, Pandey AV, Trippel M, Tapia C, Müller M, et al. Genes and proteins of the alternative steroid backdoor pathway for dihy-drotestosterone synthesis are expressed in the human ovary and seem enhanced in the polycystic ovary syndrome. Mol Cell Endocrinol.2017 05; 441: 116–23.
[9] O'Reilly MW, Kempegowda P, Jenkinson C, Taylor AE, Quanson JL, Storbeck K-H, et al.11-Oxygenated C19 Steroids Are the Predominant Androgens in Polycystic Ovary Syndrome. J Clin Endocrinol Metab.2017 01; 102 (3): 840–8.
[10] Rojas J, Chávez M, Olivar L, Rojas M, Morillo J, Mejías J, et al. Polycystic Ovary Syndrome, Insulin Resistance, and Obesity: Navigating the Patho-physiologic Labyrinth. Int J Reprod Med [Internet].2014 [cited 2019 Aug 7]; 2014.
[11] Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev.2012 Dec; 33 (6): 981–1030.
[12] Zhao H, Lv Y, Li L, Chen Z-J. Genetic Studies on Polycystic Ovary Syndrome. Best Pract Res Clin Obstet Gynaecol.2016 Nov; 37: 56–65.
[13] Dabadghao P. Polycystic ovary syndrome in adolescents. Best Pract Res Clin Endocrinol Metab.2019 Apr 13;
[14] McAllister JM, Legro RS, Modi BP, Strauss JF. Functional genomics of PCOS: from GWAS to molecular mechanisms. Trends Endocrinol Metab.2015 Mar; 26 (3): 118–24.
[15] Diamanti-Kandarakis E, Bourguignon J-P, Giudice LC, Hauser R, Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev.2009 Jun; 30 (4): 293–342.
[16] Rosenfield RL. The Diagnosis of Polycystic Ovary Syndrome in Adolescents. Pediatrics.2015 Dec; 136 (6): 1154–65.
[17] Ibáñez L, Oberfield SE, Witchel S, Auchus RJ, Chang RJ, Codner E, et al. An International Consortium Update: Pathophysiology, Diagnosis, and Treatment of Polycystic Ovarian Syndrome in Adolescence. Horm Res Paediatr.2017; 88 (6): 371–95.
[18] Witchel SF, Oberfield S, Rosenfield RL, Codner E, Bonny A, Ibáñez L, et al. The Diagnosis of Polycystic Ovary Syndrome during Adolescence. Horm Res Paediatr.2015 Apr 1;
[19] Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. Am J Obstet Gynecol.2010 Sep; 203 (3): 201. e1-5.
[20] Youngster M, Ward VL, Blood EA, Barnewolt CE, Emans SJ, Divasta AD. Utility of ultrasound in the diagnosis of polycystic ovary syndrome in adolescents. Fertil Steril.2014 Nov; 102 (5): 1432–8.
[21] Kenigsberg LE, Agarwal C, Sin S, Shifteh K, Isasi CR, Crespi R, et al. Clinical utility of magnetic resonance imaging and ultrasonography for diagnosis of polycystic ovary syndrome in adolescent girls. Fertil Steril.2015 Nov; 104 (5): 1302-1309. e1-4.
[22] Deans R. Polycystic Ovary Syndrome in Adolescence. Medical Sciences.2019 Oct; 7 (10): 101.
[23] Kowalik A, Rachoń D. Dietary inter-ventions in the treatment of women with polycystic ovary syndrome. Nutri-tion, Obesity & Metabolic Surgery.2014 Jan 1; 1: 14–9.
[24] Hestiantoro A, Natadisastra M, Wiweko B. Current Updates on Poly-cystic Ovary Syndrome Endome-triosis Adenomyosis. Jakarta: Sagung Seto; 2014.
[25] Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the internati-onal evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril.2018; 110 (3): 364–79.
[26] Mastorakos G, Koliopoulos C, Creatsas G. Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. Fertil Steril.2002 May; 77 (5): 919–27.
[27] Hoeger K, Davidson K, Kochman L, Cherry T, Kopin L, Guzick DS. The Impact of Metformin, Oral Contra-ceptives, and Lifestyle Modification on Polycystic Ovary Syndrome in Obese Adolescent Women in Two Randomi-zed, Placebo-Controlled Clinical Trials. The Journal of Clinical Endocrinology & Metabolism.2008 Nov; 93 (11): 4299–306.
[28] Ladson G, Dodson WC, Sweet SD, Archibong AE, Kunselman AR, Demers LM, et al. Effects of metformin in adolescents with polycystic ovary syndrome undertaking lifestyle therapy: a pilot randomized double-blind study. Fertil Steril.2011 Jun 30; 95 (8): 2595-2598. e1-6.
[29] de Zegher F, Ibáñez L. Therapy: Low-dose flutamide for hirsutism: into the limelight, at last. Nat Rev Endocrinol.2010 Aug; 6 (8): 421–2.