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Review Article

Polycystic Ovarian Syndrome- Revisited

Najimudeen, M[1*], Myo HLA Myint[1], Anisah, J[1], Winson, S. M[1], Thavamani, R. M[1]

[1]International Medical School (IMS), Management and Science University, Malaysia

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***Corresponding author:** Najimudeen, M
International Medical School (IMS), Management and Science University, Malaysia

Abstract

Polycystic ovarian syndrome (PCOS) is a complex condition. In PCOS the metabolic and endocrine components are affected. The PCOS is an evolving condition and therefore has variable ultrasound presentations. Inappropriate gonadotrophin secretion causes ovarian dysfunction. Increased level of plasma testosterone is a common feature in PCOS. Women with PCOS have abnormalities in the metabolism of androgens and oestrogen. PCOS is a genetically heterogeneous syndrome. The abnormal menstruation patterns in PCOS is attributed to chronic anovulation. Women with PCOS should be assessed for their cardiovascular risk. The lifestyle modifications such as reducing the weight, increasing the exercise and restriction of carbohydrate intake consistently reduce the risk of diabetes. Medical management of PCOS is aimed at the treatment of metabolic derangements, anovulation, hirsutism and menstrual irregularity. The surgical management of PCOS is aimed mainly to improve ovulation. PCOS has many long-term complications. Therefore the patients need regular follow-up with their physicians for early detection and management of any untoward sequelae associated with the syndrome.

Keywords: Polycystic, ovary, insulin resistance, androgenism.

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the most common endocrinopathy, affecting women in reproductive age group. The PCOS is poorly understood. The aetiology is unknown. The diagnostic criteria are changed from time to time. The PCOS terminology itself a misnomer since it can be diagnosed without a single cyst in the ovary. The management is not uniform and only the symptoms are treated. PCOS is a condition that has long term implications on women's health, from adolescence to menopause.

Pathophysiology

The inherent ovarian dysfunction affects the hypothalamic-pituitary-ovarian (HPO) axis. This results in hyperinsulinemia. Exaggerated gonadotrophin releasing hormone (GnRH) pulsatility results in hypersecretion of luteinising hormone (LH), This disturbs both on ovarian androgen production and oocyte development. The deranged ovarian-pituitary and hypothalamic feedback accentuates the gonadotrophin abnormalities. Hyperinsulinemia is secondary both to insulin resistance at the periphery and to abnormal pancreatic beta cell function [1].

In the year 1935, Stein and Leventhal were the first to recognize an association between the presence of polycystic ovaries and signs of hirsutism and amenorrhea [2]. They named this condition as Stein-Leventhal syndrome. In women with Stein-Leventhal syndrome, their symptoms were improved after wedge resection of the ovaries. Their menstrual cycles became regular. They were able to conceive [3].

The PCOS can result from the unusual function of the HPO axis. Inappropriate gonadotropin secretion leads to ovarian dysfunction. Serum testosterone level is also increased in many patients [4].

The pathogenesis of PCOS is not clear. The endocrinology abnormality can be attributed to an increase in luteinising hormone (LH) release which results in the increase in ovarian androgen production, a process that can be aggravated by insulin resistance [5].

The PCOS involves endocrine and metabolic changes. The endocrinal changes include derangement of androgen and luteinizing hormone. The metabolic components involve insulin and lipid metabolism.

The luteinizing hormone (LH) stimulates the ovarian theca cells to produce androgen such as testosterone, androstenedione in excess. Due to the decreased level of follicle-stimulating hormone (FSH), the ovarian granulosa cells cannot aromatize the androgens to oestrogens. This leads to low level of oestrogen and anovulation. The Growth hormone (GH) and insulin-like growth factor–1 (IGF-1) may also augment the effect on ovarian function [6].

Studies of family members with PCOS indicate that an autosomal dominant mode of inheritance occurs for many families with this disease. The fathers of women with PCOS can be abnormally hairy; female siblings may have hirsutism and oligomenorrhea; and mothers may have oligomenorrhea. Research has suggested that in a large cohort of women with PCOS, a family history of type 2 diabetes in a first-degree family member is associated with an increased risk of metabolic abnormality, impaired glucose tolerance, and type II diabetes [7].

An important link between PCOS and obesity was corroborated genetically for the first time by data from a case-control study in the United Kingdom. 463 patients with PCOS were compared with 1300 female controls [8]. The investigators demonstrated that a variant within the FTO gene (rs9939609, was shown to predispose to common obesity). This was significantly associated with susceptibility to the development of PCOS.

The Insulin-like growth factor-2 (*IGF2*) stimulates androgen secretion in the ovaries and adrenal glands [9].

Myo-inositol (MI) and D-chiro-inositol (DCI) MI-derived phosphoinositol-3-phosphate (PIP3) enhances glucose transport inside the cells through the stimulation of GLUT4 translocation to the cell membrane. MI regulates glucose uptake and FSH signaling [10].

Prevalence

The prevalence vary from 2.2% to 26%. According to the diagnostic criteria [11]. The prevalence rate of PCOS in the Asian regions has a range of 2.4-9% in China, Sri Lanka and India [12].

Clinical presentation

History

(a) Family history

The family history of patients with polycystic ovarian syndrome (PCOS) may include the following:

Menstrual disorders
Adrenal enzyme deficiencies
Hirsutism
Infertility
Obesity and metabolic syndrome
Diabetes

(b) Menstrual abnormalities

Patients with PCOS have abnormal menstruation patterns attributed to chronic anovulation. The patient usually has a history of menstrual disturbance dating back to menarche. Some women have oligomenorrhea (Menstrual bleeding that occurs at intervals of 35 days to 6 months, with less than 9 menstrual periods per year) or secondary amenorrhea (an absence of menstruation for 6 months). Dysfunctional uterine bleeding and infertility are the other consequences of anovulatory menstrual cycles. The menstrual irregularities in PCOS usually present around the time of menarche.

A retrospective study by Maslyanskaya *et al*., reported that PCOS was the most common aetiology seen in adolescent patients hospitalized for abnormal uterine bleeding accounting for 33% of 125 hospital admissions [13].

(c) Infertility

A substantial number of women with PCOS are infertile. Most women with PCOS ovulate intermittently. Conception may take longer than in other women, or women with PCOS may have fewer children than they had planned. In addition, the rate of miscarriage is also higher in affected women.

(d) Sleep apnoea

Many women with PCOS have obstructive sleep apnoea syndrome (OSAS). This is an independent risk factor for cardiovascular disease. Excessive daytime somnolence should be inquired. Individuals with obstructive sleep apnoea experience apnoea/hypopnea episodes during sleep [14]. For women with PCOS with suspected OSAS, there should be a low threshold for referral for sleep assessment. Patients may also be screened for OSAS in the clinic using such tools as the Epworth sleepiness score.

Physical Examination

(a) Hyperandrogenism

Hyperandrogenism clinically manifests as excess terminal body hair in a male distribution pattern. Hair is commonly seen on the upper lip, on the chin, around the nipples, and along the linea alba of the lower abdomen. Some patients have acne and/or male-pattern hair loss (androgenic alopecia).

Other signs of hyperandrogenism (example: clitoromegaly, increased muscle mass, voice deepening) are more characteristic of an extreme form of PCOS termed hyperthecosis. These signs and symptoms could also be consistent with androgen-producing tumours,

exogenous androgen administration, or virilizing congenital adrenal hyperplasia.

Premature adrenarche is a common occurrence and, in some cases, may represent a precursor to PCOS. Hirsutism and obesity may be present in premenarchal adolescent girls with PCOS.

Hirsutism and virilizing signs

Patients may have excessive body hair in a male distribution pattern, as well as acne. Some patients have virilizing signs, such as male-pattern balding or alopecia, increased muscle mass, deepening voice, or clitoromegaly; these findings should prompt a search for other causes of hyperandrogenism. The modified Ferriman-Gallwey (mFG) score grades 9 body areas from 0 (no hair) to 4 (frankly virile), including the upper lip, chin, chest, upper abdomen, lower abdomen, thighs, back, arm, and buttocks. A total score of 8 or more is considered abnormal for an adult white woman; a score of 36 is the most severe.

(b) Obesity

Approximately 50% of women with PCOS have abdominal obesity, characterized by a waist circumference greater than 88 cm.

(c) Acanthosis nigricans

Acanthosis nigricans is a diffuse, velvety thickening and hyperpigmentation of the skin. It may be present at the nape of the neck, axillae, area beneath the breasts, intertriginous areas, and exposed areas (example: elbows, knuckles). In patients with PCOS, acanthosis nigricans is thought to be the result of insulin resistance, although syndromic and familial variants are described. Acanthosis nigricans can also be a cutaneous marker of malignancy.

Acanthosis nigricans is staged according to the scoring system below:

Absent (0): Not detectable on close inspection
Present (1): Clearly present on close visual inspection, not visible to the casual observer, extent not measurable
Mild (2): Limited to the base of the skull, usually does not extend to the lateral margins of the neck
Moderate (3): Extends to the lateral margins of the neck but not visible anteriorly
Severe (4): Visible anteriorly
Severe (5): Circumferential

(d) Blood pressure

Patients with signs and symptoms of metabolic syndrome may have elevated blood pressure, with a systolic blood pressure of 130 mm Hg or higher and a diastolic blood pressure of 85 mm Hg or higher.

Diagnostic Considerations

Although no agreed-upon diagnostic criteria currently exist for adolescent polycystic ovarian syndrome (PCOS), hyperandrogenemia is essential for the diagnosis in adolescent age group [15].

All conditions that mimic PCOS should be ruled out before a diagnosis of PCOS is confirmed. Consider the following in the differential diagnosis of PCOS:

Ovarian hyperthecosis
Congenital adrenal hyperplasia (late-onset)
Drugs (example: danazol, androgenic progestins)
Hypothyroidism and hyperthroidism
Patients with menstrual disturbances and signs of hyperandrogenism
Idiopathic hirsutism
Familial hirsutism
Masculinizing tumours of the adrenal gland or ovary (rapid onset of signs of virilization)
Cushing syndrome (low K+, striae, central obesity, high cortisol; high androgens in adrenal carcinoma)
Hyperprolactinemia
Exogenous anabolic steroid use
Stromal hyperthecosis (valproic acid)

3-Beta-Hydroxysteroid Dehydrogenase Deficiency
Amenorrhea
Gigantism and Acromegaly
Iatrogenic Cushing Syndrome
Ovarian Tumours

Investigation

The baseline screening tests for women with suspected PCOS include Thyroid function test, serum prolactin level and free androgen index (defined as total testosterone divided by sex hormone binding globulin [SHBG] × 100, to give a calculated free testosterone level).

The diagnosis of PCOS requires the exclusion of all other disorders that can cause menstrual irregularity and hyperandrogenism. Examples are adrenal or ovarian tumours, thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinemia, acromegaly, and Cushing syndrome.

Biochemical and imaging studies must be done to rule out these other possible disorders and ascertain the diagnosis. A karyotype usually excludes mosaic Turner syndrome as a cause of the primary amenorrhea.

Late-onset congenital adrenal hyperplasia due to 21-hydroxylase deficiency can be ruled out by measuring serum 17-hydroxyprogesterone levels after a cosyntropin stimulation test. A 17-hydroxyprogesterone level of less than 1000 ng/dL—measured 60 minutes after cosyntropin stimulation—rules out late-onset congenital adrenal hyperplasia.

Women with PCOS should be screened for Cushing syndrome or acromegaly only if there is a clinical suspicion of these conditions. Cushing syndrome can be ruled out by checking a 24-hour urine sample for free cortisol and creatinine. levels of urinary free cortisol that are 4 times the upper limit of normal are diagnostic for Cushing syndrome [16]. An overnight dexamethasone suppression test is also useful for screening for Cushing syndrome.

A small percentage of patients with PCOS have elevated prolactin levels (typically >25 mg/dL). Hyperprolactinemia can be excluded by checking a fasting serum prolactin concentration.

The American College of Obstetricians and Gynaecologists (ACOG) recommends screening with 17-hydroxyprogesterone levels in women suspected of having PCOS who are at an increased risk for nonclassical congenital adrenal hyperplasia [17].

Modified Glucose tolerance test (MOGTT)

The prevalence of impaired glucose tolerance and type 2 diabetes mellitus is high in women with polycystic ovarian syndrome (PCOS),particularly in those who have a body mass index (BMI) greater than 30 kg/m^2, have a strong family history of type 2 diabetes and older than 40 years. Therefore a 75-g oral glucose-tolerance test (OGTT) should be performed at least in this group of people. Women who are diagnosed with pre pregnancy PCOS should be screened for gestational diabetes before 20 weeks' gestation. These women have a higher rate of gestational diabetes than women in the general population.

Hormone Levels

Androgens

Androgen excess can be tested by measuring total and free testosterone levels or a free androgen index. An elevated free testosterone level is a sensitive indicator of androgen excess.

Other androgens, such as dehydroepiandrosterone sulfate (DHEA-S), may be normal or slightly above the normal range in patients with PCOS. The levels of sex hormone–binding globulin (SHBG) are usually low in patients with PCOS.

FSH and LH levels

The FSH level should be checked to rule out primary ovarian failure. In patients with PCOS, the FSH levels are within the reference range or low. The LH levels are elevated for Tanner stage, sex, and age. The LH-to-FSH ratio is usually greater than 3.

Thyroid-stimulating hormone (TSH) and free thyroxine levels

Thyroid dysfunction may be a source of amenorrhea and hirsutism. In patients with PCOS, thyroid function tests are within the reference range.

Antimullerian hormone (AMH) is not required to diagnose PCOS

Diagnosis

The diagnostic criteria had changed from time to time. The diagnostic Rotterdam criteria and National Institutes of Health (NIH) criteria are different.

The Rotterdam criteria [18] have suggested a broader definition for PCOS, with two out of three of the following criteria being diagnostic of the condition:

1. Polycystic ovaries (either 12 or more follicles or increased ovarian volume [> 10 cm3])
2. Oligo-ovulation or anovulation
3. Clinical and/or biochemical signs of hyperandrogenism

In October 2013, the Endocrine Society released practice guidelines for the diagnosis and treatment of PCOS. The following were among their conclusions [19]:

Use the Rotterdam criteria for diagnosing PCOS.

Presence of 2 of the following:

1. Androgen excess
2. Ovulatory dysfunction
3. Polycystic ovaries

During that initial meeting at the National Institutes of Health (NIH) in Bethesda, Maryland, there was considerable discussion with little consensus, although a questionnaire led to the current diagnostic criteria that stand today. Based on the majority opinion rather than clinical trial evidence, the following diagnostic criteria were put forth:

1. Clinical or biochemical evidence of hyperandrogenism,
2. Chronic anovulation and exclusion of other known disorders [20].

From that time there has been a gradually increasing awareness that the clinical expression of PCOS may be broader than that defined by the 1990 NIH criteria.

1990 Criteria (both 1 and 2)

1. Chronic anovulation and
2. Clinical and/or biochemical signs of hyperandrogenism and exclusion of other aetiologies.

Revised 2003 criteria (2 out of 3)

1. Oligo- or anovulation,
2. Clinical and/or biochemical signs of hyperandrogenism,

3. Polycystic ovaries and exclusion of other aetiologies (congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome)

In 1990, an expert conference sponsored by the National Institute of Child Health and Human Disease (NICHD) of the United States National Institutes of Health (NIH) proposed the following criteria for the diagnosis of PCOS:

(a) Oligo-ovulation or anovulation manifested by oligomenorrhea or amenorrhea
(b) Hyperandrogenism (clinical evidence of androgen excess) or hyperandrogenaemia (biochemical evidence of androgen excess)
(c) Exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism

The Androgen Excess and PCOS Society (AE-PCOS) published a position statement in 2009 [21] emphasizing that, in the society's opinion, PCOS should be considered a disorder of androgen excess, as defined by the following:

(a) Clinical/biochemical evidence of hyperandrogenism
(b) Evidence of ovarian dysfunction (oligo-ovulation and/or polycystic ovaries)
(c) Exclusion of related disorders

The Society of Obstetricians and Gynaecologists of Canada (SOGC) indicated that a diagnosis of polycystic ovarian syndrome (PCOS) is made in the presence of at least 2 of the following 3 criteria, when congenital adrenal hyperplasia, androgen-secreting tumors, or Cushing syndrome have been excluded [22].

(a) Oligo-ovulation or anovulation
(b) Clinical/biochemical evidence of hyperandrogenism
(c) Polycystic ovaries on ultrasonograms (>12 small antral follicles in an ovary)

Based on the Rotterdam Classification system abdominal obesity, insulin resistance nor dyslipidemias are not included as a criteria for a diagnosis of PCOS . However, because of the increasing evidence that these abnormalities are common features of PCOS, comments have been made about the need to broaden the diagnostic criteria by including them.

Diagnostic features for adolescent girls are menstrual irregularity, clinical hyperandrogenism, and/or hyperandrogenemia. Pelvic ultrasound findings are not needed for the diagnosis of PCOS in adolescent girls [23].

Complications

Polycystic ovarian syndrome (PCOS) may be at increased risk for cardiovascular and cerebro-vascular disease. Women with hyperandrogenism have elevated serum lipoprotein levels similar to those of men [24].

Many patients with PCOS have characteristics of metabolic syndrome. Azziz *et al*., showed a 43% prevalence of metabolic syndrome in women with PCOS [25].

The metabolic syndrome is characterized by abdominal obesity (waist circumference >35 in) dyslipidaemia (triglyceride level >150 mg/dL high-density lipoprotein cholesterol (HDL-C) level < 50 mg/dL) elevated blood pressure proinflammatory state characterized by an elevated C-reactive protein level prothrombotic state characterized by elevated plasminogen activator inhibitor-1 (PAI-1) andfibrinogen levels.

Women with PCOS have an increased prevalence of coronary artery calcification and thickened carotid intima media, which may be responsible for subclinical atherosclerosis. Prospective, long-term cardiovascular-outcome studies in PCOS are needed to assess whether the increased cardiovascular risk in PCOS results in the higher cardiovascular-event rates.

Approximately 40% of patients with PCOS have insulin independent of body weight. These women are at increased risk of developing type 2 diabetes mellitus and consequent cardiovascular complications [26].

The American Association of Clinical Endocrinologists and the American College of Endocrinology recommend screening for diabetes by age 30 years in all patients with PCOS, including obese and nonobese women [27].

At risk women should be screened before 30 years of age. Patients who initially test negative for diabetes should be periodically reassessed throughout their lifetime.

Patients with PCOS are also at an increased risk for endometrial hyperplasia and carcinoma [28]. The chronic anovulation in PCOS leads to constant endometrial stimulation with unopposed oestrogen without progesterone, and this increases the risk of endometrial hyperplasia and carcinoma.

Approximately 10% of women with PCOS have type 2 diabetes mellitus, and 30-40% of women with PCOS have impaired glucose tolerance by 40 years of age [29].

PCOS patients are at a higher risk of developing infertility, dysfunctional uterine bleeding and endometrial carcinoma, and a number of metabolic disorders including insulin resistance,

hyperinsulinaemia, Type 2 Diabetes Mellitus, hypertension, dyslipidaemia and cardiovascular disease [30].

Management

Medical management of PCOS is aimed at the treatment of metabolic derangements anovulation (Infertility) hirsutism, and menstrual irregularity.

Pharmacologic treatments are reserved for metabolic derangements, such as anovulation, hirsutism, and menstrual irregularities

The first-line medical therapy usually consists of an oral contraceptive to induce regular menstrual period. The contraceptives not only inhibits ovarian androgen production but also increases sex hormone-binding globulin (SHBG) production. ACOG recommends use of combination low-dose hormonal contraceptive agents for long-term management of menstrual dysfunction [31].

First-line treatment for ovulation induction when fertility is desired is clomiphene citrate [32].

A randomized study suggested that combined metformin/letrozole and bilateral ovarian drilling are similarly effective as second-line treatment in infertile women with clomiphene citrate–resistant PCOS [33].

Improvement of insulin resistance and reduction of circulating insulin are key therapeutic targets in PCOS enhancing fertility and reducing the lifelong risk for type 2 diabetes and early cardiovascular disease. If the patient develops type 2 diabetes mellitus, oral antihyperglycemic drugs such as metformin are valuable. Clinical trials have shown that metformin can effectively reduce androgen levels, improve insulin sensitivity, and facilitate weight loss in patients with PCOS as early as adolescence [34].

If symptoms such as hirsutism are not sufficiently alleviated, an androgen-blocking agent may be added. Antiandrogens like spironolactone, leuprolide, finasteride are commonly used. Topical hair-removal agents eflornithine are usuful.

Topical acne agents like benzoyl peroxide, tretinoin topical cream (0.02–0.1%)/gel (0.01–0.1%)/solution (0.05%), adapalene topical cream (0.1%)/gel (0.1%, 0.3%)/solution (0.1%), erythromycin topical 2%, clindamycin topical 1%, sodium sulfacetamide topical 10% are widely used.

Oligo- or amenorrhoea in women with PCOS may predispose to endometrial hyperplasia and later carcinoma. It is good practice to recommend treatment with gestogens to induce a withdrawal bleed at least every 3 to 4 months. The Royal College of Obstetricians and Gynaecologists (RCOG) recommends induction of withdrawal bleeding with progestogens a minimum of every 3-4 months [35].

Surgery

Surgical management of PCOS is aimed mainly at restoring ovulation. Various laparoscopic methods include electrocautery and laser drilling. Ovarian electrocautery should be considered for selected anovulatory patients, especially those with a normal BMI, as an alternative to ovulation induction.

CONCLUSION

Polycystic ovary syndrome (PCOS) is a hormonal disorder common among women of reproductive age. Women with PCOS may have infrequent or prolonged menstrual periods or excess male hormone (androgen) levels. The ovaries may develop numerous small collections of fluid (follicles) and fail to regularly release eggs.

The exact cause of PCOS is unknown. Early diagnosis and treatment along with weight loss may reduce the risk of long-term complications such as type 2 diabetes and heart disease .It is recommended that lifestyle changes, including diet, exercise and weight loss, are initiated as the first line of treatment for women with PCOS for improvement of long-term outcomes. Pharmacologic treatments are reserved for so-called metabolic derangements, such as anovulation, hirsutism, and menstrual irregularities.

REFERENCE

1. Balen, A. (2004). The pathophysiology of polycystic ovary syndrome: trying to understand PCOS and its endocrinology. *Best practice & research clinical obstetrics & gynaecology*, *18*(5), 685-706. DOI: 10.1016/j.bpobgyn.2004.05.004
2. Stein, I. F., & Leventhal, M. L. (1935). Amenorrhea associated with bilateral polycystic ovaries. *American journal of obstetrics and gynecology*, *29*(2), 181-191.
3. Stein, I. F. (1964). Duration of infertility following ovarian wedge resection. *West J Surg*, 72, 237.
4. Barber, T. M., & Franks, S. (2010). Genetic basis of polycystic ovary syndrome. *Expert Review of Endocrinology & Metabolism*, 5(4), 549-561.
5. Westerveld, H. E., Hoogendoorn, M., de Jong, A. W. F., Goverde, A. J., Fauser, B. C. J. M., & Dallinga-Thie, G. M. (2008). Cardiometabolic abnormalities in the polycystic ovary syndrome: pharmacotherapeutic insights. *Pharmacology & therapeutics*, *119*(3), 223-241.
6. Dunaif, A., Wu, X., Lee, A., & Diamanti-Kandarakis, E. (2001). Defects in insulin receptor signaling in vivo in the polycystic ovary syndrome (PCOS). *American Journal of Physiology-Endocrinology and Metabolism*, *281*(2), E392-E399.

7. Ehrmann, D. A., Kasza, K., Azziz, R., Legro, R. S., & Ghazzi, M. N. (2005). Effects of race and family history of type 2 diabetes on metabolic status of women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism*, *90*(1), 66-71.
8. Barber, T. M., Bennett, A. J., Groves, C. J., Sovio, U., Ruokonen, A., Martikainen, H., ... & McCarthy, M. I. (2008). Association of variants in the fat mass and obesity associated (FTO) gene with polycystic ovary syndrome. *Diabetologia*, *51*, 1153-1158.
9. San Millán, J. L., Cortón, M., Villuendas, G., Sancho, J., Peral, B., & Escobar-Morreale, H. F. (2004). Association of the polycystic ovary syndrome with genomic variants related to insulin resistance, type 2 diabetes mellitus, and obesity. *The Journal of Clinical Endocrinology & Metabolism*, *89*(6), 2640-2646.
10. Bizzarri, M., Fuso, A., Dinicola, S., Cucina, A., & Bevilacqua, A. (2016). Pharmacodynamics and pharmacokinetics of inositol (s) in health and disease. *Expert opinion on drug metabolism & toxicology*, *12*(10), 1181-1196.
11. March, W. A., Moore, V. M., Willson, K. J., Phillips, D. I., Norman, R. J., & Davies, M. J. (2010). The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Human reproduction*, *25*(2), 544-551.
12. Li, R., Zhang, Q., Yang, D., Li, S., Lu, S., Wu, X., ... & Qiao, J. (2013). Prevalence of polycystic ovary syndrome in women in China: a large community-based study. *Human reproduction*, *28*(9), 2562-2569.
13. Maslyanskaya, S., Talib, H. J., Northridge, J. L., Jacobs, A. M., Coble, C., & Coupey, S. M. (2017). Polycystic ovary syndrome: an under-recognized cause of abnormal uterine bleeding in adolescents admitted to a children's hospital. *Journal of pediatric and adolescent gynecology*, *30*(3), 349-355.
14. Vgontzas, A. N., Legro, R. S., Bixler, E. O., Grayev, A., Kales, A., & Chrousos, G. P. (2001). Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. *The Journal of Clinical Endocrinology & Metabolism*, *86*(2), 517-520.
15. Baldauff, N. H., & Arslanian, S. (2015). Optimal management of polycystic ovary syndrome in adolescence. *Archives of Disease in Childhood*, *100*(11), 1076-1083.
16. Nieman, L. K. (2002). Diagnostic tests for Cushing's syndrome. *Annals of the New York Academy of Sciences*, *970*(1), 112-118.
17. American College of Obstetricians and Gynecologists. Polycystic ovary syndrome. Washington, DC: American College of Obstetricians and Gynecologists; 2009. ACOG practice bulletin; no. 108.
18. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and longterm health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19–25
19. Legro, R. S., Arslanian, S. A., Ehrmann, D. A., Hoeger, K. M., Murad, M. H., Pasquali, R., & Welt, C. K. (2013). Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, *98*(12), 4565-4592.
20. Zawadski, J. K., & Dunaif, A. (1992). Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif, A., Givens, J. R., Haseltine, F, eds. Polycystic ovary syndrome. Boston: Blackwell Scientific, 377–384
21. Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., Futterweit, W., ... & Witchel, S. F. (2009). The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertility and sterility*, *91*(2), 456-488.
22. Vause, T. D., Cheung, A. P., Sierra, S., Claman, P., Graham, J., Guillemin, J. A., ... & Wong, B. C. M. (2010). Ovulation induction in polycystic ovary syndrome. *Journal of Obstetrics and Gynaecology Canada*, *32*(5), 495-502.
23. Witchel, S. F., Oberfield, S. E., & Peña, A. S. (2019). Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. *Journal of the Endocrine Society*, *3*(8), 1545-1573.
24. Christian, R. C., Dumesic, D. A., Behrenbeck, T., Oberg, A. L., Sheedy, P. F., & Fitzpatrick, L. A. (2003). Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism*, *88*(6), 2562-2568.
25. Azziz, R., Woods, K. S., Reyna, R., Key, T. J., Knochenhauer, E. S., & Yildiz, B. O. (2004). The prevalence and features of the polycystic ovary syndrome in an unselected population. *The Journal of Clinical Endocrinology & Metabolism*, *89*(6), 2745-2749.
26. Dokras, A. (2008, January). Cardiovascular disease risk factors in polycystic ovary syndrome. In *Seminars in reproductive medicine* (Vol. 26, No. 01, pp. 039-044). © Thieme Medical Publishers.
27. American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists position statement on metabolic and cardiovascular consequences of polycystic ovary syndrome. National Guideline Clearinghouse. Available at http://guideline.gov/summary/summary.aspx?doc_id=7108..
28. Hardiman, P., Pillay, O. S., & Atiomo, W. (2003). Polycystic ovary syndrome and endometrial carcinoma. *The lancet*, *361*(9371), 1810-1812.
29. Legro, R. S., Kunselman, A. R., Dodson, W. C., & Dunaif, A. (1999). Prevalence and predictors of

risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *The journal of clinical endocrinology & metabolism*, *84*(1), 165-169.

30. Azziz, R., Woods, K. S., Reyna, R., Key, T. J., Knochenhauer, E. S., & Yildiz, B. O. (2004). The prevalence and features of the polycystic ovary syndrome in an unselected population. *The Journal of Clinical Endocrinology & Metabolism*, *89*(6), 2745-2749.
31. American College of Obstetricians and Gynecologists. Polycystic ovary syndrome. Washington, DC: American College of Obstetricians and Gynecologists; 2009. ACOG practice bulletin; no. 108.
32. Vause, T. D., Cheung, A. P., Sierra, S., Claman, P., Graham, J., Guillemin, J. A., ... & Wong, B. C. M. (2010). Ovulation induction in polycystic ovary syndrome. *Journal of Obstetrics and Gynaecology Canada*, *32*(5), 495-502.
33. Abd Elgafor, I. (2013). Efficacy of combined metformin–letrozole in comparison with bilateral ovarian drilling in clomiphene-resistant infertile women with polycystic ovarian syndrome. *Archives of gynecology and obstetrics*, *288*, 119-123.
34. Otta, C. F., Wior, M., Iraci, G. S., Kaplan, R., Torres, D., Gaido, M. I., & Wyse, E. P. (2010). Clinical, metabolic, and endocrine parameters in response to metformin and lifestyle intervention in women with polycystic ovary syndrome: a randomized, double-blind, and placebo control trial. *Gynecological Endocrinology*, *26*(3), 173-178.
35. Royal College of Obstetricians and Gynaecologists. Long-term consequences of polycystic ovary syndrome. London, UK: Royal College of Obstetricians and Gynaecologists; November 2014. Green-top Guideline No. 33.