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Review

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Unravelling Polycystic Ovary Syndrome and Its Comorbidities

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Polycystic ovary syndrome (PCOS) is a chronic multisystem endocrine disorder that affects women of reproductive age. In the ovary, the dynamic balance between dormant and growing follicles that culminates in ovulation becomes dysfunctional in the presence of excessive androgen production (ovarian/adrenal/peripheral). Moreover, hyperandrogenicity in pregnancy affects fetal development in utero and is linked to maternal pregnancy complications. Hormonal imbalance, ovarian dysfunction, and central obesity often emerge in these patients during adolescence. Once disordered physiological changes develop in PCOS, a vicious cycle ensues, leading to reproductive, metabolic, and psychological comorbidities. With the alarming increase of the number of young adults with a high degree of obesity in Korea, the prevalence of PCOS has also considerably increased. Timely and accurate screening, multicomponent healthy lifestyle modifications for both patients and family members, and comprehensive medical interventions based on international evidence-based guidelines are essential for curtailing PCOS and its comorbidities.

Key words: Polycystic ovary syndrome, Androgens, Adrenal gland, Insulin resistance, Anti-Müllerian hormone

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most commonly diagnosed endocrine disorder, with a prevalence of up to 20%[1] among reproductive-aged women worldwide. PCOS affects women's health starting before conception and extending throughout the lifespan[2] (Fig. 1). Despite its prevalence, PCOS is a challenging condition to diagnose and manage, and guidelines can vary along with patient age. The initial manifestations of PCOS, such as irregular menstruation, acne, and multi-follicular ovarian morphology, may develop during adolescence.[2] Subsequently, reproductive comorbidities (subfertility and pregnancy complications), metabolic comorbidities (dyslipidemia, impaired glucose tolerance, type 2 diabetes mellitus, hypertension, and cardiovascular disease), and psychological comorbidities (low self-esteem, anxiety, depression, eating disorders, psychosexual dysfunction, and poor quality of life) that are associated with PCOS also emerge.[3]

Obesity and the prevalence of PCOS are highly correlated with each other. The accompanying obesity rate in PCOS patients varies from 50% to 80%, depending on ethnicity and the study population.[4] The prevalence of overweight or obesity has nearly tripled in the last 40 years;[5] in Korean, there has been an alarming increase in young adults (20–39 years of age) with a high degree of obesity.[6] Furthermore, Asian women tend to accumulate more visceral fat than Caucasian women.[5] From 2005 to 2015, the incidence rates of PCOS increased by 3.5- to 4.0-fold according to the increase in waist circumference and body mass index (BMI) based on the Korean National Health Insurance Service cohort.[7] This paper will re-

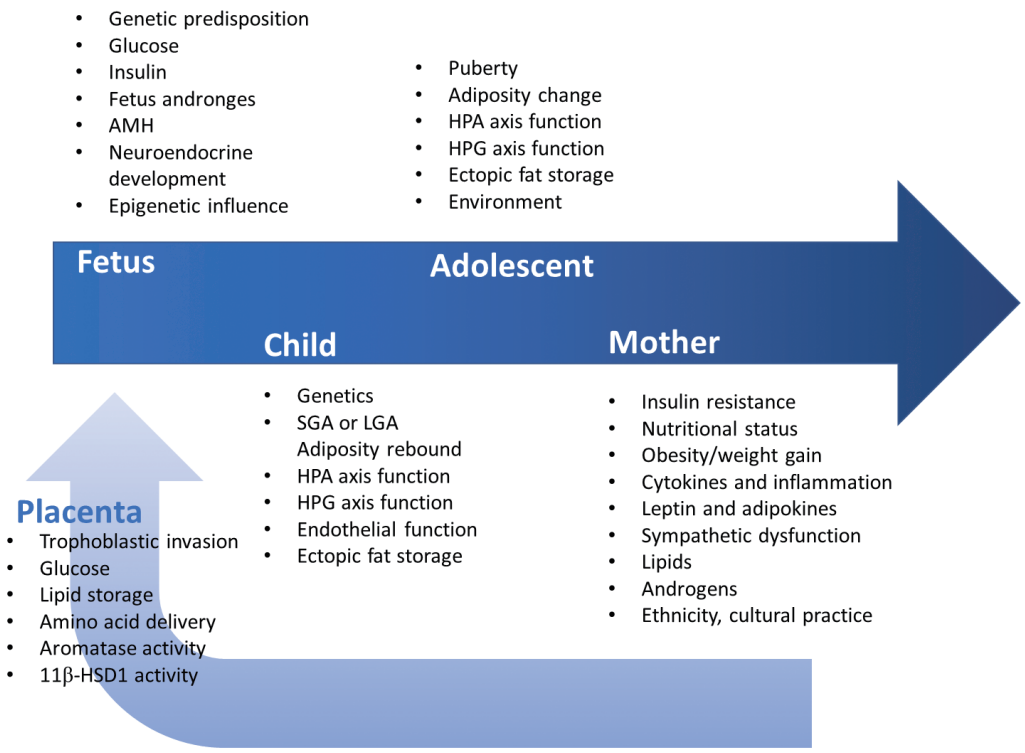

Figure 1. The life cycle of women with polycystic ovary syndrome. The complexities and interactions of some of the relevant modulating factors are listed from the perinatal period into adolescence and adulthood.[2] AMH, anti-Müllerian hormone; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; SGA, small for gestational age; LGA, large for gestational age; 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1.

view the precise pathophysiology of PCOS, its challenging diagnosis, and evidence-based treatments for the condition and its comorbidities.

PATHOPHYSIOLOGY

The pathogenesis of PCOS is complex and includes genetic, environmental, and transgenerational components. Dysfunction in multiple aspects of the hypothalamic-pituitary-ovarian/adrenal axis that interacts with genetic influences, epigenetic changes, nutrient excess, insulin resistance/hyperinsulinemia, inflammatory factors, ectopic fat storage, and intrinsic differences in steroidogenesis can lead to the development of PCOS.[8]

An evolutionary perspective

An evolutionary origin involving thrifty genotypes and phenotypes with a survival advantage has been suggested to explain prevalent insulin-resistant metabolic disorders including obesity and diabetes mellitus.[9] Such a benefit has also been proposed to be present in carriers of 21-hydroxylase deficiency[10] (the most common form of congenital adrenal hyperplasia, which is typified by adrenal androgen excess) and PCOS.[10-12] Early maturation of the reproductive axis, increased androgen secretion with forceful behavior, subfertility that extends the interval between pregnancies, and oligo-ovulation that leads to pregnancies at older ages are the causes of the survival advantage in women with PCOS and their offspring.[10-12]

Recently, Kim and Choi[13] reviewed the embryonic development and adult regeneration of the adrenal gland. Interestingly, the fetal development of both the adrenal cortex and gonads is established from clusters of bipotential adrenal gonadal precursors, called the adrenogonadal primordium, 4 to 6 weeks after conception in humans. The fetal zone of the adrenal gland emerges in the inner cortex, synthesizing dehydroepiandrosterone (DHEA) and its sulfated derivative (DHEAS). These androgens serve as sources of placenta-derived 17β-estradiol, which is essential for maintaining pregnancy. At 8 to 9 weeks after conception, early cortisol synthesis from the translational zone located in the intermediate region plays

a role in protecting normal female sexual development by inhibiting the production of adrenal androgens under the negative regulation of the fetal hypothalamic-pituitary-adrenal axis. Three months after birth, adrenal androgen secretion rapidly decreases. Subsequently, the innermost zona reticularis of the adrenal gland gradually forms and begins to synthesize androgens again from approximately 6 to 8 years of age, a period known as adrenarche in humans.[13]

During the first acceleration of growth and maturation, an exaggerated adrenarche may occur during childhood (4 to 9 years of age), resulting in a relatively tall stature, early pubarche (appearance of pubic hair driven by high levels of circulating DHEAS), and an advanced bone age.[14] The second of growth and maturation may result from early and/or rapidly advancing puberty (i.e., breast development driven by luteinizing hormone [LH] hypersecretion and ovarian estrogen secretion) and could potentially lead to early menarche.[15] Many associations between an earlier menarche and augmented morbidity in adulthood may be based on even closer associations between greater central adiposity in childhood and greater morbidity later in life.[16]

The interplay between insulin resistance and androgen excess

PCOS results from a vicious cycle of abdominal adipose tissue deposition and visceral adiposity by inducing insulin resistance and compensatory hyperinsulinism, which further facilitate excess androgen secretion by the ovaries and adrenal glands.[17] Conversely, as PCOS is mainly a hyperandrogenic disorder, increasing evidence suggests that androgen excess is not only a major mechanism in the oligo-ovulation of the syndrome but is also a facilitator in insulin resistance and metabolic dysfunction development by favoring abdominal and visceral adiposity (Fig. 2).[17,18]

Under normal circumstances, the ovaries and adrenal glands have an almost equal contribution to testosterone production. Approximately half of testosterone production originates from direct testosterone secretion by the ovaries and adrenal glands, whereas the other half is derived from the peripheral conversion of circulating androstenedione, which itself arises from approximately equal ovarian and adrenal secretion. Androgens are secreted by both the ovaries and adrenal glands in response to their respective tropic

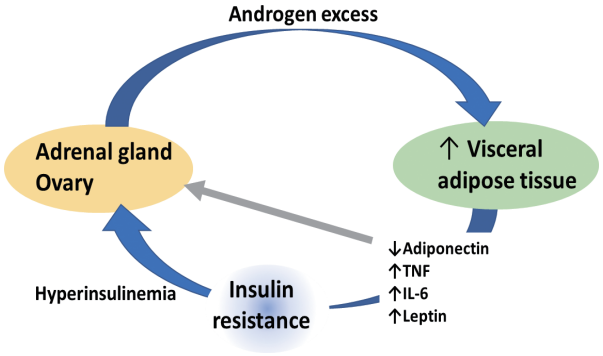

Figure 2. The vicious cycle between androgen excess and abdominal adiposity (blue arrows). Androgen excess of ovarian and/or adrenal origin is observed through the direct effects (gray arrow) of several autocrine, paracrine, and endocrine mediators (downregulation of adiponectin and upregulation of tumor necrosis factor [TNF], interleukin [IL]-6, and leptin) or indirectly through the induction of insulin resistance and hyperinsulinemia of abdominal visceral adiposity.[17,18]

hormones: LH and adrenocorticotropic hormone (ACTH). Intraglandular paracrine and autocrine mechanisms seem to play a major role in modulating androgen secretion in response to tropic hormone stimulation.[19]

In the ovary, androgens are dependent on LH and insulin within the theca cells, and estrogens from androgen substrates that are under the control of follicle-stimulating hormone (FSH) within the granulosa cells promote follicular maturation. Androgen excess hinders ovulation and stimulates the excess proliferation of early phase small antral follicles. Antral follicle growth is accompanied by an increased production of anti-Müllerian hormone (AMH), which normally functions as a gatekeeper that inhibits both the recruitment of primordial follicles to the primary follicle stage and FSH stimulation of aromatase activity. Excess insulin is an extraovarian modulator that has the potential to override the normal intraovarian downregulatory mechanisms that control ovarian androgen production.[19]

In the adrenal gland, the zona reticularis resembles the theca cell compartment of the ovary in its expression of the core enzymatic pattern for androgen production. Adrenarche represents a change in the pattern of adrenocortical secretory responses to ACTH. It is characterized by a disproportionately increasing responsiveness of Δ5-steroid intermediates (17-hydroxypregnenolone and DHEA) compared with Δ4-steroids (e.g., 17-hydroxyprogesterone [17OHP] and androstenedione) over time in the presence of stable cortisol responses.[20,21] Adiposity is strongly related to adrenarche; insulin,

Table 1. Test procedures to determine the source of female androgen excess[19,22]

Test	Rationale	Method	Outcome measure	Interpretation
GnRHag	Endogenous LH and FSH stimulates the coordinated function of ovarian follicles.	Leuprolide acetate 10 μg/kg sc (for maximum stimulation)	Ovarian steroid secretion peaks at 20–24 hours.	17OHP >152 ng/dL without steroidogenic block indicates typical FOH (PCOS-T).
hCG	Exogenous administration of an LH analog stimulates theca-interstitial cells.	hCG 3,000 IU/m^2 IM (for maximum stimulation)	Ovarian steroid secretion peaks at 24 hours.	17OHP >152 ng/dL without steroidogenic block indicates typical FOH (PCOS-T).
LDAST	Dexamethasone profoundly suppresses adrenal androgens over several days.	Dexamethasone 0.5 mg QID orally ×4 or 7 day (>100 kg)	Free testosterone, DHEAS, cortisol: sample early morning subsequent day 5 or day 8	Free testosterone ≥8 pg/mL with DHEAS <70 μg/dL and cortisol <1 μg/dL are characteristic of FOH.
SDAST	Dexamethasone rapidly suppresses adrenal testosterone and cortisol.	Dexamethasone 0.25 mg/m^2 orally at 12 PM	Total testosterone, cortisol: sample at 4 PM (4 hours later)	Total testosterone >26 ng/mL and cortisol <5 μg/dL suggest FOH.
ACTH	Exogenous ACTH stimulates adrenal steroidogenesis.	Cosyntropin ≥1.0 μg/1.7 m^2 IV (for maximum stimulation)	DHEA, 17OHP, steroid intermediates, cortisol peak at 30–60 minutes.	DHEA 1,500–3,000 μg/dL without steroidogenic block indicates FAH.

Testing is performed during the early follicular phase of the menstrual cycle.
GnRHag, gonadotropin-releasing hormone agonist; LH, luteinizing hormone; FSH, follicle-stimulating hormone; sc, subcutaneous; 17OHP, 17-hydroxyprogesterone; FOH, functional ovarian hyperandrogenism; PCOS-T, typical polycystic ovary syndrome; hCG, human chorionic gonadotrophin; IM, intramuscular; LDAST, long (4–7 days) dexamethasone androgen-suppression tests; QID, four times a day; DHEAS, dehydroepiandrosterone sulfate; SDAST, short (4 hours) dexamethasone androgen-suppression tests; ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; FAH, functional adrenal hyperandrogenism.

Table 2. The functional classification of PCOS according to the source of androgen excess[19,22]

Functional type of PCOS	Androgen source	GnRHag test 17OHP response	DAST testosterone response	ACTH test DHEA response	Prevalence among PCOS cases
PCOS-T	Primary FOH (typical FOH)	High	High in 92.5%	High in 28% (associated FAH)	67%
PCOS-A	Primary FOH (atypical FOH)	Normal	High	High in 30% (associated FAH)	20%
	Primary FAH (isolated FAH)	Normal	Normal	High	5%
	PCOS without FOH or FAH (PCOS-A of obesity or idiopathic PCOS-A)	Normal	Normal	Normal	8%

PCOS, polycystic ovary syndrome; GnRHag, gonadotropin-releasing hormone agonist; 17OHP, 17-hydroxyprogesterone; DAST, dexamethasone androgen-suppression test; ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; PCOS-T, typical PCOS; FOH, functional ovarian hyperandrogenism; FAH, functional adrenal hyperandrogenism; PCOS-A, atypical PCOS.

insulin-like growth factor-1, and leptin have been suggested as determinants of this relationship.[19]

Approximately half of testosterone production is derived from the peripheral metabolism of secreted precursors in the liver, skin, and fat. Although the factors that regulate these conversions are unclear, insulin has been proven to stimulate testosterone formation in fat cells.[19]

Sources of androgen excess in PCOS

In an attempt to understand the pathophysiology of PCOS, Rosenfield and Ehrmann[19] and Rosenfield et al.[22] functionally categorized PCOS patients according to whether the source of androgen excess is primarily the ovaries, the adrenal glands, both, or neither (Tables 1 and 2, Fig. 3). The ovarian hyperandrogenism that is present in PCOS is directly demonstrated by the gonadotropin-releasing hormone agonist (GnRHag) test or the human chorionic gonadotrophin (hCG) test and indirectly demonstrated by the dexamethasone androgen-suppression test (DAST). In the absence of evidence of a steroidogenic block, an elevated 17OHP response is typical of PCOS. The DAST indirectly evaluates ovarian androgenic function by suppressing ACTH-dependent adrenal androgen production. In the presence of normal adrenocortical suppression, an inappropriately elevated post-DAST serum testosterone level indicates an ACTH-independent source of androgen, which is ordinarily of ovarian origin. Adrenal hyperandrogenism is demonstrated by a rapid ACTH test. DHEAS is a simple correlate of this adrenal androgenic dysfunction (Table 1).[19,22] Rosenfield and Ehrmann[19] and Rosenfield et al.[22] reported that approximately two-thirds of cases had typical PCOS (PCOS-T) due to classic functional ovarian hyperandrogenism (FOH) along with hyper-

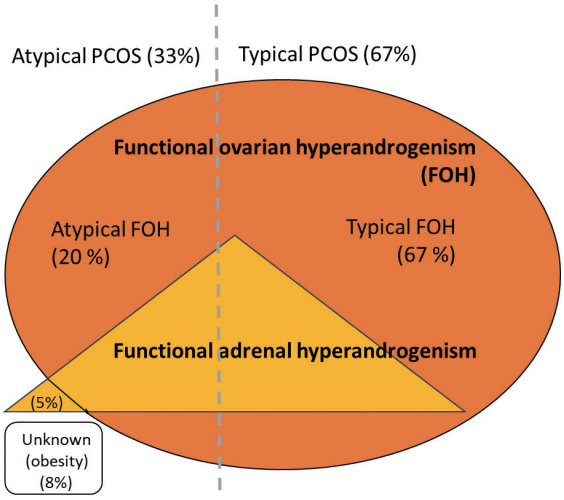

Figure 3. The sources of androgens in polycystic ovary syndrome (PCOS).[19] Approximately two-thirds of cases have functionally typical PCOS that is due to typical functional ovarian hyperandrogenism (FOH) and is characterized by hyper-responsiveness of 17-hydroxyprogesterone (17OHP) to the luteinizing hormone (gonadotropin-releasing hormone agonist or human chorionic gonadotrophin) test. The remaining one-third of PCOS cases are functionally atypical and therefore lack 17OHP hyper responsiveness. This is a heterogeneous group, most of which have atypical FOH in which ovarian androgen excess is indicated only by a dexamethasone androgen-suppression test. A small number is due to isolated functional adrenal hyperandrogenism (FAH). In a minority of cases, the source of androgen cannot be identified as either ovarian or adrenal. Most of these cases are associated with obesity. Approximately 28%–30% of FOH cases also demonstrate FAH.

sensitivity to LH that is characterized by hyperresponsiveness of 17OHP to the GnRHag or hCG test. The remaining one-third of PCOS cases are atypical PCOS (PCOS-A), which lack 17OHP hyperresponsiveness to LH and are a heterogeneous group. Approximately one-quarter of FOH cases also demonstrated functional adrenal hyperandrogenism (FAH). A small number was due to isolated FAH. In a minority of cases, the androgen source cannot be identified as either ovarian or adrenal; most of these patients are obese (Table 2, Fig. 3).[19,22]

PCOS-T patients with 17OHP hyperresponsiveness demonstrated more severe hyperandrogenism than PCOS-A cases, and the majority (92.5%) also had abnormally short DAST results and a polycystic ovarian morphology (PCOM). The serum AMH levels increased in 81%, and this increase was significantly greater than that in any other group. Coincidental FAH was also present in 28% of the cases. Impaired glucose tolerance and frank diabetes were significantly more often present in PCOS-T than in PCOS-A patients.[19,22] At the same time, PCOS-A cases made up a functionally heterogeneous group; 60% had an abnormal DAST. PCOM (65%) and AMH elevations (39%) were significantly less frequent in PCOS-A than in PCOS-T patients. FAH coexisted with FOH in 30% of this subgroup. The prevalence of glucose intolerance was significantly lower than that documented in PCOS-T patients. The other 40% of PCOS-A cases had a normal DAST; that is, there was no evidence of an ovarian source of androgen. They also had significantly milder hyperandrogenemia. Rosenfield et al.[22] identified "isolated FAH" in 15% and excessive peripheral testosterone formation by abundant adipose tissue in 85% of the nonovarian PCOS-A subgroup (25% of PCOS-A patients).

Roles of AMH

In women, AMH expression begins at approximately the 25th week of gestation and continues until menopause.[23] To prevent the exhaustion of follicles/oocytes, AMH exerts an inhibitory effect on cyclic follicular recruitment by reducing follicle sensitivity to FSH.[24] PCOS is characterized by the premature arrest of antral follicles, and this phenotype can be treated by increasing the circulating levels of FSH.[25] The serum AMH level, an indicator of the number of growing follicles and the intrafollicular androgenic status,[26] is two- to four-fold higher in women with PCOS than in healthy women, likely because androgens stimulate the early phases of follicular growth.[27-29] In addition, the serum AMH level has been strongly correlated with the number of growing follicles and is more sensitive than an ultrasonographic evaluation to the antral follicular count, which reflects preantral and small antral follicles (< 2 mm) that are rarely seen upon ultrasound.[30] Further insights into the possible role of both neuroendocrine and local ovarian factors of AMH have provided the genesis of abnormal GnRH activity and resultant increases in LH and androgens.[31] Moreover, increased maternal AMH levels (which typically decrease during pregnancy in women with normal fertility) decrease placental Cyp19a1 expression, preventing aromatization of elevated maternal testosterone levels, which, in turn, results in a hyperandrogenic intrauterine environment, masculinization of the female fetus,[32] and a PCOS-like reproductive and neuroendocrine phenotype in adulthood.[33]

Hyperandrogenicity in pregnancy

Although hyperandrogenicity is abundantly documented in non-pregnant women with PCOS, androgen status in pregnancy is less

well documented. Recent data show that pregnant women with PCOS have significantly higher androstenedione, testosterone, and free testosterone index levels than healthy control women in the first, second, and third trimesters of pregnancy.[34,35] Increasing evidence suggests that women with PCOS expose their fetuses to a hyperandrogenic environment in utero. A long anogenital distance, a marker for prenatal androgenization, has been observed in infant girls born to mothers with PCOS, and daughters of mothers with PCOS also have higher metabolic and androgenic risks.[36,37] This evidence suggests that hyperexposure to testosterone in utero can have an influence later in life.

In particular, exacerbated androgen production could be a mediator of increased vascular resistance and placental insufficiency during pregnancy due to reduced uterine blood flow, spiral artery elongation, and placental oxygenation.[38] Therefore, PCOS is linked to several pregnancy complications, including miscarriages (relative risk [RR], 2.9), preterm births (RR, 1.52),[39] pregnancy-induced hypertension (RR, 3.43), and preeclampsia (RR, 2.17).[40] In addition, increased maternal testosterone levels seem to alter placental function by affecting amino acid nutrient delivery to the fetus by downregulating specific amino acid transporter activity,[41] diminishing circulating fetal free fatty acids,[42] and possibly leading to a somewhat lower birth weight. However, PCOS in pregnancy has been associated with a greater risk of gestational diabetes mellitus[39] (RR, 2.78), probably owing to insulin hypersecretion that is induced by excess androgen[43] (Fig. 4).

DIAGNOSIS

The diagnostic features of PCOS vary across the lifespan and by ethnicity, which complicates the categorization and natural history of this condition. The international evidence-based guidelines[44]

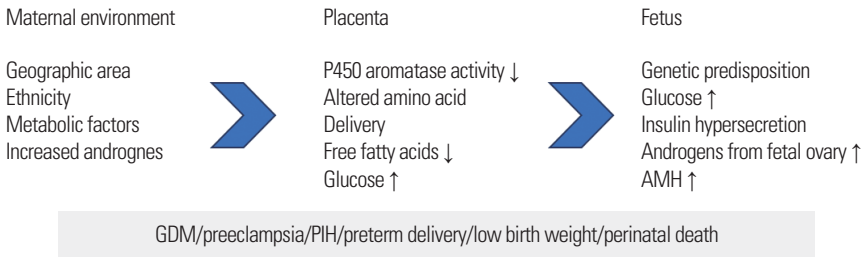

Figure 4. The influence of the maternal environment of a woman with polycystic ovary syndrome on the placenta, fetus, and incidence of pregnancy complications.[43] AMH, anti-Müllerian hormone; GDM, gestational diabetes; PIH, pregnancy-induced hypertension.

Table 3. Recommendations for diagnosing PCOS[3,44]

Category	Definition
Irregular cycles and ovulatory dysfunction	1 to <3 years after menarche: <21 or >45 days
	>3 years after menarche: <21 or >35 days or <8 cycles/yr
	>1 year after menarche: any cycle >90 days
	Primary amenorrhea at age 15 years or >3 years after thelarche (breast development)
Biochemical hyperandrogenism	Use the calculated free testosterone or free androgen index, or the calculated bioavailable testosterone level.
	Remember that liquid chromatography-mass spectrometry with extraction is the preferred assay; reference range upper limits of normal: free testosterone 1.06 ng/dL, total testosterone 60 ng/dL.
	Consider androstenedione or DHEAS if testosterone is normal and with a high index of suspicion for hyperandrogenism.
Clinical hyperandrogenism	Examine specifically for acne, alopecia, and hirsutism.
	Identify adolescents with severe acne and hirsutism.
	Use a standardized visual scale of mFG ≥4–6 while also recognizing that there are ethnic variations that are not well defined.
Ultrasound criteria	Ultrasound should not be used in those <8 years after menarche.
	Ultrasound should be transvaginal and with a high resolution.
	In this setting, the follicle count per ovary should be ≥20 or the ovarian volume should be ≥10 mL.

PCOS, polycystic ovary syndrome; DHEAS, dehydroepiandrosterone sulfate; mFG, modified Ferriman-Gallwey.

(Table 3) endorsed the use of the Rotterdam criteria,[45] which require the presence of two of the three diagnostic criteria for a PCOS diagnosis in adult women. Exclusion of thyroid disease (thyroid-stimulating hormone [TSH]), hyperprolactinemia (prolactin), and nonclassic congenital adrenal hyperplasia (screening with 17OHP) is recommended. Further evaluation is also recommended in those with amenorrhea and more atypical features, including an assessment for hypogonadotropic hypogonadism or Cushing disease. In the presence of a more severe androgenic picture, evaluation of androgen-producing tumors should be considered. Severe androgenic profiles are present if the serum androgen levels are elevated by more than twice the upper limits of normal for the local clinical assay standard.[44] The AMH level has been considered a surrogate marker or an alternative to ultrasound measurement of the follicle number per ovary for the diagnosis of PCOM. However, currently, the lack of standardized assays, variations across the reproductive lifespan, and overlap between PCOS and hypothalamic hypogonadism[46] limit the use of AMH for the diagnosis of PCOS in adult women and adolescents.

MANAGEMENT

It is important to consider that the prevalence of gestational diabetes, impaired glucose tolerance, and type 2 diabetes (five-fold in Asia, four-fold in the Americas, and three-fold in Europe); endometrial cancer (two- to six-fold); and psychological distress (five-fold) are significantly increased in PCOS patients, with the onset occurring several years earlier than in other women.[44] In addition, ethnic variations should also be considered, with a lower BMI (>23 kg/m^2), milder hirsutism, and significantly increased (five-fold) impaired glucose tolerance being distinct in Asians.[3]

The international evidence-based guidelines[3] for the assessment and management of PCOS recommend the following: (1) regular monitoring of weight changes and excess weight through measurements of weight, height, and waist circumference at each visit or at a minimum of every 6–12 months; (2) fasting lipid profiling tests at diagnosis; (3) blood pressure measurement at a minimum of annually; and (4) glycemic status monitoring (glucose, glycated hemoglobin, or oral glucose tolerance test [OGTT] in high-risk women and in those planning pregnancy or seeking fertility treatment), regardless of age and BMI, at baseline and then again after every 1 to 3 years. During pregnancy, an OGTT should initially be performed in the first trimester and then repeated in the second trimester (at 24–28 gestational weeks) if the first-trimester results were normal.[44] Additionally, all adolescent and adult women with PCOS should be routinely screened for anxiety and depressive symptoms at diagnosis.[3]

Weight management before and during pregnancy

Excess weight before conception and excessive gestational weight gain (GWG) are highly related but modifiable risk factors for reproductive outcomes in PCOS.[47] The evidence-based guidelines for the general population recommend that women should aim for a healthy BMI or lose a modest amount of weight (5%–10%) before becoming pregnant.[48] Although pregnancy can occur later in life in women with PCOS, waiting to conceive until a healthy lifestyle and a modest weight loss are achieved is worth considering,[49] as the adverse impact of obesity on maternal and fetal health is not entirely corrected by lifestyle management during pregnancy.[50]

The Institute of Medicine has developed recommendations for GWG in the general population based on women's preconception BMI in singleton pregnancies: GWG 12.5–18 kg for underweight (BMI <18.5 kg/m^2), 11.5–16 kg for normal-weight (BMI 18.5–24.9 kg/m^2), 7–15 kg for overweight (BMI 25–29 kg/m^2), and 5–9 kg for obese (BMI >30 kg/m^2)[48] patients. As the impacts of a higher GWG in women with PCOS are still unclear, limiting early GWG to 0–2 kg is even more crucial in women with PCOS who

Table 4. An overview of the effects of different medical treatment regimens for PCOS[52]

Variable	Hirsutism	Insulin resistance	BMI	Lipids	Ovulation	Safe during pregnancy
Anti-androgen						
Oral contraceptive	↓	↑?	(↑)	↑	→	NA
Spironolactone	↓	↓	→?	?	↑	No
Insulin sensitizer						
Metformin	→	↓	(↓)	↓	↑	Yes?*
GLP-1 agonist	→	↓	↓	↓	↑	No
Other						
Statin	→	↓↑	→?	↓	↑	No

*The drug should probably be stopped at positive pregnancy test.
↓, decreased; ↑, increased; →, neutral; ?, debated; (), only modest; PCOS, polycystic ovary syndrome; BMI, body mass index; GLP-1, glucagon-like peptide 1.

have preexisting insulin resistance.[51]

Antiandrogen treatment

Table 4 lists medical interventions for PCOS and also includes related comorbidities based on an updated review by Glintborg and Andersen.[52]

Oral contraceptive pills (OCPs) are widely used in PCOS to regulate menstrual cycles and prevent endometrial hyperplasia. However, due to the risk of thromboembolism and metabolic side effects (such as weight gain, development of type 2 diabetes, cardiovascular disease, and autoimmune disease), the use of OCPs should be balanced against the possible metabolic side effects in each patient.[52]

Spironolactone is a nonselective mineralocorticoid receptor antagonist that suppresses testosterone levels. The antiandrogen effects of spironolactone are comparable with those of OCPs in the treatment of hirsutism;[53] however, spironolactone could have additional benefits with respect to the risk of cardiovascular disease. Furthermore, combining spironolactone with metformin has been shown to be superior to monotherapy with either drug in terms of improved menstrual cycles, glucose level during OGTT (assessed using the area under the curve), and testosterone levels.[54] The duration of biological effects is 24–58 hours.[55]

Insulin-sensitizing medications

Metformin is probably the most commonly prescribed insulin sensitizer in patients with PCOS. Metformin increases insulin sensitivity and improves ovulatory function in PCOS, whereas androgen levels and hirsutism scores are only mildly improved.[56] In a recent meta-analysis, the effect of metformin on weight was only modest in studies with a maximum duration of 24 weeks;[57] in contrast, 12 months of metformin treatment induced a median weight loss of 3 kg.[58]

The use of metformin rather than insulin during pregnancy was associated with a lower risk of weight gain, late miscarriage, and preterm birth, as well as with reduced rates of maternal hyperandrogenism in women with PCOS;[59] however, the first follow-up study of metformin-exposed versus placebo-exposed offspring showed increased occurrences of overweight and central adiposity at a mean age of 8 years in the metformin-exposed offspring of mothers with PCOS.[60] A recent meta-analysis concluded that metformin exposure results in smaller neonates with accelerated postnatal growth, leading to a higher BMI in childhood.[61] The underlying mechanism is that metformin is transported by organic cation transporters into the mitochondrial membranes in both the fetus and placenta (in the second and third trimesters) and inhibits the mechanistic target of the rapamycin (mTOR) pathway, a primary nutrient sensor in the placenta, which, in turn, could attenuate nutrient flux and fetal growth. These effects could have consequences on fetal growth and differentiation and potentially even on childhood development, especially if relative nutrient restriction in utero is followed by later exposure of the offspring to an obesogenic environment.[62] Therefore, when used to treat PCOS and induce ovulation, metformin should be discontinued by the end of the first trimester according to the 2021 Standards of Medical Care in Diabetes from the American Diabetes Association.[63]

Glucagon-like peptide 1 (GLP-1) agonists may be a promising group of insulin sensitizers that exert neuroendocrine effects on the reproductive axis and anti-inflammatory and anti-fibrotic effects in PCOS-associated subfertility.[64] GLP-1 agonist treatment has been shown to decrease BMI and testosterone levels and to improve the ovulation rate in obese women with PCOS.[65,66] The average weight loss during 6 months of GLP-1 treatment (1.8 mg/day) was 5 kg.[66] Combined GLP-1 (1.2 mg/day) and metformin treatment was associated with a more moderate weight loss than high-dosage GLP-1 (3 mg/day) but had fewer gastrointestinal side effects.[67] After subcutaneous administration, the half-life of liraglutide was found to be 11–15 hours.[68]

Management of dyslipidemia: statins

Dyslipidemia is present in more than 70% of newly diagnosed women with PCOS.[69] Recent studies suggest that statin treatment may improve PCOS-related symptoms other than dyslipidemia. Statins can decrease the androgen levels in PCOS[70] and could have an anti-inflammatory effect.[71]

Antihypertensive medication

The treatment of hypertension in PCOS is complicated by the fact that treatment should be adjusted before pregnancy. Hyperandrogenism may be a predisposing factor for hypertension in PCOS.[72]

Therefore, a spironolactone prescription could be the first choice for improving hyperandrogenic symptoms, decreasing blood pressure, and improving endothelial function in women with PCOS.[73] However, clinical studies are required to further examine this relationship.

Thyroid dysfunction in PCOS

The rates of positive thyroid autoantibodies were reported to be higher in women with PCOS than in controls,[74] and subclinical hypothyroidism was present in 10%–25% of women with PCOS.[75] The presence of overt thyroid disease was 3.6-times higher in PCOS patients than in controls, and prescriptions for thyroid medicine were three times higher.[69] Screening for overt thyroid disease is relevant in PCOS, and the measurement of TSH levels is part of the routine evaluation in women clinically suspected to have PCOS. Furthermore, TSH measurement should be repeated at the time of pregnancy planning and also during the postpartum period.[76]

CONCLUSIONS

The prevalence of PCOS has also considerably increased along with the alarming increase in the number of young adults with a high degree of obesity in Korea. Once disordered physiological changes develop in PCOS, a vicious cycle ensues, leading to reproductive, metabolic and psychological comorbidities. Timely and accurate screening, multicomponent healthy lifestyle modifications for both patients and family members, and comprehensive medical interventions based on international evidence-based guidelines across the reproductive lifespan are essential for curtailing PCOS and its comorbidities.

CONFLICTS OF INTEREST

The author declares no conflict of interest.

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