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Review article

Hyperandrogenemia and insulin resistance: The chief culprit of polycystic ovary syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the most common systemic reproductive endocrine diseases, which has a variety of effects on a woman's health. Because of the involvement of multiple pathways and the lack of common clues, PCOS demonstrates multifactorial properties and heterogeneity of symptoms. Recent studies have demonstrated that the core etiology and primary endocrine characteristics of PCOS are hyperandrogenemia (HA) and insulin resistance (IR). HA and IR are the main causes of PCOS and they can interplay each other in the occurrence and development of PCOS. Just because of this, the study about the effects of HA and IR on pathophysiology of various related symptoms of PCOS is very important to understand the pathogenesis of PCOS. This paper reviews the main symptoms of PCOS, including neuroendocrine disorders, reproductive processes, dyslipidemia, obesity, hypertension, nonalcoholic fatty liver disease (NAFLD), and sleep disordered breathing, which seriously affect the physical and mental health of PCOS women. The increasing knowledge of the development pattern of HA and IR in PCOS suggests that changes in diet and lifestyle, and the discovery of potential therapeutic agents may improve PCOS. However, further studies are needed to clarify the mutual influence and relation of HA and IR in development of PCOS. This review provides an overview of the current knowledge about the effects of HA and IR on PCOS.

1. Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic abnormality common in women of childbearing age, with chronic anovulation (ovulation dysfunction or loss), hyperandrogenemia (HA) and polycystic ovarian morphology (PCOM) under B-ultrasound [1]. Because Stein and Leventhal first reported PCOS in 1935, it is also called Stein-Leventhal syndrome. The main clinical manifestations of PCOS are irregular menstrual cycle, infertility, hairy and/or acne. The incidence of PCOS is as high as 5-15%, which causes a heavy burden in the world and is a common cause of female reproductive infertility [2]. Overall PCOS can lead to menstrual dysfunction, subfertility, and increase the risk of type II diabetes, endometrial adenocarcinoma and potential vascular diseases [2,3].

Under the examination of B-ultrasound, the bilateral ovarian uniformly increase, the echo of the capsule is enhanced, the contour is smooth, and the interstitial echo is enhanced. Most characteristically, the size of ovary increased more obviously than the normal one. In detail, the ovary volume is higher than 10 cm^3 or the antral follicles number is more than 12 and at least one with 2-9 mm in diameter [4]. Besides, these arranging in the shape of a wheel are called “necklace sign” and the endometrium proliferated to varying degrees [5].

The diagnostic criteria for PCOS are provided by three groups, as follows in Table 1. The National Institutes of Health/National Institute for Child Health and Human Diseases (NIH/NICHD) first suggested that the main criteria for PCOS should contain (in order of importance): androgen excess and/or HA, anovulation and exclude other diseases, those cause PCOS to be a rule of exclusion androgen abnormalities with ovarian causes and/or consequences [6]. The consensus reached by the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) enacted diagnostic criteria, including at least two of the following three characteristics: clinical and/or biochemical HA, anovulation or rare ovulation and PCOM, excluding other endocrine diseases [7]. The Rotterdam PCOS criteria include all patients defined by the 1992 NIH standard, as well as women with clinical and/or biochemical HA and ovulatory PCOS or PCOM together with ovulatory dysfunction (but without androgen excess signs). The Androgen Excess-PCOS Association, in 2006, presented

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Table 1
The different diagnostic criteria for PCOS.

	NIH/NICHD (1992)	ESHRE/ASRM (Rotterdam criteria, 2004)	Androgen Excess-PCOS Association (2006)
Anovulation/rare ovulation	+	+/-	+/-
HA (Biochemical and/or clinical)	+	+/-	+
PCOM	-	+/-	+/-

Common to all diagnostic criteria: PCOS is an exclusion diagnosis. Other causes of high androgen, such as congenital adrenocortical hyperplasia (CAH), Cushing's syndrome, androgen producing tumors, are excluded.
Abbreviations: NIH/NICHD: National Institutes of Health/National Institute for Child Health and Human Diseases; ESHRE/ASRM: European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; HA: hyperandrogenemia.

that PCOS be defined by clinical and/or biochemical HA, including rare ovulation and/or PCOM, to exclude relevant illnesses [8]. The 1992 NIH and the Androgen Excess-PCOS society criteria emphasize HA, making these definitions helpful for comprehending metabolic disturbance in PCOS. The Rotterdam criteria are available for the diagnosis of PCOS in ethnic groups without exhibiting clinical androgen excess (e. g. Asian patients). No matter what HA is a core and necessary criterion for PCOS diagnosis.

The heterogeneity of PCOS as it is currently defined, such as variable clinical phenotypes of neuroendocrine disorders, reproductive processes, dyslipidemia, obesity, hypertension, nonalcoholic fatty liver disease (NAFLD), and sleep disordered breathing, has led to multiple mutually inconsistent theories regarding its etiology, in which HA and hyperinsulinemia/insulin resistance (IR) play an irreplaceable role. Here, our main goal is to review current literature about the impact and interaction between HA and IR on pathophysiological changes in regard to the clinical presentation of PCOS.

1.1. The possible causes of PCOS

The reason for affecting PCOS is the combination of environmental and genetic factors. PCOS is closely related to the following factors: high androgen exposure during embryonic period, reaction oxidation state (ROS), immunity, endocrine disorders et al. [9,10]. At the same time, PCOS appears to originate from multiple genes or oligomers. By studies based in family, twin, genome-wide association (GWAS), genes related with certain loci and fetal program, which indicate the genetic origins of HA, IR and possible role of environmental components in PCOS [3,11,12]. Changes in PCOS genes, such as DNA methylation, microRNA expression and the SNP, rs10830963, in the melatonin receptors (*MTNR1B*) gene is partially associated with PCOS [13–15]. Genetic changes in the 3′-untranslated region of *SLC18A2* are related to serum FSH level in PCOS patients and regulate gene expression in vitro [16]. The *GG* allele in PCOS is closely relevant with body-mass index (BMI), waist to hip ratio, IR, luteinizing hormone (LH), and LH/FSH ratio, and showed high basal FSH densities [17].

2. HA in PCOS

2.1. The key reason that HA appears in PCOS

CAG repeat polymorphisms in the *AR* gene, *PDE8A*, the SNP rs3797297 from follistatin (*FST*) gene may contribute to HA in women with PCOS [18–20]. But a studie has shown that CAG microsatellite repeat polymorphism in the AR gene may not be the main determinant of PCOS development [21]. Intrauterine growth retardation (IUGR), excessive androgen exposure and androgen receptors (AR) (particularly neuronal AR) in pregnancy, and unhealthy lifestyle, for example sedentariness, eating more and less exercise are hyperandrogenic origins of PCOS [22].

Although the hypoandrogenemia is characteristic of, in part, adrenal origin and autoimmuneetiology [23], it is reported that major alterations in the local ovarian immune system of PCOS ovaries to reactive oxygen species or cytokines and chemokines may lead to HA [24,25]. Inflammation-related gene, such as interleukin-1 beta (*IL1B*), *IL8*, leukemia inhibitory factor (*LIF*), *NOS2* and prostaglandin-endoperoxide synthase 2 (*PTGS2*), are over-expressed in GCs of PCOS patients, which indicates account of inflammatory responses of ovarian GCs [25]. WNT5a acts as a proinflammatory factor in PCOS patients ovarian granulosa cells (GCs). Up-regulated expression of WNT5a in PCOS primarily increases inflammation and oxidative stress in the PI3K/AKT/NF-κB signaling pathway. Inducible pro-inflammatory cytokines may further enhance NF-κB dependent regulation of WNT5a expression [26]. Above all, it is suggested that GCs of PCOS patients may cause HA under inflammatory response [27].

2.2. HA is a critical cause of PCOS

HA is not only the clinical manifestation of PCOS, but also its core etiology. Fetuses in utero with high levels of androgen may have PCOS. It is reported that prenatal DHT treatment (prenatal androgenization; PNA) causes some endocrine phenotypes closely related with PCOS, for example irregular estrus cycles and resistance to progesterone (P4) in the LET-induced mouse model of PCOS [19,28]. Because of excessive secretion of precocious androgen, girls with premature babies is also prone to PCOS development and visceral obesity and IR are found early. Girls who born at small gestational age (SGA) and develop premature adrenarche has the highest chance of developing PCOS [29]. According to reports that the contents of anti-Mullerian hormone (AMH) in daughters of PCOS women is higher during infancy, early childhood and prepuberty. In addition, a study has suggested that the common missense polymorphism enzymatic (rs710059) is associated with susceptivity to PCOS [30]. And the activity of type I 3β-hydroxysteroid dehydrogenase (3β-HSD) and aromatase (CYP19) in placenta of PCOS women was lower. IR/hyperinsulinemia in patients with PCOS, and insulin may contribute to AMH elevation in PCOS and that AMH counteracts insulin-promoted CYP19 expression in GCs [31,32]. By comparing age-matched obese and lean patients, obese patients show a higher degree of HA, indicating adverse effects of obesity. However, lifestyle adjustment and weight reducing always ameliorate PCOS women metabolism and reproductive abnormality [33]. HA can reduce the sensitivity and expression level of glucose transporter protein-4 (Glu-4), inhibit the degradation of insulin by the liver, and exacerbate central obesity, which is an important potential mechanism of insulin resistance [4]. In summary, HA may cause IR.

3. IR/hyperinsulinemia in PCOS

3.1. Biogenetic mechanism of IR in PCOS

PCOS shares several traits with the metabolic syndrome, including IR (50-70% of PCOS patients) [34], central obesity, hypertension and dyslipidemia [35]. IR is a common characteristic of PCOS women, regardless of BMI [36]. IR is commonly present in obesity, particularly in its central or android form, which is the characteristic form of obesity in PCOS [37]. Some PCOS women show increased phosphorylation of the serine residue of the insulin receptor substrate-1 molecule, thereby inhibiting insulin receptor signaling [38,39]. Genetic change of

MTNR1B in PCOS may impair insulin secretion and increase fasting blood glucose levels [14]. Vit D deficiency in PCOS may lead IR [40]. Vit D promote the maturation of adipose cells and affect the activation of enzymes involved in lipid and carbohydrate metabolism and increase adipose tissue breakdown [41].

IR is closely related to HA. Prenatal androgen (PA) female infants exhibit relatively high insulinemia, indicating an androgen excess for the sequelae of glucose metabolism and antecedents of future metabolic diseases. In addition, androgen can stimulate adipose cell hypertrophy [33]. The average islet size of PA female infants decreased, the number of islets increased correspondingly, and the islet fraction area was preserved. Infants also showed an increase in the proliferative marker Ki67 and an increase in the ratio of β-α cells in the islets, suggesting an increase in β cell proliferation [42]. Insulin stimulates ovarian theca cells to produce and secrete androgens both directly and indirectly [36]. IR stimulates the production of androgens in the ovaries and reduces the production of sex hormone binding globulin (SHBG) in the liver, which increases the amount of free testosterone (FT) available to the body [33]. These results indicate that IR can lead to HA.

3.2. IR/hyperinsulinemia is a key factor in PCOS

PCOS women usually appear dermatological signs (hirsutism, acne, and alopecia), irregular menses, biochemical alterations associated with high levels of testosterone, increased dehydroepiandrosterone (DHEA), androstenedione (ASD), LH and LH/FSH ratio, reduction of SHBG and insulin-like growth factor binding protein (IGFBP). These alterations are because of IR/hyperinsulinemia [24].

IR and endothelial dysfunction are associated with PCOS from the beginning. Children born to mothers with PCOS show increased oxidative stress compared with offspring of gestational diabetes [41]. The gene expression levels of CD11c (*ITGAX*) and tumor necrosis factor alpha (*TNFα*) are higher in subcutaneous adipose tissue of PCOS women. TNFα, as a pro-inflammatory factor, may aggravate the development of IR in women with PCOS. IR decreases in nitric oxide (NO) and increases in endothelin-1 (ET-1) in arterial endothelial cells. At the same time, increased synthesis of vasoconstrictors and impaired vasodilation of insulin. Therefore, IR increases the risk of cardiovascular metabolic diseases in PCOS.

Also, IR increases the likelihood of developing type II diabetes. IR in PCOS women causes a compensatory increase in insulin secretion from pancreatic β-islet cells. IR increases liver synthesis and increased mobilization of adipose tissue, resulting in elevated plasma levels of free fatty acids (FFA). In turn, excess FFA causes IR by inactivating key enzymes such as pyruvate dehydrogenase (PDH) or reducing glucose transport activity. This process may be a sequence that alters insulin signaling by decreasing insulin receptor substrate-1 (IRS-1)-associated PI3 kinase activity. That is to say, hepatic glucose output and its insulin-mediated inhibition are also altered, consistent with hepatic IR [24].

4. HA and IR cause neuroendocrine abnormalities of adrenal glands and ovaries in PCOS

4.1. HA and IR lead to the imbalance of hypothalamic-pituitary-adrenal (HPA) axis regulation

In PCOS women, HA primarily results from dysregulated steroid biology, such as the imbalance function of adrenal cortex and ovary [43]. The prevalence of adrenal hyperandrogenism (AH) ranges from 15-45% in women with PCOS. Adrenal DHEA is primarily converted to DHEAS by the action of sulfotransferase 2A1 (SULT2A1) [44]. Since this enzyme has a limited expression in ovarian tissue, the adrenal gland is the source for most of circulating DHEAS. In humans, DHEA is the most of steroid precursor and the adrenal gland is responsible for up to 97% of circulating DHEAS. The level of DHEAS in the serum of patients with classic anovulatory PCOS increased [33]. But far more importantly, the diagnostic use of DHEA in PCOS is limited because of its diurnal variation, its inter-subject variability and increased stress. Therefore, elevated DHEAS suggests that too much androgen is from the adrenal glands.

Defects in adrenal steroid production (functional adrenal androgen excess [FAH]) lead to HA in some PCOS women. Androgen biosynthesis of the adrenal reticular band is regulated by adrenocortical hormone (ACTH). The high reactivity of adrenaline to ACTH is a common feature of patients with PCOS and AH. Although variants in the type I 11β-hydroxysteroid dehydrogenase (*HSD11B1*) genes is not associated with PCOS [45], because of IR, reducing liver HSD11B1 dependent peripheral regeneration of cortisol may cause compensatory activation of the HPA axis. Moreover, ovarian testosterone may reduce liver enzyme activity, which is a major source of adrenal cortisol regeneration. But insulin can induce HSD11B1 activity in adipocytes via the p38 mitogen-activated protein kinase (MAPK) signaling pathway. Importantly, on account of IR, HPA axis overactivity may also be associated with increased liver 5β-reduced peripheral cortisol clearance in women with PCOS [46]. IR/hyperinsulinemia may underlie these findings.

The compensatory activation of the HPA axis is an attractive mechanism for explaining AH in PCOS patients. One possible for AH in PCOS may involve an exaggerated Δ5-17α-hydroxylase (CYP17) and/or Δ5-17,20 lyase activity of P450c17α, which is induced by an acquired mechanism such as IR/hyperinsulinemia. However, a research has found that variants in the *CYP17* genes is not related to the quantitative trait characteristic of PCOS [45]. Δ5-P450c17 is regulated by post-translational mechanisms [47], including: (I) availability of reducing equivalents donated by NADPH-CYP oxidoreductase (P450-oxidoreductase; POR); (II) the molar abundance of the POR; (III) the allosteric works with cytochrome b5 (CYB5A), by acting as an allosteric factor promoting 17,20-lyase activity; (IV) phosphorylation of the serine/threonine residue with P450c17α that appears to selectively promote 17,20-lyase activity and promotes POR-P450c17α interaction [48].

Since P450c17α serine/threonine phosphorylation promotes POR-P450c17α interaction to increase adrenal 17,20-lyase activity, a common deficiency in serine kinase activity may explain the accumulation of HA (including AH) and IR in PCOS patients. For PCOS women, short-term infusion of high insulin doses increased the response of 17-hydroxypregnenolone and 17α-hydroxyprogesterone (17OHP) to ACTH stimulation, while metformin and pioglitazone reduced ACTH-stimulated 17OHP and ASD secretion. Hyperinsulinemia and/or other factors associated with obesity may promote or exacerbate these defects [49].

In addition, adrenal reticular cells synthesize DHEA from pregnenolone in response to ACTH stimulation because their limited expression of type II 3β-HSD precludes the dominant synthesis of cortisol characteristic of fasciculata cells [50]. The main synthesis of cortisol is characteristic. Partial functional defects in 3β-HSD lead to an increase in the ratio of Δ5 to Δ4 for some PCOS women. This finding is associated with IR [51], and even a simultaneous condition in the regulation of P450c17α and 3β-HSD upstream of the MEK/ERK signaling pathway are a reasonable candidate for AH in PCOS. Besides, race may also affect the popularity of AH, as defined by increased circulating dehydroepiandrosterone-sulfate (DHEAS) levels.

Some research suggested that T might cause AH basally and in response to ACTH. It is reported that administration of testosterone to the human adrenocortical cell line NCI-H295R increases DHEA and decreases DHEAS concentration. However, T has not let levels of DHEA or DHEAS increase in fresh adrenal tissue from normal women [46]. In conclusion, the direct effects of ovarian steroids on adrenal steroid production need to be further studied.

It is worth mentioning that metformin, as one of the insulin sensitizers, can ameliorate IR in PCOS [52,53]. Some research found that metformin treatment could reduce glucose-mediated or fasting insulin concentrations in PCOS women [54–58]. Furthermore, although metformin did not change the PCOS women's fetus insulin concentrations, the PCOS women who took metformin during pregnancy had lower

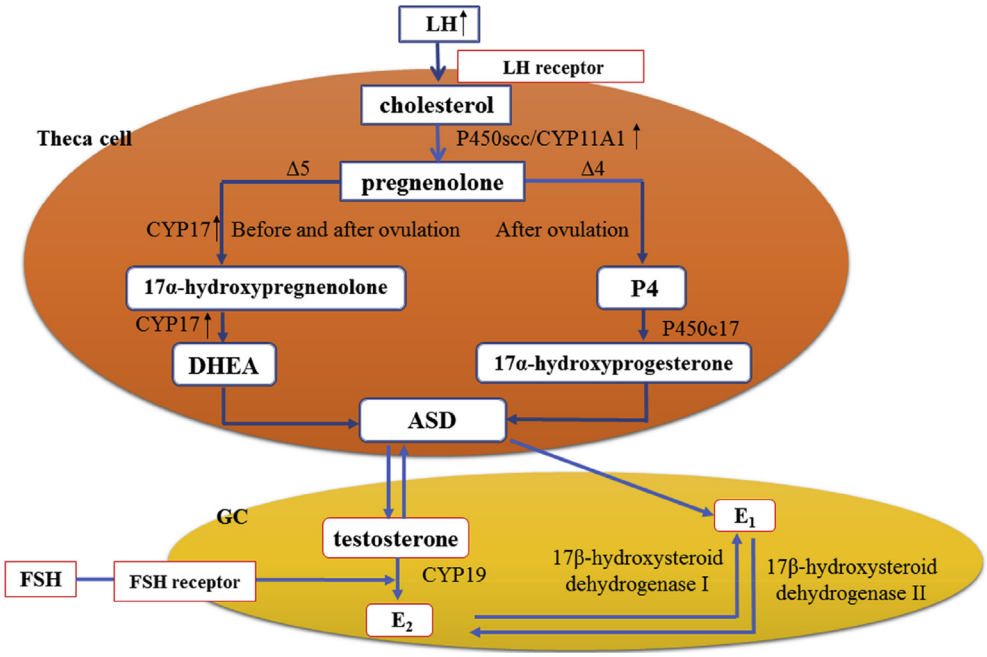

Fig. 1. The synthesis of PCOS ovarian hormones.

Depiction of the organization and regulation of the major steroid biosynthetic pathways in the small antral follicle of PCOS according two-cell-two-gonadotropin compartment theory. In PCOS patients, due to the up-regulation frequency of GnRH by hypothalamus releasing, increased sensitivity of pituitary to GnRH and excessive insulin acting on insulin receptors of pituitary, excessive LH is secreted, stimulating ovarian stroma and follicular membrane cells to produce excessive androgen. Meanwhile, IR can promote adrenal secretion of androgen, inhibit the synthesis of SHBG, and increase free testosterone. All of these are make the high androgens in the ovary inhibit the maturation of follicles and prevent the formation of dominant follicles. However, the small follicles in the ovary can still secrete E_2 equivalent to the level of early follicular stage. In addition, androstenedione is converted into E_1 under the action of CYP19 in peripheral tissues, resulting in high estrone. Continuous secretion of E_1 and a certain level of E_2 on the hypothalamus and pituitary gland, giving positive feedback to LH secretion, increasing LH secretion amplitude and frequency, showing a continuous high level, no periodicity, does not form LH peak in the middle of menstruation, so anovulation occurs. Estrogen also gives negative feedback to the secretion of FSH, reducing the level of FSH and increasing the proportion of LH/FSH. The high level of LH promotes the secretion of androgens in the ovary, while the low level of FSH continues to stimulate, which stops the development of small follicles in the ovary and leads to the formation of no dominant follicles, thus forming a vicious cycle of excessive androgens and continued anovulation, leading to polycystic changes in the ovary.

Abbreviations: GCs: granular cell; LH: luteinizing hormone; FSH: follicle stimulating hormone; DHEA: dehydroepiandrosterone; P4: progesterone; ASD: Androstenedione; E_2: estradiol; E_1: estrone.

insulin concentrations in childbirth [59]. But it has been reported that impaired insulin activity in PCOS women may be different from type II diabetes or obese women without classical characteristics of PCOS, as well as whether metformin increases insulin secretion, especially during the first stage of secretion, is not known [54]. So, the relationship of metformin on insulin concentrations is necessary to do further research. Interestingly, metformin treatment can improve HA, possibly due to lower insulin levels in PCOS [58,60–63]. This also implies the close relationship between HA and IR.

4.2. HA and IR lead to the imbalance of hypothalamic-pituitary-ovary (HPO) axis regulation

The regulation of HPO axis is abnormal in PCOS, which is exhibited in the schematic representation of Fig. 1. Both follicular theca cells and follicular GCs are required for the production of steroid hormones, although GCs first perform this function in the developmental stage of sinus follicles. GCs could respond first to FSH and then to LH in the menstrual cycle, whereas the follicular cells express only the LH receptor in response to LH. Both the follicular theca cells and GCs, as well as LH and FSH, are essential for the production of androgens, which produce the two-cell-two-gonadotropin compartment theory. Under the influence of LH, the ovarian membrane cells express three key steroidogenic enzymes, CYP11A, 3β-HSD and CYP17, which are essential for the conversion of steroid precursor cholesterol to androgens. Hydroxylation then cleaves the cholesterol side chain by the mitochondrial CYP11A (or P450scc) enzyme to produce pregnenolone, which can readily diffuse out of the mitochondria. Once converted to pregnenolone, it can be further metabolized to 17α-hydroxypregnenolone or P4 through CYP17 or 3β-HSD, separately. The CYP17 enzyme converts 17α-hydroxypregnenolone to DHEA. DHEA is as a precursor to ASD as a 3β-HSD reaction; ASD secreted by follicular theca cells are the most important precursor of dihydrotestosterone and testosterone. ASD diffuses into GCs through the basal layer, and under the role of FSH, CYP19 converts testosterone into the main estrogen (estradiol) [33]. Then, estradiol (E_2) is converted to estrone (E_1) by 17β-hydroxysteroid dehydrogenase type I, which in turn is converted to estradiol by 17β-hydroxysteroid dehydrogenase type II.

Under the effect of IR, PCOS is characterized by a distinct neuroendocrine phenotype involving sustained, rapid GnRH pulsation, which facilitates the synthesis and secretion of LH and promotes FSH. This leads to an increase in the ratio of LH to FSH [19]. Increased CYP11A1 and CYP17 expression may increase androgen biosynthesis in PCOS women [46]. Importantly, the LH dependence of ovarian hypertension may explain why PCOS usually manifests in the puberty time when the reproductive hypothalamus-pituitary axis reawakens and LH secretion increases [49,64]. IR therefore plays a central and significant role in regulating the HA occurrence of PCOS.

Excess testosterone of follicular origin is a common characteristic of PCOS. It is reported that tissue explants and GCs exposed in androgen lead to circadian misalignment dependent actions on phase distribution [65]. Androgen-treated mice have disrupted estrous cycles. But flutamide treatment can restore estrous cycling in PCOS mice, reduce the number of ovarian cyst-like follicles in LET females and ameliorate many PCOS symptoms in patients, involving responsiveness to P4. Loss of androgen receptor (AR) signal can improve the phenotype of the PCOS animal model. Therefore, excessive androgen may affect the hypothalamic-pituitary-gonadal axis through AR, thereby reducing the sensitivity to negative feedback of P4. These in turn causes neuroendocrine dysfunction and leads to ovarian function in PCOS [19].

5. HA and IR promote reproductive failure in PCOS

Reproductive disorders, the most serious problem in PCOS patients of childbearing age, are manifested as: infertility (PCOS accounted for 75% in anovulatory infertility) and increased risk of abortion [66–68]. The mechanisms of reproductive disorders include ovulation disorders caused by abnormal endocrine metabolism, impaired potential

development of ovum, and poor endometrial receptivity (ER).

5.1. Damaged follicles mature and ovulation disorder in PCOS

Ovarian function is primarily affected, where HA and IR can disturb the growth and development of the ovarian follicle, as well as the generation of a fertilizable oocyte [68]. PCOS with anovulatory is more likely to have IR than the classic PCOS phenotype.

GCs of the dominant follicle in the normal follicular phase produce large amounts of IGF-II to follicular fluid. IGF-II levels in follicular fluid are positively related with follicular diameter and E_2 levels in follicular fluid, and negatively related with androgen levels. The IGF-II in the follicular fluid of non-dominant follicles is low and does not amplify this effect, leading to developmental disorders of follicles. HA in PCOS women causes lower IGF-II in follicular fluid. Estrogen generated by multiple follicles can hindrance the apoptosis of follicular theca cells, evoking sinus follicles stagnation during growth, but not occlusion in PCOS. In PCOS women, elevated LH leads to ovarian theca cells to produce excess androgens, and low FSH contributes to impaired folliculogenesis and anovulation.

IR/hyperinsulinemia in PCOS women directly excites androgen synthesis in the ovary and adrenal glands, eventually aggravating follicular maturation and causing anovulatory infertility. Interestingly, IR/hyperinsulinemia stimulates the release of pituitary LH (thus increasing the LH/FSH ratio), increases androgen production in ovarian follicular cells, and reduces SHBG synthesis, resulting in increased levels of FT [24]. So, ovarian function and ovulation are upset [41]. It is the most common reason of barren secondary to ovulatory dysfunction [36].

The changes in genes of the LH chorionic gonadotropin hormone receptor (LHCGR) may lead ovarian failure in PCOS [17]. Also, exotropinism can cause ovarian collagen fibrosis, leading to abnormal thickening of the tunica albuginea, making follicles less prone to rupture, leading to luteinized follicle unruptured syndrome (LUFS), which also is easy to infertility. Vit D deficiency is associated with poor outcomes of ovarian stimulation in PCOS [40]. Vitamin D_3 ($VitD_3$) substitution induces normalization of serum AMH and promotes follicular development [69]. This indicates that the development of PCOS oocytes is closely related to Vit D. In general, HA, IR and high levels of LH are meaningfully trouble to ovarian follicle maturation and may lead to anovulatory cycles [24].

5.2. Impaired potential development of ovum in PCOS

Oocyte quality is a key factor in determining fertilization, division, and embryo implantation, and is the primary condition for successful pregnancy. Stem cell factor (SCF) has an important role in promoting cell proliferation and differentiation. SCF is an important cell factor that reflects the ovarian microenvironment and reflects the quality of the ovum itself. SCF secreted by oocytes in PCOS patients may be reduced [70]. The research has found that the dysregulated expression of a disintegrin and metalloproteinase with thrombospondin-like motifs (ADAMTS-1) in PCOS might affect oocyte quality through GCs-oocyte paracrine and endocrine mechanisms [71]. These results suggest that there are multiple factors affecting the oocyte of PCOS patients.

5.3. Poor endometrial receptivity (ER) in PCOS

ER refers to that the ability of the endometrium can undergo blastocyst implantation and blastocyst can develop into an embryo. The ER of patients with PCOS is worse than that of normal women. IR may occur in the endometrium of patients with PCOS. Low pregnancy rates in patients with PCOS are inversely associated with IR [72,73]. Concomitantly, the insulin pathway and endometrial energy homeostasis are also impaired. The levels and activities of insulin signaling pathway molecules (such as IRS-1/AS160/PKCζ) are reduced, which can lead to a decrease in the number of GLUT4 translocations on cell surface, thereby reducing glucose uptake by cells. Metformin (insulin sensitizer) can increase GLUT4 endometrial levels and improve patient fertility. Therefore, under IR/hyperinsulinemia ER may be aggravated in PCOS [68]. Besides IR, the PCOS endometrium is also affected by the proinflammatory environment. Proinflammatory molecules can interfere with the insulin signaling pathway by promoting phosphorylation in serine residues rather than tyrosine of IRS-1 [68].

The level of adiponectin (APN), an important function of increasing insulin sensitivity, in PCOS patients is lower than that in normal people under the effect of HA [74,75]. Single-nucleotide polymorphisms (SNPs) in 45G15G (G/T) and 276 (A/C) of *APN* gene are related to PCOS incidence [76]. Serum APN levels in patients with PCOS are inversely associated with IR [72,73]. In vitro, the research found that obese PCOS patients, under HA and IR/hyperinsulinemia, had impaired endometrial APN signaling pathways, which might affect endometrial function and implantation [77]. In animal experiments, APN enable to improve metabolic abnormalities, hormone secretion disorders, estrous cycle disorders, polycystic ovarian changes, and low pregnancy rates in PCOS rats [78,79]. So, APN may improve PCOS ER.

Meaningfully, oral treatment of metformin in PCOS women can restore this abnormality and improve reproductive outcomes. It has been found that taking metformin during pregnancy does not have demonstrably negative impacts on the fetus [80,81], and also ameliorates immediate pregnancy outcomes in PCOS [61,82,83]. The mechanism of action of the commonly used drug metformin involves the AMPK signaling pathway, the mechanism of action of the endometrial APN partially exerts energy metabolism through this pathway [84], and its serum APN concentration may increase after administration [72]. So, APN may play a role in improving ER of PCOS through AMPK-related signaling pathway, which is associative with IR. However, some studies found that the use of prolonged metformin might have no therapeutic effect for PCOS women after pregnancy [85,86]. In pregnant PCOS women, not only placenta transport of metformin was effective, allowing higher fetal exposure to it, but also the adverse effects of metformin on intrauterine exposed germ cell populations and their offspring were not clear [61,83,85,87]. Therefore, whether metformin is applied to pregnant PCOS women should be determined on a case-by-case basis.

6. HA and IR cause the disorder of lipid metabolism in PCOS

6.1. Dyslipidemia, obesity and hypertension in PCOS

In addition to reproductive failure, it is obvious that PCOS women have a higher risk of the disorder of lipid metabolism [88]. Dyslipidemia is one of the most common characteristics of PCOS patients [89]. IR and androgen excess affect lipid abnormalities in PCOS patients [90,91]. Obesity does appear to exacerbate many aspects of the PCOS phenotype, particularly those risk factors related to metabolic syndrome (Mets) [37]. Mets is closely related to hirsutism in PCOS women [92,93]. The adipose cells of PCOS patients are hypertrophic [41]. Although the pathogenesis of HA in some obese girls is not clear, it may be related to the etiology of PCOS, and increased fat mass may also play a role [49]. Furthermore, obesity itself may not cause HA. However, simple obesity can sometimes lead to a slight picture of PCOS, which is atypical because it is inhibition of LH leading to anovulation [94].

Although variants in the *HSD11B1* genes is not associated with PCOS [45], in a subgroup of lean PCOS patients, genetic variation in *HSD11B1* is associated with enhanced cortisol clearance and lower LDL-cholesterol levels [95]. Increased cortisol regeneration in adipose tissue leads to increased adipocyte differentiation and increased visceral obesity and IR, further contributing to the metabolic consequences of PCOS, such as dyslipidemia. DHEA and DHEAS have demonstrated anti-glucocorticoid effects on vivo [96,97]. But DHEA significantly inhibits preadipocyte proliferation and differentiation, independent of sex steroid and glucocorticoid receptor activation [96]. DHEA inhibits the

amplification of glucocorticoid action mediated by HSD11B1. DHEAS is metabolized to 7α-hydroxy-DHEAS by CYP7B1 in the liver. 7α-hydroxy-DHEAS is a substrate for HSD11B1, which has a competitive inhibitory effect on the reduction of cortisone [98]. AH may partially reduce the effects of glucocorticoids in arterial tissue, thereby improving the effects of obesity-induced dyslipidemia. FT levels and free androgen index are positively correlated with intraperitoneal adipose measurements in normal and PCOS patients [46]. Therefore, the extensive association of high DHEAS concentrations with high testosterone levels may be the reason for these conflicting findings in PCOS.

Obesity and HA can cause hypertension. Testosterone can activate the renin-angiotensin system directly leading to an increase in sodium retention and blood pressure in animal models. In women with PCOS, testosterone can over-sympathize the sympathetic nerves, which may lead to increased tubular sodium reabsorption and vasoconstriction [99]. But DHEA and DHEAS can induce vascular smooth muscle relaxation by directly inhibiting voltage-dependent calcium channels in tissue preparations, by opening potassium channel-mediated effects. In contrast, the DHEAS/FT ratio is considered to be an independent predictor of blood pressure in healthy young women. In addition, DHEA and DHEAS levels are positively correlated with systolic and diastolic blood pressure in middle-aged women through menopausal transition. However, AH increases the pre-hypertension and hypertension prevalence of pre-menopausal PCOS patients. For instance, in PCOS patients with elevated DHEAS concentrations, office systolic and diastolic blood pressure will be higher with elevated levels of FT [100]. However, the blood pressure values of PCOS women with increased FT and DHEAS levels were significantly higher than those with FT alone [46]. PCOS alters metabolic status, increases ROS production, and correlates endoplasmic reticulum stress with leukocyte-endothelial cell interactions, all of which are associated with hypertension [101,102]. The presence of hypertension in PCOS patients has multiple causes.

6.2. NAFLD in PCOS

Recent studies have shown a link between PCOS and another metabolic complication: nonalcoholic fatty liver disease (NAFLD). It can progress to nonalcoholic steatohepatitis (NASH), which is characterized by hepatocyte damage and apoptosis. NASH may progress to cirrhosis. The pathophysiology of NAFLD in PCOS involves IR, androgen, abnormally high expression of proprotein convertase subtilisin/kexin type 9 (PCSK9) [89], apoptosis, dysfunctional adipose tissue, adipokines, inflammatory mediators, estrogen, bisphenol A (BPA), and genetics. NAFLD and NASH have also been related with increased chance of CVD [103]. Many potential links between PCOS and NAFLD have been proposed, and the most important of these is IR and HA. Whether the PCOS represents an independent risk factor for NAFLD or whether the increased risk in this population is due to obesity, IR, metabolic syndrome or HA, the data are contradictory [104].

6.3. Sleep disordered breathing in PCOS

It has been reported that sleep disorders in patients with PCOS are doubled, and obstructive sleep apnea is a common feature in patients with polycystic ovary syndrome [14]. Fogel found that obese women with PCOS had an increased risk of obstructive sleep apnea (OSA) compared with matched, normal-reproductive women. Gopal studied the prevalence of OSA in patients with PCOS and found that the strongest predictor of OSA was the fasting insulin level and the ratio of glucose to insulin [105]. Women with PCOS tend to be overweight/obese, but sleep problems also occur in women with PCOS of normal weight. Sleep disturbances of PCOS is associated with deterioration in cardiometabolic health in the longer term and increased risk of type II diabetes [106]. Overweight/obese is an important clinical manifestation of IR. The above shows that IR is closely related to sleep disordered breathing.

7. Advanced glycosylation end products (AGEs) and endocrine disrupting chemicals (EDCs) are relevant to HA and IR in PCOS

Advanced glycosylation end products (AGEs) are elevated products of glycation or glycooxidation of proteins and lipids. AGEs can induce oxidative stress and be used as proinflammatory cytokines by activating key intracellular signaling pathways, leading to adverse health effects of PCOS [107]. Serum AGEs in women with PCOS are positively correlated with ET-1 concentration and play a role in endothelial dysfunction. Serum testosterone is positively correlated with AGEs in PCOS, suggesting a link between metabolism and reproduction [41]. In women with PCOS, Vit D3 may play a protective role in the inflammatory response of AGEs by increasing circulating soluble receptor for AGEs (sRAGE) [69]. That is to say, AGEs are relevant to HA and IR in PCOS.

Endocrine disrupting chemicals (EDCs), another potential aggravating factor, that indeed cross the placental barrier as possible environmental contributors to PCOS pathogenesis may cause irreversible changes in differentiated tissues and are the main factors affecting prenatal dysplasia. Also, since the fetal liver has not matured in the maternal uterus to decompose EDCs, it may increase the harm of EDCs. Pregnancy rats are exposed to EDCs, and their third generation offspring still can appear similar symptoms of PCOS [108]. In human or animal studies, elevated BPA or Bisphenol S(BPS) concentrations in women with PCOS, respectively are positively associated with HA [109]. In experiments on the function of β-pancreatic cells, long-term exposure to BPA a could lead to IR. In experimental models, perinatal and gestational exposure to BPA is associated with impaired glucose tolerance and IR in adult male offspring. More specifically, in human fat storage, BPA stimulates the release of cytokines (e. g. IL-6 and TNF-α) in favor of obesity and IR while inhibiting the release of APN [107]. Importantly, EDCs exposure is related with menstrual cycle abnormalities and has dose-dependent implant failure in human in vitro fertilization (IVF) [27].

7.1. Current clinical treatment of PCOS

Because the clinical characteristics of PCOS women are complicated and different, it is difficult to find specific medicine for PCOS [110]. Most therapeutic regimens suggest that PCOS women should change their lifestyles, including exercise, diet adjustment and loss of weight. PCOS women can take oral contraceptives (OCPs) as first-line treatment of PCOS menstrual disorder and hirsutism/acne. Anti-androgens are used to control the performances of androgen excess. Insulin-sensitizing medicines can treat impaired glucose tolerance or symptoms of metabolic diseases. Clomiphene citrate or similar estrogen modulators such as letrozole (LET) is used to treat anovulatory infertility in women with PCOS [111]. Surgical intervention consists of laparoscopic ovarian drilling (LOD) and ovarian wedge resection [112]. The treatment progress of PCOS patients should be adjusted by the patients' and the physicians' goals of treatment, as no single therapy is useful at the moment [113].

8. Conclusion and future perspectives

PCOS is a highly complex pathology that exhibits multiple phenotypes and is therefore sometimes difficult to diagnose and treat. That's the reason why the consensus criteria established by several groups around the world. This article reviews the physiopathological mechanism of PCOS, which is associated with HA and/or IR mediated symptoms, but is also associated with an independent pathway, as shown in Fig. 2. The etiology of PCOS androgenism is complex and closely related to the ovary and adrenal glands. HA and IR in PCOS can affect the development of systemic diseases. They are closely related to neuroendocrine disorders, reproductive processes, dyslipidemia, obesity, hypertension, NAFLD, sleep disordered breathing, and the impacts

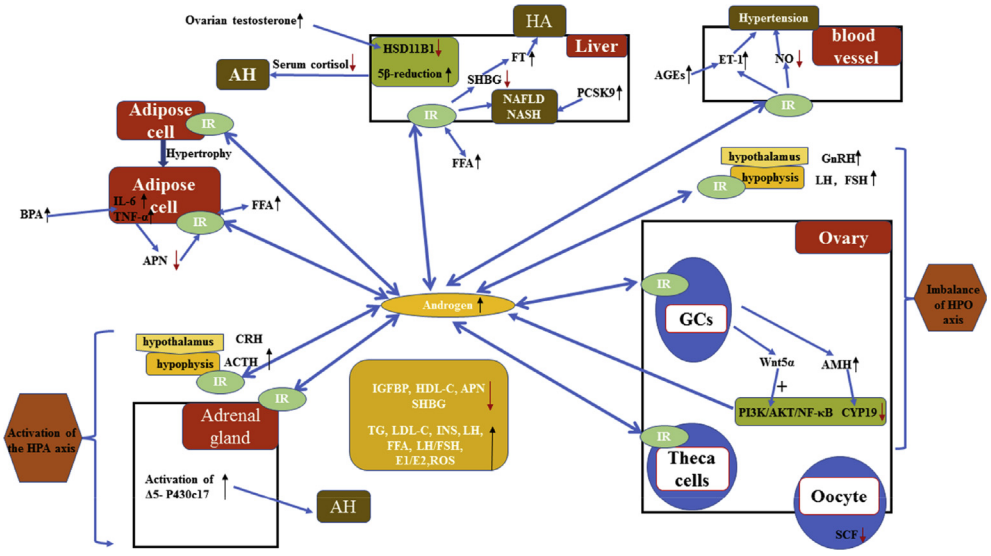

Fig. 2. The effects of HA and IR on pathophysiology of various related symptoms of PCOS.

PCOS is one of the most common systemic reproductive endocrine diseases. The reason that HA and IR in PCOS can affect the development of systemic diseases. The endocrine characteristics and pathophysiology of PCOS were as follows. PCOS is closely related to upregulate IGFBP, HDL-C, APN, SHBG, TG, LDL-C, INS, LH, ACTH, BPA, FFA, LH/FSH, E_1/E_2, Δ5- P430c17, AMH, ROS, HSD11B1, FT,ET-1,NO, GnRH, which induce a series of typically clinical manifestations such as reproductive barriers, neuroendocrine disorders, dyslipidemia, obesity, and hypertension. Eventually these even are accelerate and/or exacerbate the nature of the syndromes throughout life cycle.

Abbreviations: HA: hyperandrogenemia; AH: adrenal hyperandrogenism; IR: insulin resistance; HSD11B1: type I 11β-hydroxysteroid dehydrogenase; FT: free testosterone; SHBG: sex hormone binding globulin; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; PCSK9: proprotein convertase subtilisin/kexin type 9: FFA: free fatty acids; ET-1: endothelin-1; NO: nitric oxide; BPA: bisphenol A; APN: adiponectin; ACTH: adrenocortical hormone; IGFBP: insulin-like growth factor binding protein; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; INS: insulin; LH: luteinizing hormone; FSH: follicle stimulating hormone; E_2: estradiol; E_1: estrone; SCF: stem cell factor; AMH: anti-Mullerian hormone; AGEs: advanced glycosylation end products.

of AGEs and EDCs. Young women with PCOS often appear in health care professionals due to irregular menstruation or infertility; in the later stages, PCOS can cause a series of metabolic complications. Psychological and behavioral pathways are also likely to play a role, as anxiety and depression, smoking, alcohol use and lack of physical activity are also common among women with PCOS, partly in response to the distressing symptoms they experience. Due to timely education and interventions to improve the quality of life. It has now been recognized that the natural history of PCOS can be modified by interactions with factors such as obesity and diet. In conclusion, future research is needed to illustrate the relationship between the underlying causes of PCOS (HA and/or IR) and clinical manifestations, and to develop new therapeutic ideas with more scientific and clinical values.

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Declaration of competing interest

The authors declare that they have no conflict of interest associated with this manuscript.

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