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Diagnosis, Pathogenesis and Management of Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common reproductive endocrine diseases occurs among women of childbearing age, which is affected by many factors, but its precise pathophysiology has not yet been determined. The heterogeneous of PCOS is reflected in its complex endocrine dysfunction of the hypothalamic-pituitary-gonadal axis (HPG axis) and its multiple clinical features, such as obesity, insulin resistance, hyperandrogenism and anovulation. Meanwhile, women with PCOS also have an increased risk of major cardiovascular events, most notably type 2 diabetes, cardiovascular disease and atherosclerosis. So far, many therapies are available for improving reproductive and metabolic abnormalities in PCOS patients, in which lifestyle modification and insulin-sensitizing agents are more effective management strategies.

Keywords: polycystic ovary syndrome, hypothalamic-pituitary-gonadal axis, obesity, insulin resistance, hyperandrogenism

1. Introduction

Polycystic ovary syndrome (PCOS) is a prevalent heterogeneous disorder linked with disturbances of reproductive, endocrine and metabolic function [1], which is characterized by insulin resistance (IR), androgen excess and ovarian dysfunction and can increase the occurrence of the risks of other diseases, but its precise pathophysiology has not yet been determined. Recent years, much more studies showed that neuroendocrine dysfunction plays an important role in the pathophysiology of PCOS [9]. In PCOS, there are complex interactions between abnormal ovarian steroidogenesis, hyperinsulinemia and endocrine dysfunction of the hypothalamic-pituitary-gonadal axis (HPG axis) [2, 3]. HPG axis plays a crucial regulatory role in various life activities in mammal and consists of a complex

network of hypothalamic neurons of gonadotropin releasing hormone (GnRH) and pituitary gonadotropin (GnRH) neurons capable of gonadotropic hormone (GH) and their target organs [4], in which hypothalamic-pituitary-adrenal axis (HPA) and hypothalamic-pituitary-ovarian axis (HPO) in the female reproductive system play a vital effect. Recent studies have found that the role of HPA and HPO axis in PCOS endocrine dysfunction, such as abnormal GnRH pulse frequency, increased LH/FSH ratio, adrenal and ovarian excess androgens [1].

PCOS patients with obesity, insulin resistance (IR), hyperandrogenism, are important pathogenic factors for the metabolic abnormalities [5]. PCOS not only can affect the female reproductive function, but also increase the incidence risk of tumors such as endometrial cancer, type 2 diabetes and cardiovascular disease [6]. PCOS is closely related to metabolic syndrome. The metabolic syndrome is significantly increased in PCOS patients; moreover, women with metabolic syndrome often suffer from PCOS, showed the related endocrine and metabolic characteristics [7] IR/compensatory hyperinsulinemia are, androgen excess/hyperandrogenism, the basic characteristics of metabolic abnormalities in PCOS patients. Obesity is recognized as the most common risk factor for IR. IR is not limited to the scope of glucose metabolism, lipid metabolism and vascular disease [5–7].

Weight loss is associated with metabolic syndrome, a key treatment of PCOS, including diet control and exercise [8]. Dietary options are low-fat foods, including the amount of protein, high carbohydrates, high fiber, whole grains, fruits, vegetables and so on. Lifestyle changes can reduce weight, even if a small part of body weight but can reduce the central distribution of fat and improve insulin sensitivity, plasma insulin levels and can also make obese patients to restore self-confidence, psychological healthy growth [9, 10]. Insulin sensitizing drugs (ISDs) not only reduce the role of obesity, but also have a good effect on obesity-induced endocrine disorders [10], and then much more studies demonstrated ISDs, such as metformin, thiazolidinediones(TZDs) and D-chiro-inositol, can improve some symptoms of PCOS patients, such as hyperandrogenism, anovulation and irregular menses [11].

2. Diagnostic criteria

PCOS was firstly described by Stein and Leventhal in 1935, which was the combination of oligo-ovulation and hyperandrogenism and accompanied by hirsutism, acne, and obesity [12, 13]. Over time, PCOS patients manifested a wide range of signs and symptoms, and there were no single diagnostic criteria in different regions or populations. So far, there are three recognized diagnostic criteria as following:

In 1990, the first formal diagnostic criteria for PCOS were come up by the National Institute of Child Health and Human Disease (NICHD), based on a majority opinion of the attendees, not clinical trial evidence. The NICHD criteria included (1) hyperandrogenism and/or hyperandrogenemia and (2) chronic anovulation. Both criteria must be present, and other diagnoses must be excluded to allow reaching a diagnosis of PCOS [14].

In 2003, a Rotterdam consensus workshop sponsored by the European Society of Human Reproduction and Embryology (ESHRE)/American Society of Reproductive Medicine (ASRM) revised the NIH diagnostic criteria according to clinical trials and familial studies. The revised criteria stated: (1) oligo- or anovulation, (2) hyperandrogenism and/or hyperandrogenemia, and (3) polycystic ovaries. PCOS remains a diagnosis of exclusion, but that two out of the following three criteria must be present. PCOS clinical manifestations may include: menstrual irregularities, signs of androgen excess, and obesity. Insulin resistance and elevated serum LH levels are also common features in PCOS [15].

In 2006, the American Androgen Excess Society (AES) and the PCOS Association systematically re-examined the key recognized features of PCOS based on the medical published literatures, the AE-PCOS criteria showed that (1) hyperandrogenism, including hirsutism and/or hyperandrogenism, (2) ovarian dysfunction, including oligo-anovulation and/or polycystic appearing ovaries, and (3) the exclusion of other androgen excess or related diseases. The AES criteria acknowledge that androgen excess is a necessary component of the diagnosis [16].

The diagnostic criteria must exclude other androgen excess diseases and ovulation dysfunctions and include androgen secreting neoplasms, Cushing's syndrome, 21-hydroxylase deficient congenital adrenal hyperplasia, thyroid disorders, hyperprolactinemia and premature ovarian failure [14–16].

3. Pathogenesis

3.1. HPA and HPO axis neuroendocrine dysfunction

3.1.1. Neuroendocrinology dysfunction of the hypothalamic-pituitary axis

In PCOS, the GnRH pulse frequency is increased to approximately one pulse per 50–60 min, and increases the total amount of GnRH [17], due to the increased endogenous GnRH response to LH. This GnRH secretion pattern leads to an increase in LH/FSH ratio [4]. The relative deficiency of FSH levels causes a decrease in aromatase activity in granulosa cells, leading to testosterone not aromatize into estrogen [18, 19]. Moreover, the ovarian sex hormones have feedback effects on the nervous system, affecting the secretion of gonadotropin and the frequency of GnRH pulse [18, 19]. Many studies have shown that low-dose E2 levels in PCOS long-term positive feedback to stimulate the hypothalamus and pituitary, leading to form high LH levels [18, 19]. Androgen in women with PCOS suppresses the negative feedback effect of progesterone on GnRH pulse frequency [20, 21].

3.1.2. Adrenal dysfunction

The type of androgen in normal women is mainly androstenedione (A2), testosterone (T), dehydroisoandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS). A2 and

T are mainly from the ovarian theca cell and luteal cell, while DHEA and DHEAS are almost from the adrenal gland [22]. About 20–30% of PCOS patients have the excess adrenal androgens, such as DHEAS, which influence the activity of P450c17α and increase the metabolism of peripheral cortisol, leading to the impaired negative feedback regulation of ACTH [23].

Early onset of adrenal function is characterized by the onset of early pubic and armpit hair and may continue to develop into PCOS, which is associated with elevated levels of DHEA, due to the CYP17A1 (P450c17α) dysfunction. Activation of CYP17A1 in the adrenal reticular region leads to an increase levels of DHEA [24]. A study has demonstrated the increased size of the adrenal reticular band and increased in normal adolescent P450c17α activity to increase the synthesis of DHEA, which is onset of premature adrenal function to the process of PCOS [25]. The adrenal androgens have feedback effect on increasing the hypothalamic secretion of LH, which, in turn, leads to increase the synthesis of ovarian androgen. Thus, the adrenal androgen may cause the changes of steroid synthesis in the ovary [26, 27].

3.1.3. Ovarian dysfunction

In fact, PCOS is the most common cause of anovulatory infertility, the morphological changes may be genetic, but ovulation or anovulation is mainly dependent on the follicular environment, may be due to excessive production of local endocrine factor [18, 28, 29]. Hyperandrogenism is one of the diagnostic criteria of PCOS, and ovarian hyperandrogenism can lead to excessive follicular atresia, follicular stasis and anovulation. In PCOS, the mechanism of ovarian androgen excess is mainly theca cells that are over-responsive to LH and excessively produced androgen [12, 13]. At the molecular level, cholesterol through a series of intermediate steps is converted to androgens in theca cell layer, and the disorganized regulation of androgen biosynthesis enzyme P450c17 results in hyperandrogenism [20, 21, 30].

In general, LH binds to its receptor to stimulate thecal cells to produce androstenedione and testosterone. In contrast, FSH mainly stimulates granulosa cells to aromatize these androgens into estrogens that is, two-cell theory [31]. In PCOS, the relative lack of FSH levels leads to a decrease in aromatase activity in granulosa cells, which prevents testosterone from converting into estrogen, while low-dose estrogen long term stimulates the hypothalamus and pituitary to form high LH levels by a positive feedback [18, 19]. Progesterone is a precursor of androgen and estrogen biosynthesis. Under the stimulation of LH, granulation cells luteinized after ovulation and increased the secretion of progesterone, but a decreased estrogen secretion promoted the failure to select the dominant follicle and accompanied by anovulation in PCOS rats and make granulosa cells could not be luteinized to reduce the serum progesterone concentration [2, 3].

In PCO, the disordered follicular development impacts oocyte development. In vitro fertilization studies found that PCOS patients have a lower oocyte implantation rate [32–34], due to oocytes which are exposed to high levels of androgens and other factors of abnormal levels, such

as high insulin levels [3]. Gene chip analysis showed that abnormal endocrine and metabolic have a effects on the gene expression in PCOS oocyte, and most of the differentially expressed genes were upregulated in oocytes of PCOS patients [28, 29, 35].

3.2. Metabolic dysfunction

3.2.1. Androgen excess/hyperandrogenism

Hyperandrogenism is one of the most important endocrine features of PCOS [36]. Higher circulating androgen levels, on the one hand, can hinder the normal growth of follicles, resulting in oligoovulation or anovulation, which mainly manifests an abnormal menstrual cycle, usually oligomenorrhea/amenorrhea [36, 37], on the other hand, can cause hirsutism, acne, female hair loss and other clinical symptoms [38]. Many animal studies have shown that intrauterine androgen excess led to their offspring would be similar to the reproductive and metabolic characteristics of PCOS patients [39], and thus, androgen plays an important role in the pathogenesis of PCOS.

These clinical manifestations of hyperandrogenism will be obvious around puberty, due to both ovarian and adrenal androgens excess [40]. Excessive ovarian and adrenal gland secretion of androgens through the circulation transport into the peripheral adipose tissue and are aromatized into estrone [41]. Serum estrone excess continuously exerts feedback effects on the hypothalamus and pituitary, which manifests positive feedback effects on LH secretion and negative feedback effects of FSH secretion, leads to increase LH/FSH ratio. Low basal levels of FSH will be contribute to promote follicle development to a certain extent, but not mature, increased LH secretion, but no cyclical fluctuations, there are no LH peak, thus is the occurrence of oligoovulation, leading to infertility [1, 31]. In particular, androgen formation is also affected by insulin and insulin growth factor system, renin-angiotensin system (RAS), adiponectin, leptin, growth hormone and other factors.

Hirsutism can affect approximately 5–10% of reproductive-age women, while approximately 80% of hirsute patients will have PCOS. The increased activity of enzyme 5-α reductase in the hair follicle has elevated circulating testosterone and contributes to a dysregulation of hair follicle growth, which converts testosterone to dihydrotestosterone (DHT). Androgen excess increases hair follicle size, hair fiber diameter, and the proportion of time terminal hairs remains in the anagen (growth) phase [42].

3.2.2. Insulin resistance/hyperinsulinemia

In recent years, a large number of studies have established IR, obesity, hyperandrogenism and vascular endothelial dysfunction contribution to the occurrence and development of PCOS [43], IR can promote elevate serum insulin levels and increase the frequency of pulsatile GnRH secretion, cause elevated serum LH levels, and further promote excess androgen production [1]. The high levels of insulin result in the increased synthesis of androgen and inhibit the synthesis of sex hormone-binding globulin (SHBG) in liver, give rise to increase serum free androgen [44] and may induce the activity of insulin-like growth factor-1 and promote

the synthesis of androgen [45]. Androgen can impact the growth and development of follicles, inhibit the formation of dominant follicles, and accumulate a large number of immature follicles, that is, the formation of the polycystic-like changes of the ovaries [46].

The interaction of insulin with its receptor results in dimerization of the receptor and facilitates recruitment and activation of downstream proteins via receptor autophosphorylation [47, 48]. Many physiological effects of insulin are mediated primarily via the phosphatidylinositol-3-kinase (PI3K) signaling pathway—metabolic effects and the mitogen-activated protein kinase (MAPK) signaling pathway—mitogenic effects [48]. Insulin no longer plays its metabolic role in insulin sensitive tissues, when insulin sensitivity is compromised in that insulin resistance occurs. When insulin insensitivity hinders glucose uptake in target tissue, insulin secretion is usually increased, leading to compensatory hyperinsulinemia [49].

Usually, the metabolic action of insulin is preferentially interfered, such as glucose uptake, while its mitogenic action can remain intact [47, 48]. In PCOS patients, insulin resistance impact on the synthesis, transport and degradation of glucose led to increase the blood glucose levels and serum insulin levels [50, 51]. At present, a large number of studies have found that PCOS patients with varying degrees of insulin resistance and compensatory hyperinsulinemia and in addition to systemic IR exist ovarian insulin resistance [52–54]. Much more studies have suggested that IR and hyperinsulinemia play an important role in the pathogenesis of PCOS [52]. IR and hyperinsulinemia are important features of chronic hyperandrogenic anovulatory women [52–54]. Therefore, PCOS is a syndrome as the combination of metabolism abnormalities and reproductive dysfunction.

3.2.3. Obesity

The development of obesity is a multifactorial and complex process, which can cause many changes in the endocrine system and thus damage to female reproductive function [55]. Obesity is one of the most common clinical manifestations of PCOS, and PCOS patients showed metabolic abnormalities that were independent of obesity and were generally associated with weight gain before menstruation or hyperandrogenism [56], thus suggesting the role of obesity in the progression of the pathogenesis of PCOS. Obesity is superimposed in PCOS, which is also associated with the hyperactivity of HPA, leading to increased adrenal androgen excess status [57]. Obese PCOS patients had lower SHBG levels than those with normal weight PCOS, which lead to translate into a higher circulating free testosterone [58]. Thus, there is a greater degree of hirsutism and menstrual disorders in obese PCOS women. It has been suggested that PCOS itself may cause weight gain [56]. More importantly, established superimposed obesity further promotes weight gain, which due to the deeper hyperinsulinism of obesity, exerts greater metabolic effects on insulin synthesis, leading to more rapid fat deposition [56].

PCOS is closely related to evaluate body fat distribution, especially abdominal fat [59, 60]. Most obese PCOS patients exhibit fat accumulation in the abdomen, especially in the viscera [59]. Abdominal obesity is strongly associated with the development of IR [59]. In particular, visceral adipose tissue is highly sensitive to lipolysis stimulated by androgens that will be contribute to the increased availability of free fatty acids (FFA) [60]. This, in turn, leads to induce the accumulation of hepatic fat, decreased hepatic insulin clearance and hepatic

insulin resistance [61]. The fasting lipid profile of obese worsening PCOS is characterized by increased triglycerides and reduced HDL-C and may also reflect the effects of deeper degree of IR in obesity [62]. Increased circulating endothelin-1 and activation of the sympathetic nervous system and renin-angiotensin-aldosterone system are also contribution to worsening hypertension as a result of obesity in PCOS. Not surprisingly, most PCOS patients meeting the criteria of the metabolic syndrome are obese. In fact, abdominal obesity is the most common feature of metabolic syndrome in the disorder.

3.2.4. Oxidative stress

In recent years, effects of oxidative stress (OS) on the female reproductive system attract much more attention, such as superoxide dismutase (SOD), which are involved in the embryo implantation process, and follicular fluid antioxidant content will directly affect in vitro fertilization success rates [63–65].

Much more studies showed that the concentration levels of OS markers in PCOS higher than normal, such as lipid peroxidation (LPO) [66]. A study reported that the advanced oxidation protein products in women with PCOS were higher than that in health women with the same age and body mass index (BMI), while the total antioxidant levels were lower [67]. Previous studies suggested that OS is associated with obesity of PCOS patients, but recent studies have found elevated OS markers levels in lean PCOS patients [66].

IR is thought to be a cause of OS, which can lead to the occurrence of hyperglycemia, thus causes related cells to release reactive oxygen species (ROS), causing OS [68]. OS can damage cells and activate the expression of proinflammatory cytokines, which in turn promotes the occurrence of IR and hyperandrogenism [69]. The malondialdehyde (MDA) levels in PCOS patients with IR higher than PCOS patients without IR, but lower levels of peroxidase and zinc, which indicate high levels of OS in PCOS patients with IR [68–70]. Zinc is essential for the biological function of metalloproteinases, which not only participates in the synthesis, secretion, conduction and metabolism of insulin, and also with copper act on SOD and peroxidase (POD). Therefore, zinc deficiency may contribute to metabolic disorder in PCOS patients by affecting insulin function and reducing antioxidant content and may aggravate the degree of IR and the degree of antioxidant deficiency in PCOS patients [71].

OS markers in PCOS patients, such as MDA, thiol, and blood zinc, are associated with whose fertility, the levels of MDA in infertility PCOS patients higher than that in pregnant PCOS patients, while the MAD, sulfhydryl and blood zinc content are lower [67–71]. Therefore, eat more fruits and vegetables containing antioxidants, increased intake of vitamins, avoid drinking, smoking and intake of caffeine to maintain the balance between oxidants and antioxidants in the body, so as to maintain the health female reproductive system, which improving female fertility.

3.2.5. Chronic low-grade inflammation

Chronic low-grade inflammation is triggered an inflammatory response by nutrient metabolism excess, and its involved molecules and signaling pathways are similar to traditional inflammatory response, leading to the occurrence of some chronic metabolic diseases [72];

moreover, its related metabolic regulations are closely to reproductive function. Some complications of PCOS are closely associated with chronic low-grade inflammation, such as obesity, diabetes type 2 and cardiovascular disease, and inflammation factors may be responsible for long-term consequences of PCOS [73], such as C-reaction protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-18 and monocyte chemoattractant protein-1 (MCP-1). The first study demonstrating elevation of CRP in women with PCOS was carried out by Kelly, which suggested inflammation may be involved in occurrence and development of PCOS [74].

The inflammatory responses are induced by hyperlipidemia and IR, which not only lead to the occurrence and development of PCOS, and are also involved in the formation of long-term complications of PCOS. Some studies suggested that hyperandrogenism may be an inducing factor for chronic low-grade inflammation of PCOS [75], in turn the inflammatory responses further promote excessive ovarian androgen synthesis in PCOS patients [75]. In cellular level, inflammation upregulates the androgen biosynthesis enzyme CYP17 activity and thus promotes androgen synthesis [69]. Another study found that the stimulation of TNF-α increased the proliferation of androgen synthesis in rat interstitial cells, resulting in increased androgen secretion, which suggested that inflammation can further aggravate the performance of PCOS patients with hyperandrogenism [69, 74]. Interestingly, recent studies have found that hyperandrogenism may play an anti-inflammatory role in obese PCOS patients and demonstrated that the cycle effects of androgen were pleiotropic, and its role depends on whether obese individuals [60, 74].

Obesity increased PCOS patients with IR. IL-6, MCP-1 and TNF-α levels in patients with PCOS were significantly higher than those in controls, which were positively correlated with body weight and IR, suggesting that chronic low-grade inflammation in PCOS patients was closely related to obesity and IR [74]. Inflammatory signaling pathways interact with insulin signaling pathway, and macrophages were showed in adipose tissue of non-obese PCOS patients, which promoted the synthesis of inflammatory cytokines such as TNF-α and IL-6, which further led to the development of IR, which suggested that inflammatory may be responsible for IR in non-obese patients with PCOS [74].

Much more evidence shows PCOS patients with elevated inflammatory factors, suggesting that the body of patients in the inflammatory environment [76]. These inflammatory reactions in addition to the occurrence and development of PCOS can also cause type 2 diabetes, atherosclerosis, cardiovascular disease and other long-term complications. Therefore, the early administration of anti-inflammatory treatment may reduce the occurrence of the long-term complications of patients with PCOS.

3.2.6. Vitamin D deficiency

There are increasing evidences showed that vitamin D deficiency plays a major role in the in the pathogenesis of metabolic syndrome of PCOS [77]. Clinical studies have shown that type 2 diabetes and insulin resistance status are closely related to vitamin D deficiency [78]. In addition, studies have shown that vitamin D deficiency in patients has the increased risk of the long-term occurrence of hyperlipidemia and IR [78, 79], and in a prospective study of

intervention, PCOS women with vitamin D supplementation, the secretion capacity of insulin was increased, and lipid levels were improved [80], suggesting the importance of vitamin D supplementation in treating patients with metabolic syndrome of the general population and PCOS population.

The correlation between vitamin D deficiency and PCOS is resulted from the deposition of 25-(OH) VD3 in adipose tissue [81]. The low level of 25-(OH) VD3 increases the risk of cancer, autoimmune diseases, diabetes and cardiovascular disease [82]. Much more researches showed that vitamin D deficiency ultimately leads to impaired insulin secretion, induces glucose intolerance, and reverses the vitamin D sufficient state [79–81]. Many studies showed that a low level of 25-(OH) VD3 was observed in type 2 diabetes, while it with insulin resistance and obesity are also confirmed in PCOS population [79–82]. So far, the mechanisms of low 25-(OH) VD3 levels and insulin resistance have not been well elucidated. First, 25-(OH) VD3 may stimulate insulin secretion by stimulating the expression of insulin receptors, thereby enhancing insulin responsiveness to glucose transport [79–82]. Second, 25-(OH) VD3 regulates intracellular and extracellular calcium ions levels, which is essential for insulin sensitive tissue such as skeletal muscle, adipose tissue mediated intracellular delivery of insulin. In addition, 25-(OH) VD3 deficiency may induce a hyperinflammatory response due to its role in regulating the immune system, which is also associated with IR [83].

A recent study confirms that high 25-(OH) VD3 levels in overweight and obese PCOS women are faster weight loss than that in women with low 25-(OH) VD3 levels due to better absorption of the low calorie diet, indicating that PCOS women with the high levels of 25-(OH) VD3, weight loss is one of the most effective treatments [84]. Therefore, vitamin D supplementation can be used as an adjunct to the treatment of PCOS.

4. PCOS management

4.1. Lifestyle changes

PCOS has become a social and psychological behavior disorder and a low risk factor for quality of life. In recent years, much more studies and treatment guidelines recommend that lifestyle intervention therapy is as a first-line treatment of PCOS [9].

Lifestyle intervention is mainly through diet and exercise methods [8, 9]. Diet therapy is mainly by controlling the total calorie intake of food, scientific and rational regulation of diet, in order to achieve the purpose of weight loss [8]. In addition to limiting calorie intake to achieve the purpose of weight loss can also be classified according to different macro nutrients, such as carbohydrates, protein and fat ratio [8]. The basic principle of exercise therapy is mainly through exercise to increase the consumption of glycogen and fat. Sports therapy is significantly able to achieve weight loss and also can enhance physical fitness. Studies have shown that women with cardiovascular disease, metabolic disorders, IR, overweight and obese can improve IR and reduce the risk of cardiovascular disease and abdominal fat by scientific, rational and regular exercise [85].

Lifestyle intervention achieves weight loss and long-term maintenance to reduce obesity for PCOS and directly improve the metabolic abnormalities, menstrual disorders, hairy acne and other symptoms [8]. A large number of studies have shown that weight loss in obese with PCOS patients, its symptoms can be improved to some extent. Low calorie diets, physical exercise and other lifestyle interventions, reduce 5–10% of body mass, can change or reduce menstrual disorders, hirsutism, acne and other symptoms, and increase the pregnancy rate, improve high blood lipids, high blood sugar IR and other symptoms and can reduce the incidence of miscarriage and cardiovascular disease.

4.2. Insulin sensitizing drugs

ISDs are used to control the hyperglycemia of type II diabetes. As time goes on, insulin resistance and compensatory hyperinsulinemia negatively affecting ovarian steroid biosynthesis and follicular recruitment and maturation were found in PCOS and play a critical role in its pathophysiology, and then, much more studies demonstrated that ISDs, such as metformin, thiazolidinediones (TZDs) and D-chiro-inositol, can improve some symptoms of PCOS patients, such as hyperandrogenism, anovulation and irregular menses [11].

Metformin is one of the most common ISDs to widely use in clinical treatment of PCOS, and as a biguanide can inhibit hepatic gluconeogenesis by affecting glucose metabolis and increase glucose uptake and reduce fatty acid oxidation in peripheral tissues, so as to achieve increasing insulin sensitivity [86, 87]. The effects of metformin on reproductive and on metabolic function of PCOS are mainly a reduction of circulating insulin levels. At the pituitary levels, hyperinsulinemia decreases SHBG synthesis, thus increasing circulating free androgens, at the muscular levels, it alters the mitochondrial oxidative metabolism, at the ovarian levels, hyperinsulinemia induces anovulation, follicular growth blockade and hyperandrogenism. Excess insulin increases the concentrations of androgen, which lead to block follicular maturation and increase cytochrome P450c17a activity [11, 86, 87]. On the other hand, metformin can improve the reproductive function at the HPO level. Insulin stimulates pituitary cells to modulate the normalize LH secretion pattern, thus hyperinsulinemia may be contribution to significantly decreasing LH plasma levels, then further impact ovarian function.

TZDs are peroxisome proliferator activating receptor γ (PPARγ) agonists, which are part of the superfamily of nuclear receptors are essential for adipocyte differentiation and growth, that in a lesser degree decrease hepatic glucose production, but more potently increase peripheral glucose uptake [87]. The metabolic effects of TZDs in PCOS are similar to metformin. Some mechanistic studies have shown that TZDS also decreases fasting glucose and insulin levels, AUCs for glucose and insulin levels, and glycosylated hemoglobin levels compared with placebo in women with PCOS, and troglitazone improves insulin-mediated glucose disposal as well as insulin-secretory defects in women with PCOS [86, 87].

D-Chiro-inositol, as a new insulin-sensitizing drug, has never been approved for clinical treatment in diabetes and PCOS but could improve insulin sensitivity by enhancing signal transduction via an alternative pathway for insulin action [87].

In a word, PCOS is usually diagnosed during the early reproductive years and still occurs in approximately 4–18% of reproductive-aged women. Although the pathophysiology of PCOS

has yet not been clearly illuminated, there are much more related clinic manifestations had been deeper detected, which showed a number of its molecular mechanisms, and provided many new theoretical basis for clinical PCOS prevention and treatment.

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