Polycystic Ovary Syndrome (PCOS), Insulin Resistance and Insulin-Like Growth Factors (IGFs)/IGF-Binding Proteins (IGFBPs)

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Polycystic ovary syndrome (PCOS) is the most frequent androgen disorder of ovarian function. Hyperinsulinemia with insulin resistance is believed to be a key link in the enigmatic generation of the symptoms of PCOS such as anovulatory infertility and hyperandrogenism. Regression of these symptoms may be achieved by reducing the hyperinsulinemia. A growing body of evidence suggests that PCOS patients with hyperinsulinemia have a higher risk to develop diabetes mellitus, hypertension and cardiovascular disease as compared to age-matched women. Although oral contraceptives, progestins, antiandrogens, and ovulation induction agents remain standard therapies, weight loss should also be vigorously encouraged to ameliorate the metabolic consequences of PCOS. In addition, insulin-sensitizing agents are now being shown to be useful alone or combined with standard therapies to alleviate hyperinsulinemia in PCOS. Finally and most importantly, early identification of patients at risk and prompt initiation of therapies, followed by long-term surveillance and management, may promote the patient's long-term health. *(Chang Gung Med J 2003;26: 540-53)*

Key words: **polycystic ovary syndrome (PCOS), hyperinsulinemia, hyperandrogenism, antiandrogens, insulin resistance, insulin-like growth factors (IGFs), IGF-binding proteins (IGFBPs), insulin-sensitizing agents.**

Polycystic ovary syndrome (PCOS), characterized by amenorrhea or severe oligomenorrhea, anovulation and hyperandrogenism, is the most frequent androgen disorder of ovarian function,[1] and affects 5%-10% of all women.[2] Clinically, PCOS is a combination of three components: hyperandrogenic state, disorder of ovulation (anovulatory) and disorder of metabolism (dysmetabolic).

There is accumulating evidence that PCOS patients have a higher risk to develop diabetes mellitus, hypertension and cardiovascular disease as compared to age-matched women.[3-6] Lifelong exposure to an adverse cardiovascular risk profile in women with PCOS may lead to premature atherosclerosis.[7] The sequelae of PCOS beyond reproductive health and the adverse health consequences associated with PCOS are substantial. Unfortunately, most women are not aware of these risks. Thus, physicians should pay much attention on the clarification of the genetics, etiology, clinical associations and assessment of treatment and later sequelae of the syndrome.

Diagnosis of Polycystic Ovary Syndrome (PCOS)

Although there has been much debate on clini-

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cal definition of the PCOS, the most widely accepted one is the association of hyperandrogenism with chronic anovulation in women without specific underlying diseases of the adrenal or pituitary glands.[8] Typically, endocrinological features are overproduction of ovarian androgens and excessive secretion of luteinizing hormone (LH), but with normal or low serum levels of follicle-stimulating hormone (FSH).[9-10] Notably, ultrasonography has not been considered an essential requirement for the diagnosis of the PCOS[11] though the early descriptions of polycystic ovary are based on ovarian morphology ultrasonographically (Fig. 1).[12] In contrast, the diagnosis of the PCOS is based on both clinical and biochemical criteria.[13-15]

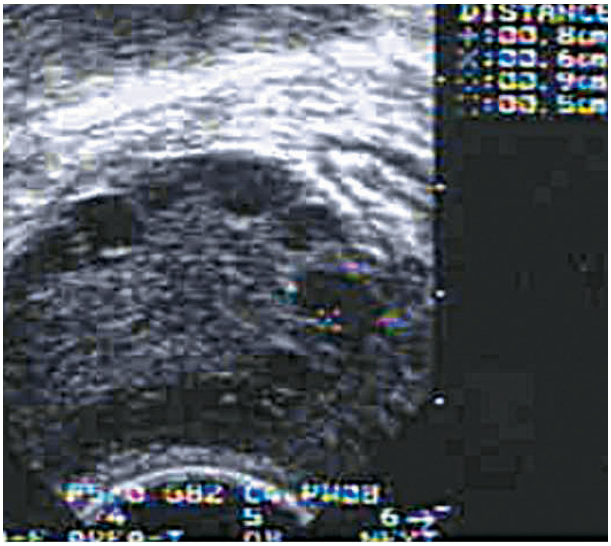

Fig. 1 Ultrasound picture of the ovary in a patient with polycystic ovary syndrome (PCOS).

PCOS can be expressed in a way of wide variety of clinical features since the definition of the syndrome has been rather vague. Thus, the criteria for diagnosis of PCOS used by clinicians and investigators are almost as heterogeneous as the syndrome itself. To meet the unanimity, a consensus on the standard for the diagnosis of PCOS has been proposed recently which needs to be universally adopted.[16] Briefly, the proposed protocol for the diagnosis of PCOS is based on the symptoms of a patient such as menstrual disturbance, hirsutism, acne and anovulatory infertility followed by an ultrasound examination. If the result of ultrasound examination

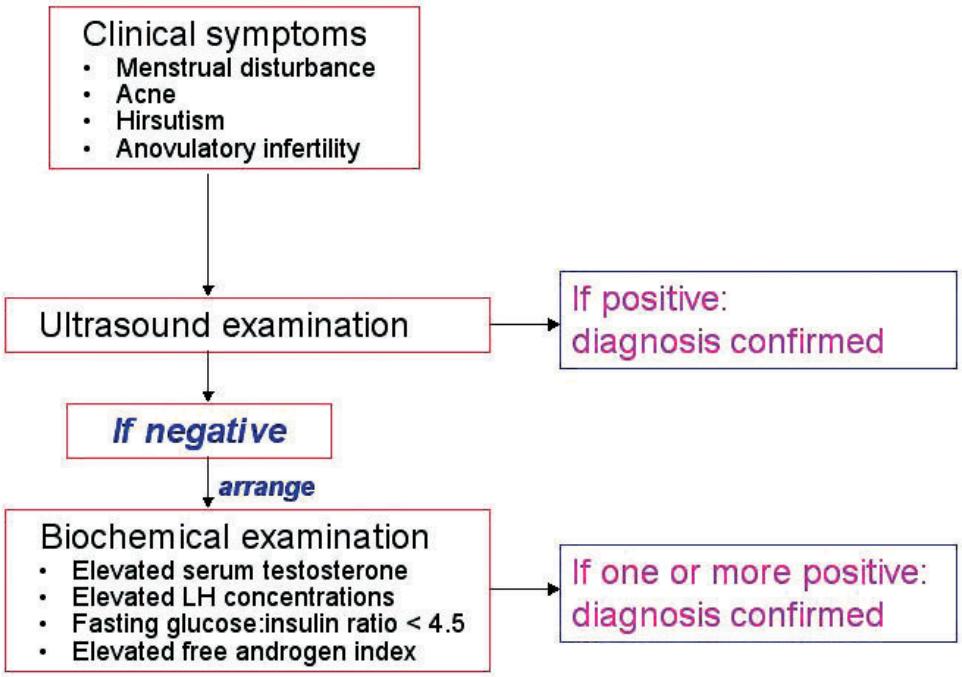

Fig. 2 A proposed protocol for the diagnosis of polycystic ovary syndrome (PCOS). Free adrogen index (FAI)=[total testosterone (nmol/L)/SHBG (nmol/L)]×100.

is positive (polycystic appearance of the ovary), the diagnosis is confirmed. In contrast, patients with negative results from ultrasound examination are further arranged biochemical examinations including determination of serum levels of LH and testosterone, as well as fasting glucose to insulin ratio. The diagnosis of PCOS is also confirmed if elevated serum LH and/or testosterone, and/or fasting glucose to insulin ratio < 4.5 are/is observed (one or more positive) (Fig. 2).

PCOS and Insulin Resistance

Polycystic ovary syndrome (PCOS) patients are known to have a high incidence of insulin resistance and glucose intolerance and tend to be at high risk of hypertension, diabetes mellitus and cardiovascular disease.[17] Insulin resistance, probably via hyperinsulinemia, results in a general augmentation of steroidogenesis and LH release in PCOS.[18] The profound insulin resistance and defects in insulin secretion, together with obesity, explain the substantially increased prevalence of glucose intolerance in PCOS. A number of obese PCOS patients display a particular metabolic pattern including an atherogenic lipid profile (dyslipidemia), glucose intolerance and an increased fasting insulin level, which is known to be closely linked with an insulin resistant state.[1,19] Approximately 75% of patients with PCOS are insulin resistant.[11] It is evident that hyperinsulinemic insulin resistance in women with PCOS is associated with an increased risk for coronary heart disease (CHD) and both types 1 and 2 diabetes.[4-6] In addition, many lipid abnormalities (most notably low high-density lipoprotein cholesterol levels and elevated triglyceride levels) and impaired fibrinolysis are also seen in PCOS patients.[17] Moreover, increased vascular stiffness and functional defects in the vascular action of insulin have been demonstrated in patients with PCOS.[20] Collectively, these observations further indicate the association among dyslipidemia, hyperinsulinemic insulin resistance and cardiovascular disease.

A growing body of evidence suggests that hyperinsulinemia resulted from insulin resistance and hyperandrogenism are reciprocal causal factors. Hyperandrogenism may contribute to hyperinsulinemia by decreasing the hepatic extraction of insulin and increasing insulin receptors.[21] In contrast, insulin stimulates androgen production in human ovarian theca and stromal cells.[22] Additionally, acute and chronic changes in circulating insulin are associated with parallel changes in circulating androgens.

Pathogenetically, the insulin resistance in at least 50% of PCOS women is believed to be related to excessive serine phosphorylation of the insulin receptor.[23] Increased insulin receptor serine phosphorylation decreases its protein tyrosine kinase activity and is one mechanism for the post-binding defect in insulin action characteristic of PCOS. Presumably, a serine/threonine kinase, that phosphrylates serine residues of insulin receptor β-subunit, causes this abnormality and is an example of an important mechanism for human insulin resistance related to factors regulating insulin receptor signaling. The serine/threonine kinase also increases the serine phosphorylation of P450c17α, the key enzyme of controlling androgen biosynthesis, leading to increased production of androgens.[24] It is thus most likely that, in some PCOS women, a single defect produces both the insulin resistance and the hyperandrogenism.[11,25] Possible mechanisms of insulin stimulation of ovarian cytochrome P450c17α activity and androgen production are shown in Fig. 3.

Genetics and PCOS

Multiple lines of independent evidence show the association among genetics, chronic hyperinsulinemia and ovarian hyperandrogenism. Specifically, mutations in the insulin receptor gene that cause severe hyperinsulinemia are proven related to ovarian hyperandrogenism.[22] In addition, adolescent girls with a history of premature pubarche have an increased incidence of functional ovarian hyperandrogenism and PCOS at adolescence, which is usually associated with hyperinsulinemia and dyslipemia, indicating that the triad of premature pubarche, hyperinsulinism and ovarian hyperandrogenism may result, at least in part, from a common early origin, rather than from a direct interrelationship later in life.[26]

Genetic studies of family clusters and relatives of affective probands have shown a high incidence of affected relatives. In this regard, a dominant mode of inheritance, rather than a recessive one, seems more likely.[27] A previous study of 50 families of PCOS probands has indicated 24% of sisters affected with PCOS, 22% of sisters with regular menstrual

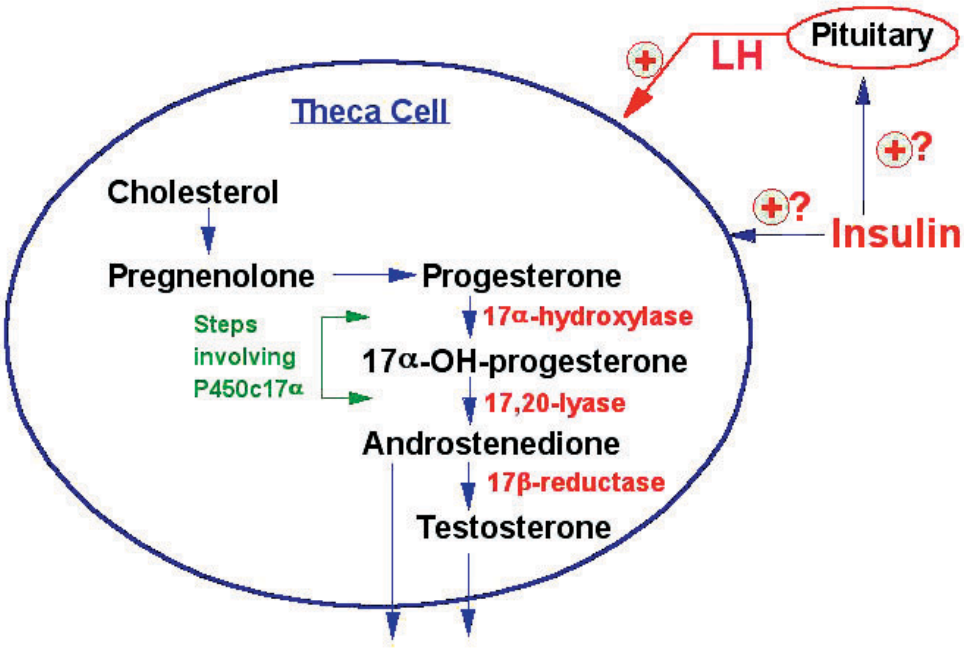

Fig. 3 Possible mechanisms of insulin stimulation of ovarian cytochrome P450c17α activity and androgen production. Insulin may stimulate the production of androgens through direct action on thecal cells and/or indirect enhancement of pituitary luteinizing hormone (LH) secretion. The enzyme, 17,20-lyase, is also named 17,20-desmolase.

cycles who are hyperandrogenic per se, and 50% of first-degree relatives having glucose intolerance (impaired glucose tolerance by oral glucose tolerance test or type 2 diabetes mellitus).[28] These findings suggest that hyperandrogenism in females and glucose intolerance may be genetic traits in PCOS kindreds. In affected sisters, only one-half have oligomenorrhea and hyperandrogenemia characteristic of PCOS, whereas the remaining one-half have hyperandrogenemia per se.[29] Thus, there is familial aggregation of hyperandrogenemia (with or without oligomenorrhea) in PCOS kindreds.

A number of candidate genes related to PCOS have been proposed and studied. In terms of steroidogenic abnormalities, CYP11a (encoding P450 side chain cleavage) appears to be a major susceptibility locus. In relation to the well-described metabolic disturbances in PCOS, the insulin gene variable number tandem repeat (VNTR) is believed to be a promising candidate.[30] Similarly, the human androgen receptor (CAG)n gene locus and/or its differential methylation patterns also influence the disease process leading to PCOS.[31] Finally, genes implicated in ovarian follicular development may have a role in the etiology of PCOS, as demonstrated by recent identification of the follistatin gene as a potential disease locus.[32]

To date, although specific gene mutations affecting androgen synthesis, insulin secretion and insulin activity may explain most of the endocrine and metabolic symptoms, environmental risk factors (either during prenatal or postnatal life) seem to play an important role in converting an occult PCOS into a clinically manifest syndrome.[33]

PCOS and Puberty

PCOS usually has a menarchal age of onset. Clinically, there is a striking resemblance between the endocrine characteristics of puberty and some forms of PCOS. Both conditions are characterized by insulin resistance, hyperpulsatile gonadotropin secretion, hyperactive ovarian and adrenal androgen synthesis, and decreased levels of insulin-like growth factor binding protein-1 (IGFBP-1) and sex hor-

mone-binding globulin (SHBG).[34-35]

Insulin and insulin-like growth factor-I (IGF-I) stimulate ovarian growth and potentiate the actions of gonadotropins on ovarian steroid synthesis. Insulin also augments the bioactive concentrations of IGF-I and androgens through regulation of the synthesis of their respective binding proteins (IGFBP-1 and SHBG) in the liver.[34] At the onset of puberty, increased pulsatile growth hormone (GH) secretion results in insulin resistance and compensatory hyperinsulinemia which in turn stimulate the growth spurts.[35-37] Insulin resistance with compensating hyperinsulinism is also a common feature of PCOS. The increased serum insulin levels further decrease hepatic synthesis of IGFBP-1 and in turn enhance the bioactivity of IGF-I.[35] Thus, it is plausible to speculate that there is an association between PCOS and puberty. Specifically, the progressively increasing insulin levels and IGF-I activity during puberty may act as inducing factors in the development of PCOS in susceptible subjects.[34]

Adrenarche, another milestone of sexual maturation, is excessively accentuated in PCOS. Recent reports have indicated that girls with premature adrenarche are at risk of developing functional ovarian hyperandrogenism and PCOS.[26,38-39] In premature adrenarche, insulin and IGF-I appear to increase the adrenal sensitivity to adrenocorticotropic hormone (ACTH), leading to overproduction of androgens.[34] Collectively, insulin and IGFs may have a role in the hyperandrogenism of premature adrenarche just as they do in PCOS (Fig. 4).[39] Thus, in certain girls with premature adrenarche, hyperandrogenism may be the first presentation of PCOS and/or insulin resistance.[38] In this respect, PCOS may be considered as a state of "hyper-puberty".

PCOS and Insulin-Like Growth Factor (IGF)/IGF Binding Protein (IGFBP) System

It is clearly evident that insulin stimulates ovarian thecal and stromal androgen secretion in vitro.[22] In women with PCOS, insulin resistance with compensatory hyperinsulinemia induces overproduction of ovarian androgens, leading to hyperandrogenism. The action of insulin on the production of androgens in the ovary is believed to be through type I IGF receptors on theca and stroma cells.[40-41]

In both normal human ovaries and polycystic ovaries, granulosa cells may or may not secrete IGFBP-1 in response to follicular stimulating hor-

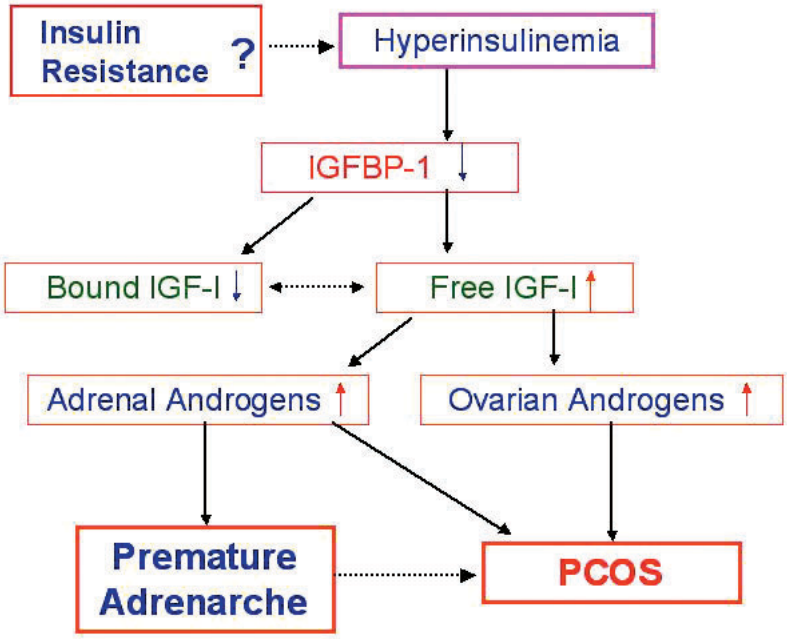

Fig. 4 Possible mechanisms involving hyperinsulinemia, insulin-like growth factor-I (IGF-I), and IGF-binding protein-1 (IGFBP-1) in premature adrenache and polycystic ovary syndrome (PCOS).

mone (FSH).[42] In contrast, the addition of IGF-I to granulosa cells incubated with testosterone or testosterone plus FSH causes complete inhibition of IGFBP-1 production.[42] Serum levels of IGFBP-1 in women with PCOS are significantly lower than in those with normal-appearing ovaries.[43-44] In addition, IGFBP-1, analyzed by Western ligand blotting, is not detected in follicular fluid in PCOS.[45] Normally, the ovarian stroma has specific binding sites both for insulin and for IGF-I.[40] In cultured human theca cells, both insulin and IGF-I potentiate LH-induced testosterone and androstenedione secretion.[41] In situ hybridization studies have shown that abundant expression of IGFBP-1 mRNA is only observed in the granulosa cells of dominant follicles and not in those of atretic follicles.[46] Additionally, in vitro studies have shown that both insulin and IGF-I inhibit IGFBP-1 production by cultured human luteinizing granulosa cells. Insulin exerts its inhibitory effect on IGFBP-1 production via insulin receptors, while IGF-I appears to exert its effect via IGF receptors.[47] These findings indicate that a decrease in IGFBP-1 produced by granulosa cells may insufficiently antagonize IGF-I bioactivity in theca-stromal cells, resulting in overproduction of androgens and in turn defective follicular maturation and ovulation.[35]

Treatment of PCOS

Conventional treatment of PCOS has been focusing on improvement of ovarian function, restoration of ovulation, and amelioration of hyperandrogenism. Although laparoscopic laser diathermy of the ovary is believed to lower circulating LH and androgen levels and induce spontaneous ovulation for PCOS patients,[48-49] this surgical procedure is reserved only for patients who are resistant to clomiphene citrate treatment[50-51] or who are unable to or unwilling to receive regular medication. In addition, correction of hyperandrogenemia by laparoscopic ovarian laser diathermy in women with PCOS is not accompanied by improved insulin sensitivity or lipid-lipoprotein levels.[52] Furthermore, postoperative adhesions and possible recurrence of hyperandrogenism may occur following laser diathermy. Currently, a prevailing trend in management of PCOS has extended to the preventive therapy, which should improve the reproductive, metabolic, and cardiovascular risks.[17] Nowadays, numerous available tools have been developed to assure early diagnosis of PCOS and close long-term follow-up as well as screening for diabetes and cardiovascular disease, further warranting early correction and prevention of metabolic and cardiovascular diseases.

Treatment with Ovulation-Inducing Agents in PCOS

In women with anovulation and PCOS, treatment should be individualized. Among ovulation-promoting agents, clomiphene citrate is an excellent one of the first choice.[53] The induction of ovulation by clomiphene citrate is believed to be the result of interaction of the drug at various levels: hypothalamus, pituitary and ovary.[54] However, low response to clomiphene citrate is frequently observed in PCOS patients with higher androgen secretion and insulin resistance.[55] In women with PCOS resistant to clomiphene citrate, gonadotropin therapy with both urinary and recombinant follicle-stimulating hormone (FSH) generally results in pregnancy.[56-59] In this respect, pituitary desensitization with gonadotropin-releasing hormone analog (GnRHa) in combination with FSH is superior to FSH-only treatment in PCOS patients who demonstrate premature luteinization during clomiphene citrate treatment.[60] However, women undergoing gonadotropin therapy with or without GnRHa are at a higher risk for multiple pregnancy and ovarian hyperstimulation syndrome (OHSS).[53,59]

Alternatively, oral administration of the aromatase inhibitor such as letrozole is effective for ovulation induction in PCOS women resistant to clomiphene citrate treatment. In addition, letrozole appears to avoid the unfavorable effects on the endometrium frequently seen with clomiphene citrate use for ovulation induction.[61]

Treatment with Antiandrogens in PCOS

In women, androgen excess per se contributes to impairment of insulin action since antiandrogen treatment partially reverses the peripheral insulin resistance associated with hyperandrogenism.[62] This is further confirmed by a study on female to male transsexuals that administration of testosterone induces insulin resistance in healthy female subjects.[63] Clinically, a number of antiandrogens including cyproterone acetate, flutamide, spironolacton, and finasteride have been used to treat hyperan-

drogenism in women with or without PCOS.[64-69]

Despite slight worsening of glucose tolerance, a combination of estrogen and cyproterone acetate is an efficient treatment for women with hyperandrogenism and hirsutism.[64,70] As with cyproterone acetate, spironolactone is effective for improving hyperandrogenism and reducing hirsutism in PCOS patients. However, for treatment of the hormonal or metabolic manifestations associated with PCOS, it is necessary to combine spironolactone with either an antigonadotrophic agent or a drug that improves peripheral insulin sensitivity.[67]

Flutamide, a non-steroid antiandrogen that specifically blocks the androgen receptor, is capable of restoring ovulation in anovulatory PCOS patients, supporting the hypothesis that flutamide reduces androgen synthesis through restoration of ovulation though a direct block of the steroidogenic enzymes of androgen biosynthesis in ovarian thecal cells cannot be excluded.[71] Although insulin resistance is not corrected, treatment with the flutamide improves the lipid profile in PCOS patients.[72] In addition, flutamide significantly blunts fasting and oral glucose tolerance test (OGTT)-stimulated secretion of insulin (reverse of hyperinsulinemia) in women with idiopathic hirsutism, but not in nonobese women with PCOS, suggesting that the efficacy of the drug is dependent on peripheral androgen hyperactivity.[65] Finasteride is also effective in the treatment of hirsutism in patients with PCOS but it is less effective than flutamide.[68]

Treatment with insulin-sensitizing agents in PCOS

Insulin resistance and increased ovarian cytochrome P450c17α activity (i.e. increased 17α-hydroxylase and, to a lesser extent, increased 17,20-lyase) are both features of the PCOS.[73] It is also evident that hyperinsulinemia stimulates ovarian P450c17α activity in obese women with PCOS. Clinically, dietary weight loss decreases ovarian P450c17α activity and reduces serum free testosterone concentrations in obese women with PCOS.[73-74] However, these changes are not observed in ovulatory obese women.[73] Collectively, it is most likely that decreasing insulin secretion may reduce ovarian hyperactivity.

Oral contraceptive pills (OC) are usually the first choice of treatment for PCOS, when fertility is not desired. However, they do not improve, or may even further induce impairment of insulin sensitivity, which is already impaired in women with PCOS.[75] Similarly, clomiphene citrate does not alleviate adverse changes in insulin resistance associated with PCOS.[54] Although treatment with antiandrogens may improve the lipid profile in PCOS women with hyperandrogenism,[72] the peripheral insulin resistance associated with hyperandrogenism can only be partially reversed.[62] Based on these observations, various insulin-sensitizing agents including metformin and troglitazone have been tried to reduce the insulin resistance and in turn lower the extent of hyperandrogenism in women with PCOS.

The insulin-sensitizing agents appear to enhance insulin action by modulating the activity of the nuclear receptor peroxisome proliferator-activated receptor-gamma (PPAR-γ). This activation results in changes in the expression of numerous genes that are critically involved in glucose and lipid metabolism, as well as in insulin signal transduction.[76-78]

Metformin, a biguanide antihyperglycemic agent that increases insulin sensitivity, has been shown to improve ovarian function and glucose metabolism in women with PCOS.[64,79] Metformin therapy not only decreases hyperandrogenism and insulin resistance but also improves ovulation rates, cervical scores, and pregnancy rates in clomiphene citrate-resistant women with PCOS.[80] Alleviation of hyperandrogenism by metformin in women with PCOS is proven to be in part through a reduction in stimulated ovarian cytochrome P-450c17α activity.[81] Adding metformin to the OC treatment significantly enhances the insulin sensitivity, and further suppresses the hyperandrogenemia in non-obese women with PCOS.[64,75] A reduction of insulin secretion with amelioration of insulin sensitivity resulted from metformin use is further confirmed by observations that a significant increase in plasma IGFBP-1 levels is induced after metformin treatment.[82] In anovulatory women with PCOS who are resistant to clomiphene citrate, metformin use significantly increased the ovulation rate and pregnancy rate from clomiphene citrate treatment.[83] A large randomized placebo-controlled trial has also shown that metformin treatment improves ovulation frequency in women with abnormal ovarian function and polycystic ovaries.[84] Furthermore, prolonged treatment of metformin decreases the risk of development of type 2 (noninsulin dependent) diabetes and also induces cardio-

protective effects on serum lipids as well as reduction in plasminogen activator inhibitor-1 (PAI-1) that leads to improvement of the fibrinolytic response to thrombosis.[84-86]

Thiazolidinediones are a new class of oral insulin-sensitizing agents. They selectively enhance or partially mimic certain actions of insulin, causing a slowly generated antihyperglycemic effect in type 2 (noninsulin dependent) diabetic patients. This is often accompanied by a reduction in circulating concentrations of insulin, triglycerides and nonesterified fatty acids.[76]

Troglitazone, one of the insulin-sensitizing compounds, thiazolidinediones, is a ligand for peroxisome proliferator-activated receptor-gamma (PPAR-γ) and is effective in the treatment of both non-insulin-dependent diabetes mellitus (NIDDM) as well as PCOS.[77] Administration of troglitazone to women with PCOS and impaired glucose tolerance ameliorates the metabolic and hormonal derangements, resulting in improvement of insulin sensitivity and hyperandrogenism as well as restoration of ovulation.[18,85,87] In addition, results from cell culture studies also indicate that the beneficial effects of troglitazone in PCOS may not be due solely to improvement of peripheral insulin resistance and hyperinsulinemia, but also to a direct effect on ovarian steroidogenesis.[88]

Metformin is classified as "category B" and its use during pregnancy is believed to be quite safe.[89] In contrast, thiazolidinediones including troglitazone are category C drugs that have been demonstrated to retard fetal development in animal studies.[90] A recent study has proclaimed that metformin therapy throughout pregnancy in women with PCOS reduces the otherwise high rate of first-trimester spontaneous abortion seen among women not receiving metformin and does not appear to be teratogenic.[89] Furthermore, use of metformin in PCOS is also associated with a 10-fold reduction in gestational diabetes. Mechanistically, metformin reduces insulin resistance and insulin secretion, thus decreasing the secretory demands imposed on pancreatic beta-cells by insulin resistance and pregnancy.[91]

CONCLUSIONS

Polycystic ovary syndrome (PCOS) is a convergence of multisystem endocrine derangements. Hyperinsulinemia is believed to be a key link in the enigmatic generation of the symptoms of PCOS such as anovulatory infertility and hyperandrogenism. Regression of these symptoms may be achieved by reducing the hyperinsulinemia.

In PCOS women with hyperandrogenism and anovulation, endometrial hyperplasia can be prevented by the oral contraceptive pill or progestins whereas hirsutism is best treated by a combination of the oral contraceptive pill and an antiandrogen. The first line of therapy for ovulation induction is clomiphene citrate, with gonadotropin or laparoscopic ovulation induction reserved for clomiphene failures. FSH together with GnRHa may decrease the risk of spontaneous abortion following ovulation induction in PCOS. In addition, weight loss should also be vigorously encouraged to ameliorate the metabolic consequences of PCOS.

The insulin sensitizing treatment allows to decrease hyperandrogenism, to reverse the menstrual cycle irregularity and to obtain spontaneous or induced ovulation (Fig. 5). The results of recent clinical studies of insulin-sensitizing agents such as metformin and troglitazone in PCOS have provided encouragement that improvement of insulin sensitivity and consequent lowering of circulating insulin levels by these agents may be of therapeutic value in the management of both anovulation and hirsutism.

Antiandrogens as a sole treatment or combined with oral contraceptives are considered the treatment of choice for the manifestations of hyperandrogenemia, but there is no agreement about their efficacy on the metabolic sequelae of PCOS (insulin resistance, hyperinsulinemia, dislipidemia) (Fig. 5). Furthermore, the improvement of insulin sensitivity by insulin sensitizers may be of therapeutic value directly and/or indirectly in the management of clinical manifestations of hyperinsulinemia and hyperandrogenemia (Fig. 5).

Although oral contraceptives, progestins, antiandrogens, and ovulation induction agents remain standard therapies, insulin-sensitizing agents are now being shown to be useful alone or combined with standard therapies. Most importantly, early identification of patients at risk and prompt initiation of therapies, followed by long-term surveillance and management, may promote the patient's long-term health.

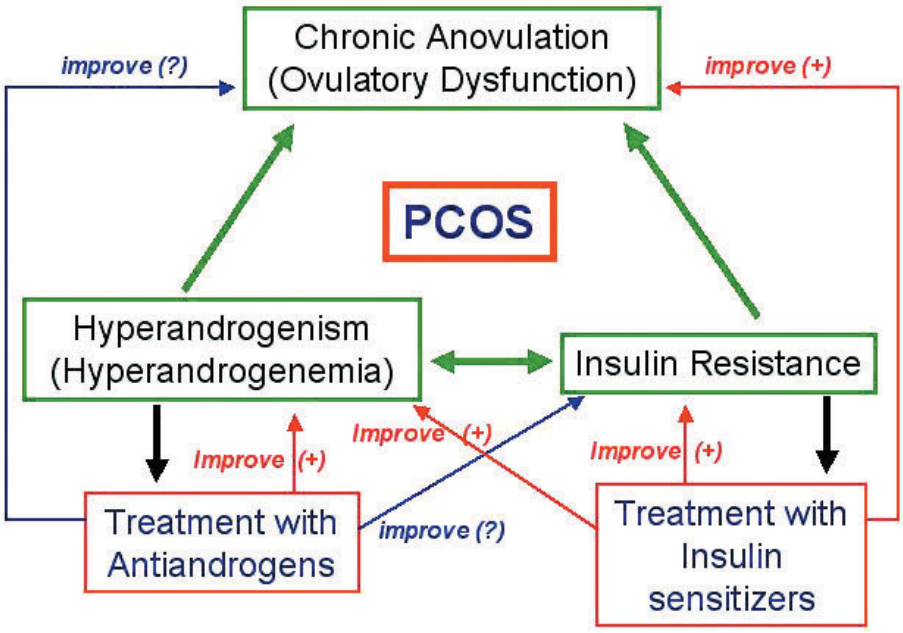

Fig. 5 In patients with polycystic ovary syndrome (PCOS), treatment with isulin-sensitizing agents ameliorates insulin resistance and hyperandrogenic status, leading to ovulation. In contrast, administration of antiandrogens in PCOS patients may in part or may not increase insulin sensitivity and resume ovulation.

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多囊性卵巢症候群、胰島素抗性、與類胰島素生長因子及類胰島素生長因子結合蛋白

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多囊性卵巢症候群 (PCOS) 是卵巢功能最常見之雄性素異常。胰島素過高血症合併胰島素抗性是誘發多囊性卵巢症候群症狀(如：無排卵性不孕、及雄性素過高血症) 最主要之關鍵，改善胰島素抗性所導致之胰島素過高血症可以緩和多囊性卵巢症候群之症狀。與正常之同年齡婦女比較，多囊性卵巢症候群之病人有較高的機率罹患糖尿病、高血壓、及心臟血管疾病。雖然口服避孕藥、黃體素、抗雄性素製劑、及促排卵藥爲多囊性卵巢症候群之標準療法，但仍須積極地鼓勵病人減肥，因減肥可以降低新陳代謝異常誘發之後遺症。目前，促胰島素敏感化製劑的單獨使用、或合併其他標準療法，能改善多囊性卵巢症候群病人之胰島素過高血症。最重要的是，儘早診斷高危險群之病人、即刻開始治療、以及長期之追蹤，可以改善及提升病患之健康。(長庚醫誌 2003;26:540-53)

關鍵字：多囊性卵巢症候群，胰島素過高血症，雄性素過高血症，抗雄性素製劑，胰島素抗性，類胰島素生長因子，類胰島素生長因子結合蛋白，促胰島素敏感化製劑。

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