

REVIEW

New concepts in pathogenesis and management of polycystic ovarian syndrome: Insulin resistance and role of insulin sensitizers

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Abstract

Polycystic ovarian syndrome (PCOS) is classically characterized by the clinical triad of androgen excess, anovulation infertility and obesity. Anovulation occurs due to functional ovarian and/or adrenal hyperandrogenism. The etiology and patho physiology of PCOS is unknown. Proposed theories include excess of gonadotropins; the effect of which is amplified by disturbances in intrinsic regulatory peptides, such as inhibin or extrinsic regulatory peptides, such as insulin or insulin like growth factor (IGF). For over 25 years insulin resistance has been known to be associated with PCOS. Improvement in insulin resistance with the use of insulin sensitizers, such as metformin and thiazolidinediones (TZDs) have been seen to be associated with better ovulation and reduced testosterone levels in patients with PCOS.

Aims: The aim of the present review is to discuss the new concepts in the pathogenesis of PCOS and to know usefulness of insulin sensitizers in such patients.

Methods: Over 50 articles extending the span of more than 25 years have been reviewed and an attempt has been made to know the etiopathogenesis of PCOS and also to assess the validity for the uses of insulin sensitizers in patients of PCOS.

Results: With the advancement of knowledge regarding etiopathogenesis, the management of PCOS has changed in recent years. In view of positive association between hyperinsulinemia and PCOS, improvement in insulin resistance through weight loss and use of insulin sensitizing drugs has been recommended.

Conclusions: Besides symptomatic treatment, recent studies recommend use of insulin sensitizers in management in PCOS for better outcome in them.

Key words: Polycystic ovarian syndrome (PCOS), Insulin resistance (IR) Insulin sensitizers (IS).

Introduction

Polycystic ovarian syndrome (PCOS), previously known as Stein –Leventhal syndrome, is classically characterized by the clinical triad of androgen excess, anovulation, infertility and obesity where anovulation occurs due to functional ovarian hyperandrogenism and / or functional adrenal hyperandrogenism. It is associated with manifestations such as enlarged polycystic ovaries, secondary amenorrhea or oligomenorrhea, hirsutism and infertility. For over 25 years insulin resistance has been known to be

associated with PCOS. The pathophysiology of PCOS is a complex and as yet not fully understood, so the management of PCOS remains a challenge.

Polycystic ovarian syndrome (PCOS) is characterized clinically by persistent anovulation and is associated with varied manifestations such as enlarged polycystic ovaries, secondary amenorrhea or oligomenorrhea and infertility. According to an estimate by Dunaif ¹ et al 5-10% of women in the reproductive age have polycystic ovarian syndrome. Besides, chronic anovulation and irregular bleeding, polycystic ovarian syndrome (PCOS)

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is characterized by hyperandrogenism which may be present in the absence of hyperandrogenemia in those women in reproductive age who have enhanced tissue sensitivity to androgens. According to the revised guidelines of the Rotterdam PCOS Consensus Workshop Group (2003), for diagnosing PCOS, a woman must show two of the following three criteria:²

1. Irregular menstruation or anovulation
2. Clinical and biochemical signs of hyperandrogenism.
3. Enlarged ovaries with a volume ≥ 10 ml; 12 or more follicles in longitudinal and anteroposterior diameter each. The multiple cysts measuring 2-9 mm cysts are arranged peripherally.

It is important to remember that polycystic ovaries are not a necessary feature of PCOS and also that many of these women with PCOS are not the ones with polycystic ovaries. A chance finding of polycystic ovary on ultrasound evaluation should not be considered as PCOS unless it is corroborated with clinical evidences. In a case of PCOS, androgen excess may be with or without skin manifestations. Approximately, 50% women with PCOS are obese and tend to have an android pattern of obesity.³

Chronic anovulation may present as irregular menstruation or amenorrhea. It is not essential to document anovulation by ultrasound or by hormonal assay, (progesterone measurements) in the presence of clear clinical history. PCOS occurs in 85- 90% of women with oligomenorrhea and in 30-40% of women with amenorrhea.⁴ Anovulation in women with PCOS is associated with steady state levels of hypergonadotrophic hyperestrogenemia. Constant exposure of estrogen leads to proliferation and hyperplasia of the endometrium and this can cause unpredictable episodes of vaginal bleeding. Unexposed estrogen exposure can be confirmed by progesterone withdrawal test done after a negative urine pregnancy test.

Gonadotropins, androgens, and ovarian steroids in PCOS

Women with PCOS have higher mean concentrations of leutinizing hormone (LH), increased bioactivity of LH and low –normal levels of follicle stimulating hormone.⁵ The precise mechanism(s) responsible for enhanced LH secretion in PCOS are not completely understood, although, studies have demonstrated a potential influence of hypothalamic gonadotropin releasing hormone (GnRH) activity and ovarian steroid feedback.⁶ Although in *in vitro* studies, insulin has been implicated as a potential regulator of LH secretion in PCOS in dose dependent manner, the similar results have not been found in vivo studies.^{7, 8} Pulsatile LH

release and gonadotropin responses to multidose GnRH were similar prior to and during a 12-h euglycemic – hyperinsulinemic clamp.⁹ It was thought that lack of insulin effect may result in insulin resistance, which is a common feature of PCOS.¹⁰ However, it was later demonstrated that even after improvement of insulin sensitivity with insulin sensitizers, like; pioglitazone treatment, there was no difference in baseline LH values, LH pulsatility, or maximally stimulated percent of LH increment following GnRH with or without insulin infusion in women with PCOS.¹¹ Although a LH:FSH ratio of >2 was part of the diagnostic criteria for PCOS, it was observed by Arroyo et al¹² that obese women with PCOS do not necessarily have elevated LH levels. Therefore, a normal LH level or LH:FSH ratio does not rule out a diagnosis of PCOS. Currently, the LH:FSH ratio is not included in the diagnostic criteria of the PCOS.

Under the influence of low but constant levels of FSH, multiple ovarian follicles are stimulated which do not achieve maturation. The life span of the follicles get extended to several months, leading to multifollicular cysts. These leutinised follicles are arrested in response to constant and relatively high levels of LH that provide a constant supply of steroids. Whereas an atretic follicle deficient in aromatase activity may become an androgenic follicle. Cultured follicular cells from the small follicles of polycystic ovaries produce small amounts of estradiol but show a dramatic increase in estrogen production when stimulated by FSH or Insulin-like growth-factor-1(IGF-1).¹³ FSH therapy induces a larger number of follicles to develop in women with PCOS as compared with other women with infertility without PCOS.¹⁴ And hence, there is the validity in proposition that a deficient *in vivo* ovarian response to FSH, possibly due to impaired interaction between signaling pathways associated with FSH and IGF-1, may be a key event in the pathogenesis of anovulation in PCOS.

The other problem hyperandrogenism is usually suggested by the presence of hirsutism (occurring in approximately 80% of PCOS sufferers) and it can be documented by measuring androgen levels in the blood. In PCOS, free testosterone is the most frequently elevated steroid in the blood. Circulating levels of total testosterone, androstenedione and dehydroepiandrosterone (DHEA) are also elevated. In obese women with PCOS sex hormone binding globulin (SHBG) levels are decreased (the effect of obesity *per se*) and this leads to an increase in free testosterone levels. Furthermore, insulin is a negative regulator of the production of SHBG by the liver, and SHBG levels are decreased in hyperinsulinemic conditions such as the metabolic syndrome and visceral obesity.¹⁵ Besides the level of DHEA Sulfate is also elevated in blood and

are exclusively secreted by the adrenal glands, the mechanism of which remains elusive. However, insulin and IGF-1 have been shown to upregulate adrenal 17-hydroxylase and 17, 20- lyase activity.¹⁶

PCOS, insulin resistance inflammation, and cardiovascular disease

Insulin resistance (IR) has been regarded as a silent condition which is known to be associated with an increased incidence of cardiovascular disease (CVD) and atherosclerosis and now it is considered to be inflammatory disorder.¹⁷ IR has been associated recently with increased levels of inflammatory mediators in the blood.¹⁸ Therefore, studies have been conducted to review the levels of inflammation in PCOS. Gonzalez¹⁹ et al. noted increased levels of tumor necrosis factor α , In cytokine that causes insulin resistance and is secreted by adipose tissue in women with PCOS compared with controls. Lean women with PCOS have higher TNF- α level than lean normal women while the levels were similar in obese women with PCOS and obese controls. Kelly et al. noted significantly increased levels of C-reactive proteins (CRP) and tissue plasminogen activators (tPA) in women with PCOS compared with healthy weight matched controls.²⁰ However when adjusted for insulin sensitivity, CRP was no longer significantly different between groups but the difference in tPA levels remained. Women with PCOS have been shown to have higher plasminogen activator inhibitor type-1(PAI-1); however, the levels were not significantly different from controls.²¹ Besides, in one study, PA-I levels were not significantly different from controls when adjusted for body mass index (BMI).²²

While the different studies suggest that PCOS is associated with a state of increased inflammation; as yet clinical studies have not shown increased rate of cardiovascular disease in PCOS.²³ However, the beneficial effect of drugs thiazolidinediones and metformin is considered partly due to the decrease in the inflammatory response associated with their uses. Troglitazone has been shown to reduce PAI-1 levels and improve endothelial – dependent vasodilation in women with PCOS may be partly due to the decrease in inflammation caused with its use. In addition, metformin too, has been shown to decrease PAI-1 and CRP levels in PCOS patients.^{24,25}

Insulin Resistance and PCOS

Burghen²⁶ et al. in 1980 noted a significant positive association between insulin, androstenedione, and testosterone levels among women with PCOS. Subsequent studies confirmed insulin-resistance to be the cause of hyperandrogenism. According to an

estimate about 20-40% of women with PCOS have impaired glucose tolerance, which is approximately 7-times higher than the rates seen in age and weight matched control.¹⁰ In addition, the prevalence of type 2 diabetes is increased in women with PCOS compared with women without PCOS (15% v/s 2.3%)²⁷. Lean women with PCOS have lower rates of carbohydrate intolerance. However, carbohydrate intolerance in lean women with PCOS have higher rates than weight- and age - matched controls. Thus, PCOS is associated with insulin resistance independently of total or fat-free body mass. Obese women with PCOS are more insulin resistant than obese non –PCOS or non –obese women with PCOS.^{10,28} Ehrmann²⁹ et al showed pancreatic α -cell dysfunction in a subset of women with PCOS. This subset of women is likely to have the highest risk of developing carbohydrate intolerance and type 2 diabetes. The Rotterdam Consensus Panel recommend oral glucose tolerance tests for obese women with PCOS.² In a study by Peppard³⁰ et al (2001), among women with type -2 diabetes, 8 were found to have PCOS.

The first step in the action of insulin involves binding to the cell surface receptor. Insulin resistance is characterized by a post receptor defect in the action of insulin, the cause of which is as yet uncertain.³¹ After insulin binding the receptor undergoes auto-phosphorylation on specific tyrosine residue (accomplished by Insulin Receptor Tyrosine Kinase [IRTK]). The activated receptors then activates insulin receptor substrates (such as IRS-1,2,3) that in turn bind to signaling molecules such as phosphatidylinositol-3) kinase and activate downstream signaling leading to insulin- mediated glucose transfer.³² Abnormalities in both IRTK activity and in mediators distal to the receptor are present in insulin resistant states. Serine phosphorylation of the insulin receptors decreases IRTK activity³³. This is the probable mechanism of TNF- α induced insulin resistance, since serine phosphorylation of P450c17- α hydroxylase (the key regulatory enzyme of androgen biosynthesis) increases enzyme activity leading to androgen biosynthesis.^{34,35} Serine phosphorylation has been noted to associate with decreased IRTK auto-phosphorylation. It is possible that a single defect (serine phosphorylation) can produce both insulin resistance and hyperandrogenism in a subgroup of PCOS women.³⁶ In the study by Lin³⁷ et al., insulin stimulated lactate production in granulosa-lutein cells was reduced in women with PCOS as compared to those women who were normal ovulatory. *In vitro*, human theca cell studies have shown that insulin has direct stimulatory effects on ovarian steroidogenesis.

Similarly, Nestler³⁷ et al. showed that insulin produced a greater increase in androgen production by theca cells isolates from women with PCOS compared with

subjects without PCOS, and that this effect was mediated specifically through the insulin receptor rather than through the IGF receptor cross-talk. There are some data to suggest that insulin enhances the effect of LH on pre-ovulatory ovarian follicles causing premature activation and subsequent follicular arrest.³⁸

Hence, it is suggested, that the hyperinsulinemia (due to insulin resistance) drives the LH effects on ovarian theca cells to cause androgen excesses that are intrinsically programmed to produce more androgen.³⁹ Excess androgens are known to interfere with the process of follicular maturation, thus, inhibiting ovulation and adding to the population of arrested follicles.⁴⁰ It has been postulated that PCOS ovaries are more resistant to the metabolic effect of insulin than to the steroidogenic effects.¹

It is known that insulin resistance has been associated with increased levels of inflammatory mediators in the blood.¹⁸ Recently; it has been shown that in response to the hyperglycemia, the generation of reactive oxygen species from mononuclear cells (MNCs) is increased in PCOS independently of obesity⁴⁰. In addition, intranuclear and inhibitory nuclear factor- κ B increase and decrease the number of MNCs respectively, independent of obesity⁴¹. This has been speculated to be a cardinal inflammatory signal that contributes to the induction of insulin resistance and hyperandrogenism in PCOS. Although, further studies are needed to clarify selective insulin resistance phenomenon.

Role of insulin sensitizers in PCOS

Metformin

Metformin is biguanide that is used to reduce plasma glucose concentrations in type 2 diabetics. In these patients, metformin does not lead to weight gain and can induce weight loss in some. Metformin primarily works by reducing hepatic glucose production, and inhibiting gluconeogenesis both directly and indirectly (by decreasing free fatty acid concentrations)^{42,43} There are some data to suggest that metformin has a favorable effect on body mass index, menstrual cyclicality and ovulation induction in women with PCOS. Studies have shown reductions in androgen levels and improvements in ovulation when metformin was given for a duration of 10-24 weeks. However, these effects were secondary to weight loss.⁴⁴ In addition; metformin has been found to reduce the high rates of gestational diabetes in those with PCOS.⁴⁵

Thiazolidinediones (TZD)

The thiazolidinediones are the peroxisome proliferator-activated receptors (PPARs) agonists. The PPARs are a subfamily of the 48-member nuclear α -receptor superfamily and they regulate gene expressions in response to ligand binding. The putative ligand mediated activation of PPAR- γ 2 by troglitazone (TZD) impairs androgen and stimulates progesterone biosynthesis in primary cultures of porcine theca cells by blocking the expressions of the cytochrome P450-17- α hydroxylase / C17-20 lyase gene and cytochrome P protein phosphorylation, which decreases the LH-insulin driven theca cell androgen production.^{47,48}

In clinical studies, TZDs lower fasting and post prandial glucose concentration.⁴⁹ Insulin concentration decreases in most studies. Such changes indicate that TZDs act as insulin sensitizers. Treatment with TZDs, like, troglitazone, for 3-6 months increases insulin stimulated glucose uptake in peripheral tissues.^{50,51} In similar studies, TZDs increase hepatic sensitivity to insulin i.e, ability of insulin to suppress endogenous glucose production, and insulin sensitivity in adipose tissue (measured from the ability of insulin to suppress free fatty acid concentrations).⁵²

In women with PCOS, TZDs have been shown to improve androgen levels, ovulation rate and enhance insulin sensitivity.

Conclusion and recommendation

As yet, etiopathogenesis of PCOS remains unsettled. Deregulation of steroidogenesis has been associated with insulin resistance, though; insulin resistance is not the part of the diagnostic criteria for PCOS. Weight loss is known to be helpful in the improving insulin resistance, but it is difficult to achieve and retain. Besides, a large number of women with PCOS are lean but insulin resistant. Antiandrogen therapy in PCOS is used for control of symptoms. Oral contraceptive hormones are used for regularization of endometrial shedding and protection. Induction of ovulation is offered to those who seek treatment for infertility. Role of insulin sensitizers are unique in PCOS due to the fact that they offer to the sufferer of PCOS both metabolic and gynaecologic benefits. And so, PCOS should be recognized as an indication for TZDs and metformin treatment, in view of insulin resistance in them.

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