IJBPAS, August, 2026, 15(8): 3671-3684

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

INSULIN RESISTANCE IN PCOS AND ITS EFFECTS ON METABOLIC HEALTH AND FERTILITY

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Received 26th June 2025; Revised 10th Aug. 2025; Accepted 12th Nov. 2025; Available online 1st Aug. 2026

https://doi.org/10.31032/IJBPAS/2026/15.8.10371

ABSTRACT

The complex endocrinology disorder known as PCOS, which stands for polycystic ovarian syndrome impacts an enormous proportion of reproductive-age women. A variety of clinical symptoms, including as irregular menstruation, anovulation, infertility, hyperandrogenism, and Metabolic conditions including adiposis and type 2 diabetes are caused by hormonal imbalances, insulin resistance (IR), and ovarian dysfunction. A hallmark of PCOS, impaired insulin sensitivity plays a significant part of the pathophysiology of the condition and its related consequences, such as metabolic disorders, endometrial cancer, and infertility. The review highlights the significance of early detection and treatment to reduce PCOS's long-term health hazards. It concludes by emphasizing the need for personalized, multidisciplinary treatment strategies and further research to fully elucidate PCOS pathophysiology and develop targeted therapies.

Keywords: Insulin resistance (IR), Hyperinsulinemia, Ovarian Dysfunction, Endometrial Cancer

INTRODUCTION

Among women of reproductive age, PCOS is a prevalent and intricate endocrine disorder. It is typified by hyperandrogenism, metabolic problems, and chronic anovulation, all of which lead to infertility. PCOS has a negative effect on reproductive health, impairing folliculogenesis and raising the incidence of comorbid conditions such endometrial cancer, type II diabetes, and hypertension. It is commonly linked to obesity. It has been suggested that inulin-type fructans (ITFs) have a beneficial effect on risk factors related to metabolic diseases. However, it is yet unknown if ITFs can help control PCOS by changing testosterone levels and impaired insulin sensitivity **[1]**. One of the primary reasons for PCOS is impaired insulin sensitivity, which leads to hyperinsulinemia and an overabundance of ovarian androgen production. Adolescents with PCOS and obesity can benefit from weight loss, individualized nutritional therapies, and lifestyle changes. Dietary supplements and medical nutrition therapy can improve reproductive function and reduce symptoms. In order to restore ovulation and fertility, early nutritional intervention is recommended. Although the fundamental causes of the differences in insulin action between various organs and signalling pathways in PCOS are not entirely understood, they might be connected to the varied functions of IRS-1 and IRS-2 in insulin signal transduction **[2]**. Insulin resistance has been observed in obese patients with polycystic ovarian syndrome who also had acanthosis nigricans. These results imply that high LH and testosterone levels may be partially responsible for the hyperinsulinemia seen in PCOS patients, suggesting a possible post-receptor malfunction.

1) The pathophysiology of insulin resistance in polycystic ovarian syndrome:

Impaired insulin sensitivity in polycystic ovarian syndrome has a complicated etiology. In PCOS, a hereditary genetic disorder with a variety of manifestation forms that manifests early in life, metabolic alterations take place prior to reproductive problems. Insulin resistance (IR) is a primary observable trait of PCOS **[3]**. Impaired insulin sensitivity is made worse by obesity. An improper reaction to insulin in peripheral tissues that are metabolically active, like skeletal muscle and adipose tissue, is the cause of the innate impaired insulin sensitivity. Hyperinsulinemia seen in PCOS **[4]**. Major impairments in insulin secretion are linked to a family history of type 2 diabetes mellitus.

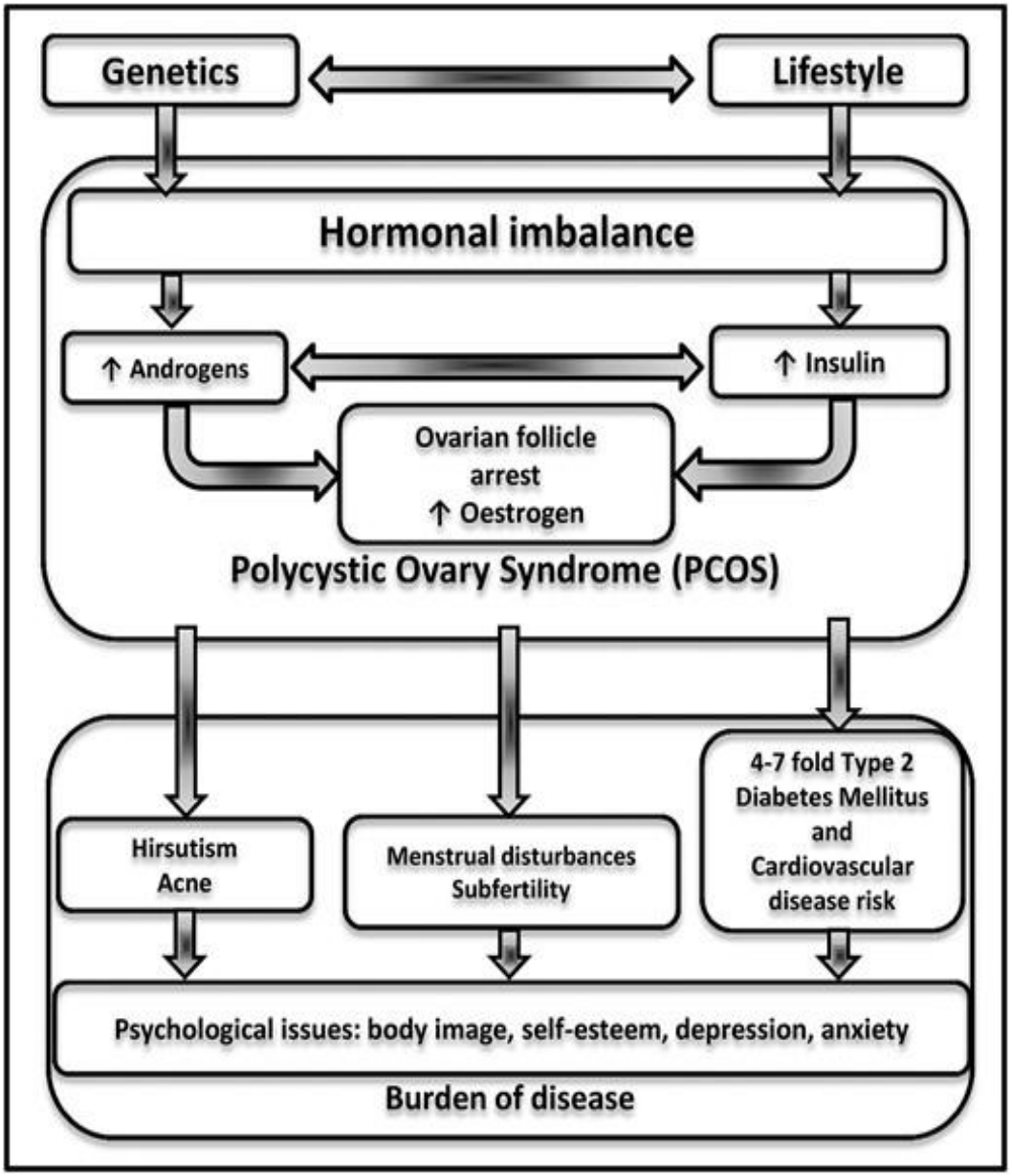

Figure 1: The aetiological, hormonal, and clinical characteristics of polycystic ovarian syndrome (PCOS)

Figure 1: The aetiological, hormonal, and clinical characteristics of polycystic ovarian syndrome (PCOS) are illustrated in this diagnostic flow chart [Teede HJ Med J Aust 2011].

(T2DM) **[5]**. While adiponectin has an insulin-sensitizing action, other substances, such visfatin, may activate the insulin receptor and show insulin-like activity. A PCOS-like phenotype may develop in the Mid-pregnancy, raising the risk of miscarriage **[7]** and it also triggers the activation of the mechanistic Target of Rapamycin (mTOR), which regulates the synthesis and destruction of proteins

1. **Hyperinsulinemia and Ovarian Dysfunction:**

Nevertheless, diagnostic criteria and genotyping methods have an impact on the genetic evaluation of insulin-related genes

[8]. A key component of PCOS pathogenesis is hyperinsulinemia brought on by tissue impaired insulin sensitivity. High levels of ovarian androgen are one of the primary features of PCOS. While the action of insulin on steroid production remains unchanged, Luteinized granulosa cells isolated from the ovaries of women with classic PCOS phenotypes demonstrate a significant decrease in the influence of insulin on glucose metabolism **[9]**. One significant metabolic factor linked to diurnal insulin exposure is fasting insulin. The tolerance to insulin and β-cell function are assessed using the hyper insulinemic-euglycemic clamp. Insulin sensitivity is not assessed, but the ability to secrete insulin in response to glucose is. The growth arrest of antral follicles after they reach a diameter of 5 to 8 mm is a distinctive sonographic appearance of the ovary in PCOS. Follicle growth inhibition results from terminal differentiation brought on by luteinizing hormone's (LH) early activation of granulosa cells **[10]**. It is thought to have an impact on several metabolic pathways, including lowering body mass index (BMI), inhibiting hepatic glucose output and gluconeogenesis, and decreasing glucose absorption **[11, 12, 13]**. Other extra-ovarian pleiotropic effects of hyperinsulinemia include reduction of hepatic sex hormone-binding globulin synthesis **[16]**, stimulation of adrenal P450c17α activity [14], and augmentation of LH pulse amplitude (as shown in rodent models) **[15]**.

2.Molecular Mechanisms of Insulin Resistance:

Insulin Resistance Molecular Mechanisms Insulin action and secretion abnormalities are part of the pathogenesis of type II diabetes **[17]**. Polycystic ovarian syndrome and resistance to insulin, about 5–10% of women who are of reproductive age suffer with pcos, an endocrine and metabolic condition marked by hormonal abnormalities that show up clinically as hyperandrogenism **[23,24]**. Insulin's molecular mechanism in PCOS has been thoroughly explained.

• Insulin attaches itself to the target cell's plasma membrane's insulin receptor (INSR):

Insulin Resistance (IR)-Related Human Diseases impaired insulin sensitivity, a condition where higher-than-normal levels of insulin are required for a normal response, directly leads to hyperinsulinemia as well diminished tolerance to glucose **[18]**. Although diabetes and obesity were covered in the preceding part, the main focus of this section is a summary of other similar metabolic disorders in humans.

• Insulin resistance and fatty liver disease (MAFLD) linked to metabolic (dysfunction):

One of the most common liver illnesses in the world is non-alcoholic fatty liver

disease (NAFLD) **[19]**. Serum free fatty acid (FFA) levels in liver cells that are too high appear to result in lipotoxic damage. **[20]**. By preventing lipogenic and esterification processes, ChREBP deficiency ameliorates insulin resistance and hepatic steatosis **[21,22]**. Therefore, MAFLD and insulin resistance may be successfully reduced by inhibiting de novo lipogenesis (DNL) and associated pathways. Increased hepatic gluconeogenesis is the main cause of fasting hyperglycaemia in individuals with diabetes mellitus type II.

3.The Effects of Inflammation and Obesity on Insulin Resistance:

A major homeostatic system is formed by the close relationship between metabolic regulation and the immunological response. Cardiovascular illness, fatty liver disease, and type II diabetes, and other metabolic problems linked to obesity can result from malfunctions in this system. The mechanisms of obesity-induced inflammation and the immune system's participation in the mechanism of diabetes and insulin resistanceare the main topics of this paper's exploration of the connection between Excess body weight, inflammation, and Impaired insulin sensitivity. Obesity can be caused by consuming too many nutrients and allowing them to build up in adipocytes **[16]**. Impaired insulin sensitivity and the Effects of Obesity and Inflammation Larger adipocyte sizes, adipose tissue expansion, and changes in pro-inflammatory cytokines are all results of increased fat deposition in adipose tissue in obesity. Interestingly, it has been shown that insulin resistance in obese animals fed a high-fat dietcan be reduced by heterogeneously deleting the inflammatory signalling intermediate IKK-β **[25]**. Through a direct interaction with INSR, SOCS3 reduces insulin-stimulated glycogen production in cultured myotubes and inhibits IRS1 tyrosine phosphorylation **[26]**. Immune cell infiltration and alterations in the liver's cytokine production in response to long-term fat exposure are the causes of insulin insensitivity **[27, 28]**. Insulin insensitivity and Inflammation Larger adipocyte sizes, adipose tissue expansion, and alterations in pro-inflammatory cytokines are all consequences of obesity's increased fat deposition in adipose tissue. Interestingly, insulin resistance in obese animals fed a high-fat diet is reduced when the inflammatory signaling intermediate IKK-β is heterogeneously deleted **[25]**. Through its direct interaction with the INSR, SOCS3 reduces insulin-stimulated glycogen production in cultured myotubes and inhibits IRS1 tyrosine phosphorylation **[26]**. Insulin resistance is linked to immune cell infiltration and modifications in the liver's cytokine production as a result of long-term lipid exposure **[27,28]**.

2)Insulin Resistance and Its Impact on Fertility in PCOS

The Effect of Insulin Resistance on PCOS Fertility a specific post-binding impairment in signal transduction is responsible for insulin insensitivity in PCOS. Insulin hypersecretion helps patients with insulin-resistant PCOS maintain normal blood glucose levels, which may put them at risk for type 2 diabetes mellitus and beta cell depletion **[36]**. The insulin receptor and insulin receptor substrate (IRS)-1 are constitutively more serine phosphorylated, which prevents metabolic signalling **[29, 30]**. A decreased sensitivity or reactivity to the metabolic effects of insulin is a common characteristic of insulin resistance (IR) **[31]**. PCOS-afflicted infertile women have higher fasting insulin levels, and the ensuing hyperinsulinemia plays a role in the development of reproductive diseases **[32, 33]**.

i)Anovulation and Ovarian Dysfunction:

Severe insulin insensitivity and ovarian hyperandrogenism are commonly observed in women who have pathogenic variants in the gene encoding the insulin receptor (INSR), autoantibodies against the insulin receptor, or genetic or acquired forms of lipodystrophy syndromes, even when obesity is not present **[34]**.

ii)Endometrial Health and Cancer Risk:

Endometrial Health and the Risk of Cancer Women with PCOS may be at higher risk for some types of cancer due to their changed metabolic and hormonal settings. Increased estrogen production, insulin insensitivity, and inflammation may be linked to endometrial cancer risk in postmenopausal women who are overweight **[35]**.Chronic systemic inflammation and elevated ROS, common in obese patients, are widely considered to be the underlying factors of pathophysiology carcinogenesis in this group of people **[36]**.Furthermore, many studies show that obesity is a risk factor for endometrial cancer and all gastrointestinal cancers, including pancreas, liver, ovary, breast, and kidney **[37]**.

iii)Oxidative Stress and Fertility:

By aggravating impaired insulin sensitivity and interfering with steroidogenesis, oxidative stress plays a pivotal role in the pathophysiology of PCOS. This, in turn, hinders follicular growth and plays a part in anovulation and infertility.

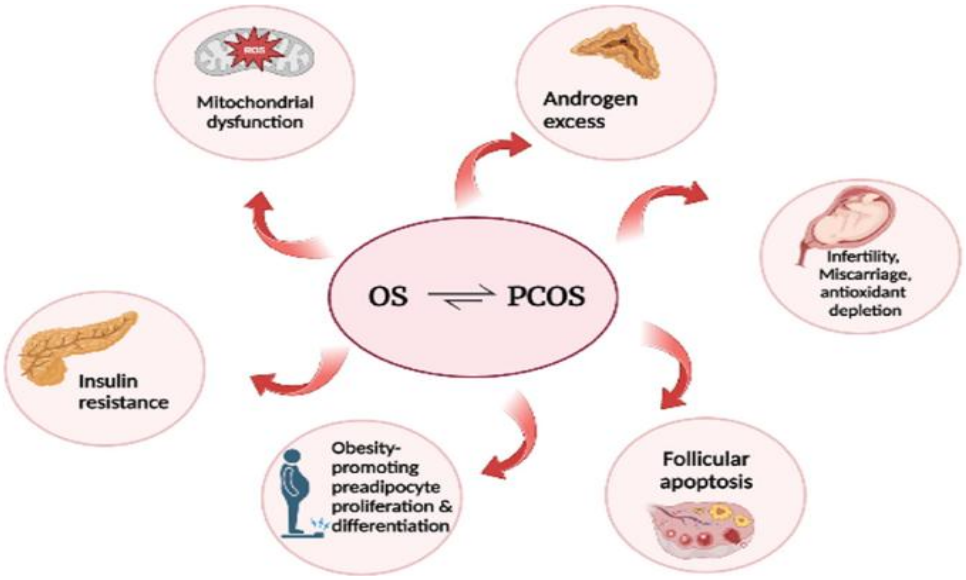

Figure 2: Diagrammatic representation of the role of oxidative stress (OS) in PCOS with main etiological factors and their interaction. Figure was generated using Bio Render software [Grymowicz M, *et al.* Int J Mol Sci. 2021]

Fertility and oxidative stress pose serious global health and social issues. Ovulation and pelvic tube problems are the main causes of infertility in women. An increased risk of infertility and irregular menstruation can result from endocrine variables that interfere with egg formation, ovulation, and endometrial receptivity at different stages. These factors include luteal insufficiency, hyperprolactinemia, polycystic ovarian syndrome, and thyroid dysfunction. Furthermore, obesity is regarded as a separate risk factor for female infertility and can reduce fertility by altering the metabolism of fat and insulin **[38].** An imbalance between the body's oxidative and antioxidant systems is a hallmark of oxidative stress (OS). Reactive oxidative material buildup can harm DNA and proteins, induce lipid peroxidation, and ultimately lead to cellular failure **[39]**. A natural substance called AOX shields live cells from ROS's damaging effects and oxidative damage **[40]**.

4)Insulin Resistance Management in PCOS

Improving metabolic health and fertility outcomes in polycystic ovarian syndrome requires addressing impaired insulin sensitivity. IR in PCOS individuals is now managed using a variety of pharmacological approaches.

Metformin:

Numerous studies have demonstrated that metformin improves menstrual cycles, restores ovulation, lowers weight and metabolic diseases, and even increases the likelihood of becoming pregnant **[41]**. Metformin has been shown time and time again to improve menstruation frequency, reduce weight, drop T levels, raise sex hormone-binding globulin (which lowers

bioavailable T levels), and make pregnancy easier **[42]**. Metformin-induced benefits persisted for up to 26 months, according to one long-term trial **[43]**.

Lifestyle Modifications:

Even if there are no appreciable changes in glucose tolerance, guidelines advise women with PCOS who have low insulin sensitivity to immediately begin insulin sensitivity treatment and modify their lifestyle **[44]**. Sleep management should be a part of lifestyle changes for women with PCOS because sleep deprivation is linked to an increased risk of IR, obesity, and type 2 diabetes **[45]**.

Incretin-Based Therapies:

Incretin-based medications are now used mostly to treat type 2 diabetes, although studies have shown that they may also be used to treat other illnesses. Incretin-based therapies may be used in the future to treat patients with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) **[46]**. In light of these factors, it would be wise to lower insulin levels pharmacologically in addition to implementing the necessary lifestyle modifications, particularly in women with PCOS who exhibit hyperinsulinism following oral glucose consumption. Although metformin reduces hepatic gluconeogenesis, it has been shown to directly affect ovarian steroidogenesis in granulosa cell cultures **[47]**.

laparoscopic ovarian drilling (LOD):

Surgical Procedures Women with PCOS, particularly those who do not react to drugs like clomiphene citrate, can benefit from laparoscopic ovarian drilling (LOD), a less invasive surgical procedure. Ovulation and pregnancy rates are greatly increased by this treatment, which entails producing multiple tiny punctures on the ovarian surface **[48]**. The method used kpr(such as laser or electrocoagulation) and the patient's unique traits can affect how well LOD works. Through a variety of methods, laparoscopic ovarian drilling (LOD) promotes ovulation in women with PCOS. It restores the hypothalamic-pituitary-ovarian axis's natural feedback loop and permits the appropriate gonadotropin stimulation required for follicular maturation by reducing the amount of androgenic substrates that can be converted into estrogen. LOD also promotes follicular development and ovulation by lowering intraovarian androgen levels. The process further promotes follicular growth by lowering inhibin levels, which raise FSH secretion. Additionally, the heat damage brought on by LOD causes growth factors like insulin-like growth factor 1 (IGF-I) to be released, which increases the ovaries' sensitivity to FSH, promotes follicular growth and maturation, and eventually improves ovulation and fertility results **[49]**. These alterations after the

laparoscopic removal of the ovaries' androgen-producing stroma are explained by a number of theories: 1) The hypothalamic–pituitary ovarian axis feedback mechanism may be restored if the substrate available for peripheral aromatization to estrogen is reduced, enabling proper stimulation by gonadotropin of follicular development and ovulation; 2) follicular maturation and ovarian ovulation may be made possible by a reduction in intraovarian androgen; 3) a drop in inhibin levels may cause a secondary increase in FSH levels, which may promote follicular expansion and ovulation in conjunction with a decrease in local androgen levels4) In reaction to heat injury, the ovary releases several growth factors, such as IGF-I, which makes the ovary more sensitive to circulating FSH and promotes follicular growth and maturation **[50, 51]**.

CONCLUSION:

One of the main characteristics of polycystic ovarian syndrome is insulin resistance and plays a significant role in its pathophysiology, impacting both metabolic health and fertility. The mechanisms underlying IR in PCOS involve disrupted insulin signalling, elevated oxidative stress, and inflammation. In women with PCOS, management techniques that increase insulin sensitivity, such as metformin, lifestyle changes, and new treatments, can lessen the consequences of insulin resistance and enhance reproductive outcomes. Further research is needed to fully elucidate the complex molecular mechanisms underlying impaired insulin sensitivity in PCOS and to develop more targeted therapeutic approaches. A multidisciplinary approach combining endocrinological, metabolic, and reproductive interventions is likely to yield the best outcomes for women with PCOS. Early diagnosis and intervention are key to preventing the progression of metabolic complications and preserving fertility. As our understanding of PCOS pathophysiology continues to evolve, personalized treatment strategies tailored to individual patient profiles may become increasingly feasible, offering hope for improved management of this complex endocrine disorder.

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