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Review Article

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# Diagnosis and Management of Insulin Resistant Polycystic Ovarian Syndrome: A Simplified Review

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**Abstract:** Polycystic Ovarian Syndrome abbreviated as PCOS is one of the common leading endocrine syndromes in middle aged women. PCOS itself is a collection of metabolic risks and symptoms such as hyperandrogenism, infertility, hyperinsulinemia, dyslipidemia, ovulatory dysfunction, type 2 diabetes and endometrial cancer and increased blood pressure Some of these metabolic risks are the physiological drivers of the syndrome and one such risk is insulin resistance. Around 50-70% of the women diagnosed with PCOS are showing the symptoms of insulin resistance. Despite obesity, insulin resistance is seen in both lean and obese PCOS patients. But obesity may be part of the reason for insulin resistance in women with PCOS. Hence hyperandrogenism is more favoured in women with obesity. Although IR associated with PCOS is a common feature, dysregulation of the insulin activity is related to the pathogenesis of PCOS. This chronic condition will escort the syndrome to major metabolic disorders substantially increasing the risk for developing diabetes (prediabetes or type2 diabetes) and furthermore increased hyperandrogenism. Various tests have been developed to determine the insulin resistance like HOMA-IR, clamp techniques, glucose and insulin levels. In addition, till to date diverse advanced markers have been proposed in the scientific literature to diagnose insulin resistance, PCOS and their association. Further research into the basic fundamentals of the syndrome is necessary to manage the disorder. The purpose of this review article is to deliver the simplified view on insulin resistance PCOS for the better understanding of the etiology, symptoms, diagnosis and therapeutic management.

**Keywords:** Polycystic ovarian syndrome (PCOS), Insulin resistance, Endocrine disorder,Hyperandrogenism, Hormonal imbalance, Biomarkers, Hyperinsulinemia.

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# 1. INTRODUCTION

## *1.1. PCOS*

Polycystic ovarian syndrome (PCOS) is one of the most common endocrinological disorders in female individuals throughout the world. In 1935 Stein and Leventhal were the first to describe the Stein and Leventhal syndrome: A curable form of sterility, in which they have stated about the diagnosis and treatment procedures. Later on Stein and Leventhal syndrome is called as polycystic ovarian syndrome (PCOS).[1,2]

## *1.2. Why is polycystic ovarian syndrome (PCOS) a menace?*

PCOS as the name itself mentions, has many ovary cysts which conceptualize PCOS as an ovarian disease but it is not completely restricted to the ovaries, rather it is a whole body endocrine disorder.[3] In detail, PCOS is an imbalance of female sex hormones (Chemical messengers) associated with common symptoms such as irregular periods, insulin resistance, acne, infertility, unwanted hair growth, Obesity and hair loss. Symptoms of PCOS are noticed usually in the women during their middle age i.e. late teens and early 20s.[4] Mechanistically polycystic ovarian syndrome (PCOS) patients encounter an abnormally high release of Luteinizing hormone (LH) form the pituitary gland into the bloodstream disrupting the regular menstrual cycle. As a result, follicles do not mature (immature follicles) this causes the cessation of ovulation leading to infertility. More or less 50% of the women diagnosed with PCOS are estimated to be obese, PCOS can affect both obese and lean women referred as Obese PCOS and Lean PCOS. But reviews conducted by some researchers have stated that obesity may be a partial reason for insulin resistance and hyperinsulinemia followed by elevated androgen levels.[5] Since PCOS is considered to be a menace, further unmanaged symptoms will lead to cardiovascular diseases (CVS), abnormal hormonal rise; Hyperandrogenism, hyperinsulinemia, Insulin resistance, ovulatory dysfunction, type 2 diabetes, endometrial cancer and increased blood pressure.[6] One of the pivotal root causes to drive the PCOS condition is insulin resistance (IR).[7]

## *1.3. What exactly is Insulin resistance PCOS?*

Insulin resistance (IR) is a condition where, the cells which utilize insulin will become highly resistant to insulin i.e. the cells in muscles, fat and liver will no longer respond to the insulin hormone and all the insulin mediated pathways are obstructed when compared to those in the healthy volunteers.[8] Insulin is a messenger hormone that stimulates the cells in the body and activates them to take up the glucose molecules in the bloodstream to generate energy. In case of insulin resistant PCOS patients, the insulin produced by pancreas cannot further stimulate the cells; this condition will cause a hindrance in the energy generation along with an abnormal increase of insulin levels in the bloodstream. During IR PCOS early phase the blood glucose levels may be normal but there is an abnormal increase in the insulin levels due to insulin resistance. Both obese and lean PCOS patients are diagnosed with insulin resistance which is not only an associated symptom but also a vital driver of the syndrome. Common symptoms in patients with insulin resistance: tiredness, fatigue etc. But in case of IR PCOS these are not the only symptoms; abnormally high insulin levels will affect other organs in the body which will intensify the PCOS effect to a greater extent. Insulin resistance affects the ovaries in such a way that they produce increased levels of androgens/testosterone which is known as a male hormone (testosterone).[9,10] Elevated levels of these male hormones or androgens will cause varying symptoms which are not acceptable by the women enduring insulin resistance PCOS like male pattern baldness, unwanted facial hair growth, acne, acanthosisnigricans, binge eating, cravings for carbohydrates, increased risk of cardiovascular diseases (CVD), gestational diabetes, prediabetes followed by Type 2 diabetes. Most of the symptoms are unnoticeable hence diagnosis of the symptoms for insulin resistance and PCOS through regular check-ups and proper management are to be adopted to improve the condition and to increase the insulin sensitivity.

## *1.4. Diagnosis*

### *1.4.1. Accessible criteria for the diagnosis of PCOS*

According to National Institutes of Health (NIH) and National Institute of Child Health and Human Development (NICHD) criteria- 1990 diagnosis of PCOS is confirmed if the patient shows hyperandrogenism and ovulatory dysfunction.[11] Rotterdam criteria- confirm the diagnosis if a patient manifests any of the two symptoms like: hyperandrogenism, ovulatory dysfunction, abnormal hormonal levels.[12,13] Women with polycystic ovaries, ovarian dysfunction along with hyperandrogenism are PCOS affected according to Androgen Excess Society criteria- 2006.[14]

## *1.5. Clinical diagnostic tests to track the body's insulin levels*

### *1.5.1. Fasting blood glucose levels*

Fasting blood glucose value is the key factor for levels of insulin resistance in the body. As the patient becomes more insulin sensitive, the fasting glucose level is likely to decrease eventually one of the primary diagnostic parameters.

## *1.6. Glucose tolerance test*

Blood glucose levels will be measured at designated time intervals after the infusion of glucose to notice the cells uptake process of the glucose molecules in the bloodstream. If the glucose levels are even on rise when compared to normal, this may be one of the indications regarding increasing insulin sensitivity or becoming more resistant to insulin.

## *1.7. Glucose clamp techniques*

### *1.7.1. Hyperglycaemic clamp techniques*

This method is used to quantify the amount of insulin secretion (beta cell sensitivity to glucose). Glucose concentration is elevated above the basal level (125mg/dl) by continulously infusing glucose. Based on the negative feedback mechanism, hyperglycemic plateau is maintained by adjusting the infusion of different glucose concentrations. It is a reliable, sensitive and reproducible physiological method.

## *1.8. Hyperinsulinemic clamp technique*

Also referred to as euglycemic clamp method in which insulin

is continuously infused into the bloodstream and the blood glucose concentration is kept constant. Using these parameters insulin resistance is measured. This test is rarely used by clinicians but most widely used by the researchers to evaluate the effects of novel medications.[15]

### *1.9. Anthropometric measurements*

Blood pressure: An evidence based research shows that hypertension is an independent risk factor for insulin resistance. In most cases hypertension or high blood pressure is caused due to hardening of the blood vessels this develops resistance against the heart. Overtime hypertension can become life threatening because it affects the heart functioning and leads to stroke. Body weight: Ideal body weight is an essential component of gaining insulin sensitivity. Overweight/obesity will elevate the risk for most of the chronic diseases. Waist circumferences, Hip circumference, waist to hip ratio are few important anthropometric parameters

### *1.10. Biomarkers for IR PCOS Diagnosis*

#### *1.10.1. Insulin resistance markers*

#### *1.10.2. HOMA- IR*

In 1985 HOMA (Homeostatic model assessment) was elucidated as a computer based method to quantify the insulin resistance and beta cell function. HMO2 an updated version, by using Radioimmunoassay insulin, fasting plasma glucose, specific insulin and c-peptide concentration can determine the insulin resistance and beta cell function.[16,17]

HOMA IR = Glucose ×Insulin/2.25 mmol/L
HOMA IR = Glucose ×Insulin/405mg/dL

### *1.11. Haemoglobin A1c*

HbA1c is a biometric marker of average glucose control and it is typically used to diagnose prediabetes, type1 diabetes and type 2 diabetes. The lower the A1c value the better the blood glucose control the lower the risk for chronic complications. Lower A1c means a strong indicator of reduced insulin resistance but A1c is a measurement of average blood glucose level not the measurement of insulin sensitivity henceforth A1c is to be interpreted in context of other biomarkers.[18]

### *1.12. Circulating cytokine markers*

Research studies stated that circulating cytokines irisin, betatrophin and zinc alpha2- glycoprotein (ZAG), anti-Mullerian hormone (AMH), inhibin A (INH-A), inhibin B (INH-B), Insulin like peptide-3, act as biomarkers to diagnose the IR PCOS. Irisin and betatrophin levels are elevated andZAG levels are lowered when compared to healthy volunteers and PCOS patients.[19, 20]

### *1.13. Oxidative stress markers*

Superoxide dismutase enzyme activity (SOD) Malondialdehyde level (MDA), reduced glutathione (GSH).[21] A lot of studies have concluded that oxidative stress has a major effect on PCOS.

### *1.14. Inflammatory markers*

Tumour necrosis factor (TNF), C reactive protein, Interleukins (IL-6, 18), Serum amyloid A in acute inflammation phase elevation is a diagnostic feature in IR PCOS patients.[22-25] A study conducted in rodents has stated that adipose tissue derived TNF-α neutralization has improved the insulin sensitivity.[26] The increased levels of this mediator will indirectly down regulate the expression of glucose transport protein GLUT4.[27]

### *1.15. Management*

#### *1.15.1. Food*

Food habits can help to manage the symptoms of IR associated with PCOS Carbohydrates and sugar are not to be administered or to be administered in low quantity,[28] but during the syndrome intense cravings for carbohydrate and sugar can be balanced by pairing high proteins, fat and fiber diet with low carbohydrates diet.[29]

### *1.16. Supplements*

One particular supplement used to treat IR is inositol, it will help to increase the insulin sensitivity by converting to myo-inositol in the presence of glucose-6-phosphate thereby trans locating the GLUT4 protein to the cell membrane via PI3K /Akt pathway.[30,31] Research studies have found that inositol will help reduce the cravings for carbohydrates and sugars at the same ovulation become regular. Menstrual cycles will follow the order. They have also noticed that infertility can be treated.[32] Vitamin-D, Magnesium and zinc are few other supplements that are used to treat insulin metabolism in PCOS patients.

### *1.17. Rest*

When the body is subjected to resting phase as such, sleep and stress management can heal the body's condition.

### *1.18. Sleep*

A research paper has stated that short durations of sleep or without enough sleep can increase the risk of insulin resistance and might exacerbate IR if it is already present.[33] Setting a regular bedtime and meditation before the bed are recommended by doctors for sleep improvement.

### *1.19. Medication*

Metformin is the only and first biguanide insulin sensitizing drug.[34] But during 1996 a study has stated that metformin does not treat insulin resistance PCOS as the IR related to PCOS is different from the IR associated with diabetes.[35] From then on immense research has been carried out and stated that metformin is used to treat insulin resistance pcos and metabolic effects hence it is the most widely prescribed medication to treat insulin resistance PCOS. Glitazones such as Rosiglitazone, Troglitazone, Pioglitazone and diuretic like low doses of spironolactone are used as an alternative medication to treat insulin resistance in PCOS women. Rosiglitazone and Troglitazone are associated with side effects which are not reported during pioglitazone administration.[36,37] Pharmacological approved clinical agent Orlistat acts as a pancreatic lipase inhibitory drug to treat IR

PCOS and also has positive effect on obesity in PCOS patients.[38,39]

### *1.20. Novel Findings*

A recent study based on nano delivery system administered curcumin to treat Insulin resistance and pancreatic deficits in wistar rats and confirmed that the nanocurcumin restored PI3K/AKT/mTOR pathway as well as neutralized the oxidative stress markers and TNF-α levels.[40] GLUT4 upregulation plays a prominent role in the treatment of PCOS associated insulin resistance, herbal extracts like berberine and Salvia officinalis[41,42] are reported to target this particular protein. Few studies have reported that berberine is a promising isoquinoline alkaloid to treat IR PCOS [43], infertility.[44] and Hyperglycaemia.[45] Auxiliary blistering data added to the berberine checklist is up regulation of GLUT4 through inactivating MAPK pathway and PI3K/AKT activation by researchers.[46]

### *1.21. Source*

Literatures form Science direct, PubMed and Scopus guided the whole review process to explore the traditional and new discoveries. Wikipedia helped to gain the basic knowledge on the particulars.

## 2. CONCLUSION

Even after the availability of a handful of diagnostic and managing tools profound research is being carried out to disseminate the neoteric findings in PCOS associated with insulin resistance. Therefore proper diagnosis and management of the symptoms play a critical role in the successful treatment to prevent the risks associated with IR PCOS. Testing for insulin resistance in patients with PCOS is a necessary criterion in order to avoid the misdiagnosis of the syndrome. In the near futuremore research in the field of insulin resistance and its association with PCOS and further more reliable diagnostic procedures are needed for therapeutic approach of the syndrome.

### *2.1 Abbreviations*

PCOS- Polycystic ovarian syndrome, IR- Insulin Resistance, LH- Luteinizing hormone, FSH- Follicle stimulating hormone, CVD- Cardiovascular diseases, HOMA- Homeostasis Model Assessment.

## 3. AUTHORS CONTRIBUTION

Data regarding insulin resistance PCOS is gathered by Ms K.Bhavana and MsSamata S Patnaik while the article is drafted by Ms K.Bhavna. Dr. Ashok Krishnan has provided valuable keynotes for completing the article. In the ultimatum the entire document is reviewed by Mrs K. Sridevi and Dr. Ashok Krishnan and necessary amendments are made.

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## 5. CONFLICTS OF INTEREST

Conflict of interest declare none

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