

# Relationship between PCOS with Infertility and Insulin Sensitivity: A Review

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## ABSTRACT

This narrative review has brought forward the recent important findings of polycystic ovary syndrome (PCOS) which is regarded as a prevalent endocrinological and metabolic disorder with several clinical features. Treatment for PCOS differs according to the presenting problems, underlying cause, age and requirements of the individuals. The review has discussed the status of PCOS in India separately, its etiologies, diagnosis and updated points of management. The phenomena of Insulin Resistance and its management have been discussed by reviewing various published works and the pathophysiologic relationship between PCOS and infertility has been discussed in detail. The role of hyperinsulinemia and Insulin Sensitivity in PCOS is discussed in detail with the relevant pathophysiological mechanism. Overall, this review is clinically significant and has discussed the essential points of a multisystem disorder (PCOS).

**Key-words:** Insulin resistance, Infertility, PCOS, Polycystic ovary, Pathophysiologic relationship

## INTRODUCTION

Polycystic ovary syndrome or PCOS is one of the most prevalent endocrinological and metabolic disorders, characterized by various clinical features including excessive androgen production, menstrual abnormalities, hirsutism, etc. Although the etiology is mostly unknown many studies have brought forward that there is a relationship between this disorder and genetic and lifestyle factors. It is seen that females, who suffer from infertility also show higher incidences of psychiatric disorders and endometrial cancer as compared to females from general masses <sup>[1-10]</sup>. Yet the picture is still not clear if infertile women have greater chances of developing cancer of mammary glands and ovaries as well <sup>[7,8,10-20]</sup>. But one fact is well established that PCOS women are at higher risk (than

normal females) of acquiring cardiovascular disorders along with metabolic health complaints like diabetes <sup>[16,21-26]</sup>.

Polycystic ovary condition (PCOS) is one of the most commonly found endocrinological disorders among females of reproductive age, manifested by hyperandrogenism, irregular ovulation and ovulation. It is considered a metabolic disorder since it is associated with a high occurrence of insulin resistance (IR), dyslipidemia, obesity, and other metabolic abnormalities. The occurrence of PCOS can be as high as 18% in reproductive females <sup>[27]</sup> and those with PCOS have a higher risk of having infertility and other medical conditions <sup>[28]</sup>. Treatment for PCOS differs according to the presenting problems, underlying cause, age and requirements of the individuals. Those females, who are undesirous of being pregnant, are treated symptomatically to relieve them from menstrual irregularities, acne and hirsutism <sup>[25-28]</sup>.

**PCOS in India-** A study done on a population of 1000 females of South India <sup>[29]</sup>, aged between 18 to 24 years and comprising of both urban and rural population, revealed that the incidence of PCOS is rising in cities and

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the urban women are more prone to acquire PCOS by 0.1% as compared to the rural women. The study showed that the overall incidence of PCOS in South India was 6% (as per Rotterdam criteria). The study also revealed that the population of women was at less risk of developing PCOS owing to their less consumption of junk food and difference in lifestyle. Family history of PCOS, smoking, sedentary lifestyle, and stress is a few of the other factors found to be associated with PCOS [28,29].

**Etiologies, Diagnosis and Management of PCOS-** There are many causes of female infertility. Most common etiologies are found to be related to improper coordination of the hypothalamus-pituitary-ovarian axis. It is seen that the components of the reproductive system like ovaries and fallopian tubes and uterus should be optimized regarding their structure and function because to achieve a healthy and successful conception there should be synchrony in the anatomical and functional aspects of the components of the female reproductive system [30]. Contraception is more common in females of developed countries, or who have had many childbirths before, or those who are starting their family at a mature age. So using intrauterine birth control measures can cause infertility both due to inflammation and damage of fallopian tubes [31,32]. The study observed that there were 10.4% of those types of cases in which the cause of infertility could not be defined despite full screening of both the male and female partners and hence they were called infertility of unknown cause [33,34]. Other common causes of infertility include improper development, displacement, of the uterus, endometritis, atrophy and malignant neoplasm of the endometrium [34]. Infertility may also occur due to failure of the ovary to release the ovum at the proper time and abnormality regarding implantation after fertilization [35]. Another study showed that 20% of infertility occurs due to menstrual disorders which can be accompanied by metabolic abnormalities. It also established the role of the thyroid gland in hormone regulation of the Hypothalamus-Pituitary-Ovary axis (HPO axis). Both over and under-functioning thyroid glands are related to infertility. Besides this other lifestyle-related elements and habits like active and passive smoking [36-39] by females, stress, obesity, exposure to radiation and chemical agents are a few more causes resulting in infertility.

**Insulin Sensitivity and Its Management-** The state of systemic cellular response towards the hormone insulin which maintains the glucose clearance is referred to as Insulin Sensitivity (IS). Normal IS enables the cellular components of the body of efficient usage of glucose present in the blood thus reducing it there and maintaining a healthy and consistent glucose level in the blood. Insulin plays an important role to regulate and maintain the level of glucose in the bloodstream. The condition of when IS is reduced/ lowered is called Insulin Resistance (IR) [38-40]. Under this circumstance, the mechanism of glucose absorption by the cell gets impaired, leading to an increased sugar level (glucose spike) in the blood. Without proper treatment, this condition can predispose to Diabetes mellitus type II. Abnormal levels of Insulin can impose a serious negative impact on fertility and embryo-development in the early stages. Metabolic homeostasis is very important for the achievement and accomplishment of a successful pregnancy. Obesity and diabetes are some of the concerns of our modern lifestyle. In these conditions, there is the consumption of high calories, which may result in diminished reproductive capacity in females. Studies from bovine models have revealed [40] that both situations whether energy excess or energy deficit have associations with the level of insulin present in the body and cause the follicular fluids to deviate from the normal limits [41].

**Pathophysiologic Relationship between PCOS and Infertility-** PCOS is self-descriptive and suggests an ovary having multiple cysts. This clinical condition causes irregular menstrual cycle, amenorrhoea and hirsutism in females [42]. Recently the definition has expanded due to the incorporation of four different phenotypes [43] along with causes of monogenic causes of hirsutism and oligomenorrhoea, accompanied with baldness similar to that of males [44]. But the monogenic cause was soon terminated as studies on twins on small cohorts of mono- and dizygotic twin pairs revealed that PCOS is a polygenic disorder linked with the X chromosome and not an autosomal dominant or monogenic kind of disorder [45,46]. Another study established that there was a '72% variance in risk of PCOS' which exhibited genetic involvement [47].

Defects in the insulin signaling pathway have been found to have an association with PCOS [48]. PCOS can change the insulin gene expression pathway [49]. A different type

of pathway related to cellular oxidative stress has come up with a possible explanation of PCOS pathology<sup>[50]</sup>. Oxidative stress can also trigger hypergonadism<sup>[51]</sup>.

**Classification Based on Phenotype-** Recently, the definition of PCOS has become more elaborative and encompasses 4 types of PCOS phenotypes, namely A-D. According to the general rule hyperandrogenism, BMI<sup>[52]</sup>, irregular menses<sup>[53]</sup> are independent predictors indicating a metabolic malfunction. Rather ovarian morphology has a lesser role to play here.

**PCOS Phenotypes A and B-** Also called classic PCOS. Women with these subtypes suffer from irregular menstruation, increased insulin production and IR and are at greater risk of developing metabolic syndrome. These women are more prone to have obesity and atherogenic dyslipidemia<sup>[54]</sup>. They are at greater risk of developing hepatic steatosis, when compared with healthy controls<sup>[55]</sup>. The classic PCOS women additionally display an extravagant elevated amount of anti-mullerian hormone (AMH)<sup>[56]</sup>. Phenotype C is also called ovulatory PCOS and typically presents the features of slightly increased insulin, atherogenic lipids, and higher levels of androgens. It is found to be associated with hirsutism and impaired metabolic functions<sup>[57]</sup>.

In 2009, a study with cohort design mentioned that phenotype C is the most prevalent one<sup>[58]</sup>. Food, rich in oil and calorie, leading to increased accumulation of fat can be the possible explanation for Khan *et al.*<sup>[59]</sup>. Phenotype D is known as Non-hyperandrogenic PCOS and it is characterized by a normal level of androgen with slightly imbalanced overall endocrine status and minimal metabolic dysfunction<sup>[60,61]</sup> in comparison to healthy controls<sup>[62,63]</sup>. Non-androgenic hormones like Sex hormone-binding globulin (SHBG), T3, T4, decreased LH/FSH ratio have been found to have an association with PCOS type D, as compared with classic PCOS<sup>[64]</sup>. Usually, patients with PCOS type D experience consistent menstrual cycles with occasional abnormalities<sup>[65]</sup>.

But this classification is not universally accepted as PCOS is a multifaceted and complicated disease; there are few exceptions that can also be considered. A German study of different types of PCOS exhibited no noticeable differences in IR, dyslipidemia, or BMI<sup>[66]</sup>. Another study from Greece showed similar findings<sup>[66]</sup>, which has found IR in those patients whose BMI was found to be more than 25 kg/m<sup>2</sup><sup>[67]</sup>. Again, studies in Sri Lanka and Brazil

exhibited no such significant variation in metabolic syndrome in females suffering from PCOS<sup>[68,69]</sup>.

**Role of Insulin Sensitivity in PCOS-** Hyperinsulinemia causes virilization affecting granulosa cells (found in theca cells & small follicles) and can induce premature ripening of immature follicles mediated by Luteinising Hormone resulting in an ovulation<sup>[70-72]</sup>. This situation can be improved by employing insulin-sensitizing agents like the biguanide class of drugs (metformin) and thiazolidinedione derivatives<sup>[73]</sup>. Hyperinsulinemia has an antagonistic effect on the endometrium both functionally and environmentally. It is also one of the leading causes of failure of implantation<sup>[74]</sup>. This condition can be treated with metformin, which enhances insulin sensitivity. Metformin is a potent agent to improve functions of 'levels of glycodelin, which is an Insulin-like Growth Factor (IGF) binding protein. It can effectively maintain the blood supply in the spiral arteries during peri-implantation.

The efficacy of Metformin in treating infertility is due to its effects on the structural and functional maintenance of the endometrium and assistance in implantation of the developing embryo<sup>[72]</sup>. Studies have pointed out that 30–50% of women with PCOS are more vulnerable to pregnancy loss in the first 3 months, which is said to be three times greater than normal pregnant women<sup>[75,76]</sup>. Using Metformin as a medication can reduce insulin levels in blood regulates plasminogen activator inhibitor activity. Hence it can reduce the risk of failure of early pregnancy. Lifestyle change is one of the fundamental measures for improving reproductive performance in addition to treatment with insulin-sensitizing agents. The inclusion of the Metformin regimen leads to the decreased rate of early pregnancy failure to 8.8% as compared to the control group with PCOS having the rate of early pregnancy loss is up to 41.9%<sup>[77]</sup>. Metformin regimen not only improves IS but also reduces the chance of losing an early pregnancy in patients with PCOS. Metformin is non-teratogenic and hence is safe for pregnant women<sup>[78]</sup>.

**Current Management Approaches of Improving Insulin Sensitivity-** For young women who have PCOS the primary line of treatment is helping them to achieve pregnancy resulting in a successful live birth. In such patients, the first line of ovulation-inducing drugs used commonly is clomiphene citrate (CC), letrozole (LZ), and

metformin<sup>[79]</sup>. CC is capable of inducing ovulation and it is anti-estrogen and non-steroidal<sup>[80]</sup>. LZ is a type of aromatase inhibitor and its function is to prevent the conversion of androgens (secreted by adrenal glands) to estrogens. Although better known for its anti-tumour properties, which can effectively treat breast cancer<sup>[81]</sup>. It additionally exhibits the properties of an ovulation induction agent. Metformin, a hypoglycemic drug that is generally used in treating diabetes<sup>[82]</sup> is also known for its features as an inducer of ovulation and improvement of pregnancy rate in women having PCOS<sup>[83,84]</sup>. A meta-analysis<sup>[85]</sup> found it to be less potent than CC. The beneficial effect of Metformin in PCOS is yet to explore. It might be possible that Metformin further develops insulin sensitivity (IS) in the liver and peripheral tissues, which might be the instrument clarifying its impact in further developing pregnancy in PCOS women. With the help of studies with larger samples, it has been established that insulin resistance is prevalent in almost 44%–70% of females with PCOS<sup>[86]</sup>.

Results extracted from familial aggregation studies reveal that PCOS can be inherited and that those gene variants that cause IR can be readily detected in PCOS patients. Other than this 'intra-uterine growth restriction (IUGR) and small for gestational age (SGA)' may result in the hypersecretion of glucocorticoids that increases the risk of developing obesity and hyperinsulinemia among children<sup>[87]</sup>. Under such situations when supra-physiological insulin was deployed it resulted in enhanced 'steroid-genesis, derange granulosa cell differentiation, with influence on the growth of follicle<sup>[88]</sup>. But, full assurance that drugs inducing IS in PCOS and help in getting them pregnant has not been achieved<sup>[89]</sup>. But according to another school of thought, various Randomized Control Trials (RCTs) brought forward that CC and other non-diabetic medicines are efficient and beneficial in IS and on the attainment of higher clinical pregnancy rate<sup>[90,91]</sup>.

About 5-10% of reproductive females have been found suffering from PCOS. Lifestyle change and reduction in body weight are vital to effectively managing PCOS. Hirsutism can be managed by using contraceptive pills, while the severe form of it will additionally need 'anti-androgens /estrogen-progestin therapy (Combined contraceptive pills or COCP). Another reason for ovulatory infertility reacts pretty well to clomiphene citrate when trailed with gonadotropins in minimal

dosages. Also, drugs that enhance insulin sensitivity have been seen to help in achieving good ovulatory performance. One such natural compound is inositol which is at par with metformin with the additional advantage of imposing lesser counter effects. Other natural and sustainable naturally occurring statins, like monacolin, can be used as mono or dual therapy (Myo-inositol) to reduce the hyperandrogenic levels in the sufferers with the least counter effects<sup>[92,93]</sup>.

Although Metformin is an effective line of treatment of PCOS for obese adolescents (also suffering from hyperandrogenemia) milder phenotypes of PCOS may not exhibit the similar pattern of IR thus presenting us the new insight that insulin-sensitizing drugs may not qualify as optimum therapy in all cases of PCOS and so the treatment should be targeted towards specific metabolic or reproductive problems<sup>[94]</sup>.

A recent study, Laganà *et al.*<sup>[95]</sup> have concluded that ingestion of insulin second messengers like Myo-inositol (MI) and D-chiro-inositol (DCI) can be beneficial to increase IS, as MI plays an important role in follicular gonadotropin pathways which coordinates and manages ovulation. MI/DCI ratio is tissue-specific and insulin is known to modulate it by aromatase this system loses its balance when the body shows signs of insulin resistance (IR), and hence epimerization of MI to DCI in insulin-sensitive tissues accordingly diminishes. This MI/DCI ratio in the ovaries is 100: 1, but its level decreases vividly and the causative reason behind this presence is an 'insulin-stimulated epimerase in hyperinsulinemic women with PCOS. Thus using Inositols have been seen as very fruitful in PCOS, as it brings about multi-faced improvement at the metabolic level, hormonal level refurbishes spontaneous ovulation. Studies on assisted reproductive technology have approved that ovarian stimulation parameters can be improved by inositol yet half-heartedly, thus further works on 'spontaneous and non-spontaneous fertility' need to be taken. Oral supplementation with MI, DCI, or their combination can improve Metabolic functioning and restoration of normal ovarian functioning in PCOS can be well achieved when they are exposed to oral dosages of MI/ DCI/ combination of both. The ideal MI: DCI ratio is 40: 1 encourages the success of fertility as an excess of DCI might be deleterious for oocyte development. Thus despite conflicting evidence, inositols stand as a promising treatment for PCOS<sup>[95]</sup>.



PCOS patients are much fragile to being obese and obesity [96] is known to disrupt their metabolic, endocrine, and reproductive functions. Many anti-obesity drugs like 'orlistat, sibutramine, and rimonabant can be incorporated into a regime of PCOS patients but except orlistat, the other two are out of circulation due to their harmful potentials and orlistat shines bright in the life of overweight and obese diabetic patients as it induced faster weight loss and rendered metabolic and cardiovascular benefits that were impossible to achieve through lifestyle changes alone [96].

## CONCLUSIONS

This review has discussed all the possible aspects of polycystic ovary syndrome (PCOS) whose prevalence has become clinically significant for conducting research. Many experimental studies are being conducted to bring new information and findings of PCOS. These newly emerged findings are updated from time to time. Clinicians need to remain updated with the several aspects of PCOS. The prevalence of this disorder is such that clinicians of the entire speciality should be informed regarding the aspects of PCOS. This multi-system disorder can affect several organ systems and the prognosis can be fatal if not managed effectively. The drug regimens are getting updated to make the prognosis better than ever. Early diagnosis and effective management are essential to bring a better prognosis and to manage any other chronic condition. The intention of this review article is the need of the hour for the medical community.

## CONTRIBUTION OF AUTHORS

**Research concept-** Soumee Das

**Research design-** Soumee Das

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