

## SYSTEMIC REVIEW

# Prediction a woman having Polycystic Ovary Syndrome (PCOS) those having Insulin Resistance (IR)

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## ABSTRACT

**Background:** "Polycystic Ovary Syndrome" (PCOS) has been identified as a hazard for growing diabetes. Although it indicates and symptoms of "Polycystic Ovary Syndrome" (PCOS) appear before the signs and symptoms of "Insulin resistance" (IR) first, According to an assumption "Insulin resistance" (IR) may have a part in developing PCOS instead of another factor. Insulin resistance caused by obesity modifies the function of the pituitary gland and hypothalamus in the brain, leading to an increase in the synthesis of androgenic hormones, which correlate to PCOS<sup>1</sup>.

**Aim:** To analyze outcomes of insulin resistance in women having polycystic ovaries

**Methodology:** A literature search was performed with the use of search engines. The following search engines provided the articles for this systematic review, PubMed, Medscape, NCBI, and Google Scholar. For article searching following keywords were used; Polycystic ovaries, insulin resistance.

**Results:** As a literature review of 45 articles and only 39 were included in this review, it is found that the Mean age of all subjects was 24-37 years. Obese females were 20-30 years and non-obese were 18-34 years. Insulin resistance occurs in 70-95% of females who were obese and had PCOS and 30-75% of females who were lean and developed PCOS. Hirsutism was observed mostly in obese patients diagnosed of having PCOS. Incidence of Amenorrhea was found higher in lean patients.

**Conclusion:** It is concluded that high insulin is not just a symptom of PCOS it's also one of the major drivers of this condition. Insulin resistance acts as a key factor of PCOS. It mostly occurs among people who are obese and had developed PCOS.

**Keywords:** (PCOS) Polycystic Ovary Syndrome, Resistance, Insulin

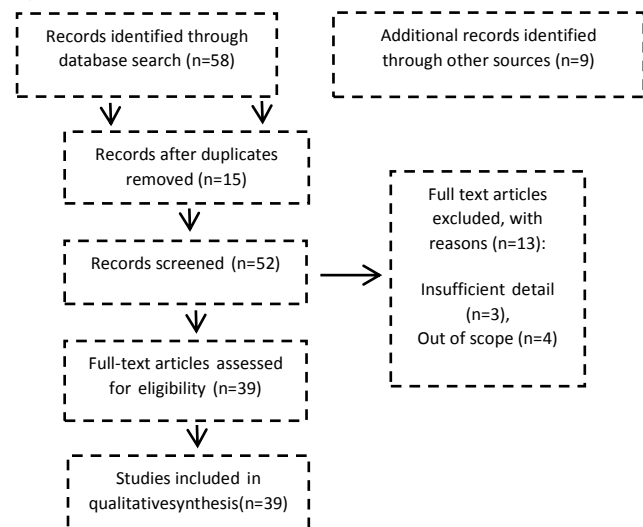
## INTRODUCTION

Leventhal and Stein initially had defined PCOS in 1935 as, hirsutism, oligo/amenorrhea and obesity, enlarged ovaries with numerous cysts, and thickened tunica. In women with anovulation, the original detection of PCOS was entirely based on the existence of thicker stroma on histological examination of bilateral ovaries, polycystic ovaries (PCO)<sup>2,3</sup>. The introduction of radioimmunoassay techniques as histological diagnosis, "serum biochemical markers" typical of PCOS, exalted aggregation of "luteinizing hormone" (LH), "androstenedione" (A) and "Testosterone" (T), minimum or regular proportions of "follicle-stimulating hormone" (FSH), and reduced "sex hormone-binding globulin" (SHBG) became alternative diagnosing technique in the 1970s<sup>4</sup>. According to "NIH/NICHD" standard, PCOS is a prevalent disease that affects 4%-8% of women of reproductive age<sup>5,6</sup>. According to several studies, the prevalence of PCOS differs and it relies on the diagnostic standard being used<sup>7</sup>. By the Inclusion of the studies, prevalence determined by Rotterdam criteria is 2-3 times higher than the occurrence determined by the NIH/NICHD requirement<sup>8,9</sup>.

However, the basic pathogenesis of the polycystic ovarian syndrome is uncertain; important symptoms include IR, aberrant, gonadotropin dynamics, and excess testosterone<sup>10</sup>. In contrast with insulin resistance, between 60% - 70% of women having PCOS are found overweight which is associated with IR<sup>11</sup>. High IR is found in females having PCOS than the obese females in public<sup>12</sup>. Early research suggested that individuals having PCOS had a much higher insulin response to an "oral glucose challenge" than skinny or less obese participants without polycystic ovary syndrome<sup>13</sup>. Dunaif et al, also found that there is a higher IR in patients having PCOS compared with control subjects was true for both obese and lean patients having PCOs<sup>14,15</sup>. PCOS also appears in 50% of the women having no extreme or awful growth of unwanted and unnecessary hair<sup>16</sup>. Acne has been found less prevalent in PCOS and not as frequent as hirsutism but it can also

be a marker of hyperandrogenism Around 15% to 30% of the adult women having PCOS have a clinical presentation of acne<sup>17,18</sup>. It is recommended to ask about the menstrual history of women presenting with acne and evaluate for the other signs of hyperandrogenism<sup>19,20</sup>.

Fig.1. Selection of articles for inclusion in the present review



Furthermore, prior research has manifested that compensatory hyperinsulinemia and insulin resistance affect a maximum number of women having PCOS<sup>21</sup>. Three multiple ideas have been tested in an attempt to understand the procedure by which PCOS is linked with the increased risk of developing IR; which might be explained in part by the fact that PCOS is frequently linked to obesity, which is commonly linked with insulin<sup>22</sup>. Throughout the pathogenesis of PCOS the tetrad of "sympathetic dysfunction", "insulin resistance hyperandrogenism" and persistent "low-grade

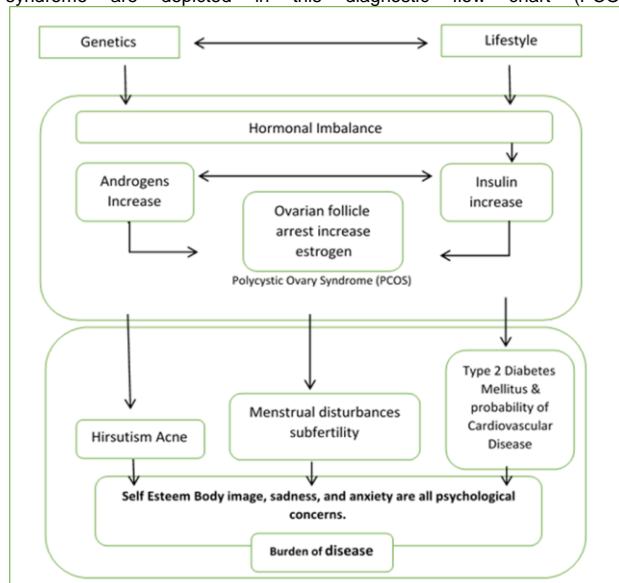
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inflammation" may play a role in the "vicious cycle". In comparison to control, women with Polycystic have more sympathetic activity, the link among systemic inflammation persistent low-grade inflammation, IR, and hyperandrogenism aren't completely understood [22]. In lean women having PCOS, Sverrisdottir et al discovered a link between cholesterol and muscular "sympathetic nerve activity" (MSNA) testosterone levels, whereas "Lambert et al" found that PCOS status was the sole forecaster of "MSNA" in overnight/chubby females having polycystic ovary syndrome<sup>23</sup>.

Especially, IR is a very typical occurrence in polycystic ovary syndrome patients. The gold standard approach for evaluating Vivo insulin action on glucose metabolism, the "hyperinsulinemic-euglycemic" clamp, and the standard for finding IR were used. Under the "hyperinsulinemic-euglycemic" clamp circumstance, glucose uptake in the lowest quartile of the background population, roughly 75% of the women shows decreased insulin sensitivity<sup>24</sup>. IR is a predictor of cardiovascular disease that is not dependent on anyone in non-selected groups. The risk is heightened with the presence of other cardiovascular disease factors. The "metabolic syndrome" (MS) or syndrome X refers to the grouping of several cardiovascular disease risk factors with IR. Because of the "obesity epidemic" the occurrence of this condition growing. Although there is considerable debate over which criteria should be included in MS, one thing is certain: IR with at least two of "dyslipidemia", "hypertension", "microalbuminuria", "central obesity", or increased fasting glucose is required<sup>25</sup>.

Fig.2. The etiology, clinical and hormonal aspects of the polycystic ovarian syndrome are depicted in this diagnostic flow chart (PCOS)



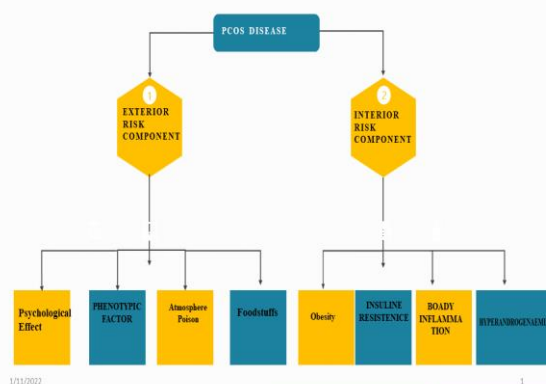
The adoption of an authentic method to characterize the morphology of polycystic ovary is required to diagnose PCOS using AES and Rotterdam criteria. The requirements that Rotterdam advocated are the existence of 12 or more follicles ranging between 2-9mm in diameter and a volume >10cm<sup>3</sup> for polycystic ovarian morphology. The polycystic ovary can be identified by this one-ovary appearance<sup>26</sup>. yet, ultrasound technology has advanced significantly over time; the most recent ultrasound technology has improved resolution, making tiny follicles observable<sup>27</sup>. As a result of these improvements, recommendations have been made to revise the criteria for defining "polycystic ovarian morphology"<sup>28</sup>. "Allemeand et al" had used three-dimensional transvaginal ultrasonography for the purpose to find the average no. of "follicles per ovary" (FNPO), this study involved the highest no. of follicles in 10 patients with PCOs and normal androgenic ovulatory control and highest no. of follicles in each sonographic plan. A mean FNPO of greater than

20.1 is recognized as PCO having 100% specificity and 70% of sensitivity. A maximum follicle present in one "sonographic plane" of 10 find out PCO having 100% specificity and with 90% sensitivity. The volume of the ovary or "Ovarian volume", which was calculated or measured by the "two-dimensional transvaginal ultrasound", of greater than 13.0 cm<sup>3</sup> is forecasted as PCO with a specificity of 100% and with a sensitivity of 50%<sup>29,30</sup>.

## METHOD

**Approaches to Research:** Some literature search was performed with the use of search engines. The following search engines provided the articles for this systematic review, PubMed, Medscape, NCBI, and Google Scholar. For article searching following keywords were used; Polycystic ovaries, diabetes, and insulin resistance. After performing unbiased searching on databases only those articles were included using keywords polycystic ovaries, obese and non-obese. Only those articles were included in which patients were suffering polycystic ovaries in the population of females. Researches were assessed for quality as well as applicability. Extraction of data was done from full journal articles. Raw data were used for summary statistics if they were not reported.

Fig 3: Explain the recognized and potential novel pathophysiological pathways that have a role in PCOS



## HAZARD LEVEL AND MORPHOLOGY

### EXTERIOR COMPONENT

**Phenotypic:** Incorporating or removing chemical components from DNA or histone without changing the level of the molecule is referred to as inherited modification. This might be linked to PCOS patients' issues with follicle growth and HA. Hypomethylation of the receptor causes an increase in gene expression and LH sensitivity<sup>31</sup>.

**Atmosphere Poison:** On interaction with hormone receptors, "Endocrine- Disrupting Chemical" can behave as agonists or antagonists. "Endocrine- Disrupting Chemical" serum levels are increased in PCOS sufferers according to the literature review<sup>32</sup>.

**Psychological Effect:** Adipocytes undergo hypertrophy and Hyperplasia as a result of chronic stress. Adipocytes production, recruitment, and activation of stromal fat immune cells are also linked to chronic stress. Which Creates psychological effects on Women's daily routine<sup>33</sup>.

**Foodstuffs:** Bodyweight combined with an improvement in "insulin sensitivity" has been showing an effective therapy for the metabolic and hormonal imbalances seen in People with PCOS<sup>34</sup>.

### INTERIOR COMPONENT

**Body Inflammation** "PCOS" is associated with low-level body inflammation, which can raise the risk of atherogenesis. Inflammation-related atherogenesis may be increased in women with PCOS who are also obsessed, in comparison to healthy women with "PCOS" or obsess controls<sup>35</sup>.

**Obesity** is a common complication of polycystic ovarian syndrome, however, it is not a distinguishing feature. Behavioral weight control is an important part of the overall therapy plan for obese women with "polycystic Ovarian Syndrome"<sup>36</sup>.

## RESULTS

As literature review of 45 articles and only 39 were included in this review, it is found that the Mean age of all subjects was 24-37 years. Obese females were 20-30 years and non-obese were 18-34 years. Insulin resistance occurs in 70-95% of females who were obese and had PCOS and 30-75% of females who were lean and developed PCOS. The statistic, however, is skewed by frequent referral bias. Hirsutism was frequently seen in polycystic ovary (PCO) patients who were obese. The prevalence of Amenorrhea was increased in lean disease-affected patients. Furthermore, there is metabolic variability across PCOS disease manifestations. The involvement of hyperinsulinemia in the overproduction of androgen, which is exacerbated by bidirectional linkages between hyperandrogenism and IR, is a major concern. According to the available research, women having PCOS may have changes in insulin action of many causes that cause unique anomalies in the individuals owing to inherent flaws.

## DISCUSSION

As literature review of 45 articles and only 39 were included in this review, it is found that the Mean age of all subjects was 24-37 years. Obese females were 20-30 years and non-obese were 18-34 years. Insulin resistance occurs in 70-95% of females who were obese and had PCOS and 30-75% of females who were lean and developed PCOS. However, frequent referral bias has an impact on this number. Hirsutism was frequently seen in PCOS patients who were overweight. Amenorrhea was shown to be more common in thin individuals. Furthermore, metabolic variability exists among PCOS clinical phenotypes. The involvement of hyperinsulinemia in the overproduction of androgen, which is exacerbated by bidirectional linkages between hyperandrogenism and insulin resistance, is a major concern. According to the available research, women having PCOS may have insulin action changes of many causes, which cause unique anomalies in these individuals attributable to inherent flaws. Obesity is frequent in these individuals, and it plays, a part in the link between IR and PCOS. Polycystic ovarian syndrome and IR have been linked by several academics and practitioners. It results in inconsistencies in the diagnosis, pathogenesis, and treatment of the disease, causing unpredictability and uncertainty<sup>37,38</sup>. Juan Wang et al. They created a research paper in which they detailed one of the most repeated "systemic reproductive endocrine illnesses" is PCOS, which has several negative consequences for a woman's health. Polycystic ovary syndrome has multifactorial features and symptoms that are heterogeneous due to the participation of many pathways and a lack of common signs. Hyperandrogenemia (HA) and insulin resistance are the basic etiology and key endocrine features of PCOS, according to recent research on IR. The major causes of polycystic ovary disease and Hyperandrogenemia insulin resistance, which can interact in the onset and progression of the condition. As a result, research into the impact of IR and (HA) on the pathogenesis of numerous PCOS-related symptoms is critical in understanding the etiology of the disease. Such articles evaluate the most common signs and symptoms of PCOS, including dyslipidemia, reproductive processes, neuroendocrine disorders, which harms (PCOS) women's physical and emotional health "hypertension", "obesity", "sleep dyspnea" and "nonalcoholic fatty liver disease" (NAFLD). The growing understanding of growth pattern of IR and HA in PCOS recommends that dietary and lifestyle modifications and identification of potential "therapeutic agents" may improve PCOS. Therefore, some further research is required to fully understand the shared impact and relationship between (IR) and (HA) in polycystic ovaries syndrome

development. That article describes summarises what is now known regarding the effect of (IR) and (HA) on PCOs<sup>39</sup>. Since the year 2019, Mudassir Maqbool et.al PCOS is one of the most recurring and frequent ovarian disorders according to a study. Therefore it is complicated, infertility is caused by an endocrine problem that affects women during their reproductive years. That syndrome is believed to be complex polygenic in origin, with several factors at play namely reproduction, multisystem dysfunction, metabolic and endocrine. Insulin resistance and Hyperandrogenism affect the value contributor to the disease pathogenesis. The routes of insulin metabolism and glucose have been explored, then disputed to determine if IR is related to a flaw in the insulin action or decreased hepatic clearance of insulin, or some initial fault present in the  $\beta$ -cell function, or all these things in conjunction. Several research has shown that chubby, controlled-weight, and lean women having PCOS have some IR which is notable and natural to PCOS. Moreover, overweight women diagnosed having PCOS have an extra burden of IR that results from their surplus "adiposity". "Hyperinsulinemia" leads to increasing in the creation of androgen directly by behaving like a "co-gonadotropin", "augmenting Luteinizing" Hormonal activity inside the ovary, and not directly by raising "serum LH pulse amplitude". Conversely, Androgens may contribute at least partially to the IR state which is associated with PCOS. We will now look at how insulin resistance plays a role in polycystic ovarian syndrome briefly in this review<sup>40</sup>.

## CONCLUSION

Enhanced insulin levels have been discovered to be a primary cause of (PCOS) as well as a symptom of the disorder. IR is a prevalent polycystic ovarian syndrome symptom. It is especially in obese women who have progressed (PCOS).

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Year of publication	Author	Title	Conclusion
2018	Soulmaz Shorakae	"Associated outcome of insulin resistance, hyperandrogenism, sympathetic dysfunction and chronic inflammation in PCOS"	Hyperandrogenism and Sympathetic dysfunction are linked with PCOS remarkably. The acute "low-grade inflammation" certainly conciliate the outcome of "sympathetic dysfunction" on IR and hyperandrogenism.
2020	N K Stepto	"Exercise and insulin resistance in PCOS: muscle insulin signaling and fibrosis"	Researchers give fresh insights about faults in the early stages of development "insulin signaling", "hyperandrogenism" and "tissue fibrosis" in PCOS-specific IR in overweight women and thin women. PCOS- defects in "insulin signaling mTOR", while "gene expression" implicated "TGFβ ligand" regulating a" fibrosis" in the "PCOS-obesity synergy" in IR and varied feedback to exercise. There was minor proof for "hyperandrogenism" as a mechanism for IR.
2019	Juan Wang	"Hyperandrogenemia and insulin resistance: the chief culprit of polycystic ovary syndrome"	PCOS is one of the most complicated pathologies that shows various phenotypes and is not easy to diagnose and treat. Which is the reason for what consensus standard was made by various cohorts in the world.
2016	H. J. Teede	"Insulin Resistance, the Metabolic Syndrome, Diabetes, and Cardiovascular Disease Risk in Women with PCOS"	There is an observation that IR has a vital role in PCOS pathogenesis. Based on studies that were case-controlled, women having PCOS show a high prevalence of "metabolic syndrome" including "dyslipidemia" and "obesity".
2015	Giovanna Muscogiuri	"Low levels of 25(OH)D and insulin-resistance: 2 unrelated features or a cause-effect in PCOS?"	Data had shown that PCOS low 25(OH)D levels are identified by the notable measure of adiposity.
2017	A Dunaif	"Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis"	PCOS appears in a menarchal age, which is suitable to inspect the ontogeny of flaws in "carbohydrate metabolism" and for ascertaining large "three-generation kindreds" for positional cloning studies to identify "NIDDM genes". Although the existence of "dysfibrinolysis", "lipid abnormalities", and IR may be forecasted to place PCOS females at maximum risk for "cardiovascular disease", suitable studies are required to evaluate it directly.
2021	P Moghetti	"Insulin resistance and PCOS: chicken or egg?"	IR and correlated "hyperinsulinemia" can produce the reproductive and endocrine features/attributes of PCOS. Still, an increase in androgen can harm "insulin action", directly and/or through various modifications happening in various tissues.
2016	Paolo Moghetti	"Insulin Resistance and Polycystic Ovary Syndrome"	IR is a regular feature in women having PCOS, even though it is not universal and varies by therapeutic setting phenotypes of PCOS. Hyperandrogenism and Insulin resistance tends to be related main factors in PCOS pathogenesis. We put an assumption that PCOS can present a common end-stage "clinical phenotype" of various procedures in which there are damaged "hyperandrogenism" and "insulin action", may be performed by particular, natural malformation of these females.
2012	Evanthia Diamanti-Kandarakis	"Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications"	PCOS is now identified as a main "reproductive" and "metabolic disorder" having a high risk for "type 2 diabetes". The females who are Affected are independent of obesity have IR.
2014	Christopher J Nolan	"Insulin resistance and insulin hypersecretion in the metabolic syndrome and type 2 diabetes: Time for a conceptual framework shift"	IR has most frequently recommended for this post and is widely regarded as a major factor for the cause of not only "metabolic syndrome" but also for its associated circumstances of PCOS, "non-alcoholic fatty liver disease" (NAFLD), "atherosclerotic cardiovascular disease" (ASCVD) and obesity-related "type 2 diabetes" (T2D).
2019	K Polak	"New markers of insulin resistance in polycystic ovary syndrome"	Patients with cardiovascular diseases endemic, PCOS and "metabolic syndrome". IR is common in women having PCOS and are independent of being overweight and are severely involved in metabolic and reproductive complications.