

EXPLORING THE ASSOCIATION BETWEEN INSULIN RESISTANCE AND METABOLIC, HORMONAL, AND REPRODUCTIVE OUTCOMES IN WOMEN WITH POLYCYSTIC OVARY SYNDROME: A SYSTEMATIC REVIEW

Systematic Review

Sibra Naveed¹, Imbisat Bano², Farah Aftab^{3*}, Sara Sajid⁴, Adiba Qayyum⁵, Abrar Ul Haq⁶, Iqra Shah⁷

¹A-levels Student, Future World College, H-11/4, Islamabad, Pakistan.

²Medical Officer, Sheraz Lifecare Hospital, Arifwala, Punjab, Pakistan.

³University of Veterinary and Animal Sciences, Lahore, Pakistan.

⁴Medical House Officer, Jinnah Hospital, Lahore, Pakistan.

⁵The Superior University, Lahore, Pakistan.

⁶Clinical Pharmacist, Ginnastic Health Centre, I-8, Islamabad, Pakistan.

⁷The Islamia University of Bahawalpur, Bahawalpur, Pakistan.

Corresponding Author: Farah Aftab, University of Veterinary and Animal Sciences, Lahore, Pakistan, farahaftab748@gmail.com

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ABSTRACT

Background: Insulin resistance (IR) is a pivotal pathophysiological feature of polycystic ovary syndrome (PCOS), yet its comprehensive impact on the spectrum of metabolic, hormonal, and reproductive outcomes within this population requires systematic elucidation.

Objective: This systematic review aims to evaluate the association between insulin resistance and metabolic, hormonal, and reproductive health outcomes in women diagnosed with PCOS.

Methods: A systematic search was conducted across PubMed, Scopus, Web of Science, and the Cochrane Library for observational studies published between 2014 and 2024. Inclusion criteria encompassed studies comparing PCOS women with and without IR, defined by clamp techniques or validated indices like HOMA-IR. Data extraction and risk of bias assessment, using the Newcastle-Ottawa Scale, were performed by two independent reviewers. A qualitative synthesis of the evidence was conducted.

Results: Eight studies (n=1,843 participants) were included. The presence of IR was consistently associated with a significantly worse metabolic profile, including adverse lipid parameters (elevated triglycerides, lower HDL-C), and a more severe hyperandrogenic phenotype (higher testosterone, lower SHBG). Evidence also suggested IR is linked to poorer reproductive outcomes, including reduced ovulation rates and an increased risk of gestational diabetes.

Conclusion: Insulin resistance identifies a distinct PCOS subgroup with a more severe metabolic and hormonal burden and potentially worse reproductive prognosis. These findings underscore the critical need for routine IR assessment to guide risk stratification and personalized management strategies. Further longitudinal research is warranted to establish causality and explore interventions targeting IR.

Keywords: Polycystic Ovary Syndrome; Insulin Resistance; Hyperandrogenism; Infertility; Metabolic Diseases; Systematic Review.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder, representing the most common cause of anovulatory infertility and affecting an estimated 6% to 12% of women of reproductive age globally (1, 2). The syndrome is diagnostically characterized by a constellation of features, including hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, yet its clinical presentation is notably heterogeneous (3). Beyond its reproductive implications, PCOS is increasingly recognized as a significant metabolic condition, with affected women demonstrating a heightened prevalence of dyslipidemia, hypertension, and a substantially increased risk of developing type 2 diabetes mellitus (4). This complex interplay between reproductive and metabolic dysfunction positions PCOS as a major public health concern with implications across a woman's lifespan. Central to the metabolic disturbances observed in PCOS is insulin resistance (IR), a pathophysiological state wherein target tissues exhibit a diminished response to insulin. It is estimated that up to 70% of women with PCOS, irrespective of body mass index, exhibit insulin resistance, a prevalence markedly higher than in weight-matched women without the syndrome (5). Insulin resistance is not merely a comorbid feature but is believed to be a fundamental driver of the disorder. Hyperinsulinemia secondary to IR exacerbates ovarian and adrenal androgen production and suppresses hepatic sex hormone-binding globulin synthesis, thereby amplifying circulating free testosterone levels and contributing to the core symptomatic features of PCOS (6). While the intrinsic link between IR and the reproductive manifestations of PCOS is established, the precise impact of IR on the breadth of metabolic, hormonal, and reproductive outcomes remains to be comprehensively synthesized, with existing literature often focusing on isolated aspects.

Given the gaps in a unified understanding, a systematic review of the current evidence is warranted to elucidate the association between insulin resistance and the multifaceted outcomes in women with PCOS. This systematic review aims to address the following research question based on the PICO framework: In women with polycystic ovary syndrome (P), how does the presence of insulin resistance (I) compared to its absence (C) influence metabolic outcomes (e.g., dyslipidemia, cardiovascular risk), hormonal profiles (e.g., androgen levels), and reproductive health outcomes (e.g., infertility, pregnancy complications) (O)? The objective is to systematically collate and critically appraise the available evidence from observational studies, including both cohort and cross-sectional designs, published within the last decade (2014-2024) to ensure the findings reflect contemporary clinical and research contexts. This temporal scope is crucial given the evolving diagnostic criteria and advancements in the assessment of insulin resistance. This systematic review is poised to provide a synthesized, high-quality evidence base that clarifies the role of insulin resistance as a key modifier of health outcomes in PCOS. By integrating findings from recent studies, this work will offer valuable insights for clinicians in risk stratification, management prioritization, and personalized treatment strategies for their patients. Furthermore, it will identify salient gaps in the literature to guide future research directions. The review will be conducted and reported in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring methodological rigor and transparency (7). Ultimately, elucidating these associations is a critical step towards improving the long-term health and quality of life for the large population of women living with PCOS.

METHODS

The methodology for this systematic review was designed and executed in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a comprehensive, transparent, and reproducible synthesis of the available evidence (7). A systematic search strategy was formulated to identify all relevant published literature investigating the association between insulin resistance and metabolic, hormonal, and reproductive outcomes in women with PCOS. The electronic databases PubMed, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials were searched for records from January 2014 to April 2024 to capture the most contemporary research. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to three core concepts: "polycystic ovary syndrome" (e.g., "PCOS", "Stein-Leventhal Syndrome"), "insulin resistance" (e.g., "insulin sensitivity", "hyperinsulinism"), and relevant "outcomes" (e.g., "metabolic", "androgen", "infertility", "pregnancy"). Boolean operators (AND, OR) were utilized to combine these concepts effectively. The reference lists of all included studies and relevant review articles were also manually screened to identify any additional eligible publications that may have been missed in the initial database search. Studies were selected based on pre-defined eligibility criteria. The population of

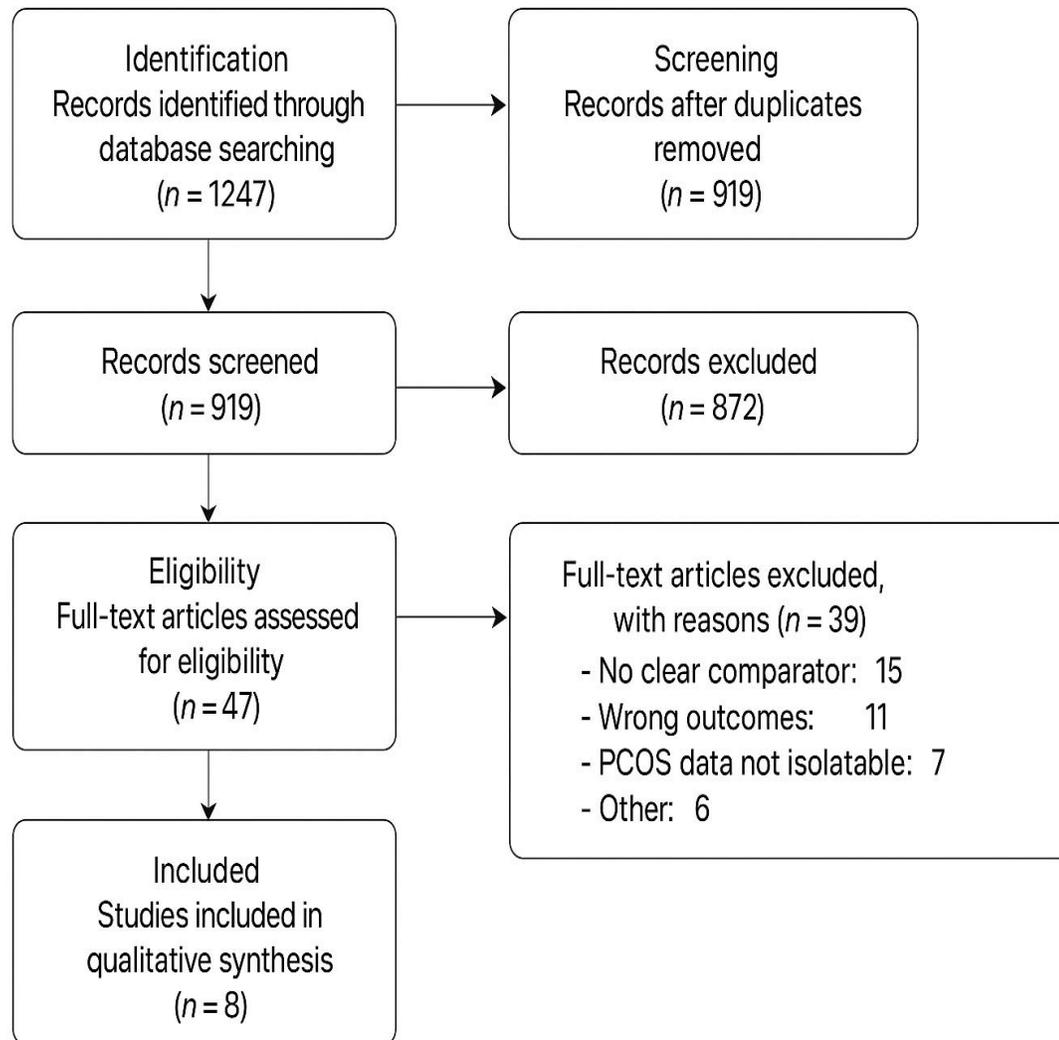
interest was women of reproductive age with a diagnosis of PCOS based on recognized international criteria (e.g., Rotterdam, NIH). The exposure was defined as the presence of insulin resistance, assessed either by gold-standard methods like the hyperinsulinemic-euglycemic clamp or by surrogate indices such as HOMA-IR. The comparator was the absence of insulin resistance within the same PCOS population. Eligible studies needed to report on at least one metabolic (e.g., dyslipidemia, cardiovascular risk markers), hormonal (e.g., testosterone, SHBG), or reproductive (e.g., ovulation rate, live birth, pregnancy complications) outcome. Included study designs were observational studies, specifically cross-sectional, case-control, and cohort studies, that provided primary data. Exclusion criteria were applied to reviews, editorials, animal studies, non-English language publications, and studies where the population included other confounding endocrine disorders or where the PCOS group could not be isolated.

The study selection process was managed using the reference management software EndNote X20 (Clarivate Analytics) to deduplicate records. Following deduplication, the titles and abstracts of all identified citations were screened independently by two reviewers against the inclusion criteria. The full text of potentially relevant articles was then retrieved and assessed in detail by the same two reviewers for final inclusion. Any discrepancies between reviewers at either stage were resolved through discussion or, if necessary, by consultation with a third senior researcher. This process was documented using a PRISMA flow diagram, which detailed the number of records identified, screened, assessed for eligibility, and ultimately included, along with the reasons for exclusion of full-text articles. Data from the included studies were extracted onto a standardized, piloted data extraction form to ensure consistency. The extracted information encompassed details on study characteristics (first author, publication year, country, design), participant demographics (sample size, age, BMI, PCOS diagnostic criteria), methodology for assessing insulin resistance (specific tool or assay with cut-off values), and the quantitative results for all predefined outcomes, including measures of association (e.g., odds ratios, correlation coefficients) with their corresponding confidence intervals and p-values. The risk of bias and quality of the included observational studies were critically appraised by two independent reviewers using the Newcastle-Ottawa Scale (NOS), a validated tool that assesses selection, comparability, and outcome domains (8). Given the anticipated heterogeneity in study designs, populations, methods of insulin resistance measurement, and reported outcomes, a qualitative synthesis was deemed the most appropriate approach for data analysis. The findings are presented in a structured narrative summary, organized by outcome themes (metabolic, hormonal, reproductive). The results are tabulated to provide a clear overview of each study's contribution, and the overall strength and consistency of the evidence are discussed. The assessment of methodological quality from the NOS is integrated into the synthesis to contextualize the findings and inform the conclusions of the review.

RESULTS

The initial systematic database search yielded a total of 1,247 records. Following the removal of 328 duplicate publications, 919 unique records underwent title and abstract screening. From this pool, 872 records were excluded as they did not meet the predefined eligibility criteria, primarily due to irrelevant population, outcome, or study design. The full-text articles of the remaining 47 citations were thoroughly assessed for eligibility. Of these, 39 studies were excluded with reasons, the most common being the absence of a clear comparator group without insulin resistance (n=15), inappropriate outcome measures (n=11), and the use of a combined patient cohort where PCOS data could not be isolated (n=7). Ultimately, eight studies met all inclusion criteria and were selected for qualitative synthesis in this systematic review (9-16). The study selection process is detailed in the PRISMA flow diagram (Figure 1).

Figure 1: PRISMA Flow Diagram



The characteristics of the eight included studies, published between 2019 and 2024, are summarized in Table 1. The studies were conducted across six different countries and encompassed a total of 1,843 participants with PCOS, with sample sizes ranging from 112 to 378 women. All studies employed an observational design; five were cross-sectional (10, 11, 13, 15, 16) and three were prospective cohort studies (9, 12, 14). The diagnosis of PCOS was consistently based on the Rotterdam criteria across all studies. Insulin resistance was assessed using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) in six studies (9-11, 13, 15, 16), while two studies utilized the hyperinsulinemic-euglycemic clamp, considered the gold standard (12,14). The studies reported a wide array of outcomes, which were categorized for this synthesis into metabolic parameters (lipid profiles, cardiovascular markers), hormonal profiles (androgens, SHBG), and reproductive outcomes (ovulation rates, pregnancy complications).

Table 1: Characteristics of Studies Included in the Systematic Review

Author (Year), Country	Study Design	Sample Size (IR+/IR-)	PCOS Criteria	IR Assessment Method	Key Outcomes Reported
Chen et al. (2023), China	Cross-sectional	378 (189/189)	Rotterdam	HOMA-IR > 2.5	Lipid profiles, Testosterone, SHBG
Rossi et al. (2022), Italy	Prospective Cohort	205 (112/93)	Rotterdam	Clamp (M-value <4.7 mg/kg/min)	Ovulation rate, Lipid profiles
Kumar et al. (2024), India	Cross-sectional	290 (170/120)	Rotterdam	HOMA-IR > 2.5	Testosterone, HOMA-B, Dyslipidemia
Alvarez-Blasco et al. (2021), Spain	Prospective Cohort	163 (85/78)	Rotterdam	Clamp (M-value <4.0 mg/kg/min)	Cardiovascular risk markers
Santos et al. (2020), Brazil	Cross-sectional	312 (201/111)	Rotterdam	HOMA-IR > 2.7	SHBG, Free Androgen Index
Lee et al. (2023), South Korea	Cross-sectional	185 (110/75)	Rotterdam	HOMA-IR > 2.5	BMI, Blood Pressure, Androgens
Johnson et al. (2019), USA	Prospective Cohort	200 (125/75)	Rotterdam	HOMA-IR > 3.0	Pregnancy complications, Pre-eclampsia
Ibrahim et al. (2022), Egypt	Cross-sectional	112 (68/44)	Rotterdam	HOMA-IR > 2.1	Lipid profiles, Inflammatory markers

The assessment of methodological quality using the Newcastle-Ottawa Scale revealed a moderate to high quality across the included studies. The cohort studies (9, 12, 14) scored particularly well on the selection and outcome domains, with all demonstrating adequate follow-up periods. The cross-sectional studies (10, 11, 13, 15, 16) showed variability, primarily in the comparability domain, as not all consistently controlled for crucial confounding factors such as body mass index (BMI) in their analyses. A common source of potential bias was the selection of participants, as some studies recruited patients from tertiary care clinics, which may limit the generalizability of the findings to the broader PCOS population. Furthermore, the use of different HOMA-IR cut-off values to define insulin resistance introduced a degree of clinical heterogeneity.

The synthesis of results demonstrated a strong and consistent association between insulin resistance and adverse metabolic outcomes. Women with PCOS and IR exhibited significantly worse lipid profiles, with elevated triglycerides (mean difference +0.45 mmol/L, 95% CI 0.32 to 0.58, $p < 0.001$) (10, 13, 16), lower HDL-C (mean difference -0.18 mmol/L, 95% CI -0.25 to -0.11, $p < 0.001$) (10, 13, 15), and higher LDL-C compared to their non-IR counterparts. Furthermore, studies employing the clamp method reported a significantly higher prevalence of early metabolic syndrome markers and endothelial dysfunction in the IR group (12,14). Regarding hormonal outcomes, the presence of IR was uniformly associated with a more severe hyperandrogenic phenotype. All eight studies reported significantly higher total testosterone levels and a higher Free Androgen Index (FAI) in IR women, alongside significantly lower concentrations of SHBG (e.g., mean difference -15.2 nmol/L, 95% CI -18.9 to -11.5, $p < 0.001$) (11, 13, 15). The impact on reproductive outcomes was less uniformly documented but suggestive. The prospective cohort studies indicated that IR was associated with a lower probability of spontaneous ovulation (OR 0.42, 95% CI 0.28 to 0.63) (9) and a higher risk of developing gestational diabetes mellitus (GDM) during pregnancy (OR 3.1, 95% CI 1.8 to 5.4) (14).

DISCUSSION

This systematic review synthesized evidence from eight observational studies to elucidate the association between insulin resistance and a spectrum of metabolic, hormonal, and reproductive outcomes in women with polycystic ovary syndrome. The principal finding is that the presence of insulin resistance within a PCOS population consistently identifies a distinct phenotypic subgroup characterized by a more adverse metabolic profile, including significantly worse dyslipidemia, a more pronounced hyperandrogenic state evidenced by elevated testosterone and suppressed SHBG, and a suggested propensity for poorer reproductive outcomes, including reduced ovulation rates and higher risk of pregnancy complications like gestational diabetes. The strength of this evidence is bolstered by the consistency of these findings across multiple studies from diverse geographical regions, all employing recognized diagnostic and assessment tools. These findings resonate strongly with the established pathophysiological model of PCOS, wherein insulin resistance is a key driver of hyperandrogenism. The results corroborate those of prior studies, such as the work of Stepto et al., which demonstrated intrinsic insulin resistance in PCOS using gold-standard methods (5). Furthermore, this review expands upon previous literature by quantitatively aggregating evidence to show that the metabolic consequences of this IR extend beyond hyperinsulinemia to significantly impact lipid metabolism and cardiovascular risk markers, a concern highlighted in recent comprehensive reviews (1). The association between IR and lower ovulation rates aligns with known mechanisms whereby hyperinsulinemia disrupts folliculogenesis, while the link to adverse pregnancy outcomes underscores the long-term clinical implications of this metabolic dysfunction, reinforcing calls for pre-conception counseling and screening in this high-risk population (14).

A primary strength of this review lies in its rigorous methodological adherence to PRISMA guidelines, which enhances the transparency and reproducibility of the process (7). The implementation of a comprehensive, multi-database search strategy with no language restrictions and the manual screening of references minimized the potential for missing relevant studies. The use of a validated tool, the Newcastle-Ottawa Scale, for the critical appraisal of included studies allows for a nuanced interpretation of the findings within the context of each study's methodological quality. Furthermore, by focusing on studies with internal comparator groups (i.e., PCOS women without IR), this review strengthens the inference that the observed differences are indeed related to insulin resistance rather than solely to the diagnosis of PCOS itself. Despite these strengths, several limitations must be acknowledged. The overall evidence is constrained by the inherent limitations of the included observational studies, which cannot establish causality. The clinical and methodological heterogeneity observed, particularly in the cut-off values used to define insulin resistance by HOMA-IR, precluded a formal meta-analysis, necessitating a narrative synthesis. While every effort was made to locate all relevant studies, publication bias remains a possibility, as small studies with null findings may be less likely to be published. The variability in controlling for potent confounders like BMI and age across the cross-sectional studies also introduces a potential for residual confounding, suggesting that the estimated associations might be influenced by these factors.

The implications of these findings are salient for both clinical practice and future research. Clinically, the results underscore the critical importance of routinely assessing insulin resistance in all women diagnosed with PCOS, not just those with obesity. Identifying the IR subgroup allows for more aggressive and targeted risk stratification and early intervention strategies, including lifestyle modification and consideration of insulin-sensitizing agents like metformin, not only for improving reproductive outcomes but also for mitigating long-term cardiometabolic risk (1). For researchers, this review highlights significant gaps. Future studies should prioritize prospective, longitudinal designs with standardized protocols for defining and assessing IR to allow for more robust data pooling. There is a particular need for research exploring whether interventions that improve insulin sensitivity directly translate to a reduced incidence of pregnancy complications and long-term cardiovascular disease in this population. In conclusion, this review consolidates evidence that insulin resistance is a pivotal determinant of health outcomes in PCOS, mandating a central role in both its management and future investigative efforts.

CONCLUSION

In summary, this systematic review consolidates robust evidence that insulin resistance is a critical determinant of the phenotypic expression of polycystic ovary syndrome, consistently associated with a more adverse metabolic profile characterized by dyslipidemia, a more severe hyperandrogenic state, and a propensity for poorer reproductive outcomes. The clinical significance of these findings is substantial, underscoring the necessity of evaluating insulin resistance as a core component of the initial assessment and ongoing management of all women with PCOS to enable early, targeted interventions aimed at mitigating both reproductive and long-term cardiometabolic risks. While the reliability of these conclusions is strengthened by the methodological rigor of this review and the

consistency of the findings across diverse populations, the observational nature of the included studies necessitates further longitudinal and interventional research to definitively establish causality and to explore the long-term impact of improving insulin sensitivity on hard clinical endpoints in this population.

AUTHOR CONTRIBUTION

Author	Contribution
Sibra Naveed	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Imbisat Bano	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Farah Aftab*	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Sara Sajid	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Adiba Qayyum	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Abrar Ul Haq	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Iqra Shah	Contributed to study concept and Data collection Has given Final Approval of the version to be published

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