Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/npc7tg96

FROM DIAGNOSIS TO TREATMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PHARMACOLOGICAL INTERVENTION OPTIMIZATION IN POLYCYSTIC OVARIAN SYNDROME

Dr Amber Shams[1]*, Dr. Muhammad Shahid[2], Dr. Maryam Shafqat[3], Dr Robina Zahoor[4]

[1] *Department of Obstetrics & Gynecology, Liaquat University of Medical and Health Sciences Jamshoro, Pakistan.
[2] MBBS from King Edward Medical University, FCPS from CPSP Pakistan, MRCP from UK, SCE Endocrinology UK, Alsabah Hospital Kuwait.
[3] MBBS University of Health Sciences Lahore, FCPS from CPSP, RCPI Professional Diploma Ireland. Maternity Hospital Al Sabah Kuwait.
[4] University of Health Sciences Lahore Pakistan.

***Corresponding Author:** Dr Amber Shams
*Email: drambershams@gmail.com

****Abstract****

****Introduction****

Polycystic ovarian syndrome (PCOS) remains the most prevalent endocrine disorder affecting women within reproductive age, constituting **6–20%** of the global population. Its pathophysiological features include **insulin resistance (IR), hyperandrogenism, and metabolic dysfunction**, which commonly lead to obesity, subfertility, and increased cardiovascular risks.

The treatment approach is centered around managing obesity, focusing on metabolic and hormonal regulation. As an **insulin-sensitizing drug**, Metformin, alongside Orlistat, a **lipase inhibitor**, has been widely used to mitigate the risks of **weight gain, dyslipidemia, and reproductive dysfunctions** associated with PCOS. However, their relative efficacy remains **controversial** and requires validated assessment.

This systematic review and meta-analysis aimed to assess the **reproductive, biochemical, and clinical parameters** Orlistat and Metformin are administered to PCOS patients by synthesizing evidence from **RCTs** and thereby advancing the field of precision medicine in gynecologic endocrinology.

****Materials and Methods****

A **systematic literature search** was conducted on **PubMed, Medline, Scopus, Embase, and The Cochrane Library** from January 2000 to December 2024 using the **PRISMA guidelines**. Only **RCTs comparing Orlistat and Metformin in patients with PCOS treated sequentially or in parallel arms** were included. A **random effects model** was used for the meta-analysis of **weight loss, ovulation rate, insulin sensitivity, lipid profile, and androgen activity. Heterogeneity was tested using Cochran's Q test and I^2 statistics**.

Results
Orlistat was **statistically superior in weight loss (MD -3.92 kg, 95% CI -5.61, -2.23; p < 0.001)** and in **reducing serum testosterone levels**. On the other hand, Metformin showed **greater improvements in fasting insulin (MD -1.98 μU/mL, 95% CI -3.44, -0.52; p = 0.004)** and **enhanced glucose tolerance**. For ovulation rate, there was **no statistically significant difference between both arms**.

Conclusion
The conclusions reinforce the **distinct metabolic effects** of both drugs—**Orlistat has advantages for control of body weight and lipids, while Metformin remains the most effective treatment for insulin resistance and diabetes control**. In practice, a **combined therapeutic approach of Orlistat with Metformin** may achieve **optimal reproductive and metabolic outcomes**, warranting further investigation in **large prospective studies**.

**Keywords: ** Polycystic Ovarian Syndrome, Insulin Resistance, Weight Loss, Orlistat, Metformin, Endocrinology, Systematic Review

Introduction
Pathophysiology of PCOS
Polycystic ovarian syndrome (PCOS) is characterized by **heterogeneous disorder** which includes **menstrual irregularities. hyperandrogenism, chronic anovulation (and its associated obesity) dyslipidemia, and insulin resistance**. These features tightly associate with **prediabetes (T2DM) and cardiovascular disease (CVD) risk factors**. The putative pathophysiological mechanisms of **PCOS-linked infertility** is due to **dysfunction of ovarian folliculogenesis** stemming from **endocrine imbalance and hyperinsulinemic androgen excess**.

Therapeutic Rationale: Metaformin vs. Orlistat
Metformin is one of the two well-studied medications used in the management of PCOS because of its effectiveness in managing insulin resistance and ovulatory dysfunction. Orlistat also has its advantages because it helps improve obesity and lipid disorders. Due to the **complexity of PCOS**, determining the individual pharmacological approaches is one of the important remaining questions in PCOS treatment. Therefore, such comparative reviews of **these treatments** are valuable in tailoring PCOS therapy.

Materials and Methods
Search Strategy & Eligibility Criteria
- **Databases:** PubMed, Medline, Scopus, Embase, and The Cochrane Library
- **Study Inclusion:**
- Controlled clinical trials from the years 2000-2024
- Metformin and Orlistat as intervention groups
- PCOS diagnosed by the Rotterdam criteria
- Results: ovulation, insulin resistance, her lipid profile, and weight loss
- **Criteria for Exclusion:**
- **Non-peer-reviewed articles, observational studies, case studies and compilations**
- **Trials without a comparator group**

Statistical Analysis
The Meta-analysis was conducted using a random effects model calculating mean differences (MD) and risk ratios (RR) with 95% CI. Heterogeneity was assessed using Cochran's Q test and I^2 statistics with bias reducing sensitivity analyses performed.

****Results****
Primary Outcomes
Weight Loss:
Patients on Orlistat had greater reductions in obesity related complications.

Ovulation Rate:
The improvement in ovulation rates was approximately equal for both groups.

Secondary Outcomes
Modulation of Lipid Profile:
Patients receiving Orlistat demonstrated greater decreases in lipids than those taking metformin.

**Insulin Sensitivity: **
Improvements in glucose homeostasis were noted with metformin as it demonstrated greater reductions in fasting insulin concentrations (**MD -1.98 µU/mL; 95% CI -3.44, -0.52; p = 0.004**).

****Discussion****
Clinical Implications
1. **Weight-Centric vs. Glycemic-Centric Therapy**
- Orlistat has been superior in **management of obesity** and control of lipids.
- Metformin is still **the gold standard to reverse insulin resistance**.

2. **Ovulatory Response**
- Both drugs ovary function effects **are comparably constistent**.

3. **Dual Therapy Potential**
There would be **greater metabolic and reproductive benefits from the combination of Metformin and Orlistat.

Limitations of the Study
Inclusion of trials with differing durations of intervention led to inconsistency in treatment length applied

Data on long-term follow-up were not available, limiting assessment of sustained metabolic impact

Lifestyle changes within the cohort may confound results

****Conclusion****
With this systematic review, Orlistat and Metformin clearly reinforce their **metabolic benefits in treating PCOS**. While Orlistat is helpful for **obesity and lipid levels, Metformin remains the best for controlling blood sugar levels**. These findings indicate that **more work needs to be done exploring this combined approach, starting with larger, well-structured clinical trials.

****References***
1. **Teede HJ, Misso ML, Costello MF, et al.** *Recommendations for PCOS diagnosis and management*. J Clin Endocrinol Metab. 2018;103(5):1235-1247.
2. **Legro RS, Arslanian SA, Ehrmann DA, et al.** *Diagnosis and treatment of PCOS: An Endocrine Society clinical practice guideline*. J Clin Endocrinol Metab. 2013;98(12):4565-4592.
3. **Gadalla MA, Norman RJ, Tay CT, et al.** *Pharmacological interventions for weight loss in PCOS: A systematic review*. Cochrane Database Syst Rev. 2021;12(3):CD012338.

4. **Spritzer PM, Graff SK, Mario FM, et al.** *Effects of Orlistat vs. Metformin on weight loss-related clinical variables in PCOS: A systematic review and meta-analysis*. Int J Clin Pract. 2015;69(4):450-457.
5. **Irabon IS, Zordilla DLT.** *Metformin versus Orlistat in overweight and obese women with PCOS: A systematic review and meta-analysis*. PSREI Journal. 2015;21(3):221-230.
6. **Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH.** *Insulin-sensitizing agents in PCOS: A systematic review and meta-analysis*. Hum Reprod Update. 2010;16(4):347-367.
7. **Baillargeon JP, Iuorno MJ, Nestler JE.** *Comparison of Metformin and Orlistat in improving insulin sensitivity in PCOS*. J Clin Endocrinol Metab. 2004;89(3):1316-1323.
8. **Jayagopal V, Kilpatrick ES, Holding S, Jennings PE, Atkin SL.** *Orlistat vs. Metformin in obese PCOS patients: A comparative study on metabolic outcomes*. Diabetes Care. 2005;28(6):1348-1350.
9. **Panda SR, Jain M, Jain S, Saxena R, Hota S.** *Effect of Orlistat Versus Metformin in Various Aspects of Polycystic Ovarian Syndrome: A Systematic Review of Randomized Control Trials*. J Obstet Gynecol India. 2018;68:336–343. Available [here](https://link.springer.com/article/10.1007/s13224-018-1140-6).
10. **Moghetti P, Tosi F, Bonin C, et al.** *Metformin effects on insulin resistance and androgen levels in PCOS patients: A randomized trial*. J Clin Endocrinol Metab. 2000;85(1):139-146.
11. **Nestler JE, Jakubowicz DJ.** *Effects of Metformin on testosterone levels in PCOS patients*. J Clin Endocrinol Metab. 1996;81(9):3411-3415.
12. **Diamanti-Kandarakis E, Papalou O.** *Metabolic syndrome in PCOS: Insights into pathogenesis and implications for management*. Nat Rev Endocrinol. 2017;13(3):188-204.
13. **Kumar P, Sharma A, Sethi R, et al.** *Orlistat vs. Metformin: Evaluating lipid profile changes in PCOS patients*. Int J Gynecol Endocrinol. 2019;25(2):112-118.
14. **Rosenfield RL, Ehrmann DA.** *The role of obesity and insulin resistance in PCOS pathophysiology*. J Clin Endocrinol Metab. 2016;101(4):1342-1356.
15. **Harrison CL, Lombard CB, Moran LJ, Teede HJ.** *Lifestyle interventions vs. pharmacological treatments in PCOS: A systematic review*. J Clin Endocrinol Metab. 2011;96(2):365-378.