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METFORMIN OR GLP 1 RECEPTOR AGONISTS? CURRENT VIEWS ON THE MANAGEMENT OF POLYCYSTIC OVARY SYNDROME

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ABSTRACT

BACKGROUND

Polycystic ovary syndrome is a heterogeneous endocrine disorder associated with insulin resistance, hyperandrogenism, and reproductive dysfunction. Pharmacological treatment commonly includes metformin and glucagon like peptide 1 receptor agonists, but their comparative effects across metabolic and reproductive outcomes remain insufficiently integrated .

AIMS

To compare the metabolic and reproductive effects of metformin and GLP-1 receptor agonists in women with PCOS and to summarize current evidence on their mechanisms of action.

METHODS

A narrative review was conducted based on a literature search in PubMed and Google Scholar for studies published between 2015 and 2025. Randomized controlled trials, meta analyses, systematic reviews, and translational studies evaluating metformin, GLP-1 receptor agonists, or their combination in women with PCOS were included. Outcomes

of interest included insulin resistance, body mass index, hormonal parameters, and reproductive outcomes .

RESULTS

Metformin was associated with improvements in insulin resistance, fasting glucose, and menstrual regularity, with modest effects on body weight and androgen levels. GLP-1 receptor agonists were associated with greater reductions in body weight, body mass index, and waist circumference, and with changes in metabolic and hormonal parameters in several studies. Improvements in ovulatory function and pregnancy outcomes were reported in some studies, although results were heterogeneous and often based on small and short term trials. Combination therapy was associated with additional improvements in metabolic and reproductive outcomes in limited studies .

CONCLUSIONS

Metformin and GLP-1 receptor agonists demonstrate different and partially overlapping effects in the management of PCOS. Current evidence supports their potential complementary use, but does not allow definitive conclusions regarding comparative effectiveness or phenotype specific treatment strategies. Further long term studies with standardized reproductive endpoints are required.

Keywords: PCOS; metformin; GLP-1 receptor agonists; insulin resistance; reproductive outcomes; obesity

INTRODUCTION

Polycystic ovary syndrome is a heterogeneous endocrine disorder affecting approximately 13% of women of reproductive age [1,2]. It is characterized by chronic anovulation, hyperandrogenism, and polycystic ovarian morphology. In addition to reproductive dysfunction, PCOS is associated with an increased risk of long term metabolic disorders, including type 2 diabetes and cardiovascular disease [1,3].

Insulin resistance and compensatory hyperinsulinemia play a central role in its pathophysiology, contributing to increased androgen production in ovarian theca cells, suppression of hepatic sex hormone binding globulin, and further disruption of ovulatory function [4]. Metformin, an insulin sensitizing agent acting through activation of AMP activated protein kinase, has been widely used to improve insulin sensitivity and restore menstrual regularity in women with PCOS [5,6].

However, its effects on body weight reduction and androgen normalization are limited, particularly in patients with obesity. In recent years, glucagon like peptide 1 receptor agonists such as liraglutide, exenatide, and semaglutide have emerged as therapeutic agents with significant effects on weight reduction and metabolic regulation, with potential benefits for reproductive function [7–9,12]. Experimental and translational studies also suggest that GLP- 1 signaling may directly influence ovarian steroidogenesis and follicular development [16–18].

Despite extensive evidence describing the metabolic and reproductive effects of metformin and GLP- 1 receptor agonists in women with PCOS, a clinically meaningful comparison between these therapeutic approaches remains unresolved. Existing studies predominantly assess metabolic outcomes such as insulin resistance and body weight separately from reproductive parameters including ovulation and fertility. This fragmented approach limits the ability to interpret how improvements in metabolic status translate into reproductive benefit.

In addition, current literature does not provide a consistent framework linking the molecular mechanisms of these agents with their clinical effects. While metformin primarily acts through AMPK activation and improvement of insulin sensitivity, and GLP- 1 receptor agonists influence appetite regulation, adiposity, and potentially ovarian steroidogenesis, it remains unclear how these distinct mechanisms determine differences in therapeutic response across heterogeneous PCOS phenotypes.

As a result, there is no clear evidence-based guidance on which treatment strategy is optimal for specific patient subgroups, particularly in the context of obesity, hyperandrogenism, and reproductive dysfunction. The lack of integration between molecular pathways, metabolic outcomes, and reproductive endpoints represents a critical gap in current knowledge.

This narrative review addresses this gap by systematically comparing metformin and GLP- 1 receptor agonists in women with PCOS, with the aim of linking their mechanisms of action to both metabolic and reproductive outcomes and identifying phenotype specific therapeutic implications.

The aim of this study is to compare the metabolic and reproductive effects of metformin and GLP-1 receptor agonists in women with PCOS and to summarize current evidence on their mechanisms of action.

RESEARCH OBJECTIVES

1. To compare the effects of metformin and GLP- 1 receptor agonists on insulin resistance, body weight, and reproductive outcomes in women with PCOS.
2. To evaluate differences in their impact on hormonal parameters, including androgen levels and ovulatory function.
3. To analyze the molecular mechanisms underlying the action of both therapies in the context of ovarian function.
4. To discuss current limitations of the evidence and potential directions for future research in PCOS treatment.

MATERIAL AND METHODS

This narrative review was conducted to synthesize current evidence on the pharmacological management of PCOS. The methodological approach was based on principles of evidence based literature analysis, without applying a formal systematic review protocol.

A literature search was performed using PubMed and Google Scholar databases covering the period from January 2015 to January 2025. The search was conducted using the following keywords: "PCOS", "metformin", "GLP-1 receptor agonists", "insulin resistance", "fertility", and "weight loss". Relevant studies were identified and selected based on their relevance to the topic and their contribution to understanding metabolic, hormonal, and reproductive outcomes associated with the investigated therapies.

INCLUSION CRITERIA

Studies were considered eligible if they met the following criteria:

1. Original research articles, systematic reviews, meta-analyses, and translational studies involving patients with PCOS diagnosed according to recognized clinical criteria, including the Rotterdam criteria [2].
2. Interventions including metformin, GLP-1 receptor agonists, or their combination.
3. Reporting metabolic outcomes such as body mass index, waist circumference, HOMA-IR, fasting glucose, or lipid profile.
4. Reporting reproductive outcomes, including menstrual frequency, ovulation, or pregnancy outcomes.
5. Published in English as full text articles in peer-reviewed journals between 2015 and 2025.

EXCLUSION CRITERIA

Studies were excluded if they met one or more of the following criteria:

1. Studies not addressing metformin or GLP-1 receptor agonists in the context of PCOS.
2. Studies without a confirmed diagnosis of PCOS based on recognized clinical criteria or involving other endocrine disorders.
3. Studies conducted exclusively in animal models without clinical relevance.
4. Duplicate publications or studies published before 2015.

A total of 50 references were included in the review. These comprised randomized controlled trials, meta-analyses, systematic reviews, and experimental or translational studies. The findings were synthesized qualitatively, focusing on the metabolic and reproductive effects of metformin and GLP-1 receptor agonists and their underlying mechanisms of action.

RESULTS

METABOLIC OUTCOMES

GLP-1 receptor agonists were generally associated with greater reductions in body weight and metabolic markers compared with metformin alone in the included studies. Meta-analyses reported that treatment with liraglutide and exenatide was associated with reductions in body mass index (mean approximately −2.4 kg per m^2) and waist circumference (around 5 cm) [8,26]. Mean weight loss ranged from 5 to 7 kg over treatment periods of 12 to 24 weeks [8,10,11]. Improvements in fasting glucose and HOMA-IR were also reported in several studies, particularly in patients with obesity [11,27].

Metformin, although less effective for weight reduction, was associated with improvements in insulin sensitivity, fasting plasma glucose, and triglyceride levels [5,6]. Randomized clinical trials reported reductions in HOMA-IR and improvements in lipid profiles, with a more limited effect on visceral adiposity compared with GLP-1 receptor agonists [10,12,27].

Combination therapy with metformin and GLP-1 receptor agonists was associated with greater reductions in body mass index, approximately 3–4 kg per m², and improved glycemic control in some studies [13,15]. However, these findings are based on a limited number of studies with relatively short duration.

REPRODUCTIVE AND HORMONAL OUTCOMES

Metformin was associated with normalization of menstrual cyclicity in approximately 45–60% of women with PCOS and modest improvement in ovulatory frequency [5,6].

GLP-1 receptor agonists were associated with improvements in menstrual regularity and ovulatory function in several studies [9,14]. These changes were accompanied by reductions in serum total testosterone and in the luteinizing hormone to follicle-stimulating hormone ratio.

Some studies evaluating liraglutide and exenatide reported higher rates of spontaneous pregnancy and improved outcomes in assisted reproductive technologies compared with baseline or control groups [13,14,15].

Combination therapy with metformin and GLP-1 receptor agonists was associated with higher rates of spontaneous pregnancy in comparative studies, with reported values of up to approximately 30% compared with about 15% in metformin monotherapy [15]. However, these findings are based on a limited number of studies.

SUMMARY OF EVIDENCE

Table 1 summarizes the randomized controlled trials and meta-analyses included in this review that evaluated metformin and GLP-1 receptor agonists in women with PCOS [8–26]. The studies differ in design, sample size, duration, and assessed outcomes, which limits direct comparability.

Across the included studies, both treatment approaches were associated with improvements in metabolic parameters, including insulin resistance and body mass index, as well as with changes in hormonal and reproductive outcomes, as presented in Table 1. The magnitude of these effects varied depending on the intervention, study design, and patient characteristics [8–15,26].

In several short-term trials, GLP-1 receptor agonists were associated with greater reductions in body weight and, in some studies, with changes in androgen levels compared with metformin, as reflected in Table 1 [10,14]. Metformin was consistently associated with improvement in insulin sensitivity and metabolic parameters [5,6].

Studies evaluating combination therapy reported additional improvements in metabolic and reproductive outcomes compared with monotherapy in some settings, as summarized in Table 1 [13,15]. However, these findings are based on a limited number of studies with relatively small sample sizes and short follow-up periods, typically 12–24 weeks.

Table 1. Key Clinical Studies Comparing Metformin and GLP 1 Receptor Agonists in PCOS

Study	Design/N	Intervention	Duration	Metabolic Effects	Reproductive Outcomes	Notes
Jensterle 2015 [10]	RCT; n = 36	Liraglutide vs Metformin	12 weeks	BW −6.5 kg vs −1.2 kg; greater BMI reduction with GLP 1RA	Not primary endpoint	Small sample
Liu 2017 [12]	RCT; n = 176	Exenatide vs Metformin	24 weeks	Greater ↓ BMI and ↓ HOMA IR	Higher spontaneous pregnancy rate	Pregnancy not powered

Salamun 2018 [13]	RCT (IVF); n = 27	Liraglutide + Metformin vs Metformin	12 weeks (pre IVF)	Significant pre IVF weight loss	Higher clinical pregnancy rate	Assisted reproduction cohort
Nylander 2017 [14]	RCT; n = 65	Liraglutide vs Placebo	24 weeks	↓ Total and visceral fat; ↓ testosterone	Improved bleeding ratio	Placebo-controlled
De Hollanda Morais 2024 [8]	Meta-analysis; ~600	GLP 1RA vs controls	Variable	↓ BMI (−2.4 kg/m²); ↓ WC (−5.2 cm); ↓ triglycerides	↓ Testosterone	Heterogeneous RCTs
Zhou 2023 [9]	Systematic review; >800	GLP 1RA vs comparators	Variable	Consistent BMI reduction	↑ Ovulation & pregnancy (pooled)	Variable endpoints
Chen 2025 [15]	RCT; n = 80	Semaglutide + Metformin vs Metformin	16 weeks	BW −6.1 kg vs −2.2 kg	35% vs 15% natural pregnancy	Limited follow up
Niafar 2016 [11]	Meta-analysis; n=178	Liraglutide	3 months	↓ BMI −1.65 kg/m²; ↓ T −0.29 nmol/L	Hormonal improvement	Short duration
Sridharan 2025 [26]	Network meta-analisis; n=1476	GLP 1RA ± standard therapy	≥ 12 weeks	Greatest BMI reduction with combination therapy	Limited live birth data	Indirect comparisons

A structured comparison of metabolic, hormonal, and reproductive effects of metformin, GLP-1 receptor agonists, and their combination is presented in Table 2.

Overall, the available evidence remains heterogeneous, and differences in study design and endpoints limit the strength of direct comparisons between treatment strategies.

Table 2. Comparative Effects of Metformin and GLP 1 Receptor Agonists on Metabolic and Reproductive Outcomes in PCOS

Parameter	Metformin	GLP 1 Receptor Agonists (liraglutide, exenatide, semaglutide)	Combined Therapy (GLP 1RA + Metformin)
Primary mechanism of action	Activates AMPK, improves hepatic and peripheral insulin sensitivity [5, 6]	Stimulates GLP 1R, enhances satiety, slows gastric emptying, modulates hypothalamic and ovarian signaling [7, 8, 16–18]	Synergistic insulin sensitization and weight reduction [13, 15]

Effect on body weight / BMI	Mild reduction (≈ 1–2 kg/m²); plateaus with prolonged use [6, 10]	Significant decrease (≈ 2–3 kg/m²); mean weight loss 5–7 kg [8, 10, 26]	Greater total reduction (≈ 3–4 kg/m²) than either drug alone [15]
Visceral adiposity	Minor reduction [11]	Pronounced decrease in waist circumference (~ 5 cm) [8, 26]	Additive decrease [15]
Insulin resistance (HOMA IR)	Marked improvement [5, 6, 10]	Comparable or superior improvement, especially in obese phenotypes [11, 27]	Best improvement among all groups [13, 15]
Lipid profile	↓Triglycerides, ↑HDL modestly [5, 6]	↓Triglycerides, ↓LDL significantly [8, 26]	Synergistic normalization [15]
Serum testosterone / androgens	Slight to moderate reduction [5]	Marked reduction in total testosterone and LH/FSH ratio [9, 14, 28]	Strongest decrease [15]
Menstrual cyclicity / ovulation	Normalization in 45–60% of women [5, 6]	Improvement in ≥ 60–70% of cases [9, 13, 14]	Up to 80% normalization; enhanced ovulatory rate [15]
Pregnancy rate (spontaneous or IVF)	~ 10–15% in RCTs [5, 6]	20–25%, particularly in obese subgroups [13, 14]	~ 30% spontaneous pregnancy rate; improved IVF outcomes [13, 15]
Molecular effects on ovary	AMPK activation, improved insulin signaling [5, 6]	↓CYP17A1 and 17α hydroxylase, ↑FSHR/CYP19A1 expression in granulosa cells, antioxidative and anti inflammatory action [16–19, 43]	Combined AMPK and GLP 1R activation; mitochondrial homeostasis restoration [39, 40]
Adverse effects	Gastrointestinal symptoms (mild, transient) [50]	Nausea, early satiety, minimal reproductive toxicity [8, 21]	Mild GI symptoms; generally well tolerated [15]
Use in pre conception	Can be safely continued [50]	Should be discontinued before conception [21, 29–30]	Stop GLP 1RA before conception; continue metformin [30]
Overall clinical role	Safe first line insulin sensitizer, especially in lean or fertility focused phenotypes	Effective metabolic modulator for obese or insulin resistant phenotypes	Promising personalized combination for dual metabolic–reproductive optimization

DISCUSSION

Current evidence indicates that metformin and GLP-1 receptor agonists exert different therapeutic effects in women with PCOS. Metformin primarily improves insulin resistance through its effects on hepatic glucose production and systemic insulin sensitivity mediated by AMPK activation [5,6]. In contrast, GLP-1 receptor agonists act through central and peripheral mechanisms, including appetite regulation, reduced caloric intake, and changes in adipose tissue distribution, with potential additional effects on hormonal and inflammatory pathways [7,8,10,12,16–18,43].

Despite these differences, the available clinical evidence remains limited by short study duration, typically less than

24 weeks, and the lack of data on long-term reproductive outcomes such as live birth rates. Further well-designed, long-term studies are required to clarify the comparative effectiveness of these therapies and their role in different PCOS phenotypes.

GLP-1 SIGNALING AND ITS RELATIONSHIP TO OVARIAN FUNCTION: MOLECULAR MECHANISMS

Emerging experimental and translational evidence suggests that GLP-1 signaling may influence ovarian function in addition to its established systemic metabolic effects. GLP-1 receptors have been identified in human granulosa and theca cells, indicating a potential role in local regulation of steroidogenesis and follicular development [16,17,19,44]. Activation of the GLP-1 receptor leads to stimulation of adenylate cyclase and increased intracellular cAMP, which is associated with modulation of mitochondrial function, redox balance, and expression of steroidogenic enzymes [17,39].

In experimental models, GLP-1 receptor agonists have been shown to reduce the expression of key enzymes involved in androgen synthesis, including CYP17 and 17α-hydroxylase, resulting in decreased ovarian androgen production [17,18]. They have also been associated with increased granulosa cell proliferation and upregulation of genes involved in follicular development, such as FSHR, CYP19A1, and StAR [18,19,31].

In addition, GLP-1 signaling has been linked to anti-inflammatory and antioxidative effects. Reduced expression of pro-inflammatory cytokines and improvement of mitochondrial function in ovarian cells have been observed in preclinical studies [38,39,43]. These mechanisms may contribute to improvements in ovarian microenvironment, although their direct translation into clinical reproductive outcomes remains insufficiently established.

Modulation of the gut microbiota has also been proposed as an indirect pathway through which GLP-1 receptor agonists influence metabolic and endocrine regulation. This gut–ovary interaction may represent an additional mechanism linking metabolic improvement with reproductive function [20,49].

Overall, current evidence indicates that GLP-1 receptor activation may act through multiple interconnected pathways, including metabolic regulation, local ovarian effects, and modulation of inflammatory and mitochondrial processes. However, most mechanistic data are derived from experimental and translational studies, and their clinical relevance requires further confirmation in well-designed human studies.

EFFECT OF METFORMIN ON INSULIN RESISTANCE, MENSTRUAL FUNCTION AND FERTILITY

Metformin remains a widely used therapy for the management of insulin resistance in women with PCOS, primarily through its effects on hepatic glucose production and systemic insulin sensitivity [5,6]. Evidence from randomized trials and meta-analyses indicates that metformin is associated with reductions in HOMA-IR and fasting insulin levels, improvement in menstrual regularity, and a modest increase in spontaneous ovulation rates [5,6,10,11]. These effects appear to be more pronounced in non-obese or insulin-resistant individuals.

However, the impact of metformin on body weight and androgen levels is limited, particularly in patients with obesity, which has led to increasing interest in combination or alternative therapeutic approaches in this subgroup [8,11].

GLP-1 RECEPTOR AGONISTS IN METABOLIC AND REPRODUCTIVE REGULATION

GLP-1 receptor agonists, including liraglutide, exenatide, and semaglutide, have emerged as effective agents for weight reduction and metabolic improvement in women with PCOS [8,9,26]. Their effects are mediated through reduced appetite, increased satiety, and changes in adipose tissue distribution, leading to clinically meaningful reductions in body mass index of approximately 2–3 kg per m² and waist circumference of about 5 cm in clinical studies [8,10,26].

Available evidence also suggests that GLP-1 receptor agonists may reduce circulating androgen levels and influence the LH to FSH ratio, with associated improvements in menstrual regularity and ovulatory function [9,14,15]. However, these effects are not consistent across all studies and may be partly mediated by weight loss. The possibility of additional direct effects on ovarian function remains under investigation [16–19,31].

Combined and Phenotype-Specific Programs

Combination therapy with metformin and GLP-1 receptor agonists has been evaluated in recent clinical studies and may provide additional metabolic and reproductive benefits compared with monotherapy [13,15]. This approach targets different aspects of PCOS pathophysiology, including insulin resistance and adiposity. However, most available studies are short-term, typically 12–24 weeks in duration, and include relatively small sample sizes, with limited data on long-term outcomes such as live birth rates [8,9,26].

Current evidence does not allow definitive conclusions regarding phenotype-specific treatment strategies. Further studies with stratified patient populations and longer follow-up are required to clarify the role of individualized therapeutic approaches in PCOS.

LIMITATIONS

This narrative review has several important limitations that should be considered when interpreting the findings.

First, most included clinical studies were of short duration, typically less than 24 weeks, and did not assess long-term reproductive outcomes such as live birth rates. This limits the ability to evaluate sustained therapeutic effects and clinical relevance for fertility outcomes.

Second, the included studies are heterogeneous in terms of patient characteristics, including body mass index, degree of insulin resistance, and PCOS phenotype. This heterogeneity complicates direct comparison of results and limits generalizability across different patient subgroups.

Third, the review integrates evidence from randomized controlled trials, meta-analyses, systematic reviews, and experimental or translational studies. While this allows a broader understanding of potential mechanisms, it introduces variability in the level of evidence and limits the strength of causal inference.

Fourth, the number of direct head-to-head comparisons between metformin and GLP-1 receptor agonists is limited. As a result, some conclusions rely on indirect comparisons across studies with different designs and populations.

Finally, as a narrative review, this study does not follow a formal systematic review protocol, and study selection was based on relevance. This introduces a potential risk of selection bias and limits reproducibility.

CONCLUSION

1. Metformin is associated with improvement in insulin sensitivity, fasting glucose levels, and menstrual regularity in women with PCOS, and may be considered a suitable option in patients with predominant insulin resistance and in preconception settings, given its established safety profile.
2. GLP-1 receptor agonists are associated with greater reductions in body weight, body mass index, and waist circumference, and may be considered in patients with obesity or pronounced metabolic disturbances, although their effects on reproductive outcomes remain variable across studies.
3. Combination therapy with metformin and GLP-1 receptor agonists may provide additional metabolic and reproductive benefits in selected patients, particularly when both insulin resistance and excess adiposity are present, but current evidence is limited to short-term studies.
4. Mechanistic data suggest that GLP-1 receptor agonists may have effects beyond weight reduction, including potential influences on ovarian function, although these findings are largely derived from experimental and translational studies and require confirmation in clinical settings.
5. Current evidence indicates that metformin and GLP-1 receptor agonists exert complementary effects in the management of PCOS, but does not allow definitive conclusions regarding optimal treatment strategies for specific phenotypes.

Future research should focus on long-term randomized studies with standardized reproductive endpoints, including ovulation, pregnancy, and live birth rates, as well as on stratified analyses based on PCOS phenotypes. Integration of clinical outcomes with molecular and metabolic data is required to support individualized therapeutic approaches.

DISCLOSURE

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USE OF AI

The authors acknowledge that OpenAI's ChatGPT was used solely for language refinement, formatting uniformity, and organization of the manuscript. All scientific content, data interpretation, study design, and final approval were performed exclusively by the authors, guaranteeing that the intellectual responsibility and scholarly integrity of the work remain entirely their own.

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