TURLEJ, Kamil, KOWALCZUK, Dmytro, KASIANIK, Viktoryia, LAZITSKAYA, Darya, SOBCHYNSKYI, Mykola, MILASHEUSKAYA, Valeryia, MYRNYI, Andrii, KIEŁBASZEWSKA, Iga, SUROSZ, Natallia and MIRANIUK, Katsiaryna. The Potential Role of Glucagon-Like Peptide-1 Receptor Agonists in Polycystic Ovary Syndrome: A Narrative Review. Quality in Sport. 2025;43:61264. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.43.61264
https://apcz.umk.pl/QS/article/view/61264

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 21.05.2025. Revised: 05.07.2025. Accepted: 05.07.2025. Published: 07.07.2025.

The Potential Role of Glucagon-Like Peptide-1 Receptor Agonists in Polycystic Ovary Syndrome: A Narrative Review

TURLEJ, Kamil, KOWALCZUK, Dmytro, KASIANIK, Viktoryia, LAZITSKAYA, Darya, SOBCHYNSKYI, Mykola, MILASHEUSKAYA , Valeryia, MYRNYI, Andrii, KIEŁBASZEWSKA, Iga, SUROSZ, Natallia and MIRANIUK, Katsiaryna

Kamil Turlej* [KT], MD

University Clinical Center of the Medical University of Warsaw
Banacha 1A, 02-097 Warsaw, Poland
kturlej99@gmail.com
https://orcid.org/0009-0008-2919-284X

Dmytro Kowalczuk* [DK], MD
Międzyleski Specialist Hospital in Warsaw
Bursztynowa 2, 04-749 Warsaw, Poland
dmytro.kovalchuk1999@gmail.com
https://orcid.org/0009-0004-1433-5052

Viktoryia Kasianik [VK], MD
Mazovian Rehabilitation Center STOCER Ltd. Saint Anna Trauma Surgery Hospital
Barska 16/20, 02-315 Warsaw, Poland
wiktoriakasianik@gmail.com
https://orcid.org/0009-0004-1540-5227

Darya Lazitskaya [DL],MD
Międzyleski Specialist Hospital in Warsaw
Bursztynowa 2, 04-749 Warsaw, Poland
datskayalo@gmail.com
https://orcid.org/0009-0007-8680-8826

Mykola Sobchynskyi [MS], MD
Międzyleski Specialist Hospital in Warsaw
Bursztynowa 2, 04-749 Warsaw, Poland
sobczynski0@gmail.com
https://orcid.org/0009-0008-1804-1114

Valeryia Milasheuskaya [VM], MD
valeryiamilasheuskaya@gmail.com
https://orcid.org/0009-0006-4126-2375

Andrii Myrnyi [AM], MD
University Clinical Center of the Medical University of Warsaw
Banacha 1A, 02-097 Warsaw, Poland
andmyrnyi@gmail.com
https://orcid.org/0009-0006-5592-259X

Iga Kiełbaszewska [IK], MD
Independent Public Healthcare Centre in Hajnówka
Doc. Adama Dowgirda 9, 17-200 Hajnówka, Poland
kielbaszewska.i@gmail.com
https://orcid.org/0009-0004-9892-4769

Natalia Surosz [NS], MD
Międzyleski Specialist Hospital in Warsaw
Bursztynowa 2, 04-749 Warsaw, Poland
natalia.surosz@gmail.com
https://orcid.org/0009-0005-1939-151X

Katsiaryna Miraniuk [KM], student
Medical University of Warsaw
Żwirki i Wigury 61,02-091 Warsaw, Poland
mironk2711@gmail.com

https://orcid.org/0009-0006-1406-9756

ABSTRACT:

This narrative review explores the potential therapeutic role of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) in the management of Polycystic Ovary Syndrome (PCOS). PCOS is a multifaceted challenge affecting women, often associated with genetic susceptibility, obesity, and insulin resistance. The review seeks to provide a nuanced understanding of the interconnected health concerns of obesity and infertility in women with PCOS and critically analyse current data on the use of GLP-1 RAs as a potential treatment strategy in comparison to standard management of PCOS. It focuses on evaluating their impact on weight loss and associated metabolic parameters, drawing upon evidence from preclinical and clinical studies. While promising results have been observed, including potential benefits on endocrine and reproductive parameters, concerns regarding long-term safety, including serious adverse events, warrant further investigation. This review aims to summarise the current understanding of GLP-1 RAs in PCOS and highlight areas requiring additional research to fully establish their place in comprehensive PCOS management

Aim of the Study:

The review seeks to provide a nuanced understanding of the interconnected health concerns of obesity and infertility in women with Polycystic Ovary Syndrome (PCOS) and critically analyse current data on the use of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) as a potential treatment strategy in comparison to standard management of PCOS, such as Metformin, Inositol or Bariatric Surgery treatment.

Key words:

Polycystic Ovary Syndrome, Glucagon-Like Peptide-1 Receptor Agonists, Obesity, Fertility

Introduction:

Polycystic Ovary Syndrome (PCOS) stands as the most prevalent endocrine disorder affecting women of reproductive age, with prevalence estimates ranging from approximately 6% to 20% globally, and affecting up to 18% in some populations. (1,2) It is recognised as one of the most widely recognised endocrine problems in this demographic. PCOS is a heterogeneous and complex condition characterised by a combination of features including chronic anovulation or oligo-anovulation, clinical or biochemical hyperandrogenism, and/or polycystic ovaries(3,4). Hyperandrogenism can manifest as hirsutism, acne, or male-pattern hair loss[5]. The disorder presents a multifaceted challenge as it extends beyond reproductive aspects to encompass metabolic and psychological dimensions.

A significant proportion of women with PCOS are either overweight or obese, ranging from 38% to 88% (1,2) and many also experience insulin resistance, estimated to affect 50% to 90%(6). These metabolic issues contribute to an increased risk of conditions such as type 2 diabetes mellitus (T2DM), hypertension, and hyperlipidemia. Reproductive disorders are also common in patients with PCOS, including infertility, miscarriages, premature birth, and gestational diabetes(6). The diverse manifestations of PCOS significantly impact health and quality of life, highlighting the importance of timely diagnosis and appropriate treatment.

Current management strategies for PCOS are often based on symptomatic treatment (7), focusing on addressing the patient's main concerns, such as ovarian dysfunction, hyperandrogenism, and metabolic alterations. Weight loss is widely considered a crucial first-line intervention, as even modest reductions can potentially improve various hormonal, cardiometabolic, and reproductive parameters. However, achieving and sustaining significant weight loss through lifestyle interventions alone can be challenging, often necessitating pharmacological support. Metformin, a drug that sensitizes cells to insulin, is frequently used, although its effectiveness can vary.

Metformin is widely used for treating hyperglycemia, hyperinsulinism, and even hyperandrogenism by improving glucose uptake and insulin sensitivity(1). It is recommended in PCOS guidelines for managing anthropometric and metabolic outcomes in women with a BMI of 25 kg/m² or higher and should be used as a first-line treatment(8). However, Metformin is associated with unsatisfactory benefits in terms of weight loss for some patients(4,9).

GLP-1 RAs have emerged as potential therapeutic options for PCOS due to their favorable effects on metabolism and weight loss(10). They mimic the effect of the GLP-1 hormone, which is responsible for stimulating insulin secretion in a glucose-dependent manner, inhibiting glucagon secretion, and slowing gastric emptying, leading to delayed glucose absorption[2]. GLP-1 RAs also promote satiety by affecting pathways in the brain, thus decreasing food-seeking behavior and increasing muscle metabolism(2). Liraglutide and semaglutide, specific GLP-1 RAs, are approved by the FDA for obesity treatment(11,12,13)

This narrative review explores the potential therapeutic role of GLP-1 Receptor Agonists in the management of PCOS. It focuses on evaluating their impact on weight loss and associated metabolic parameters, drawing upon evidence from preclinical and clinical studies. While promising results have been observed, including potential benefits on endocrine and reproductive parameters, concerns regarding long-term safety, including serious adverse events, warrant further investigation. This review aims to summarise the current understanding of GLP-1 RAs in PCOS and highlight areas requiring additional research to establish their place in comprehensive PCOS management.

Materials and Methods:

PubMed and Google Scholar databases were searched using appropriate keywords to identify relevant studies published from January 1, 2021, to May 7, 2025. Titles and abstracts were initially screened for relevance, followed by a thorough review of selected full-text articles. Studies were included based on their clinical significance and methodological rigor. No restrictions were applied regarding study design (e.g., prospective, retrospective, case series, or review articles).

Results:

Recent investigations have illuminated a multitude of potential mechanisms through which GLP-1 RAs may exert influence on the management of PCOS. Within this comprehensive review, we have employed a structured approach, categorizing the extant literature into distinct thematic sections to facilitate a systematic analysis of the diverse facets under investigation.

Weight Loss:

Studies investigating GLP-1 RAs in overweight or obese women with PCOS consistently report effects on body weight and related measures, frequently comparing these effects to those of Metformin monotherapy. Anthropometric outcomes commonly evaluated include body weight[2], Body Mass Index (BMI)(2), Waist Circumference (WC)(2), Abdominal Girth (AG)(10), and Waist-to-Hip Ratio (WHR)(10).

Studies indicate that GLP-1 RAs are effective for weight loss in women with PCOS. Liraglutide, a GLP-1 RA, at a dose of 1.8 mg/day for 26 weeks, resulted in a significant body weight loss of over 5% in overweight women with PCOS, also leading to substantial reductions in liver fat (44%) and visceral adipose tissue (18%)(7). Even a smaller dose of liraglutide (1.2 mg/day) for 12 weeks was associated with significant weight reduction and improved eating behaviour in women with PCOS. Another study found that liraglutide or roflumilast resulted in significantly greater BMI reductions compared to metformin in women with obesity and PCOS. Semaglutide, another GLP-1 RA, has shown a stronger weight-loss effect than liraglutide in mouse models. GLP-1 RAs like liraglutide and semaglutide regulate appetite and food desirability by acting on the hypothalamus, where GLP-1 receptors are expressed, contributing to their weight loss effects. Semaglutide at 2.4 mg once weekly has demonstrated efficacy for weight loss in adults with overweight or obesity in clinical trials (18). Tirzepatide, another related medication, has also shown significant weight loss effects. The weight loss achieved with medications like semaglutide and tirzepatide can be on par with that typically seen after bariatric surgery procedures like the gastric sleeve or Roux-Y procedure, which usually results in around 60–70% of excess weight loss. However, weight regain can occur after the withdrawal of semaglutide(19). Data from an observational study focusing on obese women with PCOS treated with metformin provides specific insights into weight regain after semaglutide withdrawal in this particular population. In this study, women with PCOS and obesity received a short-term intervention (16 weeks) with semaglutide (up to 1 mg weekly) as an adjunct to metformin therapy (2000 mg/day) and lifestyle intervention. Following the 16-week semaglutide phase, the medication was discontinued, but treatment with metformin (2000 mg/day) and promotion of lifestyle intervention were continued for a two-year follow-up period(21). During the semaglutide treatment phase, these women achieved significant body weight loss. Over the two years after discontinuing semaglutide, they regained about one-third of their prior weight loss(21). The authors noted that this regain of approximately one-third contrasts with the two-thirds regained by participants in the STEP 1 extension study over one year after stopping semaglutide. Despite this regain, there was still a statistically significant net weight loss from baseline to the end of the two-year follow-up period in this PCOS/metformin group. At the conclusion of the study, 21 out of 25 subjects (84%) had lower body weight compared to their baseline weight(21). The study also highlighted highly heterogeneous individual responses to weight trajectory after stopping semaglutide; some individuals continued to lose weight, some remained stable, and some regained weight but stayed below their starting weight.

Researchers in this study hypothesised that metformin might partially prevent weight regain after semaglutide-induced weight loss, particularly in insulin-resistant populations like women with PCOS. They noted that some studies suggest metformin could help stabilise progressive body weight regain in women with PCOS and proposed that their observational study provided initial insights into a potential strategy for partially overcoming adaptive mechanisms leading to weight regain. Further exploration is needed to confirm the role of metformin in attenuating weight regain after semaglutide discontinuation(21).

Semaglutide works, in part, by delaying gastric emptying, which contributes to feelings of fullness and reduced food intake. Upon stopping the medication, this effect may diminish, potentially contributing to weight regain(21,22).

Another scenario where semaglutide withdrawal occurs is when planning for pregnancy. For women attempting to conceive, it is recommended to stop semaglutide two months before trying to conceive. Similarly, tirzepatide requires a two-month stopping period, while liraglutide requires two weeks. While these sources specify the

duration for stopping, they do not provide details on the pattern or extent of weight regain specifically in the context of discontinuing for conception(22).

In summary, while weight regain is a known effect after stopping semaglutide, the degree of regain can vary. In obese women with PCOS who continued metformin and lifestyle interventions, regain was observed but a significant portion of the initial weight loss was maintained over two years, contrasting with potentially greater regain seen in other studies. Continued use of the medication is typically required to maintain the weight loss achieved with GLP-1 RAs. The long-term safety implications of weight fluctuations after discontinuing these medications also warrant consideration.

Metformin, while not explicitly FDA-approved as a primary weight loss medication, has been widely used for weight management in specific populations, including women with PCOS. Metformin is recommended in PCOS guidelines for managing anthropometric and metabolic outcomes in women with a BMI of 25 kg/m2 or higher(21).

When comparing GLP-1 RA monotherapy to Metformin monotherapy in women with PCOS, the results regarding weight loss outcomes have varied across studies. One study found that both Exenatide (10 μg BID) and Metformin (1000 mg BID) led to significant decreases in body weight, BMI, and abdominal girth over 12 weeks, but there was no significant difference between the two groups for these anthropometric outcomes (6). In contrast, another study comparing Exenatide (10 μg BID) to Metformin (1000 mg BID) over 12 weeks in overweight or obese women with PCOS (BMI $\geq$ 24) found that Exenatide resulted in greater weight loss (-4.29 $\pm$ 1.29 kg) compared to Metformin (-2.28 $\pm$ 0.55 kg) (25). This latter study also observed decreases in android fat mass % and total fat mass % with Exenatide, which were not noted with Metformin.

Combining GLP-1 RAs with Metformin has also been investigated for its effects on weight loss in women with PCOS. A meta-analysis focusing on overweight and obese women with PCOS found significant reductions in BMI with Exenatide plus Metformin combination therapy compared to Metformin monotherapy (7). A study comparing Metformin alone, Exenatide alone, and a combination of Metformin plus Exenatide in overweight, insulin-resistant, oligoovulatory women with PCOS over 24 weeks reported different degrees of body weight loss: -1.6 $\pm$ 0.2 kg with Metformin, -3.2 $\pm$ 0.1 kg with Exenatide, and a more substantial loss of -6.0 $\pm$ 0.5 kg with the combination therapy (28). Based on these findings, this study concluded that the combination therapy was superior in terms of body weight reduction compared to either medication alone (15). However, other studies comparing Liraglutide plus Metformin to Metformin alone over 12 weeks in women with PCOS found significant decreases in body weight, BMI, and waist circumference within both groups, but reported no significant difference between the combination and Metformin alone groups for these anthropometric changes (25). Similarly, another 12-week study comparing Metformin alone to Metformin plus Liraglutide in women with PCOS undergoing IVF also observed weight loss in both groups, with no significant difference in weight change between the groups (6).

Regarding other weight loss interventions, lifestyle changes including a balanced and monitored diet and physical activity are considered crucial.(1,7,22) A ketogenic or low-carbohydrate diet has been reported to improve weight in women with PCOS. Bariatric surgery is recognised as an effective long-term solution for sustained weight loss, especially for individuals with higher BMIs.(22)

As for surgical management, the most common procedure is gastric sleeve which typically results in about 60–70% of excess weight loss, which can be comparable to the weight loss achieved with semaglutide and tirzepatide(22). It is associated with successful treatment of morbid obesity and leads to significant weight loss(28). Following bariatric surgery, studies have highlighted benefits in women with PCOS, including metabolic improvements such as significant weight loss and enhanced glucose homeostasis, as well as hormonal improvements, notably significant reductions in total testosterone levels(6).

There is evidence suggesting improved fertility in women who lose weight after bariatric surgery compared with women with severe obesity(6). A recent multicentre randomised trial, the BAMBINI trial, assessed the effectiveness of bariatric surgery compared to medical treatments in promoting spontaneous ovulation in obese women with PCOS and either oligomenorrhea or amenorrhea. The study enrolled 80 women and demonstrated superior ovulation rates in the bariatric surgery group, suggesting a potential improvement in spontaneous fertility(10).

Hormonal changes occur after bariatric surgery, including an increase in levels of anorexigenic hormones like GLP-1 and PYY, and a reduction in ghrelin, an orexigenic hormone(6). These changes are potentially beneficial

in the context of PCOS due to their positive effects on appetite regulation, metabolism, and the hormonal imbalances associated with the condition. However, it remains to be determined whether the benefits on fertility following bariatric surgery are solely mediated by weight loss or also by these hormonal changes, such as the increase in GLP-1 levels. Furthermore, it is unclear whether the improved fertility outcomes are solely due to significant weight loss, which can now be accomplished via non-surgical means with GLP-1 RAs, or through possible direct effects on the female reproductive tract itself.

According to the American Society for Metabolic and Bariatric Surgery, bariatric surgery should be considered for individuals with a BMI > 35, regardless of comorbidities, or > 30 with any obesity-related conditions. It might be considered a "last resort option" for patients who have already unsuccessfully attempted other forms of treatment.(27)

However, bariatric surgery is a major surgical intervention that carries potential risks and complications affecting various bodily systems. (27)These can include nutritional deficiencies, hepatobiliary complications, gastrointestinal issues, neurological complications, and gynaecological complications. Close monitoring and regular follow-up appointments are necessary to manage these risks(32).

For women planning conception, most recommendations advise waiting 1–2 years after bariatric surgery before attempting pregnancy. This waiting period is intended to allow for maximum preconception weight loss and to identify and treat any concomitant nutritional deficiencies. This recommended wait time may not be an option for women of advanced age or women with diminished ovarian reserve who wish to conceive in a shorter period(22).

Compared to GLP-1 RAs, bariatric surgery offers high efficacy for weight loss but carries a greater risk of complications(32). While GLP-1 RAs are also effective for weight loss and improving metabolic parameters in women with PCOS, one study suggested endoscopic sleeve gastroplasty might be cost-saving compared to semaglutide over 5 years for class II obesity, but data on other surgeries is lacking(25). Furthermore, GLP-1 RAs are now being used as a safe and effective treatment for weight regain or insufficient weight loss in patients who have previously undergone metabolic bariatric surgery(32).

Other pharmacological options include Qsymia (phentermine/topiramate), which demonstrated significant weight loss in studies (e.g., 10.9% average weight loss compared to 1.6% with placebo over 56 weeks)(22). Phentermine alone has shown efficacy for short-term weight loss, with patients losing around 5% of their starting weight. Orlistat, a lipase inhibitor, has been shown to reduce weight in women with PCOS(22). A meta-analysis found that liraglutide promotes higher weight loss rates than the combination of orlistat plus metformin in women with overweight/obesity and PCOS(12).

Naltrexone/Bupropion is another medication for chronic weight management that has shown effectiveness in trials. In contrast to these agents, a meta-analysis comparing Myo-inositol to Metformin found no significant difference between the two regarding changes in BMI, weight, or waist circumference (30). Dulaglutide combined with a calorie-restricted diet resulted in a 7% weight loss in a significantly shorter time compared to the diet alone, although there was no notable difference in visceral adipose tissue reduction between the groups

Metabolic impact

Metabolic dysfunction is a core feature of PCOS, often driven by insulin resistance and abdominal obesity, significantly increasing the risk of conditions like type 2 diabetes mellitus and cardiovascular diseases (CVD)(1,23). Therefore, reporting the impact of GLP-1 RAs on these metabolic parameters is crucial.

Glucose Metabolism

Among women with PCOS, a prevalent metabolic feature is insulin resistance, often accompanied by hyperinsulinaemia (2). This metabolic dysfunction affects glucose metabolism, which fundamentally involves the processes of glucose breakdown for energy, synthesis, and storage, largely regulated by insulin (2). Treatments for PCOS, including Metformin and GLP-1 RAs, target these metabolic pathways. GLP-1 RAs activate GLP-1 receptors throughout the body, leading to a variety of effects including enhanced insulin sensitivity. GLP-1, along with Glucose-dependent Insulinotropic Polypeptide, are incretin hormones that stimulate insulin release in a glucose-dependent manner (2). They have also been shown to stimulate insulin gene expression and increase cyclic AMP levels in beta cells. Exenatide, a GLP-1 RA, is noted for its resistance

to degradation by the DPP-4 enzyme. Metformin, in contrast, primarily reduces hepatic glucose production and improves peripheral insulin sensitivity (25).

Studies comparing these interventions in women with PCOS have assessed various metabolic outcomes, including Fasting Plasma Glucose (FPG), Fasting Insulin (FINS), 2-hour Postprandial Blood Glucose (2hPBG), 2-hour Insulin (2hINS), and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)(2,14). A study by Xing et al. comparing Liraglutide plus Metformin to Metformin alone over 12 weeks in women with PCOS found that both groups showed significant decreases in FPG and HOMA-IR, but there was no significant difference between the combination group and the Metformin group in the extent of these decreases(2).. Similarly, a 2019 study by Zheng et al. comparing Exenatide and Metformin for 12 weeks in women with PCOS also reported significant decreases in Body weight, BMI, abdominal girth, and HOMA-IR in both groups, with no significant difference between the groups for these decreases.(6)This specific finding from the 2019 Zheng study regarding HOMA-IR appears to contrast with the results of another study, which indicated a greater decrease in HOMA-IR and insulin levels with Exenatide than with Metformin[(6). Despite these variations in findings regarding comparative efficacy for insulin resistance markers, a study by Tao et al. specifically in women with PCOS and prediabetes found that the remission rate of prediabetes was significantly higher in the Exenatide group and the combination (Exenatide plus Metformin) group compared to the Metformin group alone(15).

Beyond standard insulin resistance metrics, studies have also evaluated broader metabolic impacts. The 2019 Zheng et al. study reported no effect on lipid profiles with either Exenatide or Metformin treatment over the 12-week period. A meta-analysis (Al-Qudah et al. 2025) of Exenatide plus Metformin versus Metformin alone in women with PCOS included evaluation of metabolic outcomes such as OGTT results, BMI changes, and detailed lipid panel components, alongside insulin resistance(6). While noting the potential for superior efficacy, this meta-analysis also highlighted that patient adherence might be lower with combination therapy compared to monotherapy. This reduced adherence may limit the actual clinical benefits, partly due to gastrointestinal disturbances such as nausea, vomiting, abdominal pain, constipation, and diarrhoea, which are identified as common adverse effects of GLP-1 RAs and tend to have a higher prevalence with combination therapy. Therefore, while both Metformin and GLP-1 RAs demonstrate beneficial effects on glucose metabolism in women with PCOS, their comparative effectiveness on specific insulin resistance markers can vary across studies, and potential side effects of GLP-1 RAs may influence their overall clinical impact(15).

Lipid Metabolism

The impact of GLP-1 RAs on lipid profiles should also be reported, focusing on Total Cholesterol (TC), triglycerides (TG), High-Density Lipoprotein cholesterol (HDL-C), and Low-Density Lipoprotein cholesterol (LDL-C)(2).

While some studies suggest beneficial effects, the results on lipid metabolism in women with PCOS treated with GLP-1 RAs are not always consistent. One study comparing CPA/EE + Metformin and GLP-1 RA + Metformin found that the GLP-1 RA + Metformin group was more effective in reducing TC[2]. A meta-analysis comparing GLP-1 RAs versus placebo showed a significant reduction in serum triglycerides, but no significant difference in total cholesterol levels[11]. Another study noted that fasting total cholesterol, HDL, LDL cholesterol, and triglycerides did not change significantly in the studies reviewed. Exenatide has been assessed for its effects on blood lipids, including TC, TG, FFA, LDL-C, and HDL-C(3).

Beyond standard lipid panels, the impact on liver fat (steatosis) is increasingly relevant given its strong association with metabolic syndrome and insulin dysfunction[20]. Although hepatocytes may not express GIPR and GLP-1R directly, incretins like GLP-1 have indirect effects on hepatic lipid and glucose metabolism(20). Animal studies suggest GLP-1 RAs might have effects on nonalcoholic fatty liver disease and endoplasmic reticulum stress[19], and new techniques for assessing liver fat non-invasively are emerging. While not explicitly stated for PCOS patients in these sources, studies on semaglutide therapy in other populations have assessed CT-based body composition change(20), which could include fat distribution.

Energy Metabolism and Body Composition

GLP-1 RAs are known for their effects on appetite and satiety(2) leading to reduced food intake and subsequent weight loss(2,25) This impact on energy balance is a key driver of the anthropometric changes observed.

Animal studies provide insight into the mechanisms. GLP-1 RAs can influence food intake(12,19). Investigations into the metabolic effects in mouse models of PCOS revealed a predominant action in suppressing food intake(4). While short-term metabolic analyses showed limited effects on energy expenditure, thermogenic function, or locomotor activity, changes in respiratory quotient indicated greater fat oxidation after treatment with certain multi-agonists[(4) These findings suggest that reduced caloric intake and potentially increased fat utilisation contribute to weight loss. The effects on food intake and body weight with GLP-1-based therapies in humans are generally not due to food aversion or malaise[(4). Some animal studies also assessed body composition, specifically fat and lean mass, using nuclear magnetic resonance technology[4]. Semaglutide showed a stronger weight-loss effect than liraglutide in PCOS model mice, despite similar reductions in food intake, suggesting other mechanisms may be involved(13)..

In summary, the metabolism section should synthesize findings across glucose and lipid profiles, highlighting improvements where observed and noting any conflicting results or areas requiring further research. Integrating insights from body composition analysis and studies on energy metabolism can provide a more complete picture of how GLP-1 RAs influence the metabolic state in women with PCOS.

Fertility

Metabolism and reproduction are fundamental and interdependent aspects of mammalian physiology(22). Adequate metabolic homeostasis is important for reproductive health(22). Both energy deficiency and hypercaloric conditions, such as obesity, are associated with decreased fertility(22). Approximately 30% of women in the United States have a pre-pregnancy body mass index classified as obese[22]. Obesity is well established as increasing the risk of numerous complications once pregnancy is achieved, including abnormalities of fetal growth, stillbirth, thromboembolism, and delivery complications(26,27). Obesity is also linked with infertility and poorer outcomes in assisted reproductive technology, even in the absence of polycystic ovary syndrome (PCOS)(26). The pathophysiology by which obesity may lead to subfertility can involve mechanisms such as elevated circulating estrogen levels due to aromatase activity in excess adipose tissue, interference with the hypothalamic-pituitary-ovarian axis, and a chronic inflammatory state that might affect folliculogenesis, oocyte quality, embryo development, and the uterine micro-environment for implantation and placentation(22).

The general fertility rate in the United States decreased by 3% from 2022, reaching a historic low(7). This decline could potentially lead to an increase in the prescribing of GLP-1s, as clinical trials have indicated an improvement in fertility rates among women with T2D, PCOS, or obesity who are on GLP-1s3.... Robust evidence from clinical trials demonstrates the multi-benefit nature of GLP-1 analogs(7). A pharmacological approach specifically targeting the metabolic dysfunction associated with PCOS is essential, and the therapeutic class of GLP-1 RAs shows promising potential(2). Current data generally support the benefits of GLP-1 RAs on several pathological aspects of PCOS, including the improvement of menstrual cycles and glucose homeostasis5. Preconception treatment with GLP-1 RAs might provide some novel strategies in obesity, diabetes, and PCOS-associated subfertility(7).

Specifically, a meta-analysis comparing Exenatide versus Metformin in women with PCOS found that Exenatide was significantly more effective than metformin in treating these patients, as demonstrated by an increased pregnancy rate and a greater ovulation rate. This study found moderate to high-quality evidence for these effects(10). The beneficial effects of Exenatide on fertility in this patient population might be related to improvements in insulin resistance and weight control[10]. Exenatide was also found to improve several aspects of follicle morphology(27). Compared to Metformin, Exenatide was more effective at increasing sex hormone-binding globulin (SHBG) and follicle-stimulating hormone (FSH) and decreasing dehydroepiandrosterone sulfate (DHEA-S), which suggests that its superior effectiveness in improving reproductive function may be due to its effects on these hormone levels, potentially indirectly by lowering insulin resistance[(10).

Specifically, a meta-analysis comparing Exenatide versus Metformin in women with PCOS found that Exenatide was significantly more effective than Metformin in treating these patients(10). This meta-analysis demonstrated an increased pregnancy rate with Exenatide compared to Metformin (relative risk (RR) = 1.93, 95% confidence interval (CI) 1.28 to 2.92, P = 0.002). It also found a greater ovulation rate with Exenatide (RR = 1.41, 95% CI 1.11 to 1.80, P = 0.004). This study found moderate to high-quality evidence for these effects. The beneficial effects of Exenatide on fertility in this patient population might be related to improvements in insulin resistance and weight control. The meta-analysis found that Exenatide was also more effective than Metformin at promoting weight loss (mean difference (MD) = -1.72 kg/m², P=0.00001) and improving insulin resistance

(standard mean difference (SMD) = -0.62, P < 0.0001). Exenatide significantly improved various metabolic parameters, including HOMA-IR, FPG, 2hPBG, FINS, and 2hINS, compared to Metformin(5). Compared to Metformin, Exenatide was more effective at increasing sex hormone-binding globulin (SHBG) and follicle-stimulating hormone (FSH) and decreasing dehydroepiandrosterone sulfate (DHEA-S). This suggests that its superior effectiveness in improving reproductive function may be due to its effects on these hormone levels, potentially indirectly by lowering insulin resistance. Both drugs had similar effects on other sex hormone indices like total testosterone (TT), luteinizing hormone (LH), and free androgen index (FAI)(10). Individual studies contributed data to such meta-analyses. For example, a study by Elkind-Hirsch et al. in 2008 compared Exenatide (10 ug BID) and Metformin (0.5g TID) over 24 weeks in women with PCOS, measuring outcomes including pregnancy rate, ovulation rate, SHBG, DHEA-S, FSH, and LH, among others(10). Another study by Zheng et al. in 2019 compared Exenatide (10 μg BID) and Metformin (1,000 mg BID) for 12 weeks in women with PCOS(6). This study found significant decreases in body weight, BMI, abdominal girth, and HOMA-IR in both groups, with no significant difference between the groups. It also found that SHBG was raised in both groups, again with no significant difference between the groups, and no effect on testosterone, LH, or the LH/FSH ratio. A study by Tao et al. in 2021 also compared Exenatide (10 μg BID) and Metformin (1,000 mg BID) for 12 weeks in women with PCOS and prediabetes, finding a significantly higher remission rate of prediabetes in the Exenatide and combination groups(6). Another study indicated that natural pregnancy rates were significantly higher following exenatide treatment compared to metformin treatment (43.60% versus 18.70%)(10). In a study involving women with PCOS undergoing controlled ovarian stimulation after preconception treatment, the pregnancy rate per embryo transfer was significantly higher in a group treated with liraglutide plus metformin compared to metformin alone (85.7% versus 28.6%)(28). The cumulative pregnancy rate over 12 months was also higher in the liraglutide plus metformin group. These results were observed even though both treatment interventions led to a comparable reduction in body weight and visceral adipose tissue, suggesting that the underlying mechanisms might extend beyond mere weight reduction(29). Studies evaluating GLP-1s or GLP-1 RAs in women with PCOS have included fertility outcomes such as conception, clinical pregnancy, pregnancy rate per embryo transfer, delivery rate, miscarriage rate, and the number of singleton and multiple pregnancies(29). It is noted that ovulation rate was improved with DCI (D-chiro-inositol) compared to placebo in a meta-analysis of two trials(17). Inositol is widely used and promoted for PCOS management(17).

In contrast, Orlistat does not appear to have a positive effect on fertility(22). Studies found no differences between Orlistat and placebo groups regarding live births, conception, clinical pregnancy, or pregnancy loss, despite Orlistat resulting in statistically significant weight loss(22). The study concluded that an intensive preconception lifestyle intervention including orlistat did not improve the rate of live birth, pregnancy rates, or time to pregnancy compared to an activity-based intervention that did not result in weight loss(22). Thus, even with weight loss, Orlistat had no positive effects on fertility outcomes. A non-significant trend toward higher rates of miscarriage was noted in the Orlistat group, which was attributed by the authors to decreased absorption of long-chain polyunsaturated fatty acids after implantation(22). The development of vitamin D deficiency with Orlistat may also play a role, as studies have shown that women with normal vitamin D levels are more likely to conceive and experience improved implantation and a decreased risk of pregnancy-related complications(22).

The impact of the newer injectable medications that cause dramatic weight loss, such as GLP-1 RAs, on future fertility in healthy non-PCOS obese women is currently unclear[30]. This is because most studies conducted to date have significant limitations or were performed in animals with conflicting findings(30). Due to the increasing use of these agents and the high rates of unintended pregnancies in the US, there will be a higher prevalence of periconceptional exposure, making it important to understand the potential ramifications better(29).

Safety

GLP-1 RAs are generally considered to have a well-established favourable risk-benefit balance. However, their use is associated with certain adverse events and potential risks that are important to consider.

One of the most frequently reported issues and a significant factor in reduced adherence to GLP-1 RA-based therapies, particularly when used in combination, is the occurrence of gastrointestinal disturbances. These side effects are well-documented (6,15). Common gastrointestinal symptoms include nausea, vomiting, abdominal pain, constipation, and diarrhoea (6). One meta-analysis noted that gastrointestinal disturbances tended to be more prevalent with combination therapy involving Exenatide plus Metformin compared to Metformin monotherapy, with nausea being particularly notable in the combination group (28). A separate comparison of Liraglutide 3.0 mg versus placebo reported a high incidence of nausea in the Liraglutide group (48.4%) compared to placebo (7.1%), alongside higher rates of gastroenteritis (23.7% vs 13.3%), constipation (18.3% vs

12.2%), diarrhoea (15.1% vs 10.2%), fatigue (14.0% vs 8.2%), and vomiting (12.9% vs 2.0%) [22]. A meta-analysis comparing Myo-inositol to Metformin also assessed gastrointestinal side effects across six randomised controlled trials (RCTs). This analysis specifically highlighted a serious risk of bias concerning the assessment of these side effects. It found that Myo-inositol was favoured over Metformin regarding GI side effects(17).

Beyond these common issues, potential serious risks have also been raised. One source references a paper from 2011 that discusses pancreatitis, pancreatic cancer, and thyroid cancer in relation to glucagon-like peptide-1-based therapies (7). While the provided sources do not offer detailed findings on the prevalence or association of these specific serious risks within the PCOS population, the contraindications listed for some medications in a comparative table (which includes GLP-1 RAs alongside other weight loss drugs) include a personal or family history of medullary thyroid cancer or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2), and a history of prior pancreatitis or biliary disease (7). This suggests that individuals with such histories may be at increased risk or should avoid these therapies.

For women with PCOS, particularly those considering pregnancy, the safety of GLP-1 RAs is a crucial aspect. Recent studies evaluating preconception interventions in overweight or obese women with PCOS using exenatide or liraglutide in combination with metformin have reported no important safety issues (28). These findings support the continuation of research in this area, provided there is careful monitoring.

However, it is essential to be aware of the recommendations for discontinuing certain GLP-1 RAs when planning a pregnancy due to potential risks, including teratogenicity. The recommended stop times before attempting to conceive are: Liraglutide: 2 weeks, Semaglutide: 2 months, and Tirzepatide: 2 months(22). While the table discussing these drugs lists "teratogenic" specifically for Qsymia (phentermine and topiramate), the requirement to stop GLP-1 RAs before conception indicates a potential risk or insufficient data to confirm safety during early pregnancy. A retrospective register-based cohort study (2010–2021) in insulin users exposed to GLP-1 RAs in early pregnancy found an adjusted relative risk (RR) for major congenital malformations of 0.95 (with a 95% confidence interval of 0.72–1.26) and for cardiac malformations of 0.68 (with a 95% confidence interval of 0.42–1.12)[31]. A prospective surveillance cohort study (2009–2022) comparing any antidiabetic medication or obesity exposure to congenital malformations found adjusted odds ratios (ORs) relative to other diabetics (OR 0.98, CI 0.16–5.82) and obese individuals (OR 0.54, CI 0.11–2.75). While these studies, rated as low risk for integrity concerns, did not show a statistically significant increase in malformations in this specific population (primarily insulin users), the general advice to stop certain GLP-1 RAs before conception remains in place (17,22).

The assessment of safety outcomes in studies can be subject to limitations. For example, the meta-analysis comparing Myo-inositol and Metformin noted a serious risk of bias for gastrointestinal side effects. Similarly, a meta-analysis evaluating Exenatide plus Metformin noted that while a funnel plot was used to assess publication bias, its interpretive value was limited by the small number of included studies (n=5). Further high-quality research is needed to fully explore the long-term safety, cost-effectiveness, and efficacy of GLP-1 RA combination therapy, particularly in diverse PCOS populations and with longer follow-up durations. Investigating patient-reported outcomes, including the impact of side effects like gastrointestinal issues on quality of life and treatment satisfaction, could provide valuable insights.

Discussion

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which are FDA-approved for weight loss, show promising potential in addressing the metabolic dysfunction associated with PCOS[03]. Current data generally support the benefits of GLP-1 RAs on several pathological aspects of PCOS, including the improvement of menstrual cycles and glucose homeostasis(3). They have also been observed to reduce testosterone levels and improve insulin resistance[03]. Studies comparing GLP-1 RAs like exenatide to metformin in women with PCOS have found that exenatide was significantly more effective than metformin in increasing pregnancy and ovulation rates(10). Exenatide also improved aspects of follicle morphology in animal models and was more effective than metformin at increasing sex hormone-binding globulin (SHBG) and follicle-stimulating hormone (FSH) while decreasing dehydroepiandrosterone sulfate (DHEA-S), suggesting its benefits on reproductive function might be mediated through effects on these hormone levels, potentially indirectly by lowering insulin resistance[10]. Natural pregnancy rates were also significantly higher following exenatide treatment compared to metformin in one study(10). Another study involving women with PCOS undergoing controlled ovarian stimulation after preconception treatment found a significantly higher pregnancy rate per embryo transfer and cumulative pregnancy rate over 12 months in a group treated with liraglutide plus metformin compared to

metformin alone(29). These results were seen despite comparable reductions in body weight and visceral adipose tissue between the groups, suggesting the mechanisms may extend beyond just weight reduction[29]. Ovulation rate has also been shown to be improved with D-chiro-inositol (DCI) compared to placebo in a meta-analysis of two trials (21).

In contrast, some weight loss interventions have not shown positive effects on fertility outcomes despite achieving weight loss. Orlistat, for instance, did not demonstrate a positive effect on fertility in studies, showing no differences compared to placebo regarding live births, conception, clinical pregnancy, or pregnancy loss(12). One study noted a non-significant trend towards higher miscarriage rates with Orlistat (12).

Despite the promising findings regarding GLP-1 RAs, particularly in women with PCOS, there are significant limitations in the current research, and many questions remain unanswered(7). The impact of these newer injectable medications on future fertility in healthy non-PCOS obese women is currently unclear, as most studies have significant limitations or were conducted in animals with conflicting results(24). Due to the increasing use of GLP-1 RAs and high rates of unintended pregnancies, increased periconceptional exposure is likely, making it crucial to understand the potential consequences(26,28,29). Safety data for GLP-1 RAs in the periconceptional period are limited(26). Animal studies have shown mixed results regarding anomalies, growth restriction, and early fetal demise, and most exposed animals throughout gestation, not just periconceptionally(30).

Possibilities for future research are numerous and necessary to fully understand the role of GLP-1 RAs in fertility. There is a need for larger, long-term, multicentre randomized placebo-controlled studies, especially those with uniform protocols targeting reproductive outcomes in diverse populations, including women with obesity, diabetes, and/or PCOS. Future studies should explore the potential impact of different doses and durations of GLP-1 RA exposure. A key question is whether the beneficial effects are primarily mediated by weight loss and metabolic improvement or through direct interactions with GLP-1 receptors in reproductive tissues. Comparing different weight reduction strategies could help elucidate this. Further evaluation is needed on the clinical relevance of the anti-inflammatory potential of GLP-1 RAs in the gonads and endometrium, including their impact on endometrium quality and receptivity. The potential impact of GLP-1 RAs on the fertility potential of younger men with diabetes and/or obesity also needs evaluation, including assessment of gonadotropin profiles and semen samples. Case reports have noted decreased semen quality with liraglutide and sitagliptin (a DPP-4 inhibitor) in men, but these are areas for future research(29). Ongoing collection of teratogenicity data in women with inadvertent GLP-1 RA exposure during pregnancy is also essential. Finally, a deeper understanding of PCOS pathogenesis and more mechanistic data explaining the potential benefits of GLP-1 RAs, including dual agonists like tirzepatide, is needed.

Conclusions

Metabolic health, characterised by anthropometric measures and metabolic parameters, is fundamentally linked to reproductive function. Conditions such as obesity and metabolic syndrome disrupt hormonal balance, contribute to insulin resistance, and induce chronic inflammation, which in turn impair fertility, particularly in women with Polycystic Ovary Syndrome (PCOS). These metabolic dysfunctions can negatively affect follicular development, oocyte quality, embryo development, and the uterine environment for implantation.

Pharmacological interventions targeting these metabolic issues have shown potential in improving fertility outcomes. Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RAs) are a class of drugs that have demonstrated benefits on several pathological aspects of PCOS, including improvements in menstrual cycles, reduction of testosterone levels, and enhancement of glucose homeostasis. Studies comparing Exenatide (a GLP-1 RA) to Metformin in women with PCOS found that Exenatide was significantly more effective in increasing pregnancy and ovulation rates. GLP-1 RAs have also been associated with improvements in anthropometric measures such as BMI and waist circumference, as well as reductions in triglycerides in overweight women with PCOS. Animal studies using semaglutide have shown alleviation of ovarian inflammation, improved insulin resistance, and normalisation of the estrous cycle in PCOS mice, suggesting effects beyond just weight loss. In contrast, while inositols are widely used and promoted for PCOS management, a high-quality systematic review and meta-analysis concluded that the evidence supporting their use is limited and inconclusive, with many outcomes related to anthropometrics, metabolism, hormones, and reproduction assessed as low to very low certainty due to small study sizes, inconsistency, and potential bias.

Despite the promising observed benefits of GLP-1 RAs, particularly in the context of PCOS, significant limitations exist in the current evidence base. Many available studies have small sample sizes and limited follow-up durations, which restrict the strength and generalisability of the findings. There is heterogeneity among

studies regarding the populations included and the specific GLP-1 RA interventions used. A major concern is the limited data on the safety of GLP-1 RAs during the periconceptional period and in early pregnancy. While some recent human studies on first-trimester exposure have been reassuring regarding the risk of major birth defects, animal studies have yielded mixed results regarding fetal anomalies and growth restriction, often involving exposure throughout gestation. The precise mechanisms through which GLP-1 RAs impact fertility, separate from their effects on weight and metabolism, also remain unclear. Specifically, while GLP-1 RAs hold promise for improving metabolic profiles and thereby addressing some of the root causes of PCOS-related infertility, the question of whether these agents also exert direct effects on the female reproductive system remains a key area of ongoing investigation.

The current evidence suggests that GLP-1 RAs can improve ovulation and pregnancy rates, and enhance hormonal profiles. However, the mechanisms behind these improvements are not fully understood. It's plausible that the primary mechanism of action is through the amelioration of insulin resistance and the consequent reduction in hyperandrogenism, which are key factors in PCOS-related infertility. GLP-1 RAs enhance insulin sensitivity, which leads to decreased insulin levels. High insulin levels stimulate ovarian androgen production, so a reduction in insulin levels results in lower androgen levels. This hormonal shift can restore normal follicular development and ovulation.

However, the presence of GLP-1 receptors in ovarian and endometrial tissues suggests the possibility of more direct effects. GLP-1 signaling within the ovary could potentially influence steroidogenesis, folliculogenesis, and oocyte maturation. In the endometrium, GLP-1 RAs might affect receptivity, creating a more favorable environment for embryo implantation. The relative contributions of these direct and indirect effects likely vary depending on the specific GLP-1 RA used, the duration of treatment, and the individual patient's characteristics. Future research should aim to disentangle these direct and indirect pathways.

The long-term safety of GLP-1 RAs, particularly in the context of conception and pregnancy, is another critical area that requires further investigation. While short-term studies have not raised major safety concerns, the potential effects of prolonged GLP-1 RA exposure on oocyte quality, endometrial function, and pregnancy outcomes are not fully elucidated. Additionally, the potential impact on the developing fetus remains a concern, given the conflicting findings in animal studies and the limited human data on periconceptional exposure. The pharmacokinetics of GLP-1 RAs, their ability to cross the placenta, and their potential effects on fetal growth and development need to be thoroughly evaluated.

Looking to the future, several possibilities for research and clinical application emerge. There is a crucial need for larger, long-term, multi-center randomized controlled trials to definitively establish the efficacy and safety of GLP-1 RAs on reproductive outcomes in diverse populations, including obese women without PCOS and potentially men. These trials should include more rigorous and standardized protocols for assessing reproductive endpoints, such as time to pregnancy, live birth rates, and miscarriage rates. Future studies should aim to understand the optimal dose and duration of treatment and whether the beneficial effects of GLP-1 RA treatment on fertility are sustained after the medication is discontinued.

Mechanistic studies, including in vitro and in vivo experiments, are needed to elucidate the precise molecular mechanisms through which GLP-1 RAs influence reproductive tissues and processes. These studies could involve the use of animal models, as well as the examination of human ovarian and endometrial tissue samples. Advanced imaging techniques and molecular biology tools can be employed to investigate the effects of GLP-1 RAs on cellular signaling pathways, gene expression, and protein synthesis in reproductive cells.

Given the increasing use of these medications, continued rigorous collection of safety data regarding periconceptional exposure and pregnancy outcomes through registries and observational studies is paramount. These studies should include detailed information on the timing and duration of GLP-1 RA exposure, as well as comprehensive follow-up of both mothers and offspring. The establishment of large, well-designed pregnancy registries can facilitate the collection of such data and provide valuable insights into the long-term safety profile of these drugs.

Research into newer incretin-based molecules, such as dual GLP-1/GIP receptor agonists like tirzepatide, also represents a promising future direction. These agents, which combine the actions of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), have shown even greater efficacy in promoting weight loss and

improving metabolic parameters compared to GLP-1 RAs alone. Their potential role in improving reproductive outcomes, particularly in women with PCOS, warrants further investigation.

For inositols, which are widely used and promoted for PCOS management, more robust study designs are needed to provide clearer evidence of their efficacy. Future trials should address the limitations of previous studies, such as small sample sizes, heterogeneity in study populations, and lack of standardized protocols. Head-to-head comparisons of inositols with other established treatments, such as Metformin and GLP-1 RAs, would be valuable in determining their relative effectiveness.

In conclusion, the link between metabolic health and fertility is well-established, with interventions like GLP-1 RAs showing promise in addressing metabolic dysfunction and improving reproductive outcomes, particularly in PCOS. However, significant limitations exist in the current evidence regarding long-term effects, mechanisms, and especially periconceptional safety. Future research needs to focus on large-scale, high-quality studies to provide definitive answers, allowing clinicians to counsel patients effectively about the risks and benefits of these increasingly common metabolic therapies in the context of fertility and pregnancy. A deeper understanding of the interplay between GLP-1 signaling and reproductive function will not only optimize the use of GLP-1 RAs in women with PCOS but also potentially lead to the development of novel therapeutic strategies for other reproductive disorders associated with metabolic dysfunction.

Disclosure

Author's Contribution:

Conceptualization: IK, DK

Methodology: VK, DL

Formal analysis: KT, MS, DW

Investigation: AM, VM, DW

Writing-rough preparation: DL, DK, KT

Writing-review and editing: NS, KM

Supervision: IK

All authors have read and agreed with the published version of the manuscript.

Funding Statement: The authors did not receive special funding.

Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of Interest Statement: The authors declare no conflict of interest.

Bibliography

1. Almhmoud H, Alatassi L, Baddoura M, Sandouk J, Alkayali MZ, Najjar H, Zaino B. Polycystic ovary syndrome and its multidimensional impacts on women's mental health: A narrative review. Medicine (Baltim£ore). 2024 Jun 21;103(25):e38647. doi: 10.1097/MD.0000000000038647. PMID: 38905372; PMCID: PMC11191963.
2. Mingyu Liao, Xing Li, Hao Zhang, Ling Zhou, Liu Shi, Weixin Li, Rufei Shen, Guiliang Peng, Huan Zhao, Jiaqing Shao, Xiujie Wan, Zheng Sun, Hongting Zheng, Min Lon
3. Bader, S., Bhatti, R., Mussa, B., & Abusanana, S. (2024). A systematic review of GLP-1 on anthropometrics, metabolic and endocrine parameters in patients with PCOS. Women's Health. https://doi.org/10.1177/17455057241234530

4. Sánchez-Garrido MA, Serrano-López V, Ruiz-Pino F, Vázquez MJ, Rodríguez-Martín A, Torres E, Velasco I, Rodríguez AB, Chicano-Gálvez E, Mora-Ortiz M, Ohlsson C, Poutanen M, Pinilla L, Gaytán F, Douros JD, Yang B, Müller TD, DiMarchi RD, Tschöp MH, Finan B, Tena-Sempere M. Superior metabolic improvement of polycystic ovary syndrome traits after GLP1-based multi-agonist therapy. Nat Commun. 2024 Oct 1;15(1):8498. doi: 10.1038/s41467-024-52898-y. PMID: 39353946; PMCID: PMC11445520.
5. Frangie Machado M, Shunk T, Hansen G, Harvey C, Fulford B, Hauf S, Schuh O, Kaldas M, Arcaroli E, Ortiz J, De Gaetano J. Clinical Effects of Glucagon-Like Peptide-1 Agonist Use for Weight Loss in Women With Polycystic Ovary Syndrome: A Scoping Review. Cureus. 2024 Aug 12;16(8):e66691. doi: 10.7759/cureus.66691. PMID: 39262529; PMCID: PMC11389649.
6. Monney, M., Mavromati, M., Leboulleux, S., & Gariani, K. (2025). Endocrine and metabolic effects of GLP-1 receptor agonists on women with PCOS, a narrative review. Endocrine Connections, 14(5), e240529. Retrieved May 9, 2025, from https://doi.org/10.1530/EC-24-0529
7. Rahim S, Pergolizzi J Jr. The Potential Role of Glucagon-Like Peptide-1 (GLP-1) Agonists for Polycystic Ovary Syndrome. Cureus. 2025 Jan 26;17(1):e77998. doi: 10.7759/cureus.77998. PMID: 40007927; PMCID: PMC11852098.
8. Fang Wang, Yici Yan, Dongying Wang, Qingnan Fan, Fangyu Yi, Xinyan Yang ,Jin Lu, Effects of Metformin on CIMT and FMD in PCOS patients: a systematic review and meta-analysis ,BMC Women's Health volume, https://doi.org/10.1186/s12905-024-03275-w
9. Svendsen PF, Nilas L, Madsbad S, Holst JJ. Incretin hormone secretion in women with polycystic ovary syndrome: roles of obesity, insulin sensitivity, and treatment with metformin. Metabolism. 2009 May;58(5):586-93. doi: 10.1016/j.metabol.2008.11.009. PMID: 19375579.
10. Ye ZR, Yan CQ, Liao N, Wen SH. The Effectiveness and Safety of Exenatide Versus Metformin in Patients with Polycystic Ovary Syndrome: A Meta-Analysis of Randomized Controlled Trials. Reprod Sci. 2023 Aug;30(8):2349-2361. doi: 10.1007/s43032-023-01222-y. Epub 2023 Mar 31. PMID: 37002532; PMCID: PMC10354168.
11. Austregésilo de Athayde De Hollanda Morais B, Martins Prizão V, de Moura de Souza M, Ximenes Mendes B, Rodrigues Defante ML, Cosendey Martins O, Rodrigues AM. The efficacy and safety of GLP-1 agonists in PCOS women living with obesity in promoting weight loss and hormonal regulation: A meta-analysis of randomized controlled trials. J Diabetes Complications. 2024 Oct;38(10):108834. doi: 10.1016/j.jdiacomp.2024.108834. Epub 2024 Aug 20. PMID: 39178623.
12. Stefanaki K, Karagiannakis DS, Peppa M, Vryonidou A, Kalantaridou S, Goulis DG, Psaltopoulou T, Paschou SA. Food Cravings and Obesity in Women with Polycystic Ovary Syndrome: Pathophysiological and Therapeutic Considerations. Nutrients. 2024 Apr 3;16(7):1049. doi: 10.3390/nu16071049. PMID: 38613082; PMCID: PMC11013286.
13. Xiong C, Wu J, Ma Y, Li N, Wang X, Li Y, Ding X. Effects of Glucagon-Like Peptide-1 Receptor Agonists on Gut Microbiota in Dehydroepiandrosterone-Induced Polycystic Ovary Syndrome Mice: Compared Evaluation of Liraglutide and Semaglutide Intervention. Diabetes Metab Syndr Obes. 2024 Feb 21;17:865-880. doi: 10.2147/DMSO.S451129. PMID: 38406269; PMCID: PMC10894520.
14. Ma R, Ding X, Wang Y, Deng Y, Sun A. The therapeutic effects of glucagon-like peptide-1 receptor agonists and metformin on polycystic ovary syndrome: A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2021 Jun 11;100(23):e26295. doi: 10.1097/MD.0000000000026295. PMID: 34115034; PMCID: PMC8202615.
15. Hu Y, Song X, Hamiti S, Ma Y, Yusufu M, Wang X, Zhang K, Guo Y. Comparison of exenatide alone or combined with metformin versus metformin in the treatment of polycystic ovaries: a systematic review and meta-analysis. BMC Endocr Disord. 2023 Nov 16;23(1):250. doi: 10.1186/s12902-023-01497-x. PMID: 37974132; PMCID: PMC10652559.
16. Ge JJ, Wang DJ, Song W, Shen SM, Ge WH. The effectiveness and safety of liraglutide in treating overweight/obese patients with polycystic ovary syndrome: a meta-analysis. J Endocrinol Invest. 2022 Feb;45(2):261-273. doi: 10.1007/s40618-021-01666-6. Epub 2021 Aug 29. PMID: 34455568.
17. Victoria Fitz, Sandro Graca, Shruthi Mahalingaiah, Jing Liu, Lily Lai, Ali Butt, Mike Armour, Vibhuti Rao, Dhevaksha Naidoo, Alison Maunder, Guoyan Yang, Vaishnavi Vaddiparthi, Selma F Witchel, Alexia Pena, Poli Mara Spritzer, Rong Li, Chau Tay, Aya Mousa, Helena Teede, Carolyn Ee, Inositol for Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis to Inform the 2023 Update of the International Evidence-based PCOS Guidelines, The Journal of Clinical Endocrinology & Metabolism, Volume 109, Issue 6, June 2024, Pages 1630–1655, https://doi.org/10.1210/clinem/dgad762

18. Price, S.A.L., Nankervis, A. Considering the use of GLP-1 receptor agonists in women with obesity prior to pregnancy: a narrative review. Arch Gynecol Obstet 311, 1241–1247 (2025). https://doi.org/10.1007/s00404-024-07849-9
19. Liu QK. Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. Front Endocrinol (Lausanne). 2024 Jul 24;15:1431292. doi: 10.3389/fendo.2024.1431292. PMID: 39114288; PMCID: PMC11304055.
20. Giangregorio F, Mosconi E, Debellis MG, Provini S, Esposito C, Garolfi M, Oraka S, Kaloudi O, Mustafazade G, Marín-Baselga R, Tung-Chen Y. A Systematic Review of Metabolic Syndrome: Key Correlated Pathologies and Non-Invasive Diagnostic Approaches. J Clin Med. 2024 Oct 2;13(19):5880. doi: 10.3390/jcm13195880. PMID: 39407941; PMCID: PMC11478146.
21. Jensterle M, Ferjan S, Janez A. The maintenance of long-term weight loss after semaglutide withdrawal in obese women with PCOS treated with metformin: a 2-year observational study. Front Endocrinol (Lausanne). 2024 Apr 11;15:1366940. doi: 10.3389/fendo.2024.1366940. PMID: 38665260; PMCID: PMC11043580.
22. Duah and Seifer Reproductive Biology and Endocrinology (2025) 23:2 https://doi.org/10.1186/s12958-024-01339-y
23. Drummond, Rosa F. et al. Glucagon-like peptide-1 receptor agonist use in pregnancy: a reviewAmerican Journal of Obstetrics & Gynecology, Volume 232, Issue 1, 17 – 25, 10.1016/j.ajog.2024.08.024 External Link
24. Liu M, Guo S, Li X, Tian Y, Yu Y, Tang L, Sun Q, Zhang T, Fan M, Zhang L, Xu Y, An J, Gao X, Han L, Zhang L. Semaglutide Alleviates Ovary Inflammation via the AMPK/SIRT1/NF-κB Signaling Pathway in Polycystic Ovary Syndrome Mice. Drug Des Devel Ther. 2024 Sep 4;18:3925-3938. doi: 10.2147/DDDT.S484531. PMID: 39247793; PMCID: PMC11380913.
25. Abdalla MA, Deshmukh H, Atkin S, Sathyapalan T. The potential role of incretin-based therapies for polycystic ovary syndrome: a narrative review of the current evidence. Ther Adv Endocrinol Metab. 2021 Jan 27;12:2042018821989238. doi: 10.1177/2042018821989238. PMID: 33552465; PMCID: PMC7844452.
26. Mandelbaum RS. Glucagon-Like Peptide-1 Receptor agonists: A magic bullet or a double-edged sword? F S Rep. 2025 Feb 12;6(1):10. doi: 10.1016/j.xfre.2025.02.007. PMID: 40201101; PMCID: PMC11973741.
27. Marinelli S, Napoletano G, Straccamore M, Basile G. Female obesity and infertility: outcomes and regulatory guidance. Acta Biomed. 2022 Aug 31;93(4):e2022278. doi: 10.23750/abm.v93i4.13466. PMID: 36043953; PMCID: PMC9534231.
28. Drummond RF, Seif KE, Reece EA. Glucagon-like peptide-1 receptor agonist use in pregnancy: a review. Am J Obstet Gynecol. 2025 Jan;232(1):17-25. doi: 10.1016/j.ajog.2024.08.024. Epub 2024 Aug 23. PMID: 39181497.
29. Impact of dramatic weight loss with the new injectable medications on reproduction in healthy non–polycystic ovary syndrome obese women, Merhi, Zaher, F&S Reports, Volume 6, Issue 1, 4 – 9
30. Naz, Y., Setna, Z., Banu, S., & Maqsood, A. (2025). Comparison of Metformin and Metformin Plus Liraglutide for Treating Metabolic Syndrome in Patients with Polycystic Ovarian Syndrome (PCOS). Indus Journal of Bioscience Research, 3(3), 238–243. https://doi.org/10.70749/ijbr.v3i3.818
31. Kuitunen I. Exposure to GLP-1 receptor agonists in early pregnancy did not increase the risk of congenital malformations. Acta Paediatr. 2024 Dec;113(12):2682-2683. doi: 10.1111/apa.17412. Epub 2024 Aug 29. PMID: 39206800.
32. Klair N, Patel U, Saxena A, Patel D, Ayesha IE, Monson NR, Ramphall S. What Is Best for Weight Loss? A Comparative Review of the Safety and Efficacy of Bariatric Surgery Versus Glucagon-Like Peptide-1 Analogue. Cureus. 2023 Sep 29;15(9):e46197. doi: 10.7759/cureus.46197. PMID: 37905277; PMCID: PMC10613430.