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# Improving Reproductive Outcomes in PCOS: The Emerging Role of GLP-1 Receptor Agonists

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**Abstract**

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder affecting a significant proportion of women of reproductive age. It is associated with infertility, metabolic abnormalities, and hormonal imbalances, including insulin resistance and hyperandrogenism. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as exenatide and liraglutide, have shown promise in improving reproductive outcomes in women with PCOS. This review evaluates the potential benefits of GLP-1 RAs in enhancing fertility, with a focus on menstrual regularity, ovulation rates, pregnancy rates, and metabolic outcomes. Studies have indicated that GLP-1 RAs improve insulin sensitivity, reduce BMI, waist circumference, and testosterone levels, and contribute to higher natural pregnancy rates. Despite the promising results, the long-term safety of GLP-1 RAs, particularly during pregnancy, remains uncertain. Patients using GLP-1 RAs are advised to use contraception, as the safety profile during pregnancy is still under investigation. Further research is necessary to establish the long-term effects and safety of these medications in women with PCOS. Overall, GLP-1 RAs offer a potential therapeutic approach for improving fertility and metabolic health in women with PCOS.

**Key words:** Polycystic ovary syndrome, PCOS, glucagon-like peptide 1 receptor agonists, glp-1, pregnancy, gestation.

## Introduction

Polycystic ovary syndrome (PCOS) is a prevalent endocrine and metabolic disorder that affects between 4% and 20% of reproductive-age females worldwide.[1,2] PCOS typically presents with ovulatory dysfunction, hyperandrogenism and hirsutism.[3] It is also associated with obesity, insulin resistance, metabolic syndrome and an increased risk of cardiovascular disease.[4] Approximately 40-80% of women with PCOS are overweight or obese, which can increase the risk of impaired glucose tolerance and type 2 diabetes mellitus.[5] PCOS is also linked to a higher risk of developing endometrial cancer.[6,7]

## Materials and Methods

This review aims to evaluate the potential benefits of GLP-1 receptor agonists (GLP-1 RAs) in improving reproductive outcomes in women with polycystic ovary syndrome (PCOS). A comprehensive literature search was conducted using the PubMed database with the following search terms: ("Polycystic ovary syndrome" OR PCOS) AND ("glucagon-like peptide 1 receptor agonists" OR GLP-1) AND (pregnancy OR gestation). Only full-text studies published in English within the past 10 years were considered for inclusion. The review focused on studies comparing GLP-1 RAs to either placebo or metformin in women aged 18 and older with a PCOS diagnosis. Reproductive outcomes such as menstrual regularity, ovulation rates, and pregnancy rates were key inclusion criteria. Animal studies were excluded. Titles and abstracts were manually reviewed to assess the relevance of the studies and their alignment with the review's objectives. The selected studies were then qualitatively analyzed and summarized to provide an overview of the findings. As this review was not designed as a meta-analysis, no statistical methods were applied.

## Diagnostic Criteria for Polycystic Ovary Syndrome

The European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) recommend diagnosing PCOS based on the Rotterdam criteria. According to these guidelines, a diagnosis is confirmed when at least two of the three specified criteria are met, after excluding other medical conditions with similar symptoms.[8,9] Table 1 summarizes the key evidence-based diagnostic criteria and their descriptions.

| Criteria | Description |
|---|---|
| Ovulatory dysfunction | Oligo-anovulation,<br>Irregular menstrual cycles defined as cycles longer than 35 days, shorter than 21 days, or fewer than 8 cycles per year. |
| Hyperandrogenism | Clinical signs of excess androgens:<br>• **hirsutism,**<br>• **acne,**<br>• **female pattern hair loss**<br>or biochemical signs of hyperandrogenism, with elevated levels of:<br>• **total testosterone**<br>• **free testosterone**<br>• **androstenedione**<br>• **dehydroepiandrosterone sulfate (DHEAS)** |
| Polycystic ovarian morphology on ultrasound | Presence of 12 or more follicles measuring 2-9 mm throughout the entire ovary and/or ovarian volume >10 mL in at least one ovary |

Table 1. Diagnostic Criteria for Polycystic Ovary Syndrome (PCOS) Based on the 2023 International Evidence-Based Guideline and Rotterdam Criteria

**The Impact of Hormonal and Metabolic Dysregulation on Fertility in PCOS**

Infertility affects 40% of women with polycystic ovary syndrome.[10] The female reproductive system relies on a complex and finely tuned interaction of neuroendocrine signals regulated by the hypothalamic-pituitary-ovarian (HPO) axis. Disruptions in this hormonal balance can lead to various metabolic and reproductive disorders.[11,12] Increased pituitary release of LH stimulates ovarian theca cells to produce androgens. Moreover, insulin resistance causes hyperinsulinemia, which enhances androgen production in the ovaries and suppresses hepatic synthesis of sex hormone-binding globulin (SHBG), leading to increased free androgen levels in the bloodstream.[4,10] This disrupts ovarian follicle maturation and inhibits ovulation.[13]

Increased BMI negatively affects fertility in women with PCOS by exacerbating insulin resistance, hormonal imbalance and impaired metabolism and ovarian function. Controlling obesity through dietary modification, regular physical activity or pharmacological interventions can increase insulin sensitivity, lower androgen levels and improve ovarian function, thereby increasing fertility in many cases.[14,15]

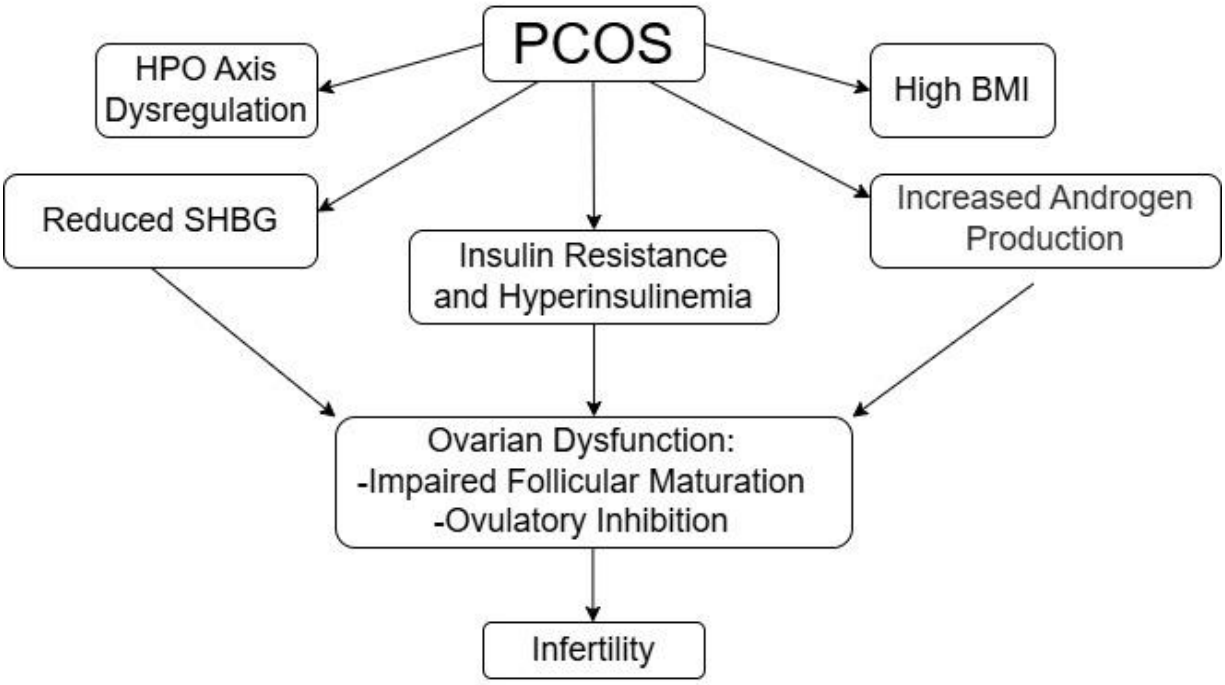


Figure 2. Schematic representation of the pathophysiology of infertility in polycystic ovary syndrome (PCOS). HPO- Hypothalamic-Pituitary-Ovarian Axis; SHBG- Sex Hormone-Binding Globulin; BMI- Body Mass Index.

**Current options for the treatment of PCOS-related infertility**

Lifestyle modifications are the primary approach to managing PCOS in women.[16,17] Quitting smoking is essential, and regular physical activity should be promoted. For overweight or obese patients, weight reduction is strongly recommended.[5,18] Additionally, The International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome (2023) recommends starting infertility treatment with non-medical interventions, which include adopting a healthy lifestyle, optimizing weight, smoking cessation, avoiding alcohol, engaging in exercise, and managing mental health issues. The guideline then outlines medical interventions for fertility management, which include treatments such as Letrozole, Metformin, Clomiphene citrate, Gonadotropins, In Vitro Fertilization (IVF), In Vitro Maturation (IVM), Laparoscopic Ovarian Surgery, Anti-obesity Pharmacological Agents, and others.[8,18]

## GLP-1 RAs: Expanding Roles Beyond Diabetes and Obesity

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) enhance glucose-dependent insulin secretion, reduce glucagon levels and slow gastric emptying, making them effective in treating type 2 diabetes (T2D).[19] Additionally, GLP1 RAs promote weight loss by suppressing appetite, leading to their investigation for obesity management.[20–22] Recent clinical trials suggest that GLP-1 RAs may also benefit women with PCOS by improving pregnancy rates, menstrual regularity, androgen levels, and insulin sensitivity. However, previous meta-analyses have primarily focused on metabolic and hormonal outcomes, with limited attention to reproductive results such as conception and pregnancy rates.[22–24] This highlights the need for further research into the potential role of GLP-1 RAs in managing reproductive health in women with PCOS, aiming to provide a more comprehensive understanding of their benefits and contribute to the development of improved clinical management strategies for this population.

## The Impact of GLP-1 Receptor Agonists on Reproductive and Metabolic Outcomes in Women with Polycystic Ovary Syndrome (PCOS)

GLP-1 receptor agonists (GLP-1 RAs), such as exenatide and liraglutide, have shown significant promise in improving reproductive outcomes in women with polycystic ovary syndrome (PCOS). GLP-1 RAs therapy was associated with a significant increase in the natural pregnancy rate, with a temporary rise in the total pregnancy rate. However, there was no improvement in the pregnancy rate after in vitro fertilization (IVF). Interestingly, longer durations of GLP-1 RA treatment have contributed to better menstrual regularity, which is a key factor for improving fertility in these patients. Additionally, GLP-1 RAs have been shown to enhance insulin sensitivity, as evidenced by improvements in HOMA-IR, increased SHBG levels, while also reducing BMI, waist circumference (WC), and total testosterone (TT). However, no significant effects on free testosterone (fT), dehydroepiandrosterone sulfate (DHEAS), or the Free Androgen Index (FAI) were observed. Subgroup analyses further revealed that while the total pregnancy rate initially increased, this effect diminished after one year following short-term GLP-1 RA usage (up to 12 weeks), suggesting that the benefits of GLP-1 RAs on fertility might be time-limited or require continuous treatment to maintain effectiveness. Furthermore, GLP-1 RAs monotherapy demonstrated similar effectiveness to metformin in reducing androgen excess, with a potential added benefit in lowering DHEAS and FAI levels.[25]

When comparing the efficacy of different GLP-1 receptor agonists, exenatide has shown more effective results than metformin in improving reproductive outcomes, promoting weight loss, and enhancing insulin sensitivity in patients with PCOS. Treatment with exenatide resulted in significantly higher pregnancy and ovulation rates compared to metformin. These improvements in reproductive function may be related to increased SHBG and FSH levels, as well as reduced DHEA-S concentrations. Additionally, BMI and HOMA-IR values were considerably lower in patients treated with exenatide compared to those receiving metformin.[26]

Among GLP-1 receptor agonists, liraglutide has shown promise in managing obesity and PCOS, improving weight loss, testosterone levels, and fertility outcomes. Studies suggest their use, alone or with metformin, can enhance in vitro fertilization (IVF) pregnancy rates and natural pregnancy rates, making them a valuable option for women struggling with infertility. These benefits are particularly important in assisted reproductive settings, where pretreatment to reduce body weight can improve reproductive success and minimize risks during pregnancy.[27]

In addition to their metabolic benefits, GLP-1 RAs have been found to influence hormonal regulation. Several studies indicate that both liraglutide and exenatide lead to a reduction in free testosterone (fT) levels and a decrease in the free androgen index (FAI), as well as significant increases in SHBG concentrations. However, whether these effects are due to the weight loss and insulin resistance suppression associated with GLP-1 receptor agonists, or if they are directly related to ovarian function, remains unclear. Both exenatide and liraglutide have been shown to increase menstrual frequency and ovulation rates. Notably, neither of these treatments was able to reduce luteinizing hormone (LH) levels. In contrast, metformin significantly reduced LH levels and total testosterone concentrations, emphasizing its role in regulating LH secretion and ovarian steroidogenesis. Given these findings, combining GLP-1 receptor agonists with metformin may offer more effective hormonal and metabolic outcomes compared to monotherapy, particularly in women with PCOS who have not responded to lifestyle changes, with or without metformin. Importantly, the higher rates of natural pregnancies following exenatide therapy and improved in vitro fertilization (IVF) pregnancy rates per embryo transfer and cumulative pregnancy rates with the liraglutide-metformin combination suggest a promising role for these treatments in addressing subfertility when administered during the preconception period.[28]

Furthermore, the combination of GLP-1 RAs with metformin has demonstrated significant benefits in improving fertility outcomes. In a study on overweight women with PCOS,

exenatide, metformin, and their combination were evaluated, with the combination proving most effective in improving ovulation rates and menstrual frequency. A correlation between weight loss and increased menstrual frequency was also observed. Similarly, liraglutide improved the menstrual bleeding ratio compared to placebo, indicating positive effects on menstrual regularity. GLP-1 receptor agonists (GLP-1 RAs) have shown promise in improving pregnancy rates in women with PCOS, particularly during the preconception period. Treatment with GLP-1 RAs, such as exenatide, has been associated with metabolic improvements, including weight loss and enhanced insulin sensitivity, both important for fertility. Following the discontinuation of GLP-1 RAs, higher natural pregnancy rates have been observed, suggesting that their use before conception can enhance fertility outcomes in women with reproductive disorders. Furthermore, liraglutide combined with metformin significantly increased IVF and cumulative pregnancy rates, including spontaneous pregnancies, compared to metformin alone. These findings underscore the potential therapeutic role of GLP-1 RAs in addressing infertility related to metabolic imbalances in PCOS.[29]

The addition of liraglutide to metformin for 12 weeks significantly increased pregnancy rates after in vitro fertilization and cumulative pregnancy rate in 12 months compared to metformin alone. Despite similar weight loss between the combined therapy and metformin alone, the beneficial effects of liraglutide on fertility may extend beyond weight reduction and improved insulin sensitivity, potentially involving the hypothalamic-pituitary axis. Liraglutide can be prescribed to young women with overweight/obesity to prevent obesity-related complications, including infertility, and improve the chances of pregnancy and a healthy pregnancy outcome.[30]

Despite these promising findings, the evidence regarding the safety of glucagon-like peptide-1 receptor agonists during pregnancy is limited, with insufficient data to determine potential risks such as fetal growth restriction, embryonic complications or fetal death. Patients should be advised to use contraception during treatment, as the safety of these medications during pregnancy remains uncertain.[31]

## Conclusions

GLP-1 receptor agonists (GLP-1 RAs), such as exenatide and liraglutide, have shown promising effects in improving reproductive outcomes in women with polycystic ovary syndrome (PCOS). These treatments have been associated with improved menstrual regularity, enhanced insulin sensitivity, and significant metabolic benefits, including weight loss and

reductions in BMI and waist circumference. Notably, GLP-1 RAs have been linked to higher natural pregnancy rates, though their impact on in vitro fertilization (IVF) outcomes remains limited. Longer durations of treatment appear to offer sustained benefits in menstrual regulation and fertility, but the effectiveness may diminish over time without continuous therapy.

When compared to metformin, exenatide demonstrates superior outcomes in terms of pregnancy and ovulation rates, likely due to its effects on SHBG levels and insulin sensitivity. Liraglutide, both alone and in combination with metformin, has also shown promise in enhancing fertility, particularly in IVF success rates and natural pregnancy outcomes. The combination of GLP-1 RAs with metformin appears to provide more effective hormonal and metabolic regulation, particularly in women who have not responded to lifestyle interventions. While the benefits of GLP-1 RAs in PCOS are clear, the long-term safety of these medications, particularly during pregnancy, remains uncertain due to limited evidence. As such, patients using GLP-1 RAs should be advised to use contraception during treatment. Overall, GLP-1 RAs offer a promising therapeutic approach for improving fertility and metabolic health in women with PCOS, although further research is needed to explore their long-term effects and safety profile during pregnancy.

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