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FROM GUT TO OVARY: THE EXPANDING ROLE OF GLP-1 ANALOGUES IN PCOS AND FERTILITY IN WOMEN

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder marked by hyperandrogenism, ovulatory dysfunction, and insulin resistance. Conventional treatments often fail to address the underlying metabolic disturbances contributing to infertility.

Aim: To critically evaluate the role of GLP-1 receptor agonists in managing metabolic and reproductive dysfunctions in women with PCOS.

Methods: A narrative review was conducted using structured searches in PubMed, Scopus, Web of Science, and ResearchGate, covering publications from 2002 to 2025. Eligible studies included original articles, randomized trials, reviews, and meta-analyses on GLP-1 receptor agonists in the context of PCOS.

Results: GLP-1 receptor agonists, particularly liraglutide and semaglutide, have demonstrated efficacy in reducing insulin resistance, lowering serum androgens, and restoring ovulation. Clinical data show improved menstrual regularity and increased pregnancy rates in both natural and assisted reproduction contexts. Safety remains favorable, with gastrointestinal side effects being most common and typically transient.

Conclusions: GLP-1 receptor agonists represent a promising therapeutic option in PCOS, offering dual metabolic and reproductive benefits. Further randomized studies are needed to define their role in fertility treatment protocols and ensure reproductive safety.

Keywords: Polycystic ovary syndrome (PCOS); GLP-1 receptor agonists; insulin resistance; hyperandrogenism; obesity; metabolic syndrome; semaglutide; liraglutide; ovulation; fertility

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting women of reproductive age. It is characterized by a combination of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. The global prevalence of PCOS ranges from 6% to 21%, depending on the diagnostic criteria used [1]. In addition to its reproductive manifestations, PCOS is closely associated with metabolic disturbances, including insulin resistance, obesity, dyslipidemia, and an increased risk of type 2 diabetes mellitus and cardiovascular disease [2]. Insulin resistance (IR) is a core pathophysiological feature of PCOS, reported in approximately 65–95% of affected women, regardless of body mass index [3].

The etiology of insulin resistance in PCOS is multifactorial, involving both genetic and environmental factors. Several candidate genes have been implicated in the dysregulation of insulin signaling in PCOS. These include INSR, which encodes the insulin receptor essential for insulin binding and downstream signaling, and IRS1/IRS2, which encode insulin receptor substrates responsible for transmitting insulin signals to key metabolic pathways. Polymorphisms in these genes may impair insulin receptor sensitivity and reduce glucose uptake in peripheral tissues. Additionally, genes such as PPARG (peroxisome proliferator-activated receptor gamma), ADIPOQ (adiponectin), and TNF-α (tumor necrosis factor alpha) have been associated with altered insulin sensitivity through their roles in lipid metabolism and chronic low-grade inflammation [1,4].

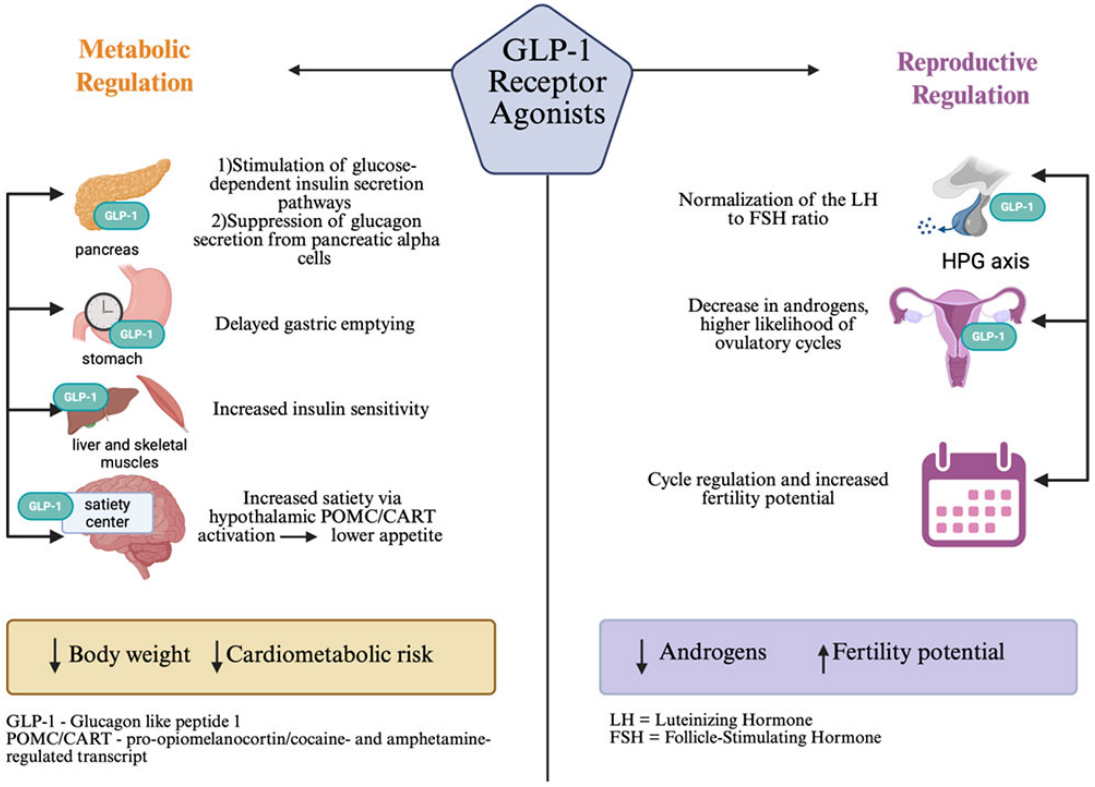
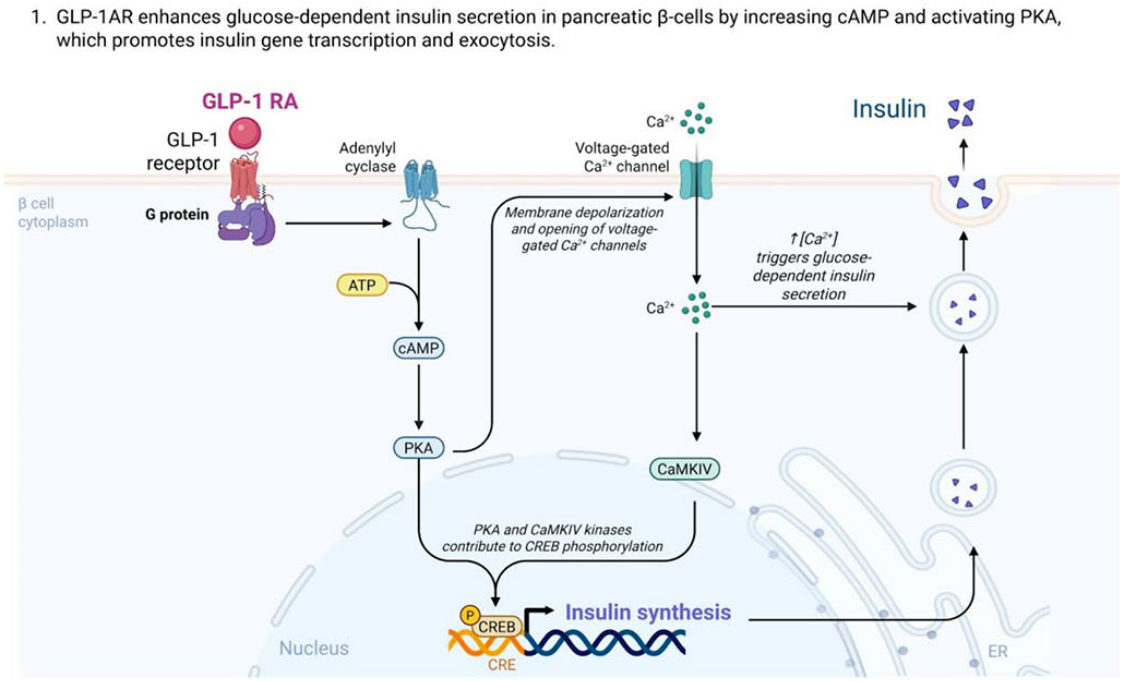


Figure 1. Pathophysiological mechanisms linking insulin resistance and hyperandrogenism in PCOS. Created in https://BioRender.com based on literature [5].

As illustrated in Figure 1, insulin resistance plays a central role in the development of hyperandrogenism in PCOS. Hyperinsulinemia exacerbates hyperandrogenism by stimulating androgen production in ovarian theca cells and by suppressing hepatic synthesis of sex hormone-binding globulin (SHBG), resulting in elevated levels of free testosterone [6,7]. These hormonal disturbances contribute to anovulation, menstrual irregularities, and infertility in women with PCOS [3].

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that enhances glucose-dependent insulin secretion, inhibits glucagon release, delays gastric emptying, and promotes satiety. GLP-1 receptor agonists (GLP-1 RAs), such as liraglutide and semaglutide, have been developed primarily for the treatment of type 2 diabetes mellitus and obesity [8]. Recent studies suggest that GLP-1 RAs may also improve reproductive outcomes in women with PCOS by ameliorating insulin resistance, promoting weight loss, and potentially exerting direct effects on the hypothalamic-pituitary-ovarian axis [9]. Figure 2 demonstrates how GLP-1 receptor agonists may influence both metabolic and reproductive pathways in women with PCOS.



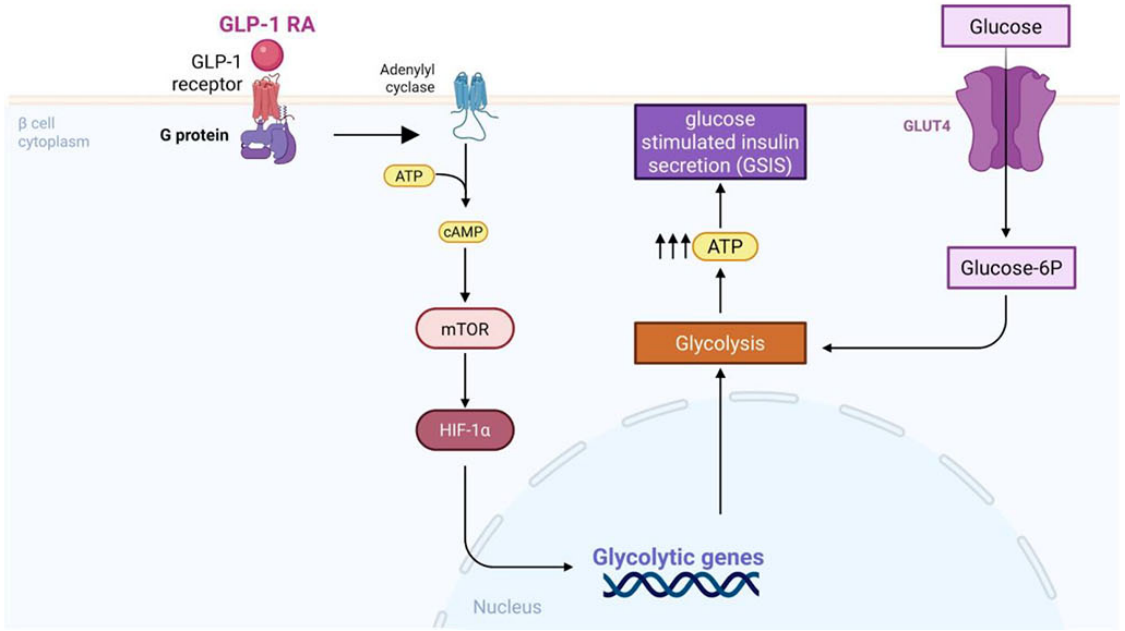


Figure 2. Mechanisms of action of GLP-1 receptor agonists relevant to PCOS pathophysiology. Created in https://BioRender.com based on literature [8].

This review aims to explore the expanding role of GLP-1 analogues in the management of PCOS, with a particular focus on their impact on fertility. By examining the underlying mechanisms, clinical evidence, and potential therapeutic applications, we seek to elucidate the benefits and considerations of incorporating GLP-1 RAs into the treatment paradigm for women with PCOS.

POLYCYSTIC OVARY SYNDROME (PCOS) – A COMPLEX METABOLIC-ENDOCRINE DISORDER

Polycystic ovary syndrome (PCOS) was first described by Stein and Leventhal in 1935, based on a series of seven women who presented with hirsutism, obesity, amenorrhea, and bilaterally enlarged polycystic ovaries observed

during surgery and confirmed histologically [10]. Since then, the clinical understanding and diagnostic criteria for PCOS have evolved significantly.

In 1990, the National Institute of Child Health and Human Development (NICHD) defined PCOS by the presence of clinical and/or biochemical evidence of hyperandrogenism in combination with oligo-ovulation or chronic anovulation [11]. Ultrasonographic features of polycystic ovaries were considered supportive but not essential. This approach was viewed as controversial, particularly in Europe, where ultrasound was widely employed as a primary diagnostic tool [12].

Since 2003, the diagnosis of PCOS has been based on the Rotterdam criteria, which require the presence of at least two out of three features: (I) infrequent or absent ovulation, (II) clinical and/or biochemical signs of hyperandrogenism, and (III) polycystic ovarian morphology (PCOM) on ultrasound, with exclusion of other etiologies [13]. Notably, these criteria do not require hyperandrogenism as a mandatory component, contrasting with the earlier NIH definition.

In 2006, the Androgen Excess Society (AES) proposed an alternative set of criteria, requiring the presence of hirsutism and/or biochemical hyperandrogenism, along with either oligo-anovulation or PCOM, thereby reinstating hyperandrogenism as a central diagnostic feature [14].

Insulin resistance (IR) is a major contributor to the pathogenesis of PCOS, with variable severity across tissues and phenotypes. It is further amplified by genetic and epigenetic mechanisms, hyperandrogenism, and obesity [1]. Hyperandrogenism, a hallmark of PCOS, refers to an excess of circulating androgens in women and plays a pivotal role not only in the development of the syndrome but also in reproductive complications. Androgens impair ovarian and endometrial function, contributing to ovulatory dysfunction, infertility, and defective implantation. Importantly, hyperandrogenism may persist during pregnancy -whether achieved spontaneously or via assisted reproductive technologies—and has been associated with adverse outcomes such as gestational diabetes, preeclampsia, preterm birth, implantation failure, and miscarriage [15].

PCOS is also linked to early-onset metabolic abnormalities, including increased risks for cardiovascular disease (CVD), obesity, impaired glucose metabolism, type 2 diabetes mellitus, dyslipidemia, and hypertension [16]. Among these, obesity is particularly prevalent and often regarded as a key clinical concern by patients. Additionally, mental health disorders are more common among women with PCOS, with elevated rates of depression, anxiety, and reduced quality of life. Low self-esteem is frequently associated with visible symptoms such as hirsutism, acne, alopecia, and excess weight [17].

Although the exact etiology of PCOS remains unclear, it is widely accepted to be multifactorial, involving a complex interplay of genetic predisposition, hormonal imbalances, metabolic dysfunction, and environmental factors. There is growing evidence that PCOS may originate during fetal development in genetically susceptible individuals, become clinically apparent during adolescence, and persist into adulthood [18].

This review examines the evolving role of glucagon-like peptide-1 (GLP-1) receptor agonists in the treatment of PCOS, with particular focus on their effects on reproductive outcomes. By integrating current mechanistic and clinical insights, GLP-1–based therapies are explored as a promising option for addressing both the metabolic and reproductive dimensions of the syndrome.

AIM OF THE STUDY

This review aims to critically examine the expanding role of GLP-1 receptor agonists in the management of polycystic ovary syndrome (PCOS), with a specific focus on their metabolic and reproductive effects. By exploring the gut-ovary axis, the study evaluates the potential of GLP-1–based therapies to enhance insulin sensitivity, promote ovulatory function, and improve fertility outcomes in women affected by PCOS.

MATERIALS AND METHODS

This narrative review was developed based on a structured literature search conducted across PubMed, ResearchGate, Scopus, and Web of Science databases, covering publications from 2002 to 2025, with the majority of the sources published between 2020 and 2025. The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text keywords, including: *"polycystic ovary syndrome (PCOS)"*, *"GLP-1 receptor agonists"*, *"insulin resistance"*, *"inflammation"*, *"hyperandrogenism"*, *"obesity"*, *"metabolic syndrome"*, *"semaglutide"*, and *"liraglutide"*. Boolean operators (AND/OR) were used to refine and expand the search where appropriate. Eligible studies included original research articles, randomized controlled trials, case series, reviews, and meta-analyses published in English. Both clinical investigations and preclinical studies were considered if they explored the metabolic, endocrine, or reproductive effects of GLP-1 receptor agonists in the context of PCOS.

Articles were excluded if they were not directly related to PCOS or its metabolic and reproductive manifestations, if they did not report on GLP-1–based interventions, or if they were published in languages other than English.

Studies lacking relevance to immunometabolic or endocrine mechanisms were also omitted. In addition, the reference lists of key publications were manually screened to identify additional pertinent sources.

Table 1summarizes the most commonly used variables reported in studies evaluating GLP-1 receptor agonists in women with PCOS.

Table 1. Key Clinical and Laboratory Variables Used in Studies Assessing GLP-1 Receptor Agonists in PCOS and Fertility

Category	Variable	Measurement / Definition	Purpose
Clinical	Body Mass Index (BMI)	Weight (kg) divided by height squared (m^2)	Assesses general adiposity
Clinical	Waist Circumference (WC)	Measured in cm at the midpoint between the lower rib and iliac crest	Evaluates central (visceral) obesity
Clinical	Menstrual Regularity	Based on self-reported cycle frequency and duration	Monitors ovulatory cycle normalization
Clinical	Ovulatory Function	Determined by mid-luteal progesterone levels, ovulation kits, or ultrasound	Confirms presence of ovulation
Clinical	Pregnancy Rate	Confirmed by ultrasound (clinical pregnancy)	Assesses fertility outcome
Laboratory	Fasting Insulin and Glucose	Measured after overnight fasting	Used to calculate HOMA-IR
Laboratory	HOMA-IR	(Fasting glucose × fasting insulin) / 22.5	Evaluates insulin resistance
Laboratory	Serum Testosterone (total/free)	Measured by immunoassay or liquid chromatography–mass spectrometry (LC-MS)	Assesses hyperandrogenism
Laboratory	LH and FSH	Measured by serum assays; LH/FSH ratio reported	Evaluates neuroendocrine function
Laboratory	Sex Hormone-Binding Globulin (SHBG)	Measured by immunoassay	Indicates availability of free androgens
Laboratory	Lipid Profile	Total cholesterol, LDL, HDL, triglycerides	Assesses cardiometabolic risk
Optional	Inflammatory Markers	C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α)	Explores low-grade systemic inflammation

Abbreviations: BMI = body mass index; WC = waist circumference; HOMA-IR = Homeostasis Model Assessment of Insulin Resistance; LH = luteinizing hormone; FSH = follicle-stimulating hormone; SHBG = sex hormone-binding globulin; CRP = C-reactive protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor alpha; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

The clinical relevance of HOMA-IR and SHBG in PCOS is well established: HOMA-IR is a validated surrogate for insulin resistance across phenotypes [1], while reduced SHBG reflects hyperinsulinemia and contributes to elevated free androgen levels [5]. Both markers are key endpoints in assessing response to metabolic therapies, including GLP-1 receptor agonists [24].

FINDINGS AND DISCUSSION

POLYCYSTIC OVARY SYNDROME (PCOS) – A COMPLEX METABOLIC-ENDOCRINE DISORDER

Polycystic ovary syndrome (PCOS) was first described by Stein and Leventhal in 1935, based on seven women presenting with hirsutism, obesity, amenorrhea, and bilaterally enlarged polycystic ovaries confirmed histologically [10]. Since then, diagnostic understanding has evolved substantially.

In 1990, the National Institute of Child Health and Human Development (NICHD) defined PCOS as the coexistence of clinical and/or biochemical hyperandrogenism with oligo- or anovulation, while polycystic ovarian morphology (PCOM) on ultrasound was considered supportive but not essential [11]. This was controversial, particularly in Europe, where ultrasonography was widely used as a primary diagnostic tool [12].

The Rotterdam criteria, introduced in 2003 and still widely used, require two of the following three features: (I) oligo/anovulation, (II) clinical or biochemical hyperandrogenism, and (III) PCOM, with exclusion of other causes [13]. Unlike the NIH definition, the Rotterdam criteria do not require hyperandrogenism. In 2006, the Androgen Excess Society (AES) proposed criteria that reinstated hyperandrogenism as essential, requiring hirsutism and/or biochemical evidence of androgen excess along with either ovulatory dysfunction or PCOM [14].

Insulin resistance (IR) plays a central role in PCOS pathogenesis and varies in severity across phenotypes. It is amplified by genetic and epigenetic mechanisms, excess androgens, and obesity [1]. Hyperandrogenism itself, a key diagnostic and pathogenic factor, contributes to ovulatory dysfunction, infertility, and impaired implantation by disrupting ovarian and endometrial function. Notably, elevated androgen levels may persist during pregnancy, increasing the risk of complications such as gestational diabetes, preeclampsia, preterm birth, implantation failure, and miscarriage [15].

Metabolic abnormalities frequently co-occur with PCOS, including obesity, impaired glucose tolerance, type 2 diabetes mellitus, dyslipidemia, and hypertension—all of which raise cardiovascular risk [16]. Obesity is particularly prevalent and often exacerbates endocrine and reproductive dysfunction. Mental health disorders, including depression and anxiety, are also more common among women with PCOS and are often linked to symptoms such as hirsutism, acne, alopecia, and weight gain, contributing to reduced quality of life [17].

Although the precise etiology remains uncertain, PCOS is recognized as a multifactorial condition involving genetic susceptibility, hormonal and metabolic dysregulation, and environmental influences. Emerging evidence suggests a developmental origin, with signs becoming clinically apparent during adolescence and persisting into adulthood [18].

This review explores the emerging role of glucagon-like peptide-1 (GLP-1) receptor agonists in the management of PCOS, with a focus on their metabolic and reproductive effects, particularly on fertility outcomes [26].

GLP-1 ANALOGUES IN PCOS: PRECLINICAL EVIDENCE FOR METABOLIC AND REPRODUCTIVE BENEFITS

Preclinical studies consistently demonstrate that GLP-1 receptor agonists exert beneficial effects on ovarian morphology and function in animal models of PCOS. In mice with DHEA-induced PCOS, liraglutide promoted granulosa cell proliferation, reduced apoptosis, improved ovarian cyclicity, and partially restored estrous regularity through modulation of FoxO1 phosphorylation in granulosa cells [27]. Another study involving both liraglutide and semaglutide showed reductions in hyperinsulinemia, hyperandrogenism, ovarian inflammation, and cystic ovarian morphology, along with enhanced browning of white adipose tissue. In rat models treated with exenatide, investigators reported normalized ovarian layer thickness, increased numbers of corpora lutea, decreased follicular cysts, and reduced endometrial fibrosis and inflammation [28]. These findings provide mechanistic support for the clinical translation of GLP-1 receptor agonists, demonstrating consistent reproductive and endocrine improvements in experimental settings.

MECHANISTIC INSIGHTS

The physiological effects of GLP-1 receptor agonists in PCOS extend beyond weight reduction and insulin sensitization. In ovarian granulosa cells, GLP-1 receptor activation promotes cell proliferation and inhibits apoptosis via FoxO1-dependent signaling pathways [27]. At the ovarian level, these agents downregulate the expression of key steroidogenic enzymes, including *STAR*, *CYP11A1*, and *CYP17A1*, and attenuate NF-κB–mediated inflammatory responses, resulting in improved steroid hormone profiles and more regular ovarian cycles [29].

Centrally, GLP-1 influences the hypothalamic-pituitary-gonadal axis by modulating gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) secretion. Increased GLP-1 receptor activity in pro-

opiomelanocortin (POMC) neurons and the pituitary may contribute to normalization of the LH/FSH ratio, a key hormonal marker in PCOS [30].

COMPARATIVE CLINICAL EFFICACY VS METFORMIN AND HORMONAL THERAPIES

Randomized clinical trials indicate that GLP-1 receptor agonists (GLP-1RAs) outperform metformin and hormonal therapies in improving metabolic, hormonal, and reproductive outcomes in women with PCOS. Agents such as liraglutide, exenatide, and semaglutide produce significantly greater reductions in body mass index (BMI), waist circumference, HOMA-IR, and free androgen index compared to metformin alone [26]. Combination therapy with GLP-1RAs and metformin has demonstrated synergistic effects, including improved menstrual regularity, increased sex hormone-binding globulin (SHBG) levels, and enhanced ovulation rates, relative to monotherapy.

Furthermore, meta-analyses and pooled clinical data suggest that GLP-1RAs improve pregnancy rates and in vitro fertilization (IVF) outcomes more effectively than standard hormonal or insulin-sensitizing treatments (see Table 2). These findings support the potential of GLP-1–based therapies to simultaneously address the metabolic and reproductive dysfunctions characteristic of PCOS.

Table 2. Comparison of GLP-1 Analogues vs Metformin and Hormonal Therapies in PCOS

Parameter	GLP-1 Analogues (e.g. Liraglutide, Semaglutide, Exenatide)	Metformin	Hormonal Therapies (e.g. OCPs, anti-androgens)
Weight Loss	Significant (−2.5 to −6.0 kg)	Mild to moderate (−1.5 to −3.0 kg)	No effect
Insulin Sensitivity (HOMA-IR)	Strong improvement	Moderate improvement	No direct effect
Androgen Levels (Testosterone, FAI)	↓ Total testosterone, ↓ FAI	↓ Slightly	↓ Strong (esp. with cyproterone acetate)
SHBG	↑ (significant)	↑ (mild)	↑ (esp. with estrogen-based OCPs)
Ovulation Rate	↑ Spontaneous and induced ovulation	↑ Slightly	Suppressed (during use)
Pregnancy Rate (natural/IVF)	Improved vs metformin	Baseline	Baseline (contraceptive)
Effect on Ovarian Morphology	↓ Cystic follicles, ↑ corpora lutea (in animals)	Mild change	No restorative effect
Impact on Menstrual Regularity	↑ Cycle frequency and normalization	Moderate improvement	Cycle control while on therapy
Adverse Effects	Nausea, GI upset, cost	GI upset, lactic acidosis (rare)	Thrombosis risk, mood changes
Pregnancy Use	Not recommended (data lacking)	Discontinue when pregnant	Contraindicated

The selected variables reflect key clinical and biochemical endpoints in PCOS. HOMA-IR serves as a validated index of insulin resistance and treatment response [1], while SHBG levels reflect hyperinsulinemia-driven androgen excess [5]. Ovulation and pregnancy rates are critical reproductive outcomes used to assess efficacy in both natural and assisted conception contexts [24].

GLP-1 ANALOGUES AND FERTILITY OUTCOMES

The distribution of glucagon-like peptide-1 receptors (GLP-1R) throughout the female reproductive system, along with findings from preclinical and clinical studies, suggests that GLP-1 analogues may serve as a critical link between metabolic and reproductive regulation. Beyond their glucose-lowering and anorexigenic effects, GLP-1 receptor agonists (GLP-1 RAs) exhibit anti-inflammatory and anti-fibrotic properties in reproductive tissues, including the ovaries and endometrium, particularly in the context of PCOS, obesity, and metabolic dysfunction.

Preclinical models have demonstrated that GLP-1 RAs and dipeptidyl peptidase-4 (DPP-4) inhibitors can reverse polycystic ovarian morphology, decrease circulating androgens and their bioavailability, and restore estrous cyclicity [31]. These agents improve ovulation frequency, normalize menstrual cycles in women with oligo- or amenorrhea, and restore hormonal balance by reducing serum androgen levels and improving LH/FSH ratios [32].

In overweight or obese women with PCOS and a history of anovulation, treatment with liraglutide or semaglutide has been associated with resumption of spontaneous ovulation and enhanced fertility potential. Importantly, emerging evidence indicates that the benefits of GLP-1 RA therapy are not limited to women with obesity. Lean women with PCOS have also shown improved reproductive outcomes, supporting the idea that these agents act via mechanisms beyond weight loss. Preclinical studies suggest central effects on the hypothalamic–pituitary–gonadal axis, including modulation of gonadotropin secretion and restoration of endocrine balance, which may contribute to improved ovulatory function and reduced hyperandrogenism [33].

Clinical data also support the use of GLP-1 RAs prior to assisted reproductive technologies (ART). Women treated with liraglutide or semaglutide before in vitro fertilization (IVF) exhibited significantly higher pregnancy rates than those receiving metformin alone [32]. One study demonstrated that a 12-week combination of liraglutide and metformin prior to IVF more than doubled the pregnancy rate compared to metformin monotherapy, despite similar weight loss in both groups [35]. Exenatide has also been reported to outperform metformin in improving natural conception rates and cycle regularity, with sustained benefits even after transition to metformin, indicating possible long-term effects [34,36].

Preliminary evidence suggests improved live birth rates and shorter time to conception in women receiving GLP-1–based therapy. However, due to limited safety data and reports of teratogenicity in animal studies, GLP-1 RAs are not recommended during pregnancy. It is advised to discontinue treatment several weeks before conception and to use reliable contraception during therapy [37]. Although current data do not indicate an increased risk of major congenital anomalies or pregnancy loss with first-trimester exposure, GLP-1 RAs remain contraindicated during pregnancy due to insufficient human data [38].

A case report included in this review describes a 32-year-old obese woman with PCOS who conceived after four months of liraglutide therapy and delivered a healthy infant following an uncomplicated pregnancy. While this outcome is encouraging, isolated case reports are insufficient to establish safety, and larger, prospective studies are needed to inform clinical guidelines for reproductive-age women using GLP-1 analogues [39].

SAFETY PROFILE OF GLP-1 RECEPTOR AGONISTS IN REPRODUCTIVE-AGE WOMEN

GLP-1 receptor agonists (GLP-1 RAs), such as liraglutide, semaglutide, and exenatide, are generally well tolerated and widely used in the treatment of type 2 diabetes and obesity. However, their safety in women of reproductive age, particularly those actively planning conception or undergoing fertility treatment, requires careful consideration.

The most common adverse effects include gastrointestinal symptoms such as nausea, vomiting, diarrhea, and reduced appetite [32]. These events are typically dose-dependent and tend to diminish over time. While the risk of hypoglycemia is low with GLP-1 RA monotherapy, it may increase when combined with insulin or sulfonylureas. Other side effects may include headache, dizziness, and localized injection-site reactions [32].

Regarding reproductive safety, preclinical studies have reported fetal growth restriction and skeletal abnormalities in animal models exposed to GLP-1 RAs during gestation [37]. Consequently, current regulatory guidelines advise against their use during pregnancy. Although recent clinical observations suggest that early pregnancy exposure may not be associated with a significantly increased risk of major congenital anomalies or pregnancy loss [38], the available human data are limited and not sufficient to change current recommendations. Therefore, GLP-1 RAs should be discontinued at least four weeks prior to conception, and effective contraception is recommended during treatment [37].

Data on lactational safety are sparse. Animal studies have shown excretion of GLP-1 RAs into milk, but human data remain lacking. As a result, these medications are not recommended during breastfeeding [37].

Long-term safety outcomes specific to reproductive-age women have not been systematically studied. While short-term benefits on metabolic and reproductive parameters are well documented, the long-term effects of sustained GLP-1 receptor activation on ovarian reserve, endometrial receptivity, and fertility potential remain uncertain [39].

In summary, although GLP-1 RAs show clear promise in improving metabolic and reproductive outcomes in women with PCOS, their use around the time of conception requires careful planning and medical supervision. Until further safety data become available, these agents should be restricted to the preconception period, and avoided during pregnancy and lactation [37–39].

REGULATORY STATUS AND OFF-LABEL USE

As of 2025, GLP-1 receptor agonists such as liraglutide and semaglutide are approved by the FDA and EMA for the treatment of type 2 diabetes mellitus and chronic weight management. They are not approved for use in the treatment of polycystic ovary syndrome (PCOS), fertility enhancement, or preconception care. Any application of GLP-1 RAs in these settings is considered off-label**.**

OFF-LABEL USE IN REPRODUCTIVE MEDICINE

Despite the absence of formal indications, GLP-1 RAs are increasingly used off-label in women with PCOS—particularly those with obesity or metabolic syndrome—due to accumulating evidence supporting their benefits in ovulation restoration and improved fertility outcomes. Off-label use should be undertaken with informed patient consent and under specialist supervision, particularly when used as part of fertility treatment protocols.

MECHANISTIC PATHWAYS LINKING THE GUT AND OVARY IN REPRODUCTIVE FUNCTION

The gut–brain–ovary axis is an emerging concept that describes the complex interaction between the gut microbiota, central nervous system, and female reproductive system. Gut dysbiosis may contribute to reproductive dysfunction by promoting systemic inflammation, metabolic disturbances, and hormonal imbalances, ultimately impairing ovulation and fertility. Through the microbiota–gut–brain axis, the gut microbiota can influence hypothalamic function, including the secretion of gonadotropin-releasing hormone (GnRH) and downstream gonadotropins, which are essential for normal ovarian activity [40].

GLP-1 receptors are expressed in multiple reproductive tissues, including the ovaries and components of the hypothalamic–pituitary axis. Preclinical studies in PCOS animal models have shown that GLP-1 receptor agonists (GLP-1 RAs), such as exenatide, improve ovarian morphology, increase the number of corpora lutea, reduce follicular cysts, and suppress inflammatory and fibrotic markers in both the ovaries and endometrium [28]. These effects suggest improved ovarian function and enhanced endometrial receptivity—two critical factors for successful reproduction.

Beyond their established metabolic effects, GLP-1 and its receptor agonists also exert central regulatory actions on the hypothalamic–pituitary–gonadal (HPG) axis. Specifically, they may stimulate the hypothalamic kisspeptin system, thereby enhancing GnRH secretion and promoting the pulsatile release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. This mechanism is particularly relevant in polycystic ovary syndrome (PCOS), where GnRH and LH pulsatility is frequently disrupted due to hyperinsulinemia and hyperandrogenism [33]. These central neuroendocrine effects may contribute to the restoration of ovulatory function in affected individuals.

CONCLUSIONS

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent a promising addition to the therapeutic arsenal for polycystic ovary syndrome (PCOS), with effects that extend beyond weight reduction and glycemic control. Their mechanisms include improved insulin sensitivity, modulation of systemic inflammation, and potential regulatory actions on the hypothalamic–pituitary–ovarian axis, reflecting a shift toward a more integrative approach to PCOS management.

Growing clinical evidence supports the role of GLP-1 RAs in improving reproductive outcomes. Meta-analyses and randomized controlled trials have shown that GLP-1–based therapies, particularly when combined with metformin, enhance menstrual regularity and increase natural conception rates [25, 32]. In women undergoing in vitro fertilization, pretreatment with liraglutide and metformin has been associated with significantly improved implantation and clinical pregnancy rates compared to metformin alone [32].

Preclinical data further support direct effects of GLP-1 on ovarian function through central neuroendocrine pathways, reinforcing its potential role in restoring ovulation and hormonal balance in women with PCOS [9].

However, safety considerations remain critical. Preclinical studies have indicated potential teratogenic effects, and current guidelines advise discontinuing GLP-1 RAs several weeks before conception [41]. Use during pregnancy is not currently recommended due to insufficient safety data in humans.

In conclusion, GLP-1 receptor agonists offer a novel dual-action strategy for PCOS—targeting both metabolic and

reproductive dysfunction. Their incorporation into personalized treatment plans may benefit women with PCOS, particularly those with infertility. Further research is essential to define long-term safety and establish evidence-based protocols for their use in reproductive-age women.

CONFLICTS OF INTEREST:

Authors have no conflict of interest to declare.

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AUTHOR CONTRIBUTION

Conceptualization: Karolina Krzyżanowska, Aleksandra Śledziewska; methodology: Julia Latocha; formal analysis: Szymon Kaźmierczak, Julia Latocha; investigation: Aleksandra Śledziewska; resources: Maciej Karasiński; data curation: Wiktoria Dzierzgowska, Aleksandra Marianowska; writing - original draft: Aleksandra Śledziewska; writing - review and editing: Wiktoria Dzierzgowska, Szymon Kaźmierczak, Aleksandra Marianowska; visualization: Julia Latocha; supervision: Maciej Karasiński, Aleksandra Śledziewska; project administration: Karolina Krzyżanowska;

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