GLP-1 receptor agonists, polycystic ovary syndrome and reproductive dysfunction: Current research and future horizons

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Abstract

Polycystic ovary syndrome (PCOS) is a disorder that involves several organ systems and cellular pathways. It is strongly influenced by environmental and epigenetic factors. The principal goal of all therapeutic approaches to individuals with reproductive abnormalities is the treatment of subfertility or the regulation of menstruation when pregnancy is not desired. Obesity is closely related to insulin resistance (IR) and subsequent hyperinsulinemia, which aggravate hyperandrogenism and impair early follicle development. Weight loss is of vital importance for overweight/obese individuals with anovulatory infertility. The GLP-1R agonists have achieved remarkable weight reduction and abdominal fat loss in patients with type 2 diabetes (T2D), as well as in overweight/obese individuals and individuals with prediabetes. They have also been shown to promote lower fasting insulin levels and insulin resistance markers. These beneficial effects have been suggested to be particularly helpful in women with PCOS, while their possible role in the hypothalamic–pituitary–gonadal axis is under intense research. This review analyzes the current evidence for GLP-1R agonists, focusing on their effects on ovarian morphology, menstrual dysfunction and fertility outcomes. It also discusses their future role in achieving targeted therapeutic approaches.

Key words: polycystic ovary syndrome, fertility, incretins, weight loss, GLP-1R agonists

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Introduction

Polycystic ovary syndrome (PCOS) is a disorder that involves several organ systems and cellular pathways. It is strongly influenced by environmental and epigenetic factors.[1] About 5–20% of women all over the world are affected during their fertility years; its prevalence depends on ethnicity, phenotype and classification system applied. The principal goal of all therapeutic approaches to women with reproductive problems is an improvement of subfertility or management of menstrual frequency in those who do not want to become pregnant.[2] Dysregulated negative feedback control of luteinizing hormone (LH), combined with insulin resistance (IR) with subsequent hyperinsulinemia, can affect ovarian hormone production and promote decreased ovulation. Hence, all treatment strategies aim to shift the balance of intraovarian steroid synthesis away from LH-insulin-driven stimulated androgen synthesis toward a follicle-stimulating hormone-driven final evolution of a dominant follicle.[1,2]

Mounting evidence has demonstrated that IR is present both in lean and obese individuals with PCOS.[3,4] Obesity, particularly the abdominal/visceral phenotype, is observed in approx. 80% of affected women.[3] It is closely related to IR and increased insulin levels, which aggravate hyperandrogenism (mainly by the stimulation of androgen synthesis from the ovarian theca cells) and impair early follicle development.[5,6] Hyperinsulinemia also stimulates androgen secretion from the adrenal glands and modulates LH release.[3,5] Furthermore, hyperandrogenemia can increase the deposition of visceral adipose tissue (VAT) and subsequently promote the resistance to insulin effects, causing a vicious cycle of feed-forward activation.[5,7] Treatment approaches that target weight loss and abdominal fat reduction do not only benefit the cardiometabolic status of these women but can also suppress this vicious cycle.

Weight loss is of vital importance in overweight/obese women with PCOS and subfertility.[1,2] The suppression of hyperinsulinemia and hyperandrogenism after weight reduction were shown to promote an improve regularity of menses and fertility potential.[1,3,5] Significant metabolic and reproductive benefits, as well as a complete resolution of this syndrome were observed in a significant percentage of obese women affected with PCOS who had undergone bariatric surgery and experienced a substantial weight loss.[8,9] Interestingly, in the latest international evidence-based practice guidelines for PCOS management, it was stated that weight loss therapies combined with lifestyle changes could be useful options for overweight/obese women after lifestyle modification alone has failed.[10]

Objectives

To explore the possible role of glucagon-like peptide-1 receptor (GLP-1R) agonists in improving menstrual dysfunction in women with PCOS.

Materials and methods

A literature search was performed systematically through PubMed, Scopus, Embase, Google, and Google Scholar until April 2022. It identified relevant preclinical and clinical peer-reviewed studies to be included in this review. Case reports and case series, as well as studies in languages other than English were not included in the study. The following Medical Subject Headings (MeSH) terms and relevant terms were used in the search process: PCOS, GLP-1, GLP-1R agonists, Liraglutide (LIRA), Exenatide (EXE), Semaglutide (SEMA), Dulaglutide (DULA), infertility/subfertility, IR, and obesity (Fig. 1).

GLP-1 and PCOS

The GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are the 2 main incretins described; they make up approx. 90% of the incretin activity.[11] The GLP-1 is a peptide that originates from proglucagon, which is synthesized and secreted from enteroendocrine L-cells after meals. It promotes weight loss and has an appetite suppressant activity due to its direct effect on the arcuate nucleus (ARC). Specifically, GLP-1 was shown to stimulate the electrical status of the hypothalamic proopiomelanocortin neurons of the ARC by enhancing the production of protein kinase A and promoting L-type calcium channel expression.[12] However, multiple regions within the central nervous system (CNS) appear to transduce pharmacological signals that connect GLP-1R activation with reduced food consumption and weight loss.[13] The GLP-1 also delays gastric secretion and intestinal motility due to its effect on the regulation of autonomous CNS function; it can also increase thermogenesis.[11–13] Dipeptidyl peptidase-4 (DPP-4) quickly breaks down native GLP-1, having 1–2 min of half-life; then, it undergoes a rapid renal clearance.[11,13]

The hypothalamic–pituitary–gonadal axis expresses GLP-1Rs, while GLP-1 has been suggested to regulate the hypothalamic neurons in order to release gonadotropin-releasing hormone (GnRH). The GLP-1 was also reported to have anti-inflammatory and anti-fibrotic activity in both the ovaries and endometrium.14 The GLP-1R knockout mice experienced disturbed estrous cycles, impaired fertility and delayed puberty compared to normal control mice.[15] The altered secretion and incretin activity were also shown in several small trials on affected women. However, the results are inconsistent and inconclusive, possibly because different protocols were utilized in metabolically heterogeneous PCOS populations.[16–22] The secretion of GLP-1 was not related to insulin levels and markers of IR per se in most of these studies.

GLP-1R agonists

The GLP-1R agonists activate GLP-1Rs and are resistant to the effect of DPP-4; reduced glycated hemoglobulin (A1C) levels and significant weight loss were observed after

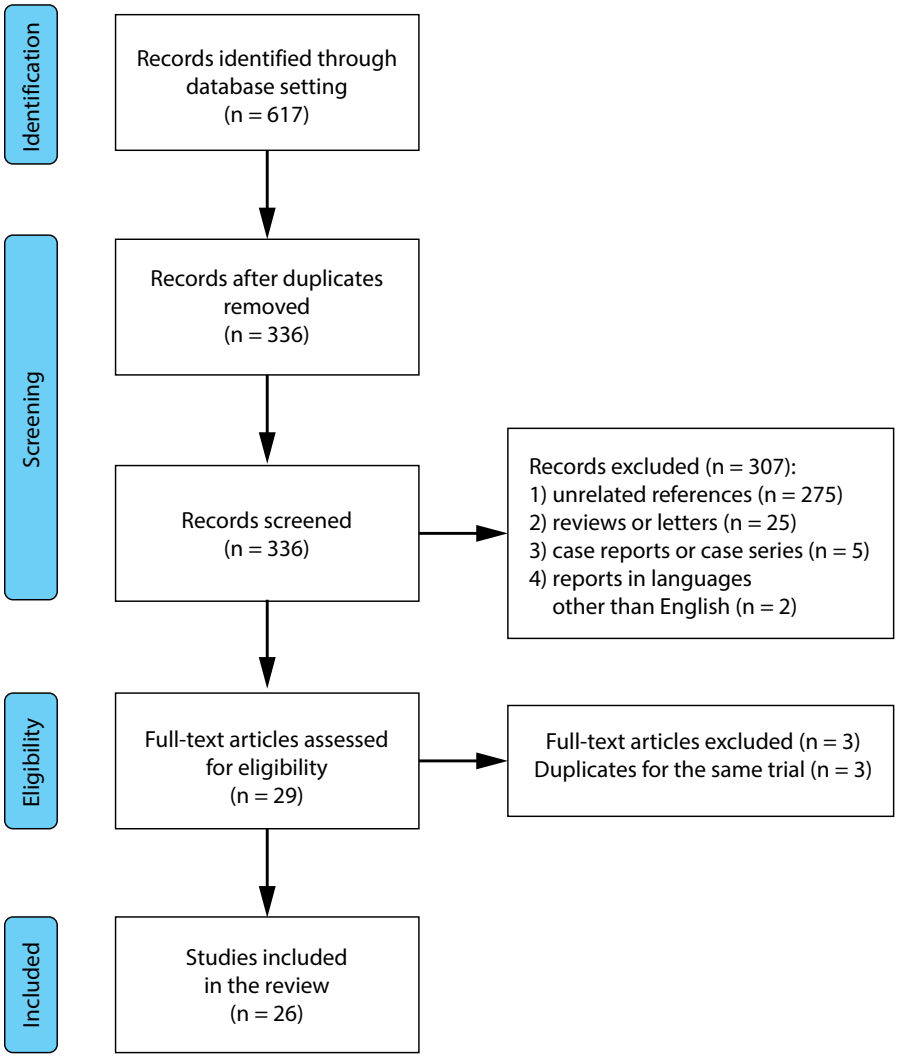

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the process of study selection

they had been administered to patients with type 2 diabetes (T2D).[23] Abdominal fat reduction, as well as improvements in IR indices and insulin levels during fasting were also described in T2D individuals, overweight/obese individuals and/or prediabetic individuals after the administration of GLP-1R agonists.[23–26] Additionally, GLP-1R agonists were shown to reduce urinary albumin excretion and mortality (cardiovascular and from any cause) in T2D patients.[27]

Liraglutide and SEMA were approved for weight reduction by both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for individuals with established obesity or overweight people with a body mass index (BMI) ≥27 kg/m^2 and at least 1 weight-related condition (e.g., hypertension, prediabetes, abnormal lipid levels, and obstructive sleep apnea) combined with lifestyle modifications.[25,28] Semaglutide was recently suggested to be the most effective of its class in terms of weight loss; it can penetrate regions of CNS, which is essential for the control of appetite and hunger, and is not impeded by the blood–brain barrier.[13,28] These beneficial effects of GLP-1R agonists were suggested to be particularly helpful in women with PCOS. Hence, their possible role has become a field of intense research in this population.[29,30]

Liraglutide

Preclinical evidence

When LIRA was administered in preclinical PCOS models, it promoted significant reductions in body weight, abdominal fat deposition and IR markers.[31–33] Liraglutide may also suppress the overexpressed Notch signaling pathway, which causes neuroinflammation and can promote cognitive dysfunction.[34] Moreover, in ovariectomized mice, LIRA was found to modulate Kisspeptin 1 neuronal populations in the ARC, which control the secretion of GnRH in a pulsatile fashion.[35,36] However, this effect was insufficient to exert LH maintenance during fasting conditions.[35]

The possible effects of LIRA administration on reproductive dysfunction were investigated in 2 studies.[31,33] In the first study, female Sprague Dawley (SD) rats (4 weeks of age) were treated with a dihydrotestosterone (DHT) pellet (DHT-induced PCOS group, n = 31), or they received sham surgery without any pellet implant (control group, n = 13).[31] In the DHT arm, a subgroup of 15 rats aged 12 weeks received LIRA, while other 16 rats received saline injections twice a day for a total of 4 weeks. Menstrual

cyclicity did not improve. However, it is unknown whether longer LIRA treatment could improve the menstrual status. In the second study, which was conducted in dehydroepiandrosterone (DHEA)-induced PCOS mice, LIRA was administered in 2 doses intraperitoneally for 2 weeks (100 μg/kg and 200 μg/kg).[33] Mice with PCOS that were given the lower dose of LIRA experienced an acyclic condition, followed by a normal menstrual cycle. Those that were given the higher dose of LIRA had 1 short acyclic period, followed by 2 normal menstrual cycles. The LIRA therapy also promoted enhanced staining in the granulosa cells, theca cells and the stroma of the ovaries.

Clinical studies

Significant reductions in BMI, abdominal circumference and body weight were reported when LIRA was administered, both as a monotherapy and together with metformin (MET), in overweight or obese women with PCOS.[37–45] Sex hormone-binding globulin (SHBG) levels were significantly increased and free testosterone (T) levels were significantly reduced in several of these studies.[38,41,43,44] A preprint version of the SAXAPCOS study (NCT03480022), in which 82 women with PCOS were randomly assigned to LIRA group (3 mg, n = 55) or placebo group (n = 27) for 32 weeks, stated that LIRA decreased the free androgen index (FAI), while it increased SHBG levels compared to placebo ($p < 0.049$ and $p < 0.006$, respectively). The frequency of menses after LIRA therapy significantly increased, as compared to the placebo group.[46] The results concerning menstrual dysfunction were reported in 5 published studies (Table 1).[37,39,40,42,44] Significant effects of LIRA were observed in 2 studies.[42,44] In the first study, the combination of 1.2 mg of LIRA every day with 1000 mg of MET twice a day or MET monotherapy were administered in obese women with PCOS and infertility.[42] Their effects on in vitro fertilization (IVF) rates, pregnancy rates (PRs) and cumulative PRs (spontaneous pregnancies and IVF pregnancies) were explored. None of the included women had experienced weight loss in the past despite changes in their daily habits. They were resistant to first-line reproductive therapeutic approaches with aromatase inhibitors or clomiphene. Twenty-eight individuals were initially enrolled, and 27 ultimately finished the medical protocol; their data were analyzed for 12 weeks (14 were treated with MET only, and 13 received the combination therapy). All participants

Table 1. Clinical studies of liraglutide in women with polycystic ovary syndrome (PCOS), in which results on menstrual dysfunction were reported

Reference	Study population	Study design	Main results
Jensterle Sever et al.[37]	36 obese women with PCOS (mean BMI: 37.1 ±4.6 kg/m^2). They were pretreated with MET for 6 months and have lost less than 5% of BW.	12-week prospective open-label trial. The individuals were randomized to receive 1.2 mg of LIRA daily (n = 11), 1000 mg of MET twice daily (n = 14) or combined 1000 mg of MET twice daily and 1.2 mg of LIRA daily (n = 11).	Combination therapy achieved a significant reduction of androstenedione levels (2.2 ±3.7 nmol/L), while LIRA and MET monotherapy promoted a significant increase of androstenedione (1.9 ±4.2 and 0.8 ±1.70 nmol/L, respectively). Menstrual frequency was not significantly changed.
Jensterle et al.[39]	32 obese women recently diagnosed with PCOS (mean BMI: 39.5 ±6.2 kg/m^2).	12-week prospective open-label study. Participants were randomized to receive 1000 mg of MET twice daily (n = 15) or 1.2 mg of LIRA daily (n = 17). A total of 28 participants completed the study (14 women in each arm) and their data were eventually analyzed.	LIRA promoted a significant increase in LH levels and no essential change in total T levels. MET caused significant LH reduction, as well as significant decrease in total T levels. No significant menstrual frequency changes were found in either group.
Jensterle et al.[40]	41 obese drug-naïve women with PCOS (mean BMI 38.6 ±6.0 kg/m^2).	12-week prospective open-label study. Participants were randomized to receive 1.2 mg of LIRA daily (n = 14), 1000 mg of MET twice daily (n = 13) or 500 mg of ROF daily (n = 14).	Menstrual frequency increased in all treatment arms and was slightly greater in patients treated with ROF.
Salamun et al.[42]	28 obese women with PCOS (mean BMI: 36.7 ±3.5 kg/m^2).	12-week prospective open-label study. Data from 27 women were finally analyzed: 13 received the combination of 1000 mg of MET twice daily and 1.2 mg of LIRA daily, while 14 were treated with MET monotherapy. The IVF protocol was offered to all women who completed the medical treatment protocol after 4 weeks of washout period.	After 1 year of follow-up, pregnancy was achieved in 69.2% of women in the combination arm and in 35.4% of women in the monotherapy arm. The PR per ET was significantly higher (85.7%) in the participants in the combination arm compared to 28.6% in the other group (p = 0.03).
Nylander et al.[44]	72 overweight or obese women with PCOS.	Prospective, double blind, placebo-controlled study. Duration of 26 weeks. All women enrolled were randomized to receive either 1.8 mg of LIRA (mean BMI (SD): 33.3 (5.1) kg/m^2) daily or placebo (mean BMI (SD): 33.3 (4.6) kg/m^2) in a 2:1 ratio. Finally, 65 participants (44 in the LIRA arm and 21 in the placebo) completed the trial.	The SHBG levels increased by 19% (p = 0.03) and free T levels decreased by 19% (p = 0.054) in the LIRA arm. When multiple regression analysis was performed with a change in bleeding ratio as dependent variable, LIRA had a significant impact on increase in menstrual frequency ($p < 0.05$). There was also a trend towards a lower stromal and ovarian volume in the drug therapy arm.

LIRA – liraglutide; MET – metformin; ROF – roflumilast; BW – body weight; BMI – body mass index; T – testosterone; LH – luteinizing hormone; SHBG – sex hormone-binding globulin; PR – pregnancy rate; ET – embryo transfer; IVF – in vitro fertilization.

who eventually completed the medical therapy were included in the IVF protocol. A 4-week washout period was an important prerequisite. Eventually, cumulative PRs were found in 69.2% of the participants in the combination group after 12 months, as compared to 35.4% in the monotherapy group. Significantly increased PRs per embryo transfer (ET) were found in the women who received LIRA/MET (85.7%), compared to those in the MET-only arm (28.6%; p = 0.03). Since the IVF PR per ET in women who experience PCOS and receive MET is approx. 30%, the possible effect of LIRA on the quality and receptivity of the endometrium was suggested.[47] Interestingly, comparable VAT reduction and body weight loss were demonstrated in both arms, suggesting that pathophysiological mechanisms other than the suppression of IR could underlie this effect. This is the first trial to show that LIRA/MET given for a short-term preconception period increased PRs per ET and cumulative PRs in this population, compared to monotherapy with MET.

In the other 26-week randomized trial, LIRA was administered to 72 women with PCOS in a daily dose of 1.8 mg (mean age: 31.4 (24.6–35.6) years; mean BMI: 33.3 (5.1) kg/m^2) compared to the placebo group (mean age: 26.2 (24.8–31.5) years; mean BMI: 33.3 (4.6) kg/m^2).[44] Sixty-five women (21 in the placebo group and 44 in the LIRA group) eventually finished the trial. The multiple regression analysis (change in the bleeding ratio was a dependent variable) suggested that the bleeding ratio at baseline ($p < 0.0001$) and LIRA ($p < 0.05$) achieved significant increases in the frequency of menses. A trend for reduced ovarian and stromal volume, which decreased by 1.6 mL after LIRA administration, was observed. Visceral adipose tissue was reduced by 18%, the proportion of fat in the liver by 44%, and the prevalence of non-alcoholic fatty liver disease by 33% in the LIRA group, as compared to the placebo group (all $p < 0.01$).[48]

Exenatide

Preclinical evidence

Significant reductions in body weight, abdominal fat deposition, fasting insulin levels, fasting glucose levels, and IR markers were observed when EXE was administered in preclinical PCOS models.[49–51] The upregulation of the molecular pathway of the AMP-activated protein kinase α-SIRT1 was also demonstrated after EXE therapy; the downregulation of this molecular pathway was associated with higher IR during a PCOS state.[49]

The possible activity of EXE on reproductive dysfunction and ovarian morphology was investigated in 2 studies.[50,51] In the first study, 45 female SD rats were randomly divided into 2 arms: the DHEA arm (n = 35) and the control arm (n = 10).[50] The DHEA group was then subdivided into 3 groups: the EXE arm (n = 10), the MET arm (n = 10) and the DHEA arm (n = 15), in which the rats were treated with saline for a total of 4 weeks. In the DHEA-treated arm, the ovarian morphology revealed several histological PCOS findings, such as increased numbers of atretic/cystic follicles and reduced corpus luteum. Both the MET-treated and EXE-treated arms had fewer cystic follicles and several other follicles, such as antral or preantral, as well as more layers of granular cells. In the second randomized study, 24 female SD rats were separated into the PCOS with IR arm group (n = 18) and the control group (n = 6).[51] The SD rats in the PCOS with IR model were randomized into 3 arms: MET (n = 6), EXE (n = 6) and PCOS with IR (n = 6) that were treated with letrozole for 3 weeks. Interestingly, 83.3% of the rats in the EXE arm and 67.7% of the rats in the MET arm recovered their regular estrous cycles, while the PCOS with IR rats experienced irregular estrous cycles.

Clinical studies

Significant improvements in BMI, body weight, abdominal circumference, and IR markers occurred when EXE was administered either alone or together with MET in women who experienced PCOS and were overweight or obese. Significant improvements in glucolipid metabolism, amino acid metabolic disorders and markers of endothelial function were also demonstrated.[52–59] Notably, the combination of EXE with dapagliflozin (DAPA) achieved the highest reductions of weight loss and total body fat compared to either drug alone (EXE or DAPA) or a combination of DAPA/MET.[57] In a recent study in which 150 women with prediabetes and PCOS received MET, EXE or a combination of both for 12 weeks (n = 50 in each group), remission rates for prediabetes were 64% in the combination arm and 56% in the EXE group. Both remission rates were significantly higher than those found in the MET arm (32%).[59] Significant reductions of LH levels, compared to baseline values, occurred in the MET and combination arms but not in the EXE arm. Androstenedione and total T levels were significantly reduced, while SHBG was significantly increased compared to the initial concentrations in all 3 treatment arms.

Any possible effects of EXE on reproductive dysfunction were investigated in 2 studies.[52,58] In the first randomized study, 60 overweight/obese oligo-ovulatory women who experienced PCOS (70% finished the study protocol) received 1000 mg of MET twice daily, 10 μg of EXE twice daily, or a combination of both for a total of 24 weeks.[52] Free testosterone levels and FAI decreased significantly in all treatment arms. Significantly lower FAI concentrations were shown in women who received EXE/MET compared to those who received MET treatment only. Increased adiponectin levels were also found in all treatment groups and were strongly associated with decreased FAI levels. More regular menses were observed in the women randomized to the EXE/MET group compared to those in the MET group; they regular menses also strongly associated with weight loss ($p = 0.018$). The ovulation rate

was higher in the women randomized to the combination arm (86%) compared with the EXE arm (50%) and the MET group (29%) ($p < 0.01$). This is the first published study to demonstrate that a combination of EXE and MET for 24 weeks was superior to single-agent EXE or MET in improving menstrual cyclicity and ovulation rates in women who experienced PCOS and were overweight or obese.

In the second 12-week randomized trial, 176 individuals who experienced PCOS and were overweight or obese received either 1000 mg of MET twice a day (n = 88) or 10 µg of EXE twice a day (n = 88); all participants were treated with MET monotherapy for another 12 weeks, after the end of the first 12 weeks of the randomized study.[58] All participants were advised to adopt the same diet and physical exercise routines. Ultimately, 158 women (89.8%; 78 on EXE therapy and 80 on MET therapy) completed the study protocol. The women who were treated with EXE experienced on average a 4.29 ±1.29 kg weight loss compared to 2.28 ±0.55 kg of weight loss in those randomized to the MET group ($p < 0.001$). In addition, the women who received EXE experienced a significantly lower android and total fat mass percentage compared to those who received MET ($p < 0.001$). Free androgen index was significantly reduced and SHBG concentrations were significantly increased in both treatment arms, with no significant difference between them (all $p < 0.001$). The menstrual frequency ratio (MFR) was 0.90 ±0.13 in the EXE arm compared to 0.68 ±0.03 in the MET arm ($p < 0.001$); this significant increase in MFR was associated with weight reduction. The PR was 43.6% in the EXE arm compared to 18.7% in the MET group ($p < 0.05$). This is the first trial to report that EXE therapy for a short time increased natural PRs more than MET therapy. The clinical and preclinical data regarding EXE administration on ovarian morphology, menstrual dysfunction and/or fertility outcomes are shown in Table 2.

Dulaglutide

The escalation of DULA given once every week in a dose of 3 mg or 4.5 mg achieved further incremental reductions in body weight, regardless of baseline A1C or BMI, compared to 1.5 mg once weekly in patients with T2D.[60] In a recent study, which was conducted in a DHEA-induced PCOS female rat model, 3 different doses of DULA were administered subcutaneously for 3 weeks in the treatment arm.[61] Fifty SD rats were randomized into either the DHEA-induced PCOS arm (n = 40) or the control arm (n = 10). Forty SD rats in the DHEA-induced PCOS model were then randomly divided into 4 arms (n = 10 in every arm): PCOS arm (model) that received normal saline; PCOS+DULA in a dose of 50 µg/kg (D-50 group); PCOS+DULA in a dose of 150 µg/kg (D-150 group); and PCOS+DULA in a dose of 450 µg/kg (D-450 group).

Insulin concentrations in the ovaries of the PCOS arm were significantly higher than those in the control arm. After DULA therapy, insulin concentrations in the ovaries in all 3 DULA groups were lower than those in the PCOS arm. The rats in all 3 DULA-treated arms experienced statistically significant reductions in serum T levels

Table 2. Preclinical and clinical studies of exenatide in polycystic ovary syndrome (PCOS), in which results on ovarian morphology and/or menstrual dysfunction were reported

Reference	Study design	Main results
Sun et al.[50]	45 SD rats were randomly divided into 2 arm groups: the DHEA arm group (n = 35) and the control arm group (n = 10). The DHEA arm group was then divided into 3 other groups: EXE group (n = 10), MET group (n = 10) and DHEA group, in which rats were treated with saline for a total of 4 weeks.	Both the MET-treated and EXE-treated arms showed decreased numbers of cystic follicles and various other follicles (such as antral and preantral follicles). Increased numbers of granular cell layers were found.
Xing et al.[51]	24 SD female rats were randomly divided into PCOS with IR group (n = 18) and the control group (n = 6). The SD rats in the PCOS with IR model were randomly divided into 3 arm groups: MET (n = 6), EXE (n = 6), and PCOS with IR (n = 6) that were treated with letrozole for a total of 3 weeks.	83.3% of the rats in the EXE arm group and 67.7% in the MET arm group recovered their regular estrous cycle, while PCOS with IR SD rats experienced irregular estrous cycles.
Elkind-Hirsch et al.[52]	60 overweight/obese oligo-ovulatory women with PCOS were randomized to receive 1000 mg of MET twice daily, 10 µg of EXE twice daily, or the combination of both medications for a total of 24 weeks.	Higher menses frequency and ovulation rates were shown in all groups after treatment. The improvement of bleeding frequency was strongly associated with weight loss. However, more regular menses were demonstrated in the combination arm compared to the MET arm. Moreover, the ovulation rate in the combination arm was significantly higher (86%) compared to the EXE group (50%) and the MET group (29%).
Liu et al.[58]	176 overweight/obese women with PCOS were randomized to receive either 1000 mg of MET twice daily (n = 88) or 10 µg of EXE twice daily (n = 88) for the first 12 weeks; all participants were treated with MET monotherapy during the next 12 weeks.	FAI was significantly reduced ($p < 0.001$) and SHBG levels significantly increased ($p < 0.001$) in both treatment arms, with no significant difference between them. The MFR was 0.90 ±0.13 in the EXE arm compared to 0.68 ±0.03 in the MET arm ($p < 0.001$); the significant increase of MFR was associated with weight reduction. The PR was 43.6% in the EXE arm compared to 18.7% in the MET group ($p < 0.05$).

EXE – exenatide; MET – metformin; DHEA – dehydroepiandrosterone; SHBG – sex hormone-binding globulin; FAI – free androgen index; PR – pregnancy rate; IR – insulin resistance; SD – Sprague Dawley; MFR – menstrual frequency ratio.

and statistically higher serum SHBG levels compared to those in the PCOS arm. There were fewer cystic follicles in the D-150 and D-450 arms, while the total population of the corpus luteum was significantly higher than in the PCOS arm. Moreover, the population of preantral follicles in all 3 DULA arms was significantly suppressed compared to the PCOS arm. Steroid hormone production-related genes, namely *3β-HSD*, *CYP19α1* and *StAR*, were significantly downregulated in the ovaries of the rats randomized to the 3 treatment groups; *StAR*- and *CYP19α1*-induced protein synthesis was significantly decreased in the ovaries after DULA therapy compared to the control arm.

Semaglutide

When administered to overweight/obese individuals, SEMA achieved remarkable reductions in body weight and significant improvements in cardiovascular and metabolic health risk factors.[62] Semaglutide decreased tongue fat tissue and fat proportion (a possible early marker of body fat deposition) compared to placebo, when given in a weekly dose of 1 mg during 16 weeks, in 25 obese women with PCOS.[63] The Treating PCOS With Semaglutide vs Active Lifestyle Intervention (TEAL) trial is active and is recruiting individuals with PCOS and obesity.[64] Participants in this study will be randomized to receive either oral SEMA (3 mg or 7 mg once daily) for 4 months or dietary modification.

Limitations

The limitations of this review are the factors that limit the quality and generability of the results of current literature, namely the short period of research, the small number of women investigated, the absence of a control arm (in some studies), and the lack of large, well-organized, double-blind, placebo-controlled studies over longer periods of time.

Conclusions

Preclinical studies on the administration of GLP-1R agonists in PCOS have shown promising results, both metabolic and reproductive. The majority of clinical studies concerning monotherapy with LIRA or EXE and their administration together with MET have demonstrated statistically significant improvements in BMI, abdominal circumference, total weight, markers of IR, and beneficial effects on glucolipid metabolism. Significant improvements in physical, psychological and social health were also reported.[65] Interindividual variations of body weight reduction could be the result of several genetic polymorphisms that contribute to GLP-1R genotype variability.[66] Most of their important effects were also illustrated in several recent meta-analyses; monotherapy with GLP-1R agonists or their combination with MET were superior to MET monotherapy in terms of reduction of waist circumference, body weight and BMI.[67–73] In order to enhance the cardiometabolic and hormonal defects associated with this syndrome, the potential combination of GLP-1R agonists/sodium-glucose co-transporter 2 (SGLT2) inhibitors is also being studied.[57,74]

Decreased free T levels and FAI have been shown both after LIRA and EXE administration. Significantly increased SHBG concentrations were also reported in numerous studies of LIRA and EXE administration.[38,41,44,52,58,59] However, the short period of research, the small number of women investigated and the absence of a control arm (in some studies) were major limitations. Whether the effect of GLP-1R agonists on increased androgen levels is the consequence of weight loss and the suppression of IR rather than an activity directly related to ovarian function per se, has not been clearly addressed. Furthermore, the rate of rebound weight gain following the cessation of this drug class is another issue that needs to be considered in future studies.

Both EXE and LIRA achieved significant increases in menstrual frequency and ovulation rates (Table 1 and Table 2). The improvement in bleeding frequency was significantly associated with weight loss in some studies. Notably, more regular menses were demonstrated after their combination with MET compared to MET monotherapy.[42,52] It should be stated that both EXE and LIRA failed to reduce LH levels.[39,59] On the contrary, MET promoted significant reductions of LH levels and meaningful reductions of total T concentrations, highlighting its key role in the regulation of LH secretion and the steroidogenesis coming from the ovaries.[75] In addition, important reductions of androstenedione concentrations were found after LIRA/MET combination therapy compared to monotherapy with LIRA, indicating the significance of their combination in this setting.[30,37] Metformin could also exhibit synergistic effects with GLP-1R agonists through the stimulation of GLP-1R expression/biosynthesis.[76] In this way, combining GLP-1R agonists with MET can be more effective compared to monotherapy of each drug class, in order to achieve significant hormonal and metabolic effects in women with PCOS, after lifestyle changes fail with or without MET.[30]

The GLP-1R agonists are classified as pregnancy class C medications and are contraindicated during pregnancy.[10,14,30] However, the higher rate of natural PRs after EXE therapy and IVF PR per ET/cumulative PRs after LIRA/MET combination suggests their promising role in the treatment of subfertility when they are administered during the preconception period.[42,58] Safety problems were unremarkable after the administration of EXE or LIRA in this setting; thus, their clinical use seems to have an acceptable profile. Close monitoring and a reasonable washout period are essential prerequisites. Interestingly, in the SEMA approval package inserts, it is stated that SEMA should be discontinued for at least 2 months before

a planned pregnancy due to its long half-life.[30] The clinical relevance of GLP-1R agonists on the hypothalamic–pituitary–gonadal axis, as well as on the quality and receptivity of the endometrium, merit future investigation.[14,30,77]

The recent dual GIP/GLP-1 receptor agonist tirzepatide promoted greater body weight loss compared to SEMA (at a dose of 1 mg) in patients with T2D. In addition, both dual GLP-1/glucagon receptor agonists and triple GLP-1/GIP/glucagon receptor agonists are under intense investigation; their possible effects on women with PCOS who are overweight or obese should be explored in future studies.[78–80]

The major adverse effects of GLP-1R agonists were nausea and vomiting, mainly during the up-titration phase; these effects were short-term and not associated with any significant termination of therapy.[25,30,66,67] In such cases, nausea and vomiting can be minimized by introducing certain treatment approaches, such as: prolonging the escalation period and titrating the LIRA dose in increments of 0.3 mg (5 click steps) rather than in increments of 0.6 mg (10 click steps), and/or dividing the dose twice a day.[25,30,81] Consistent with other interventions that cause substantial weight loss, cholelithiasis has also been reported and must be taken into consideration during the therapy and follow-up periods.[25,30] Another issue with GLP-1R agonist therapy is the high cost. The early cessation of the administration of GLP-1R agonists in individuals unlikely to experience any beneficial metabolic effects can help medical specialists reduce any probable adverse effects in the future, enhance the risk/benefit ratio and decrease the entire financial cost.[82]

Longer, larger, well-organized, multicenter, double-blind, placebo-controlled studies with thorough design and prolonged post-interventional follow-up are recommended in order to investigate the safety and activity of this drug class in women with PCOS who are overweight or obese. Convincing data with sufficient power to detect the risk/benefit profile of their use remain to be obtained. Hormonal, metabolic and fertility outcomes must be thoroughly explored. This will provide clinicians with valuable information helpful in clarifying their future role and adapting targeted therapeutic approaches in order to be successful in obtaining beneficial long-term outcomes.

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