Impact of dramatic weight loss with the new injectable medications on reproduction in healthy non–polycystic ovary syndrome obese women

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The intake of glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) in obese women with polycystic ovary syndrome (PCOS) demonstrated improvement in metabolic and reproductive symptoms; however, their impact in non-PCOS state is unclear. This review critically analyzes data pertaining to GLP-1 RAs in non-PCOS females in both humans and animals, with a focus on their impact on the hypothalamic-pituitary-ovarian axis and the uterine function. In animal models, studies showed controversial results. The intracerebroventricular GLP-1 administration caused stimulatory reproductive effects, where it increased the amplitude of the luteinizing hormone surge, follicle-stimulating hormone (FSH) secretion, serum progesterone levels, up-regulation in *Kiss-1r* expression in the hypothalamus, and increase in ovarian Graafian follicles and corpora lutea. However, the intracerebroventricular GLP-1 RA Exendin-4 and the subcutaneous GLP-1 RA liraglutide resulted in opposite effects. Even though GLP-1 up-regulated FSH receptor messenger ribonucleic acid expression in granulosa cells, it led to a suppression in FSH-induced progesterone synthesis. The effect of GLP-1 RA on the uterus also showed controversial findings. Although some data showed that GLP-1 RA had a beneficial antifibrotic effect in intrauterine adhesions model by reducing the deposition area of collagen fibers, other data showed that exposure to GLP-1 RA resulted in destruction of the luminal epithelium with shrinkage in muscle fiber. It is unclear how these GLP-1 RA medications impact future fertility in humans because most studies to date had significant limitations and were performed in animals with contentious findings. There is a clear need to study this relationship because many reproductive-aged women without PCOS are resorting to these medications for weight loss purposes. (F S Rep® 2025;6:4–9. ©2025 by American Society for Reproductive Medicine.)

Key Words: GLP-1, PCOS, obesity, reproduction, ovaries

INTRODUCTION

According to the Centers for Disease Control and Prevention reports, 2023 data showed that almost 1 in 5 women experienced infertility compared with 1 in 8 women in 2002, indicating almost a 60% increase in infertility in the last 2 decades (1). Additionally, according to the 2020 Society for Assisted Reproductive Technology data, the number of assisted reproductive technology (ART) cycles have surged 114% (from 140,795 in 2008 to 301,316 in 2020). Overweight and obesity have increased globally and surged in the United States in the last decade (2), and reproductive-aged women with obesity are also more likely to need ART services (3); however, they could be denied in vitro fertilization (IVF) because most fertility centers have a body mass index (BMI) cutoff.

Many obese women with infertility resort to invasive procedures such as bariatric surgery, which, although has several health benefits, is invasive and could positively or negatively impact different aspects of female reproduction (4). For instance, bariatric surgery has been shown to negatively impact ovarian reserve by causing a decrease in the serum antimüllerian hormone (AMH) levels (5). Although still contentious, this acute decrease in ovarian reserve after bariatric surgery may be a result of postoperative stress and micronutrient deficiencies theoretically causing damage to ovarian follicles (6).

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The injectable glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) such as semaglutide (sold under the brand name Ozempic, Novo Nordisk) are being recently found as a quick-fix solution for weight loss before IVF when previous attempts seemed too slow because time is of the essence especially in women with diminished ovarian reserve. Additionally, most fertility clinics have a BMI cutoff to qualify for IVF; thus, patients above the BMI cutoff are more inclined to use these medications so that they would meet the criteria. The use of GLP-1 RAs is rapidly gaining popularity especially with its recent outbreak on social media (7). The GLP-1 RAs are antihyperglycemic medications used mainly in the treatment of type 2 diabetes; however, they are easily available to purchase online without medical oversight (7) and are been used by healthy, nondiabetic, obese women worldwide.

Because GLP-1 receptors exist in the reproductive organs and the brain (8), one would expect an impact of the GLP-1 RAs on the hypothalamic-pituitary-ovarian (HPO) axis and uterine function. Short-term studies have shown that GLP-1 RAs can be of metabolic and reproductive benefits for women with polycystic ovary syndrome (PCOS) (9)—the most common endocrine disorder among reproductive-aged women (10). This narrative review critically summarizes and analyzes data pertaining to the impact of GLP-1 RAs medication intake in non-PCOS females with a focus on their impact on the HPO axis.

Data extraction

PubMed search using the keywords "obesity, GLP-1, GLP-1 receptor agonist, reproduction, luteinizing hormone (LH), FSH, PCOS, ovaries, granulosa cell, steroidogenesis, hypothalamus, uterus, uterine adhesions, ovarian reserve, and anti-Mullerian hormone (AMH)" was performed. From the search results, each manuscript including original studies, case reports, and review articles, was read in detail to extract data pertaining to healthy overweight and obese females, both humans and animals, who do not have PCOS. The question in mind was as follows: can these medications that cause dramatic weight loss at a rate relatively close to some bariatric surgery procedures (e.g., endoscopic sleeve gastroplasty) negatively or positively impact oocyte quality or endometrial receptivity in *healthy obese non-PCOS women*?

WHAT DO WE KNOW ABOUT GLP-1 RA AND PCOS?

For overweight/obese women with PCOS, weight loss of $\geq 5\%$ could improve metabolic and reproductive symptoms, thus restoring ovulation, decreasing insulin resistance, and reducing serum androgen levels (11). Glucagon-like peptide-1 RAs, known for their glucose-dependent insulin release, have been shown to offer benefits such as increased satiety and reduced appetite, thus constituting a promising avenue for PCOS treatment (12). For instance, a meta-analysis study of 8 randomized trials compared metformin with GLP-1 RAs in women with PCOS and concluded that GLP-1 RA was significantly better than metformin in improving insulin sensitivity and lowering BMI and abdominal circumference (9). Glucagon-like peptide-1 RA was also better than metformin in improving menstrual cyclicity, serum total testosterone and free androgen index, sex hormone binding globulin, androstenedione, LH, dehydroepiandrosterone sulfate), Ferriman-Gallwey scores, fasting blood glucose and insulin, triglycerides, total cholesterol, and blood pressure (9). Several review articles to date have nicely summarized the literature pertaining to the impact of GLP-1 RA on metabolic and reproductive disturbances, and all of them have included women with PCOS only as the target patient population (13, 14). Few studies have evaluated the effect of GLP-1 RA on menstrual irregularities in women with PCOS where some have shown an improved bleeding ratio in women with PCOS, defined as the number of menstrual bleedings divided by the study period in months, whereas other studies have shown unaltered bleeding ratio (14). A common conclusion among these review articles was that the treatment of women with PCOS should be part of a comprehensive, multidisciplinary approach aiming at weight management especially in those planning to conceive using ART.

One randomized open-label study explored the impact of preconception intervention with the GLP-1 RA liraglutide on fertility potential in obese women with PCOS who had poor responses to first-line treatment options (15). That study was conducted on 28 obese women with infertility and PCOS, assigning them to either metformin alone or metformin with low-dose liraglutide (COMBI) for 12 weeks, followed by a 4-week medication-free period and then ovarian stimulation for IVF (15). Weight loss was similar in both groups (metformin and COMBI); however, the pregnancy rate after embryo transfer was significantly higher in the COMBI group (85.7%) than in the metformin alone group (28.6%, $P=.03$). Additionally, the pregnancy rate, cumulative over 12 months, was 69.2% in the COMBI group, compared with 35.7% in the metformin group ($P<.05$). That study concluded that preconception intervention with low-dose GLP-1 RA, in combination with metformin, was superior to metformin alone in increasing pregnancy rates after IVF in obese women with infertility and PCOS. The comparable weight reduction in both groups suggests that the observed benefits are attributed to the potential direct, rather than via weight loss, impact of the GLP-1 RA liraglutide on the reproductive system, emphasizing the need for further exploration, particularly focusing on the GLP-1 impact on endometrial receptivity.

Because the therapeutic effects of GLP-1 RAs on PCOS are well acknowledged, basic science studies investigated the regulatory role of GLP-1 RA signaling in the proliferation and antiapoptotic processes of PCOS-associated granulosa cells (16). That study revealed that GLP-1 serves as a regulator of both proliferation and antiapoptosis in mural granulosa cells within PCOS mouse ovaries, both in vitro and in vivo, notably via mechanisms that involve forkhead box protein O1 (16). These data, taken together, are reassuring for PCOS state because most of both human and animal studies showed improvements in reproductive potentials.

WHAT DO WE KNOW ABOUT THE EFFECT OF GLP-1 RA ON THE HPO AXIS IN NON-PCOS STATE?

At the time of writing this manuscript, literature search resulted in a few studies in non-PCOS animal model (Table 1)

TABLE 1

Summary of findings pertaining to the impact of glucagon-like peptide-1 receptor agonists on reproductive organs in non–polycystic ovary syndrome animal models.

Study	Animal model and target organ(s)	Results
Saber and Abd El-Rahman (17)	Albino female rats: • Ovaries • Uterus	• Liraglutide at escalating doses increased the reactive oxygen species levels by impairing the concentration of superoxide dismutase, glutathione, and catalase. • Liraglutide caused apoptotic changes in granulosa cells and caused more follicular atresia. • These changes were mostly reversible after drug discontinuation. • Liraglutide resulted in destruction of the luminal epithelium and hypercellularity of the endometrial stroma as well as shrinkage in muscle fiber indicating apoptosis.
Nishiyama et al. (8)	Sprague-Dawley female rats: • Granulosa cells	• GLP-1 had no effect on estradiol synthesis or on aromatase enzyme. • GLP-1 suppressed progesterone synthesis in the presence of FSH by altering StAR, P450scc, and 3βHSD enzyme activity.
Outeiriño-Iglesias et al. (18)	Sprague-Dawley female rats: • HPO axis • Vaginal opening • Litter size and weight of pups	• Opposite to the effect of the native GLP-1 administration, the GLP-1 RA Exendin-4 (Ex4) caused a suppression of the LH surge by reducing the hypothalamic *Kiss-1* and *Kiss-1r* expression levels. • Ex4 caused a significant reduction in ovarian and uterine weight as well as a delay in vaginal opening. • Ex 4 did not affect ovulation rate or the number of ovarian follicles at all stages. • Ex 4 did not affect the number of implanted fetuses, litter size, or weight of the pups.
Wang et al. (19)	Female C57BL/6J mice: • Intrauterine adhesions	• Dulaglutide increased endometrial thickness and the number of glands and significantly reduced the area of collagen fiber deposition in the endometrium. • It significantly reduced the COL1A1, IL-1β, IL-6, TNF-α, C-C motif chemokine ligand 2, F4/80 (macrophage), vimentin, and TGF-β mRNA levels as well as the COL1A1, IL-1β, IL-6, TNF-α, F4/80, vimentin, E-cadherin, TGF-β, and p-Smad2 protein expression levels.
Ma et al.(20)	Female C57BL/6J mice: • Intrauterine adhesions	• Ex4 caused an increase in the size of the endometrial glands and caused a significant reduction in the deposition area of collagen fibers in the endometrial tissue. • Ex4 caused a significant reduction in the mRNA expression levels of TGF-β1 and α-SMA in the endometrial tissue and a significant up-regulation of MMP-9 mRNA levels. At the protein level, Ex4 caused a significant reduction in the protein expression of TGF-β1, α-SMA, and collagen 1.

Note: COL1A1 = collagen type I A 1; FSH = follicle-stimulating hormone; GLP-1 = glucagon-like peptide-1; IL = interleukin; LH = luteinizing hormone; mRNA = messenger ribonucleic acid; TGF = transforming growth factor; TNF = tumor necrosis factor.

Merhi. Injectable weight loss medications in non-PCOS condition. F S Rep 2025.

(8, 17–20) and, surprisingly, no studies in humans pertaining to the effect of GLP-1 RAs on fertility status in females without PCOS.

Impact on the ovaries and uterus in the non-PCOS model

One study explored the impact of GLP-1 RA liraglutide on ovarian and uterine tissues of female rats (17) with a focus on hormone levels, oxidative stress, and tissue integrity. That study used 30 female rats that were divided into 3 groups as follows: a control group, which received only saline through a subcutaneous injection; a GLP-1 RA liraglutide group, which received escalating doses of liraglutide over 5 weeks; and a recovery group, which received GLP-1 RA liraglutide followed by 2 weeks of drug withdrawal. Ovarian tissue oxidative stress was examined for levels of antioxidant markers (glutathione, superoxide dismutase, and catalase) as well as malondialdehyde, which is a lipid peroxidation product. Histological examinations of both the ovaries and uterus provided detailed insights into tissue architecture and any potential damage. Their results showed alterations in reproductive hormone levels, in particular a decrease in the serum LH, follicle-stimulating hormone (FSH), estradiol, and

progesterone (P4) levels but an increase in the serum testosterone level. The exposure to liraglutide resulted in a decrease not only in body weight but also in ovarian weight, whereas the recovery group exhibited an increase in both body and ovarian weight. Liraglutide treatment significantly decreased the levels of key antioxidant molecules within ovarian tissues; the glutathione, catalase, and superoxide dismutase levels declined in the liraglutide group compared with those in the control group. Moreover, the study demonstrated deleterious effects of liraglutide on granulosa cells and follicles (17) where the liraglutide group had fewer developing follicles and an increased number of disorganized and atretic follicles compared with controls. Granulosa cells within these compromised follicles exhibited apoptosis and increased amounts of fibrous tissue within the follicles. Corpora lutea displayed fatty degenerative changes and hyaline body formation, indicative of impaired functionality. Additionally, exposure to liraglutide resulted in destruction of the luminal epithelium and hypercellularity of the endometrial stroma as well as shrinkage in muscle fiber with pyknotic nuclei indicating apoptosis (17). These deleterious effects were observed to subside after liraglutide administration was discontinued, as observed in the recovery group, which demonstrated partial restoration of body and ovarian weights, rebounding of hormone levels, and significant recovery of antioxidant markers. However, persistence of some atretic follicles, degenerative changes in corpora lutea, and mild vacuolation of the uterine epithelium suggest incomplete recovery or potentially permanent damage. That study had few significant limitations. The investigators used a 5-week incremental dosing of GLP-1 RA that was increased from 0.06 mg/kg/rat in the first week of treatment to significantly higher doses of 0.3 mg/kg/rat in the fifth week of treatment; however, there was no justification of the doses used throughout the experiments. Another limitation was that there is no mention to whether the animals were killed at the same phase of the estrous cycle because it is well known that the outcomes of interest could vary significantly with various estrous phases.

Another study explored the effects of GLP-1 on steroidogenesis using rat granulosa cells (8). That study revealed that GLP-1 caused a significant suppression of FSH-induced P4 synthesis. The cyclic adenosine monophosphate production induced by FSH was suppressed by 48-hour treatment with GLP-1, whereas FSH receptor messenger ribonucleic acid (mRNA) expression was significantly increased by GLP- 1 treatment for 48 hours. Additionally, GLP-1 reduced the mRNA expression levels stimulated by FSH of the progesterogenic enzymes StAR, P450scc, and 3βHSD. Glucagon-like peptide-1 did not cause any significant alterations in estradiol synthesis by rat granulosa cells (8). The investigators concluded that GLP-1 could disrupt steroidogenesis in rat granulosa cells, in particular the FSH-induced P4 production.

The effect of GLP-1 RA on ovarian reserve markers such as serum AMH, to our knowledge, has never been investigated before in humans or animals without PCOS. One study showed a trend toward decreased AMH levels over time in women with PCOS while taking the GLP-1 RA liraglutide (21); however, this cannot translate to non-PCOS condition.

Impact on the hypothalamus and puberty in the non-PCOS model

Studies on animals have shown that central or peripheral administration of GLP-1 RA reduces food and water intake, leading to weight loss. One of the mechanisms by which GLP-1 causes anorexigenic effects is by altering the kisspeptin system at the level of the hypothalamus (18). Kisspeptin is well known to be a stimulant for gonadotropin-releasing hormone secretion that leads to an increase in LH secretion and ultimately blood steroid levels (22). Interestingly, the synthetic GLP-1 RAs have different effects than the native gastrointestinal GLP-1 peptide in different tissues/organs in both prepubertal and adult female rats. One study evaluated the changes in Glp-1r expression at the levels of the hypothalamus during different phases of the estrous cycle and evaluated the effects of GLP-1 RA administration on the onset of puberty. It was noted that central administration of the native GLP-1 caused a stimulatory effect on the gonadotrophic axis and increased the efficiency of the reproductive system. The results showed that the intracerebroventricular GLP-1 administration had stimulatory reproductive effects, where it increased the amplitude of the LH surge by approximately twofold and significantly increased FSH secretion and serum P4 levels and caused an up-regulation in *Kiss-1r* expression in the hypothalamus. The intracerebroventricular GLP-1 administration also induced an increased in ovarian Graafian follicles and corpora lutea. On the other hand, the GLP-1 RA Exendin-4 (Ex4) had opposite effects than the native GLP-1 by blocking effects on the HPO axis system (18) where it caused a 2.7-fold decrease in the LH levels, causing a suppression of the LH surge most likely by reducing the hypothalamic *Kiss-1* and *Kiss-1r* expression levels. Finally, although the administration of the native GLP-1 to prepubertal rats synchronized vaginal opening (i.e., puberty onset), exposure to the GLP-1 RA Ex4 produced a significant reduction in ovarian and uterine weight as well as delay in vaginal opening (18). However, Ex4 did not affect the number of implanted fetuses, litter size, or weight of the pups. Overall, the investigators concluded that GLP-1 and Ex4 acted differently on the HPO axis, involving the kisspeptin system, to influence reproductive efficiency in female rats. The significant 30% reduction in food intake caused by Ex4 could potentially explain the negative impact on the reproductive system. It is important to note that ex4, a hormone found in the saliva of the Gila monster, has only 50% homology in amino acids with the native GLP-1 and has a significantly longer half-life than the native GLP-1; thus, its impact may not translate to the injectable GLP-1 RAs used in humans.

Impact on uterine adhesions in the non-PCOS model

The effect of the GLP-1 RA dulaglutide on the uterus has been assessed in a study pertaining to intrauterine adhesions (IUAs) (19), a state of excess fibrotic tissue, given the background that GLP-1 RA could attenuate liver fibrosis (23), kidney fibrosis (24), and lung fibrosis (25). In that study, a mouse animal model of IUAs was used where IUAs were caused by

using mechanical curettage (scraping injury) and inducing inflammation by lipopolysaccharide. Then, the treatment group was injected subcutaneously with 3 doses of GLP-1 RA dulaglutide (150, 300, and 600 μg/kg) once a week for 2 weeks. The uterine tissue was extracted and quantified using histopathological analysis, reverse transcription polymerase chain reaction, and western blot. In the dulaglutide treatment group, the endometrial thickness increased, the endometrial glands increased in size, and the deposition area of collagen fibers in the endometrial tissue was reduced significantly compared with controls. The GLP-1 RA dulaglutide significantly down-regulated collagen type I A 1, interleukins (ILs) (e.g., IL-1β and IL-6), tumor necrosis factor-α, and transforming growth factor (TGF)-β mRNA and protein expression levels. The investigators concluded that the GLP-1 RA dulaglutide could reduce inflammatory factor release and could lessen fibrosis via TGF-β/Smad2 signaling pathway.

In another study (20) that used the same mouse model of IUAs, the GLP-1 RA exenatide was injected subcutaneously for 2 weeks after which the uterine tissue was evaluated histomorphologically and histopathologically and reverse transcription polymerase chain reaction and western blot were performed for gene quantification of TGF-β1, MMP-9, and α-SMA (genes related to fibrogenesis). The GLP-1 RA Ex4 caused a significant increase in the endometrial glands size; on the other hand, it caused significantly lower deposition of collagen fibers in the endometrial tissue (20). Ex4 caused a significant reduction in the mRNA expression of TGF-β1 and α-SMA in the endometrial tissue and a significant up-regulation of the MMP-9 mRNA levels. At the protein level, Ex4 caused a significant reduction in the protein expression of TGF-β1, α-SMA, and collagen 1. The investigators concluded that the GLP-1 RA exenatide could exert an anti-fibrotic effect in the IUA mouse model.

CONCLUSION

Accessing justice-based fertility treatments overweight/obese women can be problematic because several of these women have reported their concerns as being overlooked by doctors or have voiced that some doctors blamed their infertility on their weight without offering any diagnostic testing or providing advice for fertility assessment and management. The correlation between weight loss and reproductive benefits have been established and well integrated into the reproductive endocrinology and infertility (REI) field especially for those who would not qualify for IVF due to clinic-dependent BMI cutoffs. However, focusing only on these obesity risks while overlooking the challenges of weight loss could be disadvantageous. Given the current obesogenic environment, vulnerability of this patient population, and wealth of online misinformation, there is a dramatic increase in the use of the quick-fix GLP-1 RA medications leading the commercial market to capitalize on this vulnerability. As of today, even though the GLP-1 RA medications seem promising and beneficial for women with PCOS, it is unclear how these GLP-1 RA medications impact future fertility in healthy obese women who do not have PCOS. The data to date have been done mostly in vitro or in animal models with mediocre designs.

What do REI doctors do in the meantime when encountering non-PCOS women on GLP-1 RA who wish to undergo ART? According to the American Society of Anesthesiologists, before procedures that involve anesthesia or sedation, such as egg retrieval, patients taking GLP-1 RA on a daily basis should stop taking the medication the day before a procedure, and patients taking GLP-1 RA on a weekly basis should stop 1 week before a procedure. The goal is to minimize the risk of aspiration of food into the lungs during anesthesia due to delayed gastric emptying caused by these medications.

Even though manufacturers recommend stopping the GLP-1 RA semaglutide at least 2 months before conception and the GLP-1 RA tirzepatide at least 1 month before conception, most clinical guidance on the optimal time to stop these medications was based on animal data. Expert opinions among REI doctors have been divided between those who would allow their patient to continue the GLP-1 RA during the ART procedures as long as the patients are not undergoing embryo transfers to directly become pregnancy, whereas others recommend that all patients use contraception to prevent unintended pregnancy while taking GLP-1 RA. The fear among the latter group stems from some studies examining small animals exposed to GLP-1 RA in pregnancy showed evidence of adverse outcomes in the offspring, including decreased fetal growth, skeletal and visceral anomalies, and embryonic death.

Clearly, future directions call for a need for supervision by the healthcare system that is not provided by online direct-to-consumer services. An attentive and rigorous effort to ensure proper care for overweight/obese women is needed to prevent unnecessary pressure on these women to blindly use these injectable weight loss medications with their unknown, although seems intuitively beneficial, reproductive consequences. Of note, evidence on the long-term concerns and outcomes of these medications in women of all ages with all types of medical conditions, with or without PCOS, is scarce, and the long-term consequences of cessation of their use remain unknown. Lessons from the impact of bariatric surgery on the female reproductive system could be helpful for researchers in this instance.

Declaration of Interests

Z.M. has nothing to disclose.

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