The Journal of Clinical Endocrinology & Metabolism, 2025, **110**, 3009–3024
https://doi.org/10.1210/clinem/dgaf401
Advance access publication 14 July 2025
Mini-Review

Effect of GLP1 Agonists on Reproduction

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Abstract

Obesity, in animals and humans, is associated with male and female reproductive dysfunction. Elucidating the mechanisms by which excessive weight affects reproduction and proving that weight loss improves reproductive function has been difficult. Data in animals and humans demonstrate improvements in reproductive function after weight loss, achieved with or without glucagon-like peptide 1 (GLP1) agonists. In preclinical studies there is evidence that GLP1 agonists have direct effects on the hypothalamus to stimulate luteinizing hormone (LH) secretion and direct beneficial effects on the gonads and the endometrium. Whether GLP-1 agonists provide an added direct beneficial effect on reproductive organs in humans, beyond the benefits mediated by weight loss, remains unclear. However, consideration of GLP1 agonists for the treatment for obesity-associated reproductive dysfunction requires caution, as any weight loss during pregnancy is associated with adverse fetal outcomes, and preclinical studies indicate fetal toxicity of the GLP1 agonist class. Here, we review the available preclinical and clinical evidence of the effects of GLP-1 agonists on human reproductive health, suggest a therapeutic strategy, and list the needs for future research.

Key Words: GLP1, weight loss, reproduction, fertility, human, male, female

Abbreviations: Ab, antibody; AC3, adenylate cyclase type III membrane enzyme; AUC, area under the curve; BMI, body mass index; BW, body weight; cAMP, cyclic adenosine monophosphate; CR, calorie-restricted; DHEA, dehydroepiandrosterone; DMED, diabetes mellitus erectile dysfunction; DPP-4, dipeptidyl peptidase IV; E2, estradiol; ED, erectile dysfunction; Exe-4, exendin-4; F4/80, murine macrophage marker (cell surface glycoprotein); FAI, free androgen index; FBG, fasting blood glucose; FH, functional hypogonadism; FSH, follicle-stimulating hormone; fT, free testosterone; GLP1, glucagon-like peptide 1; GLP1a, glucagon like peptide 1 receptor agonist; GLP1R, GLP1 G protein–coupled receptor; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; HFD, high-fat diet; IP, intraperitoneal; IV, intravenous; Kiss, kisspeptin; Kitl, Kit receptor ligand; LDH, lactate dehydrogenase; LH, luteinizing hormone; MCP-1, monocyte chemoattractant protein-1; MET, metformin; MGO, methylglyoxal; mRNA, messenger RNA; MS, metabolic syndrome; MW, molecular weight; NA, not applicable; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; OCP, oral contraceptive pill; OS, oxidative stress; PCOS, polycystic ovary syndrome; PKA, protein kinase A; ROS, reactive oxygen species; SC, subcutaneous; SGLT2, sodium-glucose cotransporter 2; SHBG, sex hormone–binding globulin; STZ, streptozotocin; T, total testosterone; T/D, testicular dysfunction; TGF, transforming growth factor; TNF, tumor necrosis factor; TRT, testosterone replacement therapy.

Less than 20 years after the discovery that the glucagon-like peptide 1 (GLP1, 7-37) stimulates insulin secretion from the rat pancreas (1, 2), the first GLP1 receptor agonist exenatide was approved by the US Food and Drug Administration for the treatment of type 2 diabetes. For simplicity, all molecules that agonize the GLP1 receptor will be referred to as GLP1 agonists in this review. Since then, the therapeutic potential of GLP1 agonists has expanded beyond glycemic control. Approved GLP1 agonizing therapeutics now include peptides, peptide conjugates, antibodies, and antibody conjugates (Table 1). Small molecules, bispecific antibodies, and combinations are in development. Different agents have demonstrated direct activity to enhance satiety (3), reduce gastric emptying (4-6), and suppress inflammation (7) in humans. All agonists have demonstrated efficacy in the treatment of type 2 diabetes and obesity, and certain agonists have recently been reported to be beneficial in the treatment of obstructive sleep apnea (8), osteoarthritis of the knees (9), renal failure (10-12), and heart failure (13, 14). This review will summarize the emerging data indicating that GLP1 agonists also improve obesity-associated reproductive dysfunction in men and women.

Materials and Methods

This is a narrative review. We searched individual terms including *GLP1* or *GLP1 receptor agonist* or *GLP1 receptor* AND *female* or *male* or *reproduction* or *fertility* or *polycystic ovary syndrome* or *PCOS* or *oral contraceptives* or *gastric emptying* or *drug interactions* or *major congenital anomalies* or *pregnancy* through March 1, 2025. We also reviewed the latest prescribing information for each approved drug from Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm) through March 1, 2025.

Results

Obesity-Associated Reproductive Dysfunction in Men and Women

Hypogonadism is prevalent in about 40% of obese men (15) and up to 75% of men with body mass index (BMI) greater than 40 (16). Hormonal and germ cell anomalies in men with obesity and/or metabolic syndrome (MS) include reduced luteinizing hormone (LH), testosterone (T), semen volume and sperm count, altered sperm morphology, as well as poor

Received: 23 March 2025. **Editorial Decision:** 10 July 2025. **Corrected and Typeset:** 1 August 2025

Table 1. List of Food and Drug Administration–approved glucagon-like peptide 1 agonists

Drug	Brand name	Indication	Date approved	Route	Dose	Molecule	MW
Liraglutide	Victoza	Type 2 diabetes	2010	SC	0.6-1.8 mg daily	Modified GLP1 peptide + fatty acid	3751.2
Liraglutide	Saxenda	Obesity	2014	SC	3 mg daily	Modified GLP1 peptide + fatty acid	3751.2
Exenatide	Byetta	Type 2 diabetes	2005	SC	10 ug twice a day	Modified GLP1 peptide	4186.6
Exenatide	Bydureon Bcise	Obesity	2017	SC	2 mg weekly	Modified GLP1 peptide	4186.6
Semaglutide	Ozempic	Type 2 diabetes	2017	SC	0.5-2 mg weekly	Modified GLP1 peptide + long carbon chain	4114
Semaglutide	Rybelsus	Type 2 diabetes	2019	Oral	3-14 mg daily	Modified GLP1 peptide + long carbon chain	4114
Semaglutide	Wegovy	Obesity	2021	SC	1.7-2.4 mg weekly	Modified GLP1 peptide + long carbon chain	4114
Tirzepatide	Mounjaro	Type 2 diabetes	2022	SC	5-15 mg weekly	Modified GLP1/GIP + fatty diacid	4813.5
Tirzepatide	Zepbound	Obesity	2023	SC	5-15 mg weekly	Modified GLP1/GIP + fatty diacid	4813.5
Lixisenatide	Adlyxin	Type 2 diabetes	2016	SC	20 µg daily	Modified GLP1 peptide	4858
Dulaglutide	Trulicity	Type 2 diabetes	2014	SC	0.75-4.5 weekly	Modified GLP1 peptide + Ab Fc fragment	59 670
Albiglutide	Tanzeum	Type 2 diabetes	2014	SC	30-50 mg weekly	2 copies modified GLP1 peptide + human albumin	72 970

Abbreviations: Ab, antibody; GLP1, glucagon-like peptide 1; MW, molecular weight; SC, subcutaneous.

fertility outcomes (17-26). However, the percentage of DNA fragmentation in sperm nuclei appears to be unaffected (27). Based on an analysis of 21 studies involving 13 077 men, there is a J-shaped relationship between BMI and the risk for developing oligozoospermia or azoospermia (20) with a nadir between 18.5 and 25. Meta-analyses have concluded that higher BMI in men correlates with a decrease in fertility and lower in vitro fertilization rates (20, 27-30) and intracytoplasmic sperm injection successes (31). Men with diabetes have been demonstrated to have reduced testicular weights and seminiferous tubule diameters, and degeneration and vacuolation of spermatogonia, spermatocytes, and spermatids (32).

Excess adipose tissue is associated with dysregulation of adipokine secretion, inflammation, and oxidative stress (OS), which disrupts the hypothalamic pituitary gonadal axis and directly affects testicular function (33-39). In preclinical studies, OS is an important driver of male infertility (40-42) and hyperglycemia has been shown to play a crucial role in upregulating OS in testicular somatic and germ cells in diabetic animals (43-45).

The detrimental effects of obesity and related comorbidities on female reproduction have also been established. There is an inverse correlation between body weight (BW) and LH secretion in normal women and those with polycystic ovary syndrome (PCOS) (46, 47). Obesity is associated with impaired ovulation, increased time to pregnancy, and lower rates of implantation and pregnancy (48, 49). Adverse pregnancy outcomes, both to the obese pregnant person and the fetus, include gestational diabetes, preeclampsia, preterm labor, and cesarean deliveries (50). Improvements in fertility with weight reduction medications such as orlistat, metformin, and phentermine (49) have been described.

Overview of Opportunities of Glucagon-Like Peptide 1 Agonists in Human Reproduction

The impressive weight loss induced by GLP1 agonists offers an opportunity to prospectively prove that weight loss improves reproductive function. A substantial amount of emerging data, mostly preclinical, suggests that GLP1 agonists also have direct beneficial effects on reproductive health independent of weight loss. Multiple anecdotal pregnancies occurring during GLP1 agonist therapy have been reported (51-55). The potential mechanisms for improved fertility include direct GLP1 action at the hypothalamus, testes, ovaries, and/or uterus; indirect effects secondary to weight loss; and/or indirect effects caused by contraceptive failure due to delayed or reduced absorption of oral contraceptives associated with reduced gastric emptying or vomiting. However, it must be considered that weight loss during pregnancy is associated with adverse fetal outcomes (56), and GLP1 agonists cause fetal harm in preclinical toxicology studies.

Effects of glucagon-like peptide 1 agonists on the hypothalamus in males and females

The GLP1 peptide appears to signal both the gonadotropin-releasing hormone (GnRH) and the kisspeptin (Kiss) neurons, possibly acting as a regulating mediator between the metabolic and the reproductive systems (57, 58). Significant animal and cellular data demonstrate that GLP1 and its agonists can directly interact with hypothalamic GnRH neurons. Expression of GLP1 peptide has been identified in vertebrate brains (59, 60). Also, rat preproglucagon neurons residing in the nucleus of the solitary tract and the reticular nucleus of the medulla oblongata of the brainstem have been shown to produce GLP1 (61, 62). The preproglucagon neurons of the lower brainstem from various species project innervating axons to the hypothalamus, thalamus, septal regions, cerebral cortex, and different nuclei in the hindbrain, which suggests a direct intracerebral function of GLP1 (63). In adult mice, peripherally injected radiolabeled exenatide can access the central nervous system by crossing the blood-brain barrier (64).

GLP1 G protein–coupled receptors (GLP1Rs) are expressed in the rodent brain (65-67) and localized to the GnRH neurons (68, 69). In adult female rat models, the highest expression of GLP1 receptor messenger RNA (mRNA) in the hypothalamus has been detected during the proestrous phase (70).

GLP1 has been shown to exert direct facilitatory actions via GLP1R on the GnRH neurons by increasing the postsynaptic

excitatory GABAergic currents in GnRH neurons (68). In experiments conducted in vitro, the administration of exenatide to immortalized rodent GnRH producing GT1 to 7 neurons resulted in a concentration dependent increase in GnRH release with an associated rise in intracellular cyclic adenosine monophosphate (cAMP) (69). In the basal forebrain of male mice, whole-mount immunocytochemistry visualized GLP1 neuronal projections in a distribution pattern along the axons of the GnRH cells, and excitation of the GnRH system was demonstrated by optogenetics (71).

GLP1 appears to also act on the Kiss neurons. GLP1 stimulates the expression of Kiss receptor mRNA in hypothalamic explants from female rats (70) and in fetal rat brain cultures (72). Electrophysiological experiments in an ovariectomized mouse model revealed that liraglutide increased action potential firing and caused a direct membrane depolarization of arcuate Kiss cells in brain slices (73).

Intracerebroventricular injection of GLP1 to male rats rapidly increased plasma LH concentrations (69), and acute central GLP1 administration to female rats during the proestrous phase doubled the amplitude of the preovulatory LH surge, and increased the number of mature graafian follicles and corpora lutea, and the number of offspring born (70). Peripherally administered GLP1 also amplified the LH response. However, central or peripheral administration of exenatide had the opposite effects, reducing gonadotropins and sex steroids, hypothesized to be secondary to the significant weight loss induced by exenatide but not GLP1 (70). These discordant findings suggest that relative concentration and potency of administered agonists is important. In female sheep, intravenous (IV) infusion of exenatide has been shown to increase mean plasma LH concentrations and LH peripheral pulse amplitude (74).

Effects of Glucagon-Like Peptide 1 on Male Reproductive Organs

GLP1R expression has been described in rodent and human testes (75-78).

In rodents, GLP1R mRNA and GLP1 protein are expressed in a mouse Sertoli cell line (TM4), a Leydig cell line (MA-10), and in germ cell lines (79), and GLP1R has been identified by immunohistochemistry in rodent testes (75). GLP1R knockout (GLP1R−/−) mice had reduced testicular weight (80). In normal human testicular tissue samples, GLP1R expression has been detected in Leydig cells by immunohistochemistry, Western blot, and polymerase chain reaction analyses (75). The receptor has also been identified in human spermatozoa by in silico analysis (81).

In nonobese, nondiabetic rats, semaglutide ameliorates ischemia-induced testicular dysfunction (82) and exenatide exerts a protective effect on the methylglyoxal (MGO) pathway involved in corpus cavernosum function (83).

GLP1 agonists improve reproductive function in obese rodents by increasing LH, follicle-stimulating hormone (FSH), testosterone, and sex hormone–binding globulin (SHBG) levels and restoring sperm DNA damage, sperm count, and motility (Table 2). These effects may be mediated through a decrease in the expression of proinflammatory cytokines in association with a reduction in BW (38, 78). The degree to which the indirect effect of weight loss is beneficial to the reproductive system in comparison to the direct effect of GLP-1 analogues remains to be determined. However, the lower percentage of sperm head defects observed in rats treated with GLP1 vs calorie-restricted (CR) control animals (87) supports a possible direct GLP1 agonist effect.

Treatment of diabetic rats with GLP1 agonists mitigated diabetes-induced suppression of the hormonal profile, abnormal testicular structure, and erectile dysfunction (ED) (86, 89-91). The relative effects due to the normalization of glycemia vs improvement in BW remain to be determined. Semaglutide appears to alleviate diabetes-induced testicular damage through improvement in lipid peroxidation and reduction in ferroptosis (91). In iron-overloaded rats, exenatide has been shown to reduce inflammation of the testis, indicating its protective role against the harmful effects of iron accumulation in the gonads (84).

Human Sertoli cells exposed to increasing concentrations of GLP1 express changes in cell metabolism including an increase in efficiency of lactate dehydrogenase (LDH) and a reduction in mitochondrial membrane potential and oxidative damage (76). In human semen studies, GLP1 and exenatide at various concentrations reduce oxidative damage (85) and tumor necrosis factor α (TNF-α) induced negative effects on sperm parameters (88), respectively. Treatment of human spermatozoa with exenatide has been shown to activate a protein kinase A (PKA)-dependent GLP1/GLP1R signaling pathway (77).

Effects of Glucagon-Like Peptide 1 Agonists in Men

The literature on GLP1 agonist therapy in men mostly pertains to the treatment of obesity, MS, and/or type 2 diabetes as previously reviewed (92-94). (Table 3). In 2 clinical studies in healthy nonobese men, GLP1 infusions over 6 and 8 hours, to 9 and 18 men, respectively, did not significantly change LH and testosterone secretion (95, 100). These studies imply that GLP1 treatment does not induce changes in male gonadotropin or sex steroid levels in the absence of baseline obesity, weight loss, or longer treatment.

Several studies have evaluated the effect of longer-term GLP1 agonist therapies on male reproductive function. In a 16-week trial studying men with obesity-associated functional hypogonadism, liraglutide significantly increased LH and FSH and induced greater weight loss compared to testosterone therapy (99). In 56 obese men who achieved weight loss by following a low-calorie diet for 8 weeks, liraglutide therapy did not further affect sperm parameters (101). Liraglutide treatment, for 4 months' duration, in 110 men with MS yielded superior weight loss and better sperm parameters compared to baseline and to gonadotropin-treated participants. In this trial, liraglutide treatment was also superior to T or gonadotropin treatments in improving gonadotropin levels and ED (102).

In 43 men with diabetes-associated hypogonadism who were treated initially with a combination of lifestyle changes, metformin and T therapies for 1 year, liraglutide treatment led not only to weight loss and glycemic control but to a greater improvement in ED (97). In 25 men with diabetes, semaglutide was more effective than T in normalizing BW and in restoring sperm parameters (103). In 176 men with type 2 diabetes, a 12-week treatment period using exenatide and metformin was superior to glimepiride and metformin in increasing T levels and correcting sexual dysfunction (98).

Lifestyle intervention–induced weight loss also improves male reproductive function (Table 4) (22, 104, 105). Thus,

Table 2. Effects of glucagon-like peptide 1 (GLP1) and GLP1 agonists on male reproductive tissues

Citation	Study design	Treatment and control groups	Effects on weight	Effects on sex steroids	Effects on gonads/semen parameter
Zhang et al, 2015 (38)	HFD-induced obese mice model, 8 wk	Control CD (n = 5), HFD obese saline control (n = 8), HFD obese exenatide (24 nmol/kg/d IP×8 wk (n = 8)	Exenatide reduced BW	Exenatide intervention did not improve markedly decreased T levels in HFD group	Obesity reduced quality of sperm and increased inflammation in testis Exenatide reduced expression of proinflammatory cytokines and improved quality of sperm
Dalaklioglu et al, 2018 (83)	Rat model of MGO-induced corpus cavernosum dysfunction, 12 wk	Control (n = 8); MGO (n = 8); MGO + low Exe-4 (0.1 µg/kg twice daily SC (n = 8); MGO + high Exe-4 (1 µg/kg twice daily SC) (n = 8)	Not reported	Not reported	Exe-4 treatment significantly reduced MGO-induced impaired corpus cavernosum relaxations independently of its glucose-lowering effect
Yesil et al, 2018 (84)	Iron overloaded rat model; immunohistochemical staining of testes, 4 wk	IP injections of saline, (n = 6; iron dextran (60 mg/kg/d IP) 5/wk (n = 6); iron dextran + exenatide (10 µg/kg in 2 divided doses IP) (n = 6)	Not reported	Not reported	Iron-overloaded rats injected with exenatide had significant reduction in caspase-8 and -3 enzyme staining in testicular stromal and endothelial cells and lower OS markers compared with controls
Martins et al, 2019 (85)	Human Sertoli cells in culture	Increasing concentration of GLP1 at physiological postprandial (0.01 nM) or pharmacological levels (1 and 100 nM)	NA	NA	Increased efficiency of conversion of glucose to lactate at lower GLP1 dose (0.01-1 nM) and reduction in mitochondrial membrane potential and oxidative damage at highest GLP1 dose (100 nm)
Rago et al, 2020 (77)	Human sperm cells of pooled semen from 3 men	Incubations with Exe-4 at various concentrations (100 pM to 10 nM)	NA	NA	Exe-4 activated PKA-dependent GLP1/GLP1R signaling pathway and stimulation of LDH and G6PDH activities. Dose-response of Exe-4 on progressive motility and cholesterol efflux peaked at 300 pM Exe-4
Yuan et al, 2020 (86)	8-wk-old rat with STZ-induced DMED (n = 30) and controls	DMED controls (n = 10); DMED + liraglutide (0.3 mg/kg/12 h SC ×4 wk) (n = 30)	No significant change in weight or glucose	Not reported	Liraglutide improved ED and reduced NADPH oxidases, ROS production, and expression of RhoA and ROCK2 in DMED group
Abdullah et al, 2022 (82)	Rat model of ischemia (spermatic torsion × 2 h)/reperfusion (detorsion × 4 h)-induced T/D	Sham ischemia + saline injections, (n = 10); sham ischemia + exendin (50 µg/kg IV × 1 dose) (n = 10); T/D + exendin (n = 10); T/D + semaglutide (12 µg/kg SC 5 min before reperfusion) (n = 10); T/D + exendin 15 min before semaglutide + semaglutide 5 min before reperfusion (n = 10)		Semaglutide increased T compared to shams. LH and FSH levels comparable between these 2 groups	Semaglutide modulated testicular GLP1/ KISS1 pathway-related genes, steroidogenesis pathway-related genes, improved testicular oxidative state, and suppressed testicular inflammation and apoptosis. Exendin, a GLP1R antagonist, before semaglutide abolished these effects
Correia et al, 2022 (87)	6-wk-old adult male rats, 28-d study	Ad libitum feeding, (n = 5); CR (30% < chow diet than controls), (n = 6); GLP1 (3.5 pmol/min/kg IP) (n = 5)	Weight gain less with CR (124 g) compared to GLP1 (174 g) and control (162 g)	Not reported	CR group had higher percentage of sperm head defects. GLP1 treatment resulted in lower percentage of sperm head defects
Castiglione et al, 2023 (88)	Human sperm cells from semen samples of 45 healthy men	1- and 2-h incubations with Exe-4 (300 pM). Samples exposed to TNF-α only or to TNF-α added after previous exposure to Exe-4			Exe-4 attenuated TNF-α negative effect on sperm parameters. Exe-4 (300 pM) significantly decreased phosphorylation of levels of "negative" kinases p-IRS-1Ser312 and p-JNK
Fathy et al, 2023 (89)	8- to 10-week-old, male albino rats, treated 8 wk	Controls (n = 8); diabetic HFD followed by streptozotocin injection (n = 8); liraglutide (0.4 mg/kg/d) injection in diabetic rats (n = 8)	Not reported	Liraglutide significantly increased T, LH, and FSH	Liraglutide upregulated testicular expression of GLP-1R, PPAR-α, PGC-1α, kiss1, kiss1R, leptin, leptinR, GnRH, GnRHR, STAR, Smad7, CYP17A1, HSD17B3, CYP19A1, and CYP11A1, and downregulated expression of TGF-β and Smad2

(*continued*)

Table 2. Continued

Citation	Study design	Treatment and control groups	Effects on weight	Effects on sex steroids	Effects on gonads/semen parameter
Qi et al, 2024 (78)	6-wk-old mice	HFD obese (n = 12); Control lean intermates (n = 12); after 12 wk ½ of each treated for 12 wk with liraglutide (100 µg/kg/d SC) or saline SC	Liraglutide decreased BW	Liraglutide decreased FBG, INS, E2, and SHBG levels; increased LH, FSH, T, and fT	Liraglutide increased sperm count; decreased sperm abnormality rate; and increased GLP-1R, AC3 expression levels, and cAMP levels and PKA activity in testicular tissue
Iida et al, 2024 (79)	Exp 1. Male mice Exp 2. Sertoli cell line (TM4) Leydig cell line (MA-10) Germ cell line GC-1 spg, GC-2 spd	Exp 1. Controls (n = 3); Exenatide (2.5 nmol/kg IP) 1 h prior to analysis (n = 3) Exp 2. Exenatide to final concentration of 10 nm in medium of TM4 cells	Not reported	Not reported	Exp 1: Exenatide significantly increased expression of Kitl and GLP1R mRNA expression in testes Exp 2: Exenatide upregulated Kitl, Pdgfa, GLP1R mRNA in Sertoli TM4 cells
Abdel-Wahab et al, 2025 (90)	Adult male rats with or without diabetes treated for 4 wk	Controls (n = 7); Semaglutide (25 nmol/kg daily SC) (n = 7); diabetes (n = 7); diabetes + semaglutide (n = 7)		In diabetic rats, semaglutide elevated T above baseline but below controls and restored low LH, and FSH levels closer to control levels	Semaglutide mitigated diabetes-induced sexual and T/D by regulating disrupted redox balance, restoring spermatogenesis gene and protein levels, modulating hormonal profiles, and mitigating testicular inflammation

Abbreviations: BW, body weight; cAMP, cyclic adenosine monophosphate; CR, calorie-restricted; DMED, diabetes mellitus erectile dysfunction; E2, estradiol; ED, erectile dysfunction; FBG, fasting blood glucose; FSH, follicle-stimulating hormone; fT, free testosterone; GLP1, glucagon-like peptide 1; GnRH, gonadotropin-releasing hormone; HFD, high-fat diet; INS, insulin; IP, intraperitoneal; IV, intravenous; LDH, lactate dehydrogenase; LH, luteinizing hormone; MGO, methylglyoxal; mRNA, messenger RNA; NA, not applicable; OS, oxidative stress; PKA, protein kinase A; ROS, reactive oxygen species; SC, subcutaneous; SHBG, sex hormone–binding globulin; STZ, streptozotocin; T, testosterone; T/D, testicular dysfunction; TGF, transforming growth factor; TNF, tumor necrosis factor.

it is difficult to determine whether a direct effect of GLP1 on GnRH neurons and/or the testis contributes additional efficacy to what is indirectly achieved by weight loss. It might be hypothesized that direct effects, if any, would be more likely with smaller molecular-weight agents that could cross the blood-brain or blood-testes barriers.

Although preclinical toxicology studies did not demonstrate male fertility issues, there is at least 1 case report of a 35-year-old obese man whose spermiogram became abnormal following liraglutide treatment (96). In addition, there have been a few isolated reports of men with reduced sperm counts associated with liraglutide therapy (eHealthMe.com).

Effects of Glucagon-Like Peptide 1 Agonists on Female Reproductive Organs and Fertility

There are scant data on the expression of GLP1 receptors in female reproductive tissues. GLP1 receptor mRNA levels have been detected in ovarian tissue in one study using female rats (70). The level of mRNA in the ovary appeared to vary throughout the estrous cycle, with the highest levels found in the diestrus phase.

Glucagon-like peptide 1 activity in ovaries

The effects of central GLP1 administration to increase gonadotropins in female rats (70) resulted in a slow rise in progesterone levels, which peaked at the end of the proestrous phase. These hormonal changes were associated with a significant increase in follicular number and corpora lutea (70). In another study, female diabetic rats treated with intraperitoneal (IP) exenatide had a significant reduction in ovarian stromal fibrosis and follicular degeneration compared to controls, though the effects on glycemic control were not reported (106).

Female GLP1R knockout mice had a statistically significantly delay in puberty and a decrease in the number of ovarian follicles compared to age-matched controls (80). A nonstatistically significant decrease in the number of corpora lutea was also observed. Despite the decrease in follicle number, these knockout mice did not have alterations of ovarian histology or an appreciable difference in fertility compared to controls.

Both rat and mice models of PCOS have been developed (Table 5) using dehydroepiandrosterone (DHEA) induction. Treatment of these animal models with GLP1 agonists has resulted in significant increases both in serum estradiol (E2) and progesterone levels (111), reductions in serum androgen levels (108, 110-112), decreased ovarian expression of steroid synthesis enzymes (110, 112), and return of estrus cyclicity (108, 110, 111).There was a significant increase in SHBG levels in one study (112) but not in another (110). Many of the PCOS animal studies investigated ovarian histology by hematoxylin and eosin staining to compare the effect of GLP1 agonist treatment with untreated controls. GLP1 agonist treatment of "PCOS" mice was associated with an increased number of follicles, thicker granulosa cell layers, increased prevalence of corpus lutea, and decreased cystic components of the ovaries (107, 108, 110, 111).

Animal studies using a PCOS model have not yet investigated the effect of GLP1 agonists on conception outcomes.

Glucagon-like peptide 1 activity in endometrium

Most studies on the endometrial effects of GLP1 agonists have been performed in the context of disease models such as

Table 3. Effects of glucagon-like peptide 1 agonists on reproductive function in men

Citation	Study design	Treatment and control groups	Effects on weight	Effects on sex steroids	Effects on gonads/semen parameter
Jeibmann et al, 2005 (95)	9 healthy men, 6-h euglycemic clamp crossover	Saline or a constant infusion of GLP1 (0.4 pmol/kg/min)		No change in pattern of LH or FSH secretion or change in mean T levels. GLP1 infusion reduced pulsatile component of T secretion	
Fontoura et al, 2014 (96)	Case report of 35-y-old man weighing 100 k	Liraglutide (0.6 mg SC daily) treatment for 5 mo followed by cessation of treatment	2-kg weight loss after liraglutide		Semen analysis normal at baseline but declined (0.2×10^6 sperm/mL) on liraglutide with no sperm motility. Spermiogram normalized 2 mo after cessation of liraglutide
Giagulli et al, 2015 (97)	Observational retrospective study in 43 obese men with diabetes and overt hypogonadism	Group 1:Lifestyle changes, metformin (2000-3000 mg/d) and T undecanoate 1000 mg every 12 wk × 1 y Group 2: (n = 26) Poor responders received liraglutide (1.2 µg/d) therapy for another y Group 3: (n = 17) Continued metformin and T therapy	Liraglutide led to reaching glycemic target and lowering BW compared to other groups		Liraglutide compared to other treatments led to considerable improvement in ED
Shao et al, 2018 (98)	12-wk observational prospective study in 176 obese men with DM	Group 1: (n = 90) Short-term combined treatment using exenatide Group 2: (n = 86) Glimepiride + metformin	BW loss of <5% to >5% in 2 groups	Exenatide + metformin superior to glimepiride + metformin in increasing serum T levels T levels highest in patients who lost BW >5% in both groups	Exenatide and metformin superior to glimepiride and metformin in correction of sexual dysfunction
Jensterle et al, 2019 (99)	Prospective open-label randomized 16-week trial in 30 middle-aged men with obesity-associated functional hypogonadism	Group 1:(n = 15) liraglutide 3.0 mg daily S Group 2: (n = 15) transdermal T 50 mg of 1% gel daily	Greater weight loss of 7.9 ± 3.8 kg in liraglutide group compared to 0.9 ± 4.5 kg in T group	Liraglutide group had significant increases in LH and FSH	Significant improvement in sexual function reported in both groups
Izzi-Engbeaya et al, 2020 (100)	Randomized, placebo-controlled crossover study in 18 healthy men	8-h intravenous infusion of 0.8 pmol/kg/min GLP-1 or rate-matched vehicle infusion		Number of LH pulses, LH AUC, FSH AUC, and T AUC did not significantly differ during vehicle and GLP-1 administration	
Andersen et al, 2022 (101)	Randomized, controlled trial in 56 obese but otherwise healthy men who followed CR diet (800 kcal/d)×8 wk then randomized.	Duration: 52 weeks: Group 1: (n = 8), placebo, habitual activity Group 2: (n = 9) placebo, exercise training Group 3: (n = 7) Liraglutide and habitual activity Group 4: (n = 7) liraglutide and exercise	16.5-kg mean BW loss after CR diet		CR diet increased sperm concentration 1.49-fold and sperm count 1.41-fold Improvements maintained for 52 wk in men who maintained weight loss Semen volume, sperm motility, and motile sperm count did not change. No additional effects of liraglutide on sperm parameters
La Vignera et al, 2023 (102)	Randomized clinical trial in 110 men with MS and hypogonadism Treated 4 mo	Group 1:(n = 35) gonadotropins (urofollitropin 150 IU, 3×/wk, and hCG 2000 IU, 2×/wk)	Liraglutide induced superior weight loss	Liraglutide group had significantly higher levels of T, SHBG, and serum	Liraglutide significantly improved sperm parameters and ED compared to baseline and other groups

(*continued*)

Table 3. Continued

Citation	Study design	Treatment and control groups	Effects on weight	Effects on sex steroids	Effects on gonads/semen parameter
		Group 2:(n = 35) Liraglutide (3 mg daily SC); group 3:(n = 40) Transdermal T (60 mg/d)		gonadotropins than other groups	
Gregoric et al, 2025 (103)	Randomized open-label trial in 25 men with obesity, type 2 DM, and functional hypogonadism	Group 1: (n = 13) Semaglutide 1 mg/wk SC Group 2:(n = 12) (T undecanoate IM) 1000 mg/ 10-12 wk for 24 wk	BW and BMI decreased significantly in semaglutide group compared to TRT group		Compared to TRT, semaglutide group had significantly higher number of morphologically normal sperm, sperm concentration and total number

Abbreviations: BMI, body mass index; BW, body weight; CR, calorie-restricted; DM, diabetes mellitus; ED, erectile dysfunction; FSH, follicle-stimulating hormone; GLP1, glucagon-like peptide 1; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; MS, metabolic syndrome; SC, subcutaneous; SHBG, sex hormone–binding globulin; T, testosterone; TRT, testosterone replacement therapy.

PCOS, diabetes, endometrial cancer, and intrauterine adhesions. GLP1 receptor expression has been identified in the human endometrium (113).

In female diabetic rats, treatment with exenatide resulted in a reduction in endometrial fibrosis and endometrial glandular degeneration (106). In two studies involving normal mice with induced intrauterine adhesions, the GLP1 agonists exenatide and semaglutide significantly reduced adhesion burden compared to controls (109, 114). These studies suggest a direct anti-inflammatory role of GLP1 agonists in reducing adhesions and fibrosis in endometrial tissue. Other studies have examined the effect of various GLP1 agonists, including liraglutide and exenatide, on endometrial cancer cells, demonstrating significant rates of autophagy in addition to inhibition of cancerous growth (113, 115, 116). While these studies demonstrate a clear role of GLP1 agonism in treating pathologic states, the effect in normal physiology is unknown.

Effects of glucagon-like peptide 1 agonists in women

Because of the association of PCOS with obesity, multiple investigators have evaluated the effects of GLP1 agonists on reproductive hormones, menstrual function, and pregnancy rates in women with PCOS (Table 6). There are minimal data on the effects of GLP1 agonists on fertility in women with obesity without PCOS.

A comparison study in overweight women with PCOS, treated with either metformin alone or metformin plus liraglutide, revealed a significant decrease in total T levels and free androgen index (FAI), and an increase in progesterone, E2, and SHBG levels in the liraglutide-treated group (123). In a similar study involving women with obesity and PCOS, combination therapy with exenatide and metformin was superior to monotherapies at reducing the FAI (117). Studies in liraglutide-treated women with PCOS found a similar normalization of the hormonal profile compared to placebo-treated participants, including reduction in the FAI (121), increase in SHBG, and decrease in free T (fT) levels (119). While there are no human studies investigating ovarian histology, Nylander et al (119) found, in women with PCOS, a significant decrease in ovarian volume with liraglutide treatment, suggesting that GLP1 agonists may also affect ovarian morphology.

In women with PCOS, combination therapy of exenatide and metformin was also superior to monotherapies at regulating menstrual cycles and improving ovulation rates (117). Several trials have demonstrated an improvement in menstrual regularity with GLP1 agonist treatment (118, 119, 123).

Clinical trials of women with PCOS compared pregnancy rates in those treated with GLP1 agonists vs other therapies. One study compared liraglutide and metformin dual therapy to metformin monotherapy on rates of successful pregnancies from assisted reproductive technologies. Rates of pregnancy per embryo transfer were significantly higher in the combined therapy group compared to metformin alone, despite equivalent weight reduction between the two groups (120). Other studies found that exenatide was associated with a significantly increased rate of spontaneous pregnancy compared to metformin alone (118, 122).

While the primary goal of these studies was to examine the effects on reproductive outcomes, secondary results showed significant weight reduction in the GLP1 agonist treatment groups. Therefore, it is not possible to determine if the beneficial effects noted in women with PCOS are solely due to weight loss or whether the direct ovarian and/or endometrial effects described in animals may also apply to women.

Finally, a recent retrospective cohort study looked at obstetrical outcomes in reproductive-aged females who had a GLP1 agonist prescription in the 2 years preceding their pregnancy (50). Even when matched for BMI, the use of preconception GLP1 agonists was associated with reduced rates of gestational diabetes, gestational hypertension, and preeclampsia. Additionally, this cohort was less likely to have preterm and cesarean deliveries. Because the cohorts were matched for BMI, the results may be interpreted as showing a direct beneficial effect of GLP1 agonists therapy prior to conception in reducing the risk of pregnancy-related complications.

Developmental Effects of Glucagon-Like Peptide 1 Agonists

Muller et al (124) reviewed 23 animal studies of preclinical effects of GLP1 agonists on pregnancies in rats, mice, and rabbits and found that GLP1 agonists were associated with reduced fetal weight and/or growth, delayed ossification, and the presence of skeletal variants (Table 7). These defects

Table 4. Effects of lifestyle intervention on reproduction in men

Citation	Study design	Treatment and control groups	Effects on weight	Effects on sex steroids	Effects on gonads/semen parameter
Håkonsen et al, 2011 (22)	Prospective cohort study in 43 severely obese men (age 20-59 y)	14-wk residential weight loss program	Median percentage weight loss 15%	Decrease in BMI associated with increase in T, SHBG, and AMH levels	Decrease in BMI associated with increase in sperm counts and volume. Largest weight loss statistically improved sperm count and morphology
Faure et al, 2014 (104)	Case series of 6 men with increased abdominal fat in couples with idiopathic infertility	Several months of lifestyle program (individualized nutritional advice and exercise)	Improved body composition with abdominal fat loss	Significant increase in T/estradiol ratio blood profile	Significant improvement in sperm DNA integrity with no change in other sperm parameters. All spouses conceived and all pregnancies were brought to term
Mir et al, 2018 (105)	Cross-sectional large cohort study in obese men	Lifestyle modifications vs baseline	Weight loss averaged 2.8 kg		Weight loss had significant positive correlation with percentage of DNA fragmentation index, improvement in sperm morphology ($P < .05$).

Abbreviations: AMH, antimüllerian hormone; BMI, body mass index; SHBG, sex hormone–binding globulin; T, testosterone.

Table 5. Effects of glucagon-like peptide 1 agonists on female reproduction in animal models of polycystic ovary syndrome

Citation	Study design and duration	Treatment and control groups	Effects on sex steroids	Effects on menstrual cycle	Effects on ovarian histology/ morphology
Tao et al, 2015 (107)	DHEA-induced PCOS rat model 4 wk	Exenatide 10 μg/kg, n = 10, Metformin 300 mg/kg, n = 10 Placebo, n = 10	—	—	Increased granulosa cell layer Thinning of theca layer Increased number of corpus luteum Decreased number of dilated follicles
Sun et al, 2020 (108)	DHEA-induced PCOS mouse model 3 wk	Liraglutide 0.2 mg/kg, n = 10 Placebo, n = 30	Decreased serum testosterone Increased serum SHBG Reduction in steroidogenesis enzyme expression	40% recovery of regular estrus cycle	Increased granulosa cell layer Decreased number of cystic follicles Decreased number of atretic follicles Increased visibility of corpus luteum
Wu et al, 2021 (109)	DHEA-induced PCOS rat model 3 wk	Dulaglutide 50 μg/kg, n = 10 150 μg/kg, n = 10 450 μg/kg, n = 10 Placebo, n = 10	Decreased serum T	—	Decreased number of cystic follicles Increased number of corpus luteum
Zhang et al, 2023 (110)	DHEA-induced PCOS mouse model 4 wk	Liraglutide 0.3 mg/kg, n = 6 Semaglutide 0.1 mg/kg, n = 6 Placebo, n = 6	Decreased T Decreased FAI No significant effect on SHBG Reduction in steroidogenesis enzyme expression	Decreased disordered estrus cycle	Decreased number of cystic follicles Increased number of corpus luteum
Liu et al, 2024 (111)	DHEA-induced PCOS mouse model 4 wk	Semaglutide 0.24 mg/kg, n = 6 0.84 mg/kg, n = 6 Placebo, n = 6	Decreased T Increased E2 Increased serum progesterone Reduction in steroidogenesis enzyme expression	Improved estrus cycling	Decreased number of cystic follicles Increased number of corpus luteum

Abbreviations: DHEA, dehydroepiandrosterone; E2, estradiol; FAI, free androgen index; PCOS, polycystic ovary syndrome; SHBG, sex hormone–binding globulin; T, testosterone.

were observed at doses that overlapped with expected human exposures. The defects were also usually associated with a reduction in maternal weight gain and decreased food consumption, which are known causes of delayed growth and ossification in animals (125, 126). Therefore, it is difficult to determine if these adverse effects would apply to women at stable weight.

Assessing the human risk of congenital malformations in infants of mothers taking GLP1 agonists is challenging due to the lack of prospective trials, and the known increased risks of fetal malformations in mothers with obesity or type 2 diabetes compared to lean and nondiabetic mothers (127). The label recommendations for use in pregnancy are therefore based on results of preclinical toxicology studies. For different members of the GLP1 agonist class, recommendations range from a contraindication to the use of liraglutide, to discontinuation if pregnant, or to consider the risks and potential benefits (Table 8). The potential benefit of treating diabetes in pregnancy may outweigh the risks, whereas the benefit risk ratio might be different in nondiabetic obese women.

Table 6. Effects of glucagon-like peptide 1 agonists on reproduction in women with polycystic ovary syndrome

Citation	Study design and duration	Treatment and control groups	Effects on weight loss	Effects on sex steroids	Effects on menstrual cycle	Effects on ovarian histology/ morphology	Effects on conception
Elkind-Hirsch et al, 2008 (117)	Randomized control trial 24 wk	Metformin 1000 mg bid, n = 14 Exenatide 10 μg bid, n = 14 Combined, n = 14	Combined: −6.0 ± 0.5 kg Exenatide: −3.2 ± 0.1 kg Metformin: −1.6 ± 0.2 kg	Decreased T; Decreased FAI; increased SHBG (though not significant)	Increased occurrence of menses Increased regularity of menses Increased rates of ovulation	—	—
Liu et al, 2017 (118)	Randomized control trial 12 wk	Exenatide 10 μg bid, n = 88 Metformin 1000 mg bid, n = 88	Exenatide: −3.12 ± 1.36 kg/m^2 Metformin: −0.98 ± 0.22 kg/m^2	Decreased FAI; increased SHBG; decreased T (though not significant)	Increased menstrual frequency Increased regularity of menses	—	Increased rate of natural pregnancy
Nylander et al, 2017 (119)	Randomized control trial 26 wk	Liraglutide 1.8 mg/d, n = 44 Placebo, n = 21	Liraglutide: −5.2 kg	Decreased fT; decreased FAI; increased SHBG	Increased bleeding ratio	Reduced ovarian volume	—
Salamun et al, 2018 (120)	Randomized control trial	Metformin 1000 mg bid + liraglutide 1.2 mg/d, n = 14 Metformin 1000 mg bid, n = 14	Combined: −0.7 ± 1.3 kg/m^2 Metformin: −2.5 ± 2.0 kg/m^2	Increased SHBG	—	—	Increased pregnancy rate per embryo transfer
Elkind-Hirsch et al, 2022 (121)	Randomized control trial 32 wk	Liraglutide 3 mg/d, n = 55 Placebo, n = 27	Liraglutide: −5.7% BW reduction ± 0.75 Placebo: −1.4% BW reduction ± 1.09	Decreased FAI	Increased menstrual frequency	—	—
Li et al, 2022 (122)	Randomized control trial Stage 1: 12 wk, stage 2: 52 wk	Exenatide 10 μg twice a day, n = 80 Metformin 1000 mg twice a day, n = 80	Exenatide: −2.16 ± 1.53 kg/m^2 Metformin: −1.39 ± 0.89 kg/m^2	—	—	—	Increased rate of spontaneous pregnancy. No significant difference in total pregnancy rate
Xing et al, 2022 (123)	Randomized control trial 12 wk	Metformin 1000 mg bid + liraglutide 1.2 mg/day, n = 27 Metformin 1000 mg bid, n = 25	Combined: −3.45 kg/m^2 Metformin: −1.92 kg/m^2	Decreased T; Decreased FAI; increased SHBG increased E2; increased progesterone	Increased rate of menstrual cycle recovery	—	—

Abbreviations: bid, twice a day; BW, body weight; E2, estradiol; FAI, free androgen index; fT, free testosterone; SHBG, sex hormone–binding globulin; T, testosterone.

Table 7. Preclinical fetal effects of maternal glucagon-like peptide 1 agonist exposure. Adapted from Muller et al (124) with permission

Drug	Reduced embryonic survival	Decreased fetal weight/growth	Increased preweaning fetal growth	Delayed ossification and skeletal variations[a]	Visceral[b] congenital abnormalities	Major skeletal congenital malformations
Liraglutide	+	+		+	+	–
Exendin-4	–	–	+	–	–	
Exenatide	–	+		+	–	–
Albiglutide	+	+		+	–	–
Dulaglutide	+	+		+	–	–
Lixisenatide	–	+		+	–	–
Semaglutide	+	+		+	+	+
Tirzepatide[c]		+		+	+	–

+ = observed, – = not observed.
[a]Skeletal variations: structural change that does not affect viability, development, or function (eg, wavy ribs) that can be found in the normal population under investigation and can be reversible.
[b]Visceral: having to do with the viscera; which are the soft internal organs of the body, including the lungs, heart, and the organs of the digestive, excretory, reproductive, and circulatory systems.
[c]Tirzepatide data from Food and Drug Administration Summary Basis of Approval.

Table 8. Pregnancy recommendations

Drug	Label wording
Liraglutide	SAXENDA is contraindicated during pregnancy because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm.
Exenatide	Use during pregnancy only if the potential benefit justifies the risk to the fetus.
Semaglutide	May cause fetal harm. When pregnancy is recognized, discontinue WEGOVY. Females and males of reproductive potential: Discontinue WEGOVY at least 2 months before a planned pregnancy because of the long half-life of semaglutide.
Tirzepatide	Based on animal study, may cause fetal harm. Females of reproductive potential: Advise females using oral contraceptives to switch to a non–oral contraceptive method or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation.
Lixisenatide	ADLYXIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Dulaglutide	Should be used during pregnancy only if the potential benefit justifies the potential risk to fetus.
Albiglutide	TANZEUM may cause fetal harm; only use if potential benefit justifies potential risk to fetus.

A recent observational population-based cohort study (128) identified pregnant women with type 2 diabetes and their infants who were followed for up to 1 year post partum. Preconceptual exposure was defined as at least one filled prescription for GLP1 agonists, sulfonylureas, dipeptidyl peptidase IV (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, or insulin up to 90 days prepregnancy until the end of the first trimester. Of the more than 50 000 infants born to mothers with type 2 diabetes, 5.3% had a major congenital malformation compared to 3.7% of all infants in the database (>3 million), confirming the known adverse effect of diabetes on fetal outcomes. The malformation rate was 8.3% (n = 938) for infants exposed to a GLP1 agonist, 9.7% (n = 1362) for sulfonylureas, 6.1% for DPP-4 inhibitors (n = 687), 7.0% for SGLT2 inhibitors, (n = 335); and 7.8% for insulin, (n = 5078). The adjusted relative risks for major congenital malformations compared to insulin were statistically similar between all the treatments (0.95 [95% CI, 0.72-1.26], 1.18 [95% CI, 0.94-1.48], 0.83 [95% CI, 0.64-1.06], 0.95 [95% CI, 0.72-1.26], and 0.98 [95% CI, 0.65-1.46] for infants exposed to GLP1R agonists, sulfonylureas, DPP-4 inhibitors, and SGLT2 inhibitors, respectively).

Other systematic reviews of pregnancies in women treated with GLP1 agonists have had similar results (127, 129, 130). The rate of major congenital malformations in offspring of mothers taking GLP1 agonists before or in early pregnancy appears to be similar to those of offspring born to mothers who are on other diabetes drugs or who are obese. Although these results are promising, there are several important limitations. Insulin is not an appropriate comparator for women without diabetes. The numbers are small and the confidence limits for a statistically significant effect are wide, suggesting that a true effect could still exist. None of the studies are corrected for glycemic control, a key confounder that increases rates of major congenital malformations. In addition, the doses of GLP1 agonists used for the treatment of diabetes are often lower than those used for the treatment of obesity, thus raising the risk that malformation rates might be higher following higher treatment doses. Finally, there may be other differences between the participants, such as duration of therapy before conception and other concomitant diseases that would influence these results.

Other Effects of Glucagon-Like Peptide 1 Agonists

Reduced gastric emptying and effect on oral drug absorption

Reduced gastric emptying contributes to the sense of satiety leading to weight loss with GLP1 agonists. However, gastric emptying measurements can vary widely between studies, depending on the dose of GLP1 agonist, its half-life, the duration of GLP1 agonist treatment prior to the gastric emptying test, and the timing of the test relative to the GLP1 agonist administration. At least one study indicated that the effect of the GLP1 agonist on gastric emptying was worse with initiation

Table 9. Drug interaction studies

Drug	Label OCP interaction	Label recommendations	Drug interaction study dose	Data
Liraglutide	No effect on bioavailability of OCPs	VICTOZA delays gastric emptying and may affect absorption of concomitantly administered oral medications (7).	1.8 mg/d steady state, OCP dosed 7 h after Victoza	12% and 13% reduction in Cmax but no decrease in AUC
Liraglutide	No effect on bioavailability of OCPs	SAXENDA causes a delay of gastric emptying and thereby has potential to affect absorption of concomitantly administered oral medications. In clinical pharmacology trials, liraglutide did not affect absorption of tested orally administered medications to any clinically relevant degree. Nonetheless, monitor for potential consequences of delayed absorption of oral medications concomitantly administered with SAXENDA	1.8 mg/d steady state, OCP dosed 7 h after Victoza	12% and 13% reduction in Cmax but no decrease in AUC
Exenatide	Diminishes therapeutic effect of OCPs	Recommend taking OCPs at least 1 h prior to exenatide	5 µg twice a day for d 1-4 then 10 µg twice a day for d 10-22, OCP dosed d 8 and then d 10-28	46% (42%-51%) and 41% (35%-47%) reduction in Cmax when given 30 min after exenatide but only 9%-15% reduction when given 1 h before
Semaglutide	No clinically significant differences in pharmacokinetics of the following drugs observed when used concomitantly with semaglutide: lisinopril, S-warfarin, R-warfarin, metformin, digoxin, ethinyl estradiol, levonorgestrel, furosemide, or rosuvastatin		Steady state: 1 mg	
Tirzepatide	May reduce efficacy of oral hormonal contraceptives due to delayed gastric emptying. This delay is largest after first dose and diminishes over time	Advise patients using oral hormonal contraceptives to switch to a non–oral contraceptive method or add a barrier method of contraception for 4 wk after initiation and for 4 wk after each dose escalation with MOUNJARO. Hormonal contraceptives not administered orally should not be affected	Single dose: 5 mg	55%-66% reduction Cmax and 20%-23% reduction of AUC
Lixisenatide	Diminishes therapeutic effect of oral contraceptives	Recommend taking OCPs at least 1 h prior OR at least 11 h after lixisenatide		
Dulaglutide	In clinical pharmacology studies, dulaglutide at dose of 1.5 mg did not affect absorption of tested orally administered medications to any clinically relevant degree. Delay is largest after first dose and diminishes with subsequent doses		1.5 mg	10%-20% reduction Cmax, minimal change in AUC
Albiglutide	TANZEUM delays gastric emptying. May affect absorption of concomitantly administered oral medications		Steady state: 50 mg weekly for 4-5 wk	Standard bioequivalence criteria met with a few exceptions not considered clinically relevant. No clinically meaningful differences in LH, FSH, or progesterone observed

Abbreviations: AUC, area under the curve; Cmax, maximum concentration; FSH, follicle-stimulating hormone; LH, luteinizing hormone; OCP, oral contraceptive pill.

of the first dose or following the first dose escalation than at steady state (131).

Pregnancies in women taking oral contraceptives while on a GLP1 agonist (reported in social media) have led to a hypothesis that oral contraceptive efficacy may be reduced due to decreased gastric emptying and subsequently reduced drug absorption. However, drug interaction study results vary between the different GLP1 agonists (Table 9) (132-137), resulting in differences in manufacturers' prescribing information recommendations. Some of the differences between

results could be explained by study design issues, since it would be expected that there would be a larger effect on contraceptive drug absorption if there was a larger effect on gastric emptying. Thus, there may be reduced oral contraceptive pill (OCP) absorption following the first dose of a GLP1 agonist compared to when the GLP1 agonist has reached a steady state. Another factor might be the timing of the OCP ingestion relative to the GLP1 agonist dosing.

Not addressed in any of the studies is the effect of vomiting, which would be expected to significantly reduce absorption of recently ingested drugs and reduce contraceptive efficacy acutely.

Drug interaction studies for other oral drugs that may be used for reproductive care such as clomiphene and letrozole were not identified in this review, but their structural similarity to oral contraceptives suggests they would have similar risks to drug absorption.

Discussion and Clinical Recommendations

The available data suggest that the administration of GLP1 agonists for the treatment of obesity or type 2 diabetes may improve reproductive function both in men and women, with evidence for increased sex steroid levels, improved sperm number and quality in hypogonadal males and reduced T and improved ovarian cyclicity and pregnancy rates in women with PCOS. Preclinical data suggest direct effects of GLP1 agonists at the level of GnRH and Kiss neurons, testes, ovaries, and endometrium. Limited evidence suggests there is minimal transfer of GLP1 or its agonists into semen or breast milk, but it may cross the placenta. Based on currently available data, GLP1 agonists may be indicated for the treatment of hypogonadism and infertility in obese men.

Women taking GLP1 agonists for weight loss or diabetes therapy should be advised that they could become pregnant due to improved reproductive function or loss of oral contraceptive efficacy. In most cases, effective contraception should be recommended. If oral contraceptives are chosen, an additional contraceptive method should be added until the dose of GLP1 therapy reaches steady state and the risk of vomiting is reduced. Timing of the oral contraceptive should follow prescribing instructions for the given GLP1 agonist therapy. Some women may choose a long-acting injectable contraceptive therapy to avoid the risks of reduced concentrations of an OCP. For women with PCOS, GLP1 agonists may further lower androgens levels and protect the endometrium, in addition to the benefits of weight loss.

For women who intend to conceive, contraception is advised in most cases when initiating a GLP1 agonist until a healthy preconception weight and/or normoglycemia have been achieved. At this time, switching to a shorter-acting GLP1 agonist that does not have a contraindication label for pregnancy is advised, in addition to using a barrier contraceptive method. Then spontaneous menstrual cyclicity can be assessed and additional fertility recommendations made. Given that weight loss during pregnancy may cause adverse fetal outcomes (56), the current common recommendation is to discontinue a long-acting GLP1 agonist 2 months before trying to conceive. However, this recommendation is likely to be difficult, as 2 months is enough time for substantial weight regain and loss of glycemic control, which reverses the prior beneficial effects achieved. Considerable emotional and lifestyle support may be needed to help the woman maintain her weight while trying to conceive with an uncertain timeline for success.

In summary, while balancing the risks and benefits, it is possible that a GLP-1 agonist with a low-dose maintenance regimen and a short half-life may be beneficial until conception occurs. It is not known whether the risks for fetal malformations would be worse with GLP1 agonist therapy as opposed to those associated with obesity and diabetes.

Recommendations for Future Research

This review clarifies several important areas needing future investigation. Safety for men taking a GLP1 agonist while trying to conceive is an important area for further research. First, studies of sperm counts and function before and during GLP1 agonist therapy in men without hypogonadism are needed to respond to the few case reports of worsening sperm counts and function. In men taking a GLP1 agonist, it would be helpful to track pregnancy rates and outcomes of their partners to evaluate any risks to offspring.

Most preclinical and clinical studies investigating the effects of GLP1 agonists on ovarian function to date have been in patients with obesity-associated diseases such as diabetes and PCOS, as opposed to obesity alone. As studies have shown direct benefits of GLP-1 agonists on the ovary and endometrium in preclinical disease states, it would be useful to understand if there are additional detectable benefits in treating obesity without these concomitant illnesses.

In humans, a key need is for well-controlled prospective studies of the effect of weight loss on reproductive function (sex hormones, sperm quality, endometrial histology, menstrual cyclicity, and conception rates). Ideally, such studies would compare the efficacy of a GLP1 agonist with an alternative therapy that achieves similar weight loss. However, there are limitations that might make such a design challenging. Currently there are no safe weight loss medications or lifestyle changes that achieve the average level of weight loss induced by GLP1 agonists. While bariatric surgery might achieve similar amounts of weight loss, it would be difficult to ethically blind such a study. It will be useful to continue to assess the minimal amount of weight loss required to benefit reproductive health both in men and women. There remains a gap in knowledge with regard to the hypothalamic and pituitary effects of GLP-1 agonists in women with obesity and metabolic dysfunction. In women, it would also be helpful to understand whether the weight loss needs are different for women who are overweight and otherwise healthy compared to obese women with PCOS, MS, or diabetes. Since there have not been studies investigating the reproductive outcomes of GLP1 agonist–induced weight loss in the absence of PCOS, it remains unclear whether the reproductive benefits are secondary to a treatment of the underlying PCOS pathophysiology or an indirect effect of weight loss on reproductive capability.

In this context, it would be useful to assess the potential for GLP1 agonist therapy to facilitate conception in nonobese women with PCOS. Finally, it is critical to understand whether a GLP1 agonist can be safely continued throughout pregnancy for the treatment of diabetes.

Better understanding of, and management strategies for, the weight regain after discontinuing GLP1 agonists is urgently needed, as well as successful methods for maintaining weight loss. This is critical for women who would like to lose weight

before conceiving to improve their chances of conception and their maternal and fetal outcomes.

Continuing pregnancy registries to assess fetal outcomes is critical. In addition, a larger study of women with diabetes in pregnancy (either preexisting or gestational) would be helpful to better understand if optimal glycemic control with a GLP1 agonist could reduce the rate of congenital malformations in offspring of diabetic mothers. Ideally such a study would match glycemic control between the GLP1 agonist and placebo or matched control groups.

Disclosures

M.C. and A.J.T. have nothing to disclose. A.E.T. receives consulting income from Crinetics Pharmaceuticals and Third Rock Ventures related to GLP1 agonist therapies.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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