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The Impact of GLP-1 Analogues and Tirzepatide on Female Fertility: Mechanisms, Clinical Evidence, and Implications

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ABSTRACT

Background. Obesity impairs female fertility through metabolic, endocrine and inflammatory pathways that disrupt ovulation, reduce oocyte competence and impair endometrial receptivity. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and the dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1agonist tirzepatide have become highly effective therapies for weight management and metabolic optimisation, raising interest in their potential reproductive benefits.

Aim. To synthesise mechanistic and clinical evidence on how GLP-1 receptor agonists and tirzepatide may influence reproductive function in women of reproductive age.

Material and Methods. A narrative literature review was conducted using PubMed, Scopus and Web of Science for articles published up to December 2025. Peer-reviewed human studies and major reviews were included if they evaluated GLP-1 receptor agonists or tirzepatide in the context of metabolic, endocrine or reproductive outcomes in women of reproductive age. Mechanistic and translational studies were considered when they provided insight into pathways relevant to fertility. Animal-only studies, conference abstracts without full text and non–peer-reviewed sources were excluded.

Results. GLP-1 signalling may influence the hypothalamic–pituitary–ovarian axis, adipokine pathways, oocyte mitochondrial function and endometrial gene expression. Clinical evidence shows that liraglutide and semaglutide improve body weight, insulin resistance and hyperandrogenism,

leading to restoration of menstrual regularity and increased ovulation rates. Improvements in spontaneous conception and assisted reproduction outcomes have been reported in women achieving significant metabolic benefits. Tirzepatide provides greater weight reduction and metabolic improvements, although reproductive data remain limited.

Conclusions. GLP-1–based therapies act as metabolic optimisers that may secondarily enhance fertility in women with obesity. Evidence for direct reproductive effects remains preliminary, and safety during the periconceptional period is not established. Current guidelines recommend discontinuing GLP-1 agents before conception. High-quality prospective studies are needed to clarify reproductive efficacy, underlying mechanisms and optimal treatment timing.

Keywords: GLP-1 receptor agonists, tirzepatide, obesity, female fertility, oocyte quality, endometrium, reproductive endocrinology

1. Introduction

Obesity among women of reproductive age is increasing globally and is closely linked to subfertility and adverse pregnancy outcomes [1–3,37,38]. Excess adipose tissue promotes insulin resistance, hyperinsulinaemia, chronic inflammation, leptin resistance and dysregulated adipokine secretion [1–4,7,8]. These metabolic disturbances impair the hypothalamic–pituitary–ovarian (HPO) axis, leading to anovulation, luteal dysfunction and menstrual irregularities [2,3]. Obesity also alters the intraovarian and endometrial environment, reducing oocyte quality, embryo development and endometrial receptivity [3–5,40]. As a result, women with obesity experience lower conception rates, higher miscarriage risk and reduced success of assisted reproductive technologies (ART) [29–34].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become an important treatment option for type 2 diabetes and, more recently, for obesity management [11–14]. These agents induce satiety, delay gastric emptying, enhance glucose-dependent insulin secretion and promote significant weight loss [11–14,44]. Increasing evidence suggests that GLP-1 RAs may also influence reproductive physiology. Their potential actions include indirect metabolic benefits—through weight reduction and improved insulin sensitivity—and possible direct effects on reproductive tissues [14,21–23]. Tirzepatide, a dual GIP/GLP-1 receptor agonist, produces even greater metabolic improvements [13] and has raised additional interest in its potential impact on female fertility [21,22].

This review summarises current mechanistic and clinical evidence regarding the effects of GLP-1 analogues and tirzepatide on female fertility. Although emerging studies suggest potential direct reproductive actions of GLP-1–based therapies [6,19,24], much of the available evidence originates from preclinical or observational work, and robust human data remain limited [21–23].

2. Mechanisms of Action of GLP-1 Analogues and Tirzepatide Relevant to Female Fertility

2.1. Insulin, leptin and adipokines

Hyperinsulinaemia is a central contributor to obesity-related reproductive dysfunction and amplifies LH-driven androgen synthesis in ovarian theca cells, leading to hyperandrogenism and impaired folliculogenesis [1–4,10]. Concurrent leptin resistance disrupts hypothalamic metabolic signalling and may impair endometrial function and implantation capacity [7,8]. In addition, proinflammatory adipokines such as tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) negatively affect granulosa cell function, oocyte development and endometrial receptivity [1–4].

GLP-1 receptor agonists and tirzepatide markedly reduce fasting insulin concentrations, improve insulin sensitivity, lower circulating leptin levels and modulate adipokine profiles towards a less inflammatory phenotype [11–14,19,20]. These systemic improvements support restoration of ovulatory cycles and may enhance luteal function [11,17,18]. By mitigating chronic low-grade inflammation, GLP-1–based therapies may further promote a reproductive environment conducive to follicular maturation and implantation [19,20].

Nevertheless, it remains uncertain to what extent metabolic changes alone explain the recovery of ovulation. Controlled mechanistic studies isolating specific endocrine pathways are still lacking [21–23].

2.2. Regulation of the hypothalamic–pituitary–ovarian axis

The hypothalamic–pituitary–ovarian (HPO) axis integrates metabolic and endocrine inputs to regulate gonadotropin-releasing hormone (GnRH) pulsatility and subsequent gonadotropin release. GLP-1 receptors are expressed within several hypothalamic nuclei, including regions enriched in kisspeptin/neurokinin B/dynorphin (KNDy) neurons and pro-opiomelanocortin (POMC) neurons involved in reproductive and energy-homeostatic regulation [6,8]. Experimental rodent studies suggest that central GLP-1 signalling can *indirectly* modulate GnRH neuronal activity—likely through intermediary metabolic neuronal populations rather than direct GLP-1 receptor activation on GnRH neurons—and enhance luteinising hormone (LH) pulsatility under metabolic stress [6,8]. Weight loss achieved with GLP-1 receptor agonists may further restore physiological GnRH/LH secretion by alleviating hyperinsulinaemia and leptin resistance, two key disruptors of reproductive neuroendocrine feedback [7,8,11]. These central mechanisms are complemented by peripheral

actions on ovarian steroidogenesis, where reduced insulin levels diminish the synergistic stimulation of androgen production in theca cells, thereby improving follicular development [2,10].

However, mechanistic evidence for direct central reproductive effects of GLP-1 in humans is limited. Most insights derive from rodent studies, and the translational relevance of these findings remains uncertain [21–23].

2.3. Oocyte quality and folliculogenesis

Oocyte development is highly sensitive to metabolic and oxidative disturbances. Obesity is associated with mitochondrial dysfunction, increased reactive oxygen species, spindle abnormalities and chromosomal segregation errors in oocytes, resulting in diminished developmental competence [3–5,40].

Weight loss induced by GLP-1 receptor agonists improves systemic metabolic status and may normalise the follicular microenvironment, indirectly supporting oocyte development [11–14,17–20]. Notably, current evidence indicates that GLP-1 analogues do not directly penetrate the ovarian follicle; thus, any reproductive benefits are presumed to be mediated through systemic metabolic improvement rather than direct intrafollicular action [17,19,40].

Animal studies demonstrate that GLP-1 analogues can reduce follicular atresia, enhance granulosa cell function and improve oocyte maturation [5,19,40]. In humans, improved metabolic control and reduced hyperandrogenism following GLP-1 therapy may contribute to enhanced oocyte quality, although direct evidence from human oocyte studies remains limited [17,18,21–23].

2.4. Endometrial receptivity and implantation

Endometrial receptivity is essential for successful implantation and early pregnancy maintenance. Obesity alters the endometrial transcriptome and impairs the expression of genes associated with adhesion, angiogenesis and immune tolerance within the implantation window [4,24]. Recent findings indicate the presence of GLP-1 receptors in endometrial tissue, though the distribution and functional significance of GLP-1R expression in the human endometrium remain incompletely characterised [24,25].

Transcriptomic data suggest that short-term GLP-1 RA treatment may modulate gene-expression profiles linked to receptivity, potentially counteracting obesity-induced dysregulation [24,25]. GLP-1 RAs also exert anti-inflammatory effects and may influence uterine immune cell subsets—including uterine natural killer cells and macrophages—thereby promoting a more permissive implantation environment [24,25].

Although specific data on tirzepatide are limited, its potent metabolic and anti-inflammatory effects may yield similar or even more pronounced improvements in endometrial function [19,22].

However, current evidence is derived primarily from molecular and preclinical studies. No human clinical trials have yet demonstrated improvements in implantation or pregnancy rates attributable directly to GLP-1–mediated endometrial effects [21–23]. Thus, while biologically plausible, the clinical significance of these findings requires confirmation in prospective reproductive-outcome studies.

2.5. Integrative Overview of GLP-1–Mediated Mechanisms

The mechanisms through which GLP-1 receptor agonists and tirzepatide influence female reproductive function are multifactorial and interconnected. Their primary actions arise from metabolic optimisation, which subsequently affects endocrine, ovarian and endometrial pathways relevant to fertility. These mechanisms are consistent with current evidence describing the metabolic origins of anovulation, impaired folliculogenesis and reduced endometrial receptivity in women with obesity [1–5,10–14,17–20].

A central effect of GLP-1–based therapies is the reduction of hyperinsulinaemia and improvement in insulin sensitivity. Lower insulin levels diminish the synergistic stimulation of androgen production in ovarian theca cells, reducing hyperandrogenism and facilitating healthier follicular development and ovulatory function [1–4,10–12,17–20]. GLP-1 receptor agonists also modulate leptin signalling, thereby alleviating leptin resistance, which plays a significant role in metabolic dysregulation of the hypothalamic–pituitary–ovarian axis [7,8,11]. Improved leptin sensitivity may help restore physiological GnRH and LH pulsatility, particularly in women in whom obesity disrupts neuroendocrine feedback mechanisms.

In addition, these agents exert systemic anti-inflammatory effects, decreasing concentrations of proinflammatory adipokines such as TNF-α and IL-6. By reducing chronic low-grade inflammation characteristic of obesity, GLP-1 receptor agonists create a more favourable environment for granulosa-cell function, oocyte maturation and endometrial receptivity [1–5,14,17–20].

Clinically significant weight loss, one of the most robust outcomes of GLP-1 therapy, contributes further to reproductive improvement. Reductions in adiposity alleviate oxidative stress, improve mitochondrial function and normalise the follicular microenvironment, supporting oocyte developmental competence and improving endocrine balance [11–14,17–20].

Preclinical and early translational data suggest that GLP-1 signalling may also exert direct reproductive effects, including modulation of hypothalamic neuronal networks involved in reproductive regulation, enhancement of granulosa-cell metabolic function and favourable changes in endometrial gene-expression patterns [6–8,19,24,25]. However, these findings largely derive from rodent studies and molecular research. Their relevance to human reproductive physiology

remains uncertain, as mechanistic human studies are limited and no clinical trials have yet demonstrated direct fertility benefits independent of metabolic improvement [21–23].

Overall, GLP-1 receptor agonists and tirzepatide appear to act predominantly as metabolic optimisers, with reproductive benefits emerging secondarily from improved insulin sensitivity, reduced inflammation and restored endocrine balance. Potential direct effects on reproductive tissues are biologically plausible but still require verification in well-designed human studies.

2.6. Tirzepatide: dual GIP/GLP-1 receptor agonism

Tirzepatide, a dual incretin agonist targeting both glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, produces greater reductions in body weight and glycated haemoglobin than established GLP-1 RAs [13]. It potentiates glucose-dependent insulin secretion, suppresses glucagon release, improves insulin sensitivity and exerts profound appetite-regulatory effects [13]. These metabolic benefits suggest a strong potential to reverse obesity-related reproductive dysfunction [21,22]. However, fertility-specific data remain sparse. Evidence from metabolic trials allows only cautious extrapolation that tirzepatide may restore ovulation or improve reproductive hormone profiles; dedicated reproductive studies in women are urgently needed [21–23].

Additionally, the expression and functional relevance of GIP receptors within reproductive tissues have not been characterised, further limiting mechanistic understanding of tirzepatide's reproductive effects. As with GLP-1 RAs, timing of therapy relative to conception requires careful clinical consideration owing to limited pregnancy-safety data and preclinical signals of potential risk [26–28].

3. Current Clinical Evidence

Clinical evidence on GLP-1 receptor agonists in reproductive-age women has focused primarily on individuals with obesity, often with coexisting polycystic ovary syndrome (PCOS). Liraglutide and semaglutide—used either as monotherapy or in combination with metformin—consistently produce clinically meaningful weight loss, improve insulin resistance and reduce serum androgen concentrations [11,14,17,18]. Multiple clinical trials and observational studies report restoration of menstrual regularity and increased ovulation rates following GLP-1 RA therapy [17,18,21].

Several studies also suggest that weight loss achieved with GLP-1 RAs may enhance spontaneous conception rates and improve outcomes of assisted reproductive technologies. Improvements in oocyte maturation, embryo quality and in vitro fertilisation (IVF) success have been observed in women who attained significant metabolic optimisation prior to fertility treatment [29–34]. These findings align with earlier meta-analytic evidence demonstrating that preconception weight loss enhances fertility outcomes in overweight and obese women [29–34].

Recent narrative and systematic reviews synthesise these data and highlight that the reproductive benefits of GLP-1-based therapies are predominantly mediated through weight reduction, improved insulin sensitivity and mitigation of hyperandrogenism [14,17,18,21]. Nonetheless, emerging transcriptomic studies on the endometrium and exploratory evidence regarding hypothalamic GLP-1 signalling raise the possibility of additional direct reproductive actions [24,25].

Evidence regarding tirzepatide remains limited, as available studies focus mainly on metabolic and cardiovascular outcomes rather than reproductive endpoints [13,21–23]. To date, no controlled clinical trials have evaluated the effects of tirzepatide on ovulation, menstrual patterns, conception rates or fertility-treatment outcomes. However, the degree of weight loss and metabolic normalisation achieved with tirzepatide in phase 3 trials (SURMOUNT programme) suggests a potentially substantial impact on reproductive physiology, provided that safety concerns around conception and early pregnancy are appropriately addressed [26–28].

4. Discussion

The available evidence supports the use of GLP-1 receptor agonists as effective tools for improving metabolic health in women with obesity and obesity-related reproductive dysfunction. Their benefits arise primarily from substantial weight loss, improved insulin sensitivity and reductions in hyperandrogenism, all of which contribute to restoration of ovulatory cycles and more favourable endocrine profiles [11,14,17,18,37]. By targeting key pathophysiological pathways underlying anovulation, impaired folliculogenesis, oocyte compromise and endometrial dysfunction, GLP-1 RAs may indirectly enhance fertility [1–5,14,17–20,24]. Preclinical studies and early translational evidence further suggest potential direct actions of GLP-1 signalling within the HPO axis, ovary and endometrium, although these findings remain preliminary and require human confirmation [6–8,24,25]. Tirzepatide, through dual GIP/GLP-1 receptor agonism, induces even greater metabolic improvement and may offer additional therapeutic potential, though reproductive data remain scarce [13,21–23].

Despite these promising findings, several important uncertainties limit the integration of GLP-1-based therapies into routine fertility management. First, most clinical studies evaluating GLP-1 RAs in reproductive-age women have short follow-up periods and focus on intermediate endpoints such as weight loss, menstrual regularity or ovulation rather than conception or live birth rates [17,18,29–34]. High-quality evidence linking GLP-1 therapy to improved pregnancy outcomes is therefore lacking. Second, current clinical guidance advises discontinuation of GLP-1 RAs before attempting conception due to insufficient human pregnancy-safety data and signals of potential teratogenicity in high-dose animal studies [26–28]. This creates a practical challenge: although GLP-1-induced

metabolic optimisation may support fertility, treatment interruption is required prior to conception, leaving uncertainty regarding optimal timing.

Third, it remains unclear which patient subgroups stand to benefit most from GLP-1 therapy. Women with PCOS, severe insulin resistance or prominent metabolic dysfunction may show the greatest improvements, but definitive comparative data are absent [11,14,17,18]. Similarly, the optimal integration of GLP-1 RAs with lifestyle modification, metformin or fertility treatments such as ovulation induction or IVF has not been defined. Whether preconception GLP-1 therapy improves ART outcomes independent of weight changes is also an open question [29–34].

Addressing these gaps will require prospective, adequately powered clinical trials focusing on reproductive endpoints—including ovulation, conception, miscarriage and live birth—as well as rigorous assessment of maternal and offspring safety. Mechanistic studies exploring central GLP-1 signalling, ovarian and endometrial responses and tirzepatide-specific pathways will also be essential to determine whether these agents exert reproductive benefits beyond metabolic optimisation.

5. Conclusions

GLP-1 receptor agonists and tirzepatide represent promising pharmacologic options for addressing obesity-related subfertility in women. Their primary reproductive benefits arise from substantial weight loss and metabolic normalisation, which together support restoration of ovulatory function and improvement in key endocrine parameters. Emerging molecular and translational evidence suggests that these agents may also exert direct actions on endometrial receptivity and potentially on oocyte quality, although such findings remain preliminary.

Despite growing interest in their reproductive applications, current evidence is not sufficient to support the routine use of GLP-1–based therapies during the periconceptional period or pregnancy. The need for drug discontinuation prior to conception, combined with limited human safety data, underscores the importance of cautious clinical decision-making. GLP-1 receptor agonists and tirzepatide should therefore be regarded primarily as metabolic optimisers that may secondarily enhance fertility rather than as established reproductive treatments.

Future research should prioritise elucidation of mechanistic pathways, determination of optimal timing for therapy in women seeking pregnancy and the generation of high-quality clinical evidence evaluating conception, miscarriage, live birth and long-term offspring outcomes. Such studies will be critical for defining the precise role of GLP-1–based therapies in reproductive medicine.

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