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The Impact of GLP-1 Receptor Agonists on Human Fertility: A Narrative Review of the Reproductive Effects of Semaglutide (Ozempic) and Tirzepatide (Mounjaro) in Men and Women

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Abstract **Review Article**

Background: Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs) have revolutionized the management of type 2 diabetes mellitus (T2DM) and obesity. Their expanding clinical use, particularly that of the single-agonist semaglutide (Ozempic/Wegovy) and the dual GLP-1/GIP agonist tirzepatide (Mounjaro/Zepbound), has led to increased exposure in the reproductive-age population, raising critical questions about their impact on human fertility. ***Objective:*** To summarize the mechanistic and clinical evidence regarding the effects of semaglutide and tirzepatide on human fertility in both sexes, focusing on the interplay between metabolic improvement and direct reproductive signaling. ***Methods:*** This narrative review synthesizes studies published between 2015 and 2025 in PubMed, Scopus, and Embase, focusing on the reproductive and endocrine effects of semaglutide and tirzepatide in men and women. ***Results:*** GLP-1 RAs show potential beneficial effects on fertility, primarily via indirect mechanisms**,** including significant weight reduction, improved insulin sensitivity, and subsequent hormonal normalization. Direct effects are suggested by GLP-1 receptor expression in the gonadal tissues. However, while clinical evidence points to improved ovulation rates in women with obesity/PCOS and better sperm parameters in men with obesity-related hypogonadism, reproductive safety data, particularly long-term safety and pregnancy outcomes, are limited. ***Conclusion:*** Evidence suggests possible fertility improvement in cases of metabolic-related infertility. However, the lack of robust human data, coupled with preclinical findings of teratogenicity, necessitates a cautious approach. Long-term safety and pregnancy outcomes require urgent further research, and clinicians must counsel patients on preconception discontinuation.

Keywords: Semaglutide, Tirzepatide, GLP-1 receptor agonists, Fertility, Reproductive Health, PCOS, Spermatogenesis, Obesity.

1. INTRODUCTION

The global prevalence of obesity and T2DM continues to rise, driving the rapid adoption of highly effective pharmacotherapies, such as GLP-1 RAs [1]. Semaglutide, a GLP-1 mono-agonist, and tirzepatide, a dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) co-agonist, represent the current frontiers in this class of drugs [2]. Their profound efficacy in promoting weight loss and improving glycemic control has led to their increasing use, including off-label use, among individuals of reproductive age [3].

Obesity is a major contributor to subfertility in both men and women, often mediated by chronic low-grade inflammation, insulin resistance, and hormonal dysregulation [4]. Consequently, fertility concerns and reproductive outcomes have emerged as critical and rapidly expanding areas of research on GLP-1 RAs.

This review aims to evaluate the current mechanistic and clinical evidence on how semaglutide and tirzepatide affect fertility and reproductive health in both men and women, providing a balanced perspective on their potential benefits and established safety concerns.

2. Mechanistic Overview: GLP-1 and Reproductive Physiology

The impact of GLP-1 RAs on fertility is multifaceted, involving both indirect effects mediated by systemic metabolic improvement and potential direct effects of receptor signaling within the reproductive axis.

2.1 GLP-1 receptor distribution and hormonal cross-talk

The GLP-1 receptor (GLP-1R) is widely expressed in central and peripheral tissues crucial for reproductive function.

- **Central Nervous System:** GLP-1R is abundant in the hypothalamus and pituitary gland, where it interacts with the hypothalamic-pituitary-gonadal (HPG) axis [5]. GLP-1 signaling in the hypothalamus can influence the release of Gonadotropin-Releasing Hormone (GnRH), which in turn regulates the secretion of Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) from the pituitary gland [6].
- **Gonadal Tissues:** GLP-1R expression has been demonstrated in the ovary (granulosa cells) and testis (Leydig cells and sperm) in both human and animal models, suggesting a potential for direct modulation of gonadal function and gamete quality [7, 8].
- **Metabolic Hormones:** GLP-1 RAs are intrinsically linked to the regulation of insulin and leptin. Improvement in insulin sensitivity is a cornerstone of GLP-1 RA action, which is particularly relevant in conditions such as Polycystic Ovary Syndrome (PCOS) [9]. Leptin, a key adipokine, signals energy status to the brain and reproductive system. GLP-1 RAs indirectly modulate leptin levels through weight loss, influencing sex steroid pathways [10].

2.2 Metabolicand Endocrine Modulation

The primary mechanism by which GLP-1 RAs influence fertility is through the correction of obesity-induced metabolic dysfunction.

- **Weight Reduction and Insulin Sensitivity:** Significant weight loss (often >15% with tirzepatide) and improved insulin sensitivity are potent indirect fertility modulators [11]. In women, this can break the vicious cycle of hyperinsulinemia, hyperandrogenism, and anovulation, which are common in PCOS [12]. In men, metabolic improvement can reduce the aromatization of testosterone to estradiol and decrease inflammation, leading to the normalization of the hormonal milieu [13].
- **Cellular Energy Homeostasis:** Obesity is characterized by low-grade chronic inflammation and impaired cellular energy production, both of which can negatively impact oocyte quality. GLP-1 RAs can modulate key cellular pathways like AMPK (AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR), by improving energy balance [14]. AMPK, a master regulator of energy, drives follicular atresia during sustained energy shortages, whereas mTOR guides follicular recruitment and oocyte maturation. By restoring metabolic health, GLP-1 RAs may indirectly support optimal oocyte and follicular development [14].

3. Evidence in Women

The majority of clinical data on GLP-1 RAs and female fertility are centered on women with obesity and/or PCOS, in whom the metabolic benefits are most pronounced.

3.1 Effects on ovulatory function and menstrual regularity

The most notable clinical effect of GLP-1 RAs is the restoration of ovulatory function and menstrual regularity in women with PCOS and obesity [15].

- **PCOS Studies:** Studies, including those involving semaglutide, have shown that substantial weight loss can lead to the resumption of spontaneous menses and ovulation [16]. A weight loss of only 5–10% is often sufficient to improve metabolic and reproductive symptoms in PCOS, and GLP-1 RAs frequently exceed this threshold [17]. Clinical trials are ongoing to rigorously assess the efficacy of semaglutide in obese infertile women with PCOS (e.g., NCT05702905) [18].
- **Tirzepatide Potential:** While direct large-scale fertility studies on tirzepatide are limited, its superior weight loss and glycemic control, stemming from its dual GIP/GLP-1 action, suggest an even greater potential for restoring ovulatory cycles compared to mono-agonists [19].

3.2 Effects on hormonal profiles and ovarian reserve markers

Metabolic improvement directly translates to favorable changes in reproductive hormones.

- **Hormonal Normalization:** Weight loss with GLP-1 RAs reduces hyperinsulinemia and subsequent hyperandrogenism, leading to decreased total and free testosterone levels [20]. This hormonal shift is critical for restoring the normal LH/FSH ratio, which is typically elevated in PCOS [21].
- **Ovarian Reserve Markers (AMH):** Anti-Müllerian Hormone (AMH) levels, which are often pathologically high in PCOS, have been observed to decrease following GLP-1 RA therapy, likely reflecting the reduction in the number of small antral follicles associated with improved ovulatory health [22]. However, AMH may also serve as a marker for stratification in PCOS, and its changes must be interpreted cautiously [22].

3.3 Reproductive and pregnancy outcomes

Data on reproductive outcomes and pregnancy safety in humans represent the most critical knowledge gap.

- **Unplanned Pregnancies:** The Significant improvements in fertility often lead to

unplanned pregnancies, underscoring the need for mandatory pre-conception counseling and effective contraception [23].

- **Preclinical Findings and Teratogenicity:** Preclinical studies in animal models (rats and rabbits) have demonstrated the potential teratogenicity and embryotoxicity of both semaglutide and tirzepatide exposure during gestation, including fetal growth restriction and structural abnormalities [24, 25].
- **Recommendations for Pre-pregnancy Discontinuation:** Due to the long half-lives of these medications and preclinical safety signals, regulatory bodies and clinical guidelines strongly recommend a **washout period** before attempting conception. The recommended period for semaglutide administration is at least **2 months (**equivalent to five half-lives) [26]. Tirzepatide, which has a shorter half-life, is also recommended for discontinuation prior to pregnancy [27].
- **Human Pregnancy Exposure:** Limited human data from pregnancy registries and post-marketing surveillance are available. While some reports have not shown a significant increase in major congenital malformations following first-trimester exposure, the overall human evidence base is too small to rule out risk, and contraindications during pregnancy and lactation remain [28].

4. Evidence in Men

Obesity-related male infertility is characterized by low testosterone levels, reduced sperm quality, and erectile dysfunction. GLP-1 RAs primarily address these issues through weight loss and metabolic correction.

4.1 Effects on testosterone levels and spermatogenesis

GLP-1 RAs have shown promising results in improving the hormonal and cellular aspects of male fertility, particularly in men with obesity and T2DM.

- **Testosterone Restoration:** Semaglutide and tirzepatide, by inducing significant weight loss and improving insulin sensitivity, lead to a reduction in sex hormone-binding globulin (SHBG) and a subsequent increase in total and free testosterone levels in men with obesity-related hypogonadism [29]. This is a crucial step in normalizing the HPG axis.
- **Spermatogenesis and Sperm Parameters:** Direct and indirect effects on sperm quality have been reported in the literature. A small pilot study in obese men with T2DM and functional hypogonadism found that semaglutide markedly improved sperm morphology and total testosterone levels after 24 weeks [30]. Furthermore, human sperm express the GLP-1 receptor, and *in vitro* studies suggest that GLP-1 RAs may enhance sperm metabolism and motility [31]. However, some larger retrospective studies have found no association between GLP-1 RA exposure and impaired semen parameters in men undergoing fertility evaluations [32].

4.2 Sexual function and reproductive hormones

The metabolic benefits of GLP-1 RAs extend to improving QoL and sexual function.

- **Sexual Function:** Weight loss and improved metabolic health, including better endothelial function, are strongly linked to improved sexual desire and erectile function [33]. Although the effect is largely indirect, GLP-1's impact on the central nervous system and vascular health contributes to overall sexual well-being [34].
- **Gonadotropins:** The effect on gonadotropins (LH and FSH) is less clear than that on testosterone. While some studies suggest that GLP-1 RAs may modulate the HPG axis centrally, the primary mechanism of testosterone increase is likely peripheral, through the reduction of obesity-related inflammation and improved Leydig cell function [35].

5. Clinical Implications and Safety Considerations

The clinical use of GLP-1 RAs in patients of reproductive age requires careful, individualized risk–benefit assessment.

- **Use in Metabolic-Related Infertility:** GLP-1 RAs are highly relevant for patients with PCOS, severe obesity, or metabolic syndrome seeking fertility. In these populations, the benefits of weight loss and metabolic correction may outweigh the risks, provided that strict pre-conception protocols are followed.
- **Preconception Counseling and Washout:** Given the preclinical teratogenicity signals and long half-lives of semaglutide and tirzepatide, counseling on the need for effective contraception and a washout period is essential [36]. A recommended washout period of at least 2 months before attempting conception remains the standard of care for semaglutide use.
- **Contraindications:** GLP-1 RAs are contraindicated in pregnancy and lactation. Patients who become pregnant while on therapy should discontinue the medication immediately and be enrolled in a pregnancy exposure registry (e.g., the Novo Nordisk registry for semaglutide) for monitoring purposes [37].
- **Individualized Assessment:** Clinicians should weigh the severity of obesity/metabolic disorders (and their associated reproductive risks) against the unestablished long-term safety profile of the medications.

6. Knowledge Gaps and Future Directions

Despite their clinical potential, significant knowledge gaps must be addressed.

- **Lack of Long-term Reproductive Outcome Data:** The most pressing gap is the absence of long-term data on reproductive outcomes, including live birth rates, in both men and women following GLP-1 RA exposure.
- **Limited Human Trials:** Most human evidence is retrospective or observational. There is a critical need for large-scale, prospective human trials that directly assess fertility endpoints, such as time-to-pregnancy and live birth rates, in women with PCOS and men with metabolic-related subfertility.
- **Mechanistic Studies on Gonadal Signaling:** Further research is needed to fully delineate the direct mechanistic roles of GLP-1 and GIP signaling in human gonadal tissues (ovaries and testes) and gamete development, independent of systemic metabolic effects.
- **Future Directions:**
  - **RCTs:** Randomized controlled trials (RCTs) comparing GLP-1 RAs to lifestyle interventions or established therapies (e.g., metformin) for ovulation and pregnancy outcomes.
  - **Post-marketing Surveillance:** Continued and enhanced post-marketing surveillance and pregnancy registries are vital for gathering robust human safety data on pregnancy exposure.

7. CONCLUSION

GLP-1 receptor agonists, particularly semaglutide and tirzepatide, hold substantial promise for improving fertility indirectly via powerful metabolic and hormonal modulation in individuals with obesity or T2DM. This indirect benefit, facilitated by profound weight loss and improved insulin sensitivity, can restore ovulatory function in women and normalize testosterone and sperm parameters in men.

However, the evidence base remains preliminary, and the safety profile during conception and pregnancy has not yet been established. Preclinical data suggest a risk of teratogenesis. Consequently, clinicians must prioritize reproductive intentions, mandate effective contraception, and enforce the recommended washout periods before initiating therapy in reproductive-age adults. Future research is essential to bridge the current knowledge gaps and provide definitive guidance on the safe and effective use of these transformative medications in human reproduction.

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