Review Article
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GLP-1 analogue as a novel approach for fertility treatment: unravelling the therapeutic potential: A narrative review

Abstract

Glucagon-like peptide-1 (GLP-1) analogues have emerged as promising therapeutic agents for the treatment of type 2 diabetes. Recent studies have suggested a potential role of GLP-1 in reproductive functions, offering new avenues for fertility treatment. This paper aims to review the current understanding of GLP-1 analogues to human reproduction, focusing on their potential application in fertility treatment, and discussing the molecular mechanisms and signalling pathways involved. Further, we highlight the challenges and future directions in the application of GLP-1 analogues for fertility treatment.

Keywords: GLP-1, fertility, reproduction, insulin resistance, PCOS

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Abbreviations: GLP-1, glucagon-like peptide-1; ARTs, assisted reproductive technologies; GLP-1Ras, GLP-1 receptor agonists; HPG, hypothalamic-pituitary-gonadal; PCOS, polycystic ovary syndrome; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; AMH, anti-müllerian hormone; IGF-1, insulin-like growth factor-1

Introduction

Infertility affects approximately 8-12% of couples worldwide, posing significant physical, psychological, and financial challenges.[1] Fertility treatments, including assisted reproductive technologies (ARTs), have revolutionized the management of infertility; however, they are often associated with high costs, limited success rates, and potential complications.[2] Thus, there is an ongoing need to explore novel therapeutic strategies to improve fertility outcomes.

Glucagon-like peptide-1 (GLP-1) is an incretin hormone mainly secreted by intestinal L-cells in response to nutrient ingestion.[3] It plays a critical role in glucose homeostasis by stimulating insulin secretion, inhibiting glucagon secretion, and delaying gastric emptying.[4] GLP-1 receptor agonists (GLP-1RAs) have been developed as therapeutic agents for type 2 diabetes due to their ability to lower blood glucose levels and promote weight loss.[5] Interestingly, accumulating evidence suggests that GLP-1 and its analogues may have potential implications in the regulation of reproductive function, opening new avenues for fertility treatment.[6]

GLP-1 and its receptor, GLP-1R, have been identified in various reproductive tissues, including the hypothalamus, pituitary, ovary, and testis.[7] GLP-1R activation has been linked to the modulation of the hypothalamic-pituitary-gonadal (HPG) axis, which plays a pivotal role in the regulation of reproductive function.[8] Moreover, studies have shown that GLP-1RAs can improve insulin sensitivity and reduce hyperandrogenism in women with polycystic ovary syndrome (PCOS), a leading cause of infertility.[9,10]

Molecular mechanisms and signalling pathways

The molecular mechanisms underlying the effects of GLP-1 analogues on reproductive function are still not fully elucidated. However, several signalling pathways have been implicated in this process. In the hypothalamus, GLP-1R activation modulates the release of gonadotropin-releasing hormone (GnRH), which in turn regulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland.[3] Additionally, GLP-1RAs have been shown to suppress the expression of kisspeptin, a key regulator of GnRH release.[11] These findings suggest that GLP-1 analogues may exert their effects on fertility through the modulation of the HPG axis.

In the ovary, GLP-1R activation has been reported to promote follicular development, enhance oocyte maturation, and improve oocyte quality. Additionally, GLP-1RAs have been shown to exert anti-inflammatory and anti-apoptotic effects in ovarian cells, which may further contribute to their beneficial impact on ovarian function.[12]

Weight loss and fertility treatment

Obesity is a well-established risk factor for infertility, with negative effects on both male and female reproductive outcomes.[13] Weight loss has been shown to improve fertility and enhance the success of fertility treatments.[14] GLP-1 analogues, known for their weight loss-promoting effects in diabetic patients, may offer a unique opportunity for the management of obesity-related infertility.[15] Studies have demonstrated that GLP-1 analogues can promote weight loss in non-diabetic overweight and obese individuals, leading to improved menstrual function and ovulation rates in women with obesity-related infertility.[16] Further research is needed to assess the optimal timing, duration, and dosing of GLP-1 analogues for weight loss in the context of fertility treatment.

There is also further evidence to suggest that GLP-1 analogues may have a positive effect on fertility outcomes in overweight and obese women. For example, a study by Salamun et al.[17] found that liraglutide, a GLP-1 analogue, improved cumulative pregnancy rates in overweight and obese women undergoing fertility treatment. Another study,[9] compared the effects of exenatide, another GLP-1 analogue, and metformin on menstrual cyclicity in overweight women with PCOS. They found that the combination of exenatide and metformin was more effective at improving menstrual cyclicity than either treatment alone.

Furthermore, GLP-1 analogues have been shown to improve reproductive outcomes in patients with PCOS. A randomized trial[10] compared the effectiveness of low-dose liraglutide plus metformin to high-dose liraglutide alone in the treatment of obese women with PCOS. They found that the combination therapy resulted in greater weight loss and better improvement in insulin resistance, menstrual cyclicity, and fertility outcomes than high-dose liraglutide alone.

Another study published in the Journal of Clinical Endocrinology and Metabolism in 2008 compared the effects of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome. The study found that the combined treatment resulted in a higher frequency of ovulatory cycles and improved insulin sensitivity compared to the single treatment.[9]

Overall, these studies suggest that GLP-1 analogues may be a potential option for weight loss and improvement of fertility outcomes in overweight and obese women undergoing fertility treatment, particularly those with polycystic ovary syndrome. However, further research is needed to fully understand the potential.

It is important to note that weight loss and lifestyle changes are still the first-line approaches for improving fertility outcomes in overweight and obese individuals. GLP-1 analogues should only be considered as an adjunct to these measures, and further research is needed to determine their optimal use in fertility treatments.

Endometrial receptivity

Endometrial receptivity plays a critical role in successful implantation and pregnancy outcomes. Emerging evidence suggests that GLP-1 may influence endometrial receptivity through the modulation of various molecular and cellular processes. For instance, GLP-1 has been shown to promote endometrial cell proliferation, enhance the expression of adhesion molecules, and regulate the secretion of cytokines and growth factors, which are essential for embryo implantation.[18] Additionally, GLP-1 analogues may improve endometrial receptivity in women with insulin resistance and PCOS by reducing inflammation and oxidative stress.[10] Further studies are needed to better understand the potential role of GLP-1 analogues in endometrial receptivity and to determine their therapeutic potential in enhancing implantation success rates during fertility treatment.

Ovarian function

GLP-1 analogues have been shown to exert various effects on ovarian function, which may contribute to their potential application in fertility treatment. GLP-1R activation has been reported to promote follicular development, enhance oocyte maturation, and improve oocyte quality, possibly through the upregulation of intrafollicular Insulin-like growth factor-1 (IGF-1) and Anti-Müllerian hormone (AMH). Moreover, GLP-1RAs have been demonstrated to improve insulin sensitivity and reduce hyperandrogenism in women with PCOS, thereby ameliorating ovulatory dysfunction and enhancing fertility outcomes.[9,10] More research is needed to fully elucidate the impact of GLP-1 analogues on ovarian function in various fertility disorders and to establish optimal treatment protocols.

AMH is a glycoprotein hormone secreted by the granulosa cells of preantral and small antral follicles in the ovary. AMH plays a vital role in ovarian folliculogenesis by regulating follicle recruitment, growth, and selection. It also serves as a valuable biomarker for assessing ovarian reserve and predicting ovarian response in ART.[19]

Polycystic ovarian syndrome

Insulin resistance and hyperinsulinemia are common features in conditions like PCOS, a prevalent endocrine disorder affecting reproductive-aged women. Hyperinsulinemia has been shown to stimulate the production of ovarian androgens and inhibit follicular development, leading to anovulation and infertility.[20]

GLP-1 plays a crucial role in regulating insulin secretion and glucose homeostasis. It has been demonstrated that GLP-1 agonists can improve insulin sensitivity and reduce hyperinsulinemia in patients with type 2 diabetes.[3,21] These beneficial effects of GLP-1 agonists on insulin sensitivity could also extend to women with PCOS, potentially restoring normal ovarian function.[9,22] Reported that treatment with exenatide, another GLP-1 analogue, improved menstrual cyclicity in overweight women with PCOS by reducing insulin resistance and hyperinsulinemia. Similarly, Jensterle et al.[10] found that low-dose liraglutide combined with metformin was more effective in restoring menstrual cyclicity in obese women with PCOS than high-dose liraglutide alone. These studies suggest that GLP-1 analogues, by ameliorating insulin resistance, may improve ovarian function and fertility outcomes in women with PCOS.

Male reproduction

In male reproduction, the presence of GLP-1R in testicular tissue suggests a potential role for GLP-1 analogues in spermatogenesis and steroidogenesis. Although limited, studies have shown that GLP-1RAs can improve sperm parameters and testosterone production in animal models, highlighting the potential for GLP-1 analogues in male fertility treatment.[23]

Safety of GLP-1 analogues in fertility treatment

As the therapeutic potential of GLP-1 analogues in fertility treatment gains attention, it is crucial to evaluate their safety profile to ensure that potential benefits are not accompanied by adverse effects. GLP-1 analogues, such as liraglutide and exenatide have been widely used in the management of type 2 diabetes and obesity with a well-established safety profile in these populations.[24] However, their safety in the context of fertility treatment requires further exploration.

Most studies on GLP-1 analogues in fertility treatment, particularly in women with PCOS, have focused on short-term treatment and demonstrated relatively mild and transient side effects, such as gastrointestinal symptoms, including nausea, vomiting, and diarrhoea.[9,10] These side effects are generally well-tolerated and tend to subside over time as the body adapts to the medication.

Although the available data on GLP-1 analogues in fertility treatment show promising results, there is limited information on their long-term safety, particularly concerning pregnancy outcomes and potential effects on the developing foetus.

Conclusion

In summary, GLP-1 analogues have shown potential as novel fertility treatments due to their effects on weight loss, endometrial receptivity and ovarian function.

Although sufficient data already support the use of GLP-1 analogues as a pre-treatment for obese or PCOS women undergoing ART to enhance pregnancy rate, additional studies are still needed. These studies should focus on evaluating the long-term effects of GLP-1 analogues on pregnancy outcomes and foetal development. Although current research shows reassurance regarding the potential impact on offspring, a deeper understanding of the safety and efficacy in this specific context is fundamental. It is important to remark

that GLP-1 analogues have a well-established safety profile in the management of type 2 diabetes and obesity but their potential effects on pregnancy require further investigation. Future studies should aim to address the challenges in the application of GLP-1 analogues in fertility treatment, such as dose optimization, molecular mechanism elucidation, combination therapies, personalized medicine and long-term safety and efficacy. By addressing these areas, the therapeutic potential of GLP-1 analogues in fertility treatment could be fully unlocked opening new avenues for couples affected by infertility.

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Conflicts of interest

The authors declare to have no conflict of interest.

References

1. Zegers–Hochschild F, Adamson GD, de Mouzon J, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology. *Fertil Steril*. 2009;92(5):1520–1524.
2. Boivin J, Bunting L, Collins JA, et al. International estimates of infertility prevalence and treatment–seeking: potential need and demand for infertility medical care. *Hum Reprod*. 2007;22(6):1506–1512.
3. Drucker DJ. Mechanisms of action and therapeutic application of glucagon–like peptide–1. *Cell Metab*. 2018;27(4):740–756.
4. Nauck MA, Vardarli I, Deacon CF, et al. Secretion of glucagon–like peptide–1 (GLP–1) in type 2 diabetes: what is up, what is down? *Diabetologia*. 2011;54(1):10–18.
5. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once–weekly semaglutide versus once–daily insulin glargine as add–on to metformin (with or without sulfonylureas) in insulin–naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open–label, parallel–group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5(5):355–366.
6. Izzi–Engbeaya C, Dhillo WS. Gut hormones and reproduction. *Ann Endocrinol (Paris)*. 2022;83(4):254–257.
7. Khan D, Ojo OO, Woodward OR, et al. Evidence for involvement of GIP and GLP–1 receptors and the gut–gonadal axis in regulating female reproductive function in mice. *Biomolecules*. 2022;12(12):1736.
8. Caltabiano R, Condorelli D, Panza S, et al. Glucagon–like peptide–1 receptor is expressed in human and rodent testis. *Andrology*. 2020;8(6):1935–1945.
9. Elkind–Hirsch K, Marrioneaux O, Bhushan M, et al. Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2008;93(7):2670–2678.
10. Jensterle M, Kocjan T, Kravos NA, et al. Short–term intervention with liraglutide improved eating behavior in obese women with polycystic ovary syndrome. *Endocr Res*. 2015;40(3):133–138.
11. Beak SA, Heath MM, Small CJ, et al. Glucagon–like peptide–1 stimulates luteinizing hormone–releasing hormone secretion in a rodent hypothalamic neuronal cell line. *J Clin Invest*. 1998;101(6):1334–1341.
12. Sun Z, Li p, Wang X, et al. GLP–1/GLP–1R signaling regulates ovarian PCOS–associated granulosa cells proliferation and antiapoptosis by modification of forkhead box protein O1 phosphorylation sites. *Int J Endocrinol*. 2020;2020:1484321.
13. Sermondade N, Faure C, Fezeu L, et al. BMI in relation to sperm count: an updated systematic review and collaborative meta–analysis. *Hum Reprod Update*. 2013;19(3):221–231.
14. Catalano PM, Shankar K. Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child. *BMJ*. 2017;356:j1.
15. Pi–Sunyer X, Astrup A, Fujioka K, et al. A Randomized, controlled trial of 3.0 mg of Liraglutide in weight management. *N Engl J Med*. 2015;373(1):11–22.
16. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non–alcoholic steatohepatitis (LEAN): a multicentre, double–blind, randomised, placebo–controlled phase 2 study. *Lancet*. 2016;387(10019):679–690.
17. Salamun V, Jensterle M, Janez A, et al. Liraglutide increases IVF pregnancy rates in obese PCOS women with poor response to first–line reproductive treatments: a pilot randomized study. *Eur J Endocrinol*. 2018;179(1):1–11.
18. Jensterle M, Janez A, Fliers E, et al. The role of glucagon–like peptide–1 in reproduction: from physiology to therapeutic perspective. *Hum Reprod Update*. 2019;25(4):504–517.
19. Iwase A, Nakamura T, Osuka S, et al. Anti–Müllerian hormone as a marker of ovarian reserve: What have we learned, and what should we know? *Reprod Med Biol*. 2016;15(3):127–136.
20. Diamanti–Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocr Rev*. 2012;33(6):981–1030.
21. Cena H, Chiovato L, Nappi RE. Obesity, polycystic ovary syndrome, and infertility: a new avenue for GLP–1 receptor agonists. *J Clin Endocrinol Metab*. 2020;105(8):e2695–709.
22. Papaetis GS, Kyriacou A. GLP–1 receptor agonists, polycystic ovary syndrome and reproductive dysfunction: Current research and future horizons. *Adv Clin Exp Med*. 2022;31(11):1265–1274.
23. Cannarella R, Calogero AE, Condorelli RA, et al. Is there a role for glucagon–like peptide–1 receptor agonists in the treatment of male infertility? *Andrology*. 2021;9(5):1499–1503.
24. Trujillo JM, Nuffer W, Ellis SL. GLP–1 receptor agonists: a review of head–to–head clinical studies. *Ther Adv Endocrinol Metab*. 2015;6(1):19–28.

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