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STATE-OF-THE-ART REVIEW

The hidden impact of GLP-1 receptor agonists on endometrial receptivity and implantation

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Abstract

Increasing infertility rates represent a growing medical challenge in modern societies resulting from a complex interplay of sociocultural trends, lifestyle factors, exposure to environmental toxins, and underlying health problems. Women's fertility is particularly vulnerable to these shifts. The obesogenic lifestyle not only accelerates weight gain, but also disrupts ovulation driving the rise in infertility. Among several medications used for treating obesity and type 2 diabetes, glucagon-like peptide-1 receptor agonists (GLP-1RAs) show promising improvement in female fertility most likely by stimulating ovulation. However, the effects of GLP-1RAs on the endometrium remain unclear. Further studies are needed to investigate the impact of GLP-1RAs on endometrial receptivity and embryo implantation and early development. The aim of this study is to address the knowledge gap regarding the effects of GLP-1RAs on human reproduction, with special focus on the endometrium. Understanding these mechanisms may help to develop new strategies for improving fertility treatment, reduce implantation failure and address potential safety concerns regarding teratogenicity

Abbreviations: ART, assisted reproduction technologies; EEOs, endometrial epithelial organoids; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; IVF, in vitro fertilization; LH, luteinizing hormone; PCOS, polycystic ovary syndrome.

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and adverse developmental outcomes for children born to women conceiving during or soon after GLP-1RA treatment.

KEYWORDS
endocrinology, glucagon-like peptide-1 receptor agonists, infertility, obesity, polycystic ovary syndrome

1 | INTRODUCTION

Obesity is a major public health problem worldwide, affecting more than 2 billion adults. It is not only a significant risk factor for many common diseases, but also leads to a direct or indirect increase in healthcare spending.[1] Although the natural conception and birth of a baby are often taken for granted, today, one in six couples faces infertility, while up to 15% of pregnancies end in miscarriage during the first trimester.[2] In this context, obesity, with its extensive systemic effects, is identified as a major fertility disruptor either alone or in combination with polycystic ovary syndrome (PCOS).[3] Obesity reduces fertility, resulting in a threefold increase in the risk of infertility and up to 40% increased risk of miscarriage.[4] Also, obesity is a main disruptor in assisted reproduction technologies (ART), negatively impacting the clinical pregnancy rate and increasing the risk of pregnancy loss, with a 20% reduction in live birth rates.[5] During ART, obese patients need prolonged ovarian stimulation with an increased gonadotropin dose, particularly those patients with PCOS, which can result in a low number of mature follicles and oocytes retrieved,[6] leading to an increased cycle cancellation rate.[4] Since age is a risk factor for obesity, it further exacerbates the impaired reproductive functions in infertile women undergoing in vitro fertilization (IVF), who are frequently of advanced age.[7] Despite the well-characterized adverse impact of obesity on female reproductive success, either without or with the accompanying infertility-associated disease like PCOS, the underlying mechanisms covering the entire spectrum of reproductive functions, from oocyte maturation to embryo implantation, have yet to be elucidated.

Glucagon-like peptide-1 receptor agonist (GLP-1RA), a medication used to treat type 2 diabetes, obesity, and PCOS, shows promise in improving female fertility. Traditionally, weight loss has been thought to improve hormonal balance and restore ovulation. Recent literature highlights the effects of GLP-1RA on the hypothalamus-pituitary-ovarian axis in alleviating female reproductive functions. However, there is a paucity of data and inconsistent findings have been reported related to the effect of GLP-1RA on endometrial function which is crucial for embryo implantation. In this review, we have consolidated the available knowledge from the published scientific literature on obesity and infertility from the perspective of endometrium and have proposed a future research agenda to elucidate the endometrial molecular mechanisms underlying the effects of glucagon-like peptide-1 (GLP-1) and its analogs used in clinical practice.

Key message

Glucagon-like peptide-1 receptor agonists hold promise for improving female fertility, especially in obese or PCOS patients. However, it is crucial to understand the limited evidence available, and their use should be approached with caution, considering potential side effects.

2 | MATERIAL AND METHODS

A comprehensive review of published literature until July 1, 2024, on the impact of GLP1-RA on the female reproductive systems, focusing primarily on the endometrium, was conducted. The literature search was performed in PubMed (MEDLINE) and Cochrane Library using keywords (GLP-1 receptor agonist, Glucagon-like peptide 1 agonist, Glucagon-like peptide, Glucagon-like peptide 1 receptor, infertility, obesity related infertility, polycystic ovary syndrome, ovulation, endometrial receptivity, female reproduction) and Boolean operators (Table S1). Additionally, in this review, we have proposed a research agenda that can be used to investigate the impact of GLP-1RAs on endometrial receptivity and embryo implantation. For this, we consolidated references using keywords transcriptome, spatial transcriptome, and endometrial organoids.

The exclusion criteria included conference abstracts, letters to the editor, study protocols, articles without full-text availability, and studies written in languages other than English. Two authors independently (A.S-.L. and A.P.) screened articles by evaluating titles and abstracts. Irrelevant articles were eliminated resolving discrepancies through discussion with another author (A.A.).

The search yielded 117 publications. After removing duplicates and irrelevant studies, a total of 59 articles including 8 animal studies, 2 randomized clinical trials, and 2 in vitro experimental studies were used for the current review.

3 | OBESITY, IN COMBINATION WITH PCOS, EXACERBATES FEMALE INFERTILITY

Obesity impacts menstrual cyclicity and female reproductive function by contributing to a complex metabolic disorder.[3] This is evidenced by the observation that up to 80% of women with PCOS

have obesity.[8] PCOS is a hormonal disorder with increased androgen production and dysregulated gonadotropin secretion, resulting in menstrual irregularities or anovulation, hirsutism, and infertility. An excess in androgen synthesis in PCOS is caused by the abnormal response to elevated luteinizing hormone to follicle-stimulating hormone (LH/FSH) ratio.[9] Metabolically, PCOS impairs insulin action and pancreatic beta-cell function, affecting insulin-mediated glucose disposal, thus causing insulin resistance, hyperinsulinemia, and increased blood glucose level. Obesity in PCOS women exacerbates these metabolic disturbances and aggravates its symptoms.[8] Hyperandrogenemia in PCOS also contributes to the deposition of visceral fat that further accentuates insulin resistance and obesity.[10]

In obese women, the accumulation of circulating free fatty acids causes imbalances in the levels of adipokines, such as elevated and decreased levels of leptin and adiponectin, respectively, which are essential for maintaining metabolic homeostasis, reproductive hormonal regulation, and inflammatory balance.[11] An elevated level of leptin causes the secretion of proinflammatory factors like TNF alpha and interleukin 6. The increase in these inflammatory markers, along with characteristics of oxidative stress, is commonly associated with low-grade systemic inflammation. This, together with other conditions such as hyperinsulinemia and hyperandrogenism, promotes ovarian dysfunction, menstrual irregularities, and other reproductive disorders.[12] Thus, adiposity influences the PCOS phenotype and disrupts the hormonal milieu, increasing the likelihood of menstrual cycle irregularities and anovulation.[13] As adiponectin is also responsible for glucose uptake, a decrease in its levels results in insulin resistance, increasing the risk of type 2 diabetes. Furthermore, as adiponectin receptors have been reported to be expressed not only in ovaries, contributing to polycystic ovarian morphology, but also in the endometrium[14]; reduced levels of adiponectin have been associated with decreased endometrial receptivity and implantation failure.[5]

Although ovulatory dysfunction is one of the major causes of infertility in PCOS, it has been shown that several disease-specific metabolic factors also have deleterious effects on the endometrium, resulting in lower implantation and pregnancy rates.[15] Hormonal imbalances in PCOS affect cyclic endometrial cellular proliferation and tissue differentiation, resulting in immune and inflammatory dysregulation, as well as altered angiogenesis, which are the major pathology pathways contributing to endometrial-factor infertility in PCOS. Moreover, obesity induces alterations in endometrial receptivity associated gene expression patterns, particularly noticeable when coupled with PCOS.[16–18] The deterioration of endometrial receptivity via abnormal endometrial stromal decidualization, linked to altered steroid hormone activity; metabolic features, such as insulin resistance and abnormal glucose and fatty acid metabolism; and tissue inflammation have been observed in transcriptome studies on obese PCOS women undergoing ART.[15] An in vitro decidualization model, in which the endometrial stromal cells were exposed to cAMP and progesterone for 4 to 14 days, has been successfully used to advance the understanding of endometrial factors associated with PCOS, particularly by identifying abnormalities in the decidualization process of endometrial stromal cells[19] and noting the decreased expression of stanniocalcin-1,[20] a marker of endometrial receptivity. In addition, obese PCOS women also showed impairment in endometrial GLUT4 expression—the insulin-regulated glucose transporter, affecting endometrial glucose metabolism[21] and likely contributing to infertility. Moreover, the co-occurrence of obesity and PCOS is not limited only to infertility, and its impact on the uterus may extend even beyond conception. PCOS and obesity have been associated with an increased risk of pregnancy complications such as pregnancy-induced hypertension, preeclampsia, and gestational diabetes mellitus, likely related to abnormal decidua function, and even elevated risk for endometrial hyperplasia and endometrial cancer.[22]

Combined oral contraceptive pills are the primary pharmacological treatment for menstrual cycle irregularities and hyperandrogenism. Additionally, metformin is recommended either as a standalone treatment or alongside other medications, primarily for managing metabolic features of PCOS.[23] Still, the use of pharmacological anti-obesity agents is considered experimental in women with PCOS when aimed at enhancing fertility,[24] thus opening new venues for clinical research on restoring fertility in obese PCOS patients.

4 | THE PHYSIOLOGICAL ROLE OF GLP-1 IN WEIGHT LOSS

GLP-1 is an incretin hormone secreted by the small intestine, alpha pancreatic cells, and brain.[25] The GLP-1 peptide is encoded by the proglucagon gene located on chromosome 2 in humans, consisting of 6 exons. GLP-1 exists in 3 active forms, GLP-1 (7–36 amino acids) amide, GLP-1 (7–37 amino acids), and GLP-1 (7–37 amino acids, with glycine extended), all products of the cleavage of the proglucagon molecule (Figure 1).[26] GLP-1 binds to and mediates the biological activation through the G protein–coupled receptor GLP-1R. Via the receptor, GLP-1 activates the cAMP signaling pathway, playing a crucial role in reducing appetite by enhancing satiety, leading to a decrease in food intake and long-term weight loss.[27] Primarily, GLP-1 (7–36) lowers blood glucose levels by promoting insulin secretion and decreasing glucagon release in a glucose-dependent manner by the mTOR-dependent HIF-1α activation pathway in pancreatic cells (Figure 1).[28] Beyond its primary role, GLP-1 has a regulatory and protective role in the "ileal brake mechanism" to optimize digestion and nutrient absorption.[29] GLP-1 also has anti-inflammatory effects, targeting GLP-1R expressed on distinct populations of circulating immune cells and reducing systemic inflammation by decreasing NF-κB signaling (Figure 1).[30] In obese patients, the secretion of GLP-1 from the gut is impaired, underscoring its role in the pathophysiology of obesity.[31] Genetic variants in the GLP-1R gene, such as rs2268641, rs6923761, and rs1042044, have been associated with various metabolic conditions, including obesity, type 2 diabetes, and gestational diabetes mellitus, owing to their negative impact on body mass, insulin secretion, and glucose metabolism.[32–34]

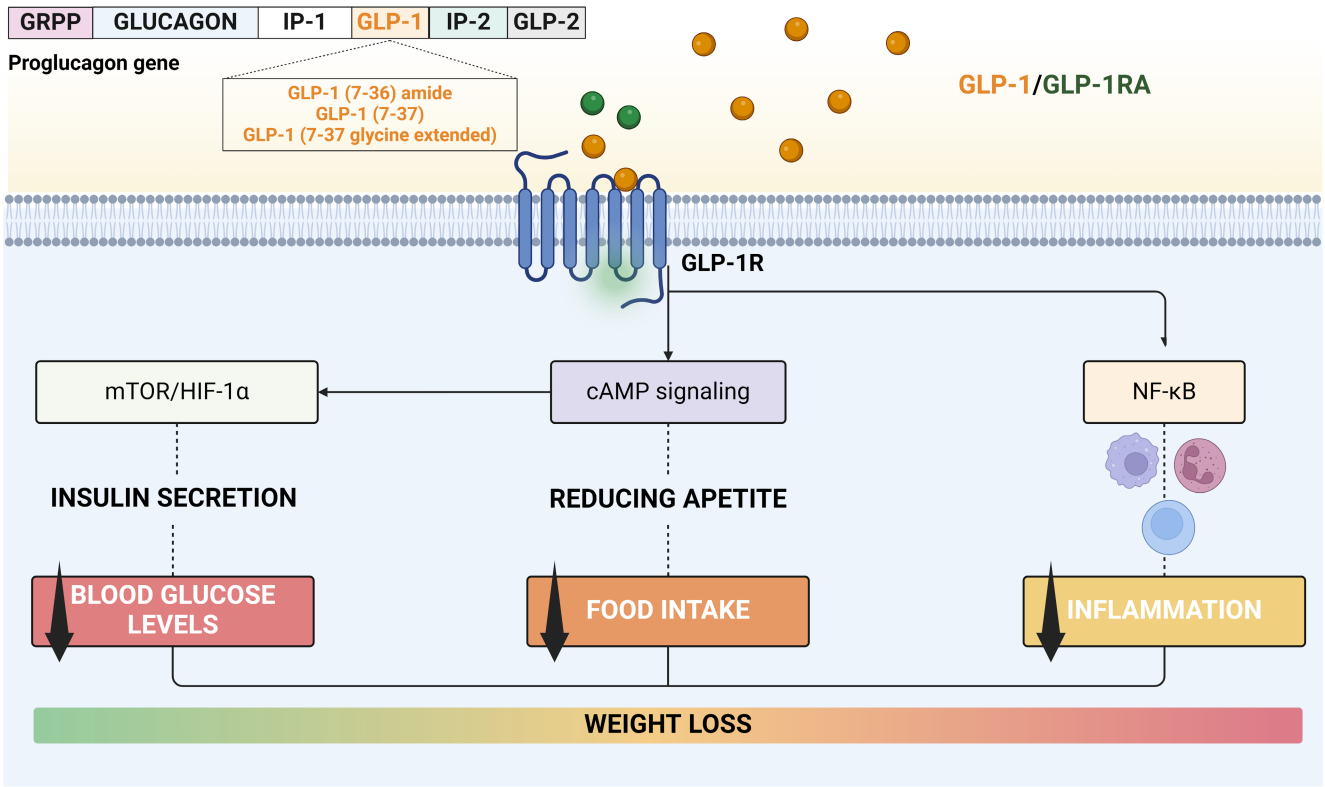

FIGURE 1 Glucagon-like peptide-1 (GLP-1) and its functional mechanisms associated with weight loss. The proglucagon gene consists of 6 exons, one on which is the encoding region of GLP-1. GLP-1 exists in 3 active forms, GLP-1 (7–36) amide, GLP-1 (7–37), and GLP-1 (7–37 glycine extended). The GLP-1 binds the G protein–coupled receptor GLP-1R and mainly promotes (i) low blood glucose levels by promoting insulin secretion by the mTOR-dependent HIF-1α activation pathway; (ii) decrease in food intake and long-term weight loss; and (iii) anti-inflammatory effects, targeting GLP-1R expressed on distinct populations of circulating immune cells and reducing systemic inflammation by decreasing NF-κB signaling. Finally, GLP-1/GLP-1R agonist (GLP-1RA) have an important role in weight loss. This figure was made using BioRender.

In vivo, the endogenous GLP-1 (7–36) amide remains active for a very short time of 1–2 mins as it is rapidly degraded to GLP-1 (9–36) amide by the dipeptidyl peptidase-4 enzyme.[35] To overcome this rapid degradation, GLP-1R agonists have been synthesized, generating supraphysiological levels of ligands that activate GLP-1R[36] and eventually enhancing the natural mechanism of GLP-1. Thus, the increasing evidence suggests that these agonists are effective tools in managing obesity and related metabolic disorders.

5 | GLP-1 MODULATION OF THE HYPOTHALAMIC-PITUITARY-OVARIAN AXIS ENHANCES FEMALE FERTILITY

As described above, obesity is associated with diabetes and insulin resistance, sharing a common link with metabolic disorders like PCOS. Thus, obesity can be considered a major disruptor of female fertility, resulting in poor reproductive outcomes. GLP-1R, the primary target of GLP-1, is detected in various tissues, including hypothalamus, pituitary, ovary, and endometrium.[37] Alongside obesity, GLP-1 and GLP-1R also directly affect on the hypothalamic-pituitary-gonadal axis, thus modulating female reproductive function.[38]

Animal model studies have revealed that the highest expression of GLP-1R occurs in the hypothalamus,[39] and high plasma levels of GLP-1 have been reported during the pro-estrous phase in rats.[39] GLP-1 is known to modulate the pulsatile release of gonadotropin-releasing hormone.[39,40] This was evidenced in female rats wherein acute central GLP-1 administration during the pro-estrous phase influenced the anterior pituitary to increase the synthesis of ovulation-promoting LH, leading to an increase in the number of mature follicles, and elevated implantation and live birth rate.[39] Furthermore, it also impacts ovarian functions. Female GLP-1R knockout mice exhibited a slightly delayed onset of puberty and a marginally decreased number of ovarian follicles without affecting estrogen and progesterone plasma levels and overall fertility.[41] Additionally, in the PCOS rat model, GLP-1RA exhibited improved morphological changes in the ovaries and biochemical markers of PCOS in terms of plasma free testosterone, LH, estradiol, and progesterone.[42,43] Also, GLP-1RA exenatide administration reduced stromal fibrosis and degeneration in ovaries with a reduction in inflammatory and oxidative stress markers, and an increase in serum anti-mullerian hormone level in diabetic rats.[39] Recently, in mice, the presence of *Bacteroides vulgatus* in the gut has been associated with the development of a PCOS-like

phenotype by reducing GLP-1 production and disrupting ovarian function. However, treatment with GLP-1R effectively restored the ovarian function.[44]

The impact of GLP-1 and its receptor on the hypothalamic-pituitary-ovarian axis in humans is less studied. Randomized controlled trials (reviewed in[38]) showed the positive impact of GLP-1RA in PCOS patients by decreasing androgen levels and increasing sex hormone-binding globulin levels. However, clinical studies have not been able to determine the exact mechanism by which GLP-1RA regulates hyperandrogenism. It also remains unclear whether GLP-1RA exerts its effects primarily by reducing obesity or whether it has a direct impact on ovaries.

6 | GLP-1 LEVELS ARE ASSOCIATED WITH FEMALE REPRODUCTIVE DISORDERS

In general, both fasting and postprandial GLP-1 levels are lower in people with obesity as compared with those in normal-weight individuals.[45] In women with PCOS, the GLP-1 level showed a significantly different time-dependent pattern in the oral glucose tolerance test, that is used to reveal the prediabetic condition. In the early phase of the test up to 1 hour, GLP-1 level was similar in PCOS and controls, whereas the incretin level was significantly lower in PCOS than in controls at 3 hours post-test, highlighting GLP-1 as an early marker of a prediabetic state in women with PCOS.[46] However, there was no significant difference in GLP-1 level between obese women with PCOS and obese women without PCOS.[10,46] Moreover, the expression of GLP-1 level was found to be significantly reduced in the peritoneal fluid of patients with endometriosis compared to controls. Decreased GLP-1 levels were also correlated with the reduced expression of pro-inflammatory CD86 macrophage marker in peritoneal fluid of endometriosis patients determined by flow cytometry, which plays a critical role in the elimination of endometrial cells after retrograde menstruation. Thus, the study concludes that the reduced GLP-1 levels can impact on the expression of pro-inflammatory markers of macrophages in the peritoneal fluid, which may contribute to the development of endometriosis.[47] A recent prospective cohort study also revealed that high levels of fasting GLP-1 were associated with a lower risk of developing obesity-related and hormone-sensitive cancers, including endometrial cancer.[48]

7 | GLP-1RA ALLEVIATES ENDOMETRIAL FUNCTION

While ovulatory dysfunction is a major cause of infertility in PCOS, several of its metabolic and biochemical features have deleterious effects on endometrium. Studies have reported a widespread expression of GLP-1R in human tissues, including normal endometrium.[37] In mice, mRNA and protein expression of GLP-1R were observed in uterine glands, luminal epithelium, and stromal cells. Furthermore, GLP-1R knockout mice exhibited a disrupted estrous cycle, reduced pregnancy outcome, and decreased litter size, indicating that GLP-1R plays a significant role in female reproductive function.[41]

In addition to the normal endometrium, GLP-1R expression is associated with endometrial cancer, a common gynecologic malignancy strongly correlated with obesity, with over half of endometrial cancer cases attributed to obesity.[37] GLP-1R mRNA and protein expression are reported to be significantly upregulated in cancer compared to normal tissue.[41,49] Patients with higher GLP-1R expression were associated with increased mRNA levels of estrogen and progesterone receptors and low histological grade of tumors.[50] Moreover, high GLP-1R expression was correlated with longer progression time and higher survival rate, suggesting a better prognosis. Furthermore, GLP-1 activity has also been shown to influence the process of autophagy—a cellular recycling process, in endometrium and endometrial cancer. The human Ishikawa endometrial cancer cell line exposed to GLP-1RA liraglutide revealed a significant induction of autophagy and a dose-dependent inhibition of cell growth.[37] This suggests that targeting autophagy in endometrial cancer cells with liraglutide could represent a novel and promising approach for oncology.

Moreover, a study using in vivo models demonstrated that GLP-1RA exenatide reduces histological degeneration and fibrosis of endometrium in diabetic rats, primarily through anti-inflammatory effects and by counteracting oxidative stress.[51] These results suggest that GLP-1 and GLP-1RA may exert anti-inflammatory and anti-fibrotic properties in the endometrium affected by obesity, diabetes, and PCOS. Given the potential for reduced fibrosis and inflammation to enhance endometrial receptivity, the effects of GLP-1RA on endometrial tissue warrant further clinical studies among cohorts of obese and PCOS patients. As an example, the combination of GLP1-RA liraglutide with metformin in infertile obese PCOS patients increased the pregnancy rate after IVF treatment compared to metformin treatment alone although weight loss was similar in these groups,[52] supporting the hypothesis of endometrium as an effective target for GLP-1RA therapy.

In summary, while the expression of GLP-1R has been explored in human endometrial cancer and various animal diabetes models, its expression pattern in the healthy human endometrium during the menstrual cycle remains unclear. Understanding this expression pattern could lay a solid foundation for deciphering the potential impact of GLP-1RA on endometrial physiology and shed light on how this information might enhance ART outcomes for individuals with obesity or PCOS.

8 | FOOD FOR THOUGHT—FUTURE PERSPECTIVES AND RESEARCH AGENDA

GLP-1RA therapy has shown potential in reversing female infertility. Previously, it was thought that weight loss could correct hormonal imbalances and consequently restore ovulation. However, the effects of GLP-1RA on endometrium, crucial for embryo implantation,

remain unclear. Future research is pivotal as it must address a significant knowledge gap regarding how GLP-1RA impacts the initial stages of human conception, including endometrial maturation and embryo implantation. Unraveling these molecular mechanisms and addressing potential safety concerns for GLP-1RA therapy are crucial for infertile women, whether they face unplanned pregnancies while using GLP-1RA or aim for conception after treatment.

It is important to highlight the growing interest in examining the effects of GLP-1RA treatment on obese populations of reproductive age, with or without PCOS. The endometrial molecular changes induced by weight loss are not fully elucidated and represent a substantial gap in our current knowledge. Consequently, there is a compelling need for research focused on this group of patients to elucidate how weight loss, facilitated by metabolic regulation via GLP-1RA, influences reproductive success. Novel research strategies must be implemented to explore in-depth the impact of GLP-1RA on endometrial receptivity and embryo implantation as outlined in Figure 2. To achieve these objectives, multiomic techniques, in vitro organoid models, and implantation assays could be utilized to bring enhanced insight and understanding (see Research Agenda Box).

RESEARCH AGENDA

- To explore the molecular effects of GLP-1RA on endometrial receptivity and embryo implantation.
- To elucidate the multiomic landscape of endometrial tissue under the GLP-1RA effect.
- To investigate the single-cell metabolic profiles of endometrium under the GLP-1RA effect.
- To exploit modern in vitro implantation models using embryo-like blastoids and endometrial models to improve understanding of GLP-1RA effects on implantation.

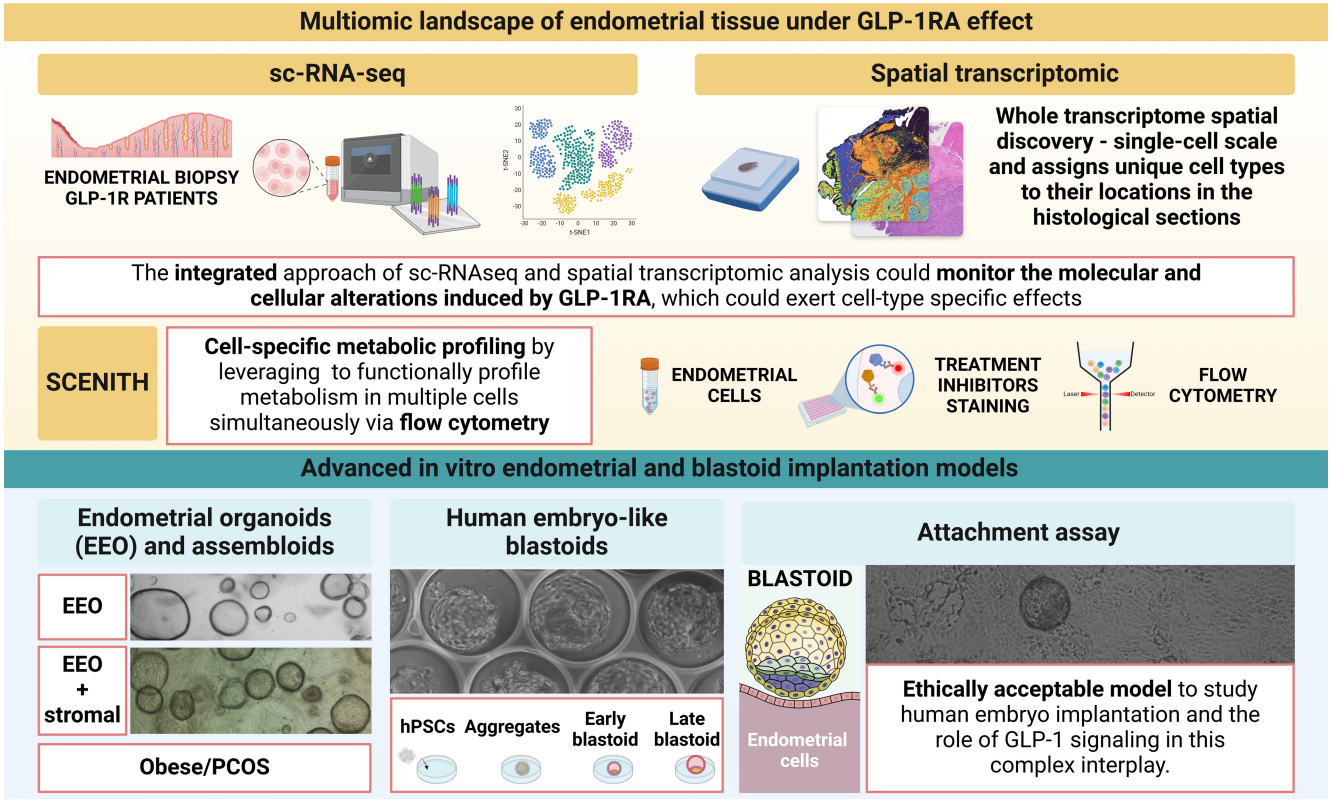

FIGURE 2 Approach to study the impact of glucagon-like peptide-1 receptor agonist (GLP-1RA) on endometrial receptivity and embryo implantation. The endometrial molecular changes induced by weight loss present a substantial gap in our current knowledge. Consequently, there is a compelling need for research focused on these groups of patients to elucidate how weight loss, facilitated by metabolic regulation via GLP-1RA, influences reproductive success. Novel strategies must be implemented to look deeper into the impact of GLP-1RA on endometrial receptivity and embryo implantation. To delineate the molecular changes occurring in endometrial tissue influenced by GLP-1RA single-cell RNA-seq (sc-RNA-seq), spatial transcriptomic and metabolic profiling of cells (using SCENITH protocol, single-cell energetic metabolism by profiling translation inhibition) will provide the capacity for molecular profiling at the single-cell resolution. Advanced in vitro models, such as endometrial epithelial organoids (EEOs), assembloids (EEOs incubated with stromal cells), and blastocyst-like structures derived from naïve human pluripotent stem cells (hPSCs), can attach to hormonally stimulated endometrial cells. This attachment replicates the initial stages of implantation and will enhance our understanding of the complex processes that lead to endometrial receptivity and mediate the molecular dialog between the embryo and the maternal endometrial cells during implantation. This figure was made using BioRender.

9 | MULTIOMIC LANDSCAPE OF ENDOMETRIAL TISSUE UNDER GLP-1RA EFFECT

In recent years, single-cell RNA sequencing and tissue spatial transcriptomic studies have transformed our ability to explore the intricate heterogeneity of RNA transcripts within individual cells of endometrial tissue.[53,54] Advanced analysis of endometrial tissue could elucidate the impact of GLP-1RA on the endometrial receptivity, essential for embryo implantation. In this new era fueled by advancements in whole transcriptome spatial discovery, it is possible to establish knowledge at the single-cell scale and assign unique cell types to their locations in the histological sections.[55,56]

Given that GLP-1RA drugs likely impact the metabolic homeostasis and energy equilibrium of the target tissue, conducting single-cell-type-specific metabolic profiling is instrumental to uncover the molecular mechanisms by which ligand binding to GLP-1R induces alterations in the target cells of endometrial tissue. Therefore, utilizing individual cell-specific metabolic profiling by leveraging the SCENITH protocol, a method designed to functionally profile metabolism in multiple cells simultaneously via flow cytometry,[57] would be beneficial for analyzing endometrial biopsies with and without GLP-1RA exposure, as well as for testing endometrial cells or organoids exposed to GLP-1RA in vitro. This approach could enhance our understanding of the metabolic shifts in endometrial tissue mediated by GLP-1RA, which would support the restoration of fertility.

10 | ADVANCED IN VITRO ENDOMETRIAL AND BLASTOID IMPLANTATION MODELS

Endometrial epithelial organoids (EEOs) are in vitro models that mimic the response of steroid hormones to endometrium and display self-organizing potential and genetic stability over extended periods of culture.[58] These organoids have been developed not only from healthy women but also from patients with conditions such as endometriosis and endometrial cancer, effectively recapitulating the disease phenotype.[59] We hypothesize that employing the EEOs derived from obese infertile women with and without PCOS would further advance our understanding of the endometrial factors that play a role in infertility within these patients' populations. The in vitro exposure of EEOs to GLP-1RA and further analysis of endometrial receptivity could help to delineate the specific role of GLP-1 in endometrial tissue function, particularly in the preparation and supporting of implantation. Additionally, upcoming experiments with endometrial assembloids, which combine primary endometrial epithelial cells with stromal cells,[60] could serve as an additional endometrial model for the role of GLP-1 in endometrial decidualization and receptivity. By exposing these models to GLP-1RA, we could understand whether the metabolic background of female infertility influences the characteristic response of the endometrial organoids in response to GLP-1RA.

Human implantation in vitro models also allow to unravel the molecular mechanisms of implantation and to investigate the impact of GLP-1RA treatment on this delicate process. A recent breakthrough in this field is the development of blastoids, blastocyst-like structures derived from naïve human pluripotent stem cells, which can attach to endometrial cells hormonally stimulated to replicate the first stages of implantation.[61,62] This ethically acceptable model provides a valuable tool to study human embryo implantation and the role of GLP-1 signaling in this complex interplay. The impact of GLP-1RA on endometrial receptivity by using the EEOs and assembloid models together with blastoid and attachment assay will uncover the mechanisms through which GLP-1RA therapy may affect human conception. Despite the great advantages of modern in vitro models, some limitations, such as the restricted cell types present in endometrial models, need to be addressed. Moreover, the question remains of how closely the blastoid model resembles the human in vivo preimplantation embryo.

11 | CONCLUSIONS

In this review, we delineate roles of GLP-1 in fertility and highlight knowledge gaps. Furthermore, we explore the potential for making use of recently developed technologies available to the reproductive research community. These advancements provide a unique opportunity to elucidate the molecular mechanisms underlying the effects of GLP-1 and its agonists on specific cell types within the endometrial tissue, helping to alleviate female infertility or enhance the success of assisted reproduction. This new knowledge could potentially impact a large population of female patients who are recommended GLP-1RA treatment due to obesity alone or a combination of obesity with PCOS and who struggle with infertility. As these infertility-related conditions are both characterized by metabolic and hormonal imbalances, suggesting more personalized GLP-1RA treatment schemes could potentially support their goal towards achieving a pregnancy. These personalized treatments have the potential not only to assist the patients to lose their weight but also to be integrated into ART protocols prior to commencing the IVF. This integration could aid in enhancing the success rates of IVF. However, it is crucial to understand the limited evidence available due to the relatively new treatments offered, and their use should be approached with caution, considering potential side effects. Furthermore, it is crucial to understand the molecular mechanisms of GLP-1RA effects on human conception to better address potential safety concerns associated with GLP-1RA therapy for women becoming pregnant during or soon after the therapy.

AUTHOR CONTRIBUTIONS

Alberto Sola-Leyva: Conceptualization, investigation, Writing—original draft, Writing—review & editing. Amruta Pathare: Conceptualization, investigation, Writing—original draft, Writing—review & editing. Apostol Apostolov: Conceptualization, Writing—review & editing.

Elina Aleksejeva: Writing—review & editing. Keiu Kask: Writing—review & editing. Triin Tammiste: Writing—review & editing. Susana Ruiz-Durán: Writing—review & editing. Sanjiv Risal: Writing—review & editing. Ganesh Acharya: Conceptualization Writing—review & editing. Andres Salumets: Conceptualization, Supervision, Resources, Writing—original draft, Writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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