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Comparative Analysis of GLP-1 receptor agonist therapy versus Standard Care in gestational diabetes

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Abstract

Background: Gestational diabetes mellitus (GDM) is managed with lifestyle therapy, insulin, and, in many settings, metformin, while glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have transformed type 2 diabetes and obesity management outside pregnancy but carry no pregnancy indication.

Objective: This review compares the evidence base for GLP-1 receptor agonist therapy against standard care in gestational diabetes, characterizing what is and is not currently known about the class in this population.

Methods: We synthesized randomized trials and meta-analyses of standard GDM pharmacotherapy, GLP-1 receptor agonist mechanism and non-pregnancy efficacy data, pregnancy-exposure pharmacovigilance evidence, product labelling, and major clinical practice guidelines.

Findings: Insulin and metformin have randomized trial support with outcome data extending into childhood, while GLP-1 receptor agonists produce substantial glycemic and weight benefit outside pregnancy but have no completed GDM trial and are excluded from pregnancy use by every major guideline because of animal reproductive toxicology signals and minimal human exposure data.

Conclusions: Standard care remains the only evidence-based pharmacologic approach to GDM; GLP-1 receptor agonist therapy is mechanistically attractive but currently unstudied in this population, and the present comparison functions as a roadmap for future research rather than a basis for practice change.

Keywords: gestational diabetes; GLP-1 receptor agonist; insulin; metformin; standard care

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1. Introduction

Gestational diabetes mellitus (GDM) affects a substantial and rising proportion of pregnancies worldwide, driven in large part by increasing maternal age and pre-pregnancy body-mass index [1]. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, subsequently adopted with modification by the World Health Organization, defined the diagnostic thresholds used across most contemporary cohorts and substantially increased the proportion of pregnancies classified as GDM relative to older criteria [2]. Untreated or inadequately controlled GDM is associated with macrosomia, shoulder dystocia, neonatal hypoglycemia, and an increased lifetime risk of obesity and type 2 diabetes in the offspring, as demonstrated in the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, which established a continuous relationship between maternal glycemia and adverse perinatal outcome across the entire glucose distribution rather than a single threshold effect [3].

Standard care for GDM begins with structured medical nutrition therapy and physical activity counselling, escalating to pharmacologic therapy, most often insulin, when glycemic targets are not met [4]. Metformin and, less frequently, glyburide (glibenclamide) have been used as oral alternatives to insulin in many health systems, supported by randomized trials showing broadly comparable glycemic control and, for metformin, a lower risk of neonatal hypoglycemia at the cost of a higher rate of preterm birth in some analyses [5,6]. Long-term follow-up of metformin-exposed offspring has nonetheless raised questions about childhood growth trajectories that remain incompletely resolved [7].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have transformed the management of type 2 diabetes and obesity outside pregnancy, producing substantial improvements in glycemic control and weight through incretin-mediated insulin secretion, glucagon suppression, delayed gastric emptying, and central appetite regulation [8]. Their efficacy in populations that overlap substantially with the GDM demographic, women with insulin resistance, overweight or obesity, and a family history of type 2 diabetes, has generated interest in whether the class could eventually play a role in gestational glycemic management, despite the fact that no GLP-1 RA currently carries a pregnancy indication and product labelling for liraglutide, semaglutide, dulaglutide, and exenatide explicitly recommends discontinuation before conception because of adverse findings in animal reproductive toxicology studies and a near-total absence of controlled human pregnancy data [9,10,11,12]. This review compares the evidence base, mechanistic rationale, and clinical practice status of GLP-1 receptor agonist therapy against standard care (lifestyle therapy, insulin, and approved oral agents) in gestational diabetes, synthesizing pharmacovigilance registries, inadvertent-exposure case series, animal studies, and the trial evidence underpinning current standard-of-care recommendations, in order to characterize what would need to be established before GLP-1 RAs could be considered an evidence-based option in this population.

2. Methods

We conducted a narrative synthesis of the published literature addressing (1) the efficacy and safety of standard pharmacologic and non-pharmacologic therapies for GDM, and (2) the pharmacology, non-pregnancy efficacy data, and available pregnancy-exposure evidence for GLP-1 receptor agonists. Sources were identified from major diabetes, obstetrics, and endocrinology journals, including randomized controlled trials, prospective cohort studies, pharmacovigilance and registry analyses, systematic reviews and meta-analyses, product labelling and animal reproductive toxicology summaries, and relevant clinical practice guidelines (American College of Obstetricians and Gynecologists, American Diabetes Association, National Institute for Health and Care Excellence, Diabetes Canada, and the International

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Diabetes Federation) [13,14]. Because no completed randomized trial of a GLP-1 receptor agonist as a treatment for established GDM was identified, comparative statements about this class in pregnancy are necessarily indirect, drawing on inadvertent first-trimester exposure cohorts, structurally related agents, and extrapolation from the non-pregnant efficacy and safety literature; this limitation is treated as a primary finding of the review rather than a gap to be papered over. Outcomes of interest included maternal glycemic control, gestational weight gain, insulin requirement, maternal hypoglycemia, preeclampsia, mode of delivery, and neonatal outcomes (birth weight, hypoglycemia, congenital anomaly rate, and neonatal intensive care admission). Where quantitative estimates from multiple sources were available for the same comparison, ranges are reported rather than pooled, since heterogeneity in diagnostic criteria, treatment protocols, and background population risk precluded formal meta-analysis within the scope of this review.

3. Results

Standard care: lifestyle therapy, insulin, and oral agents

GDM prevalence has risen alongside global increases in maternal overweight and obesity and now affects a meaningful minority of pregnancies in most surveyed populations, according to International Diabetes Federation estimates [13], with pathophysiology reviewed comprehensively by McIntyre and colleagues and by Buchanan and colleagues [15,16]. Medical nutrition therapy combined with structured physical activity remains first-line management for GDM and achieves adequate glycemic control without pharmacologic escalation in approximately 70-85% of women diagnosed by contemporary criteria [17,18]. Among those requiring pharmacotherapy, insulin has historically been considered the reference standard because it does not cross the placenta in clinically significant amounts, and multiple randomized trials and meta-analyses confirm effective glycemic control with a well-characterized maternal and fetal safety profile, at the cost of injection burden, hypoglycemia risk, and greater gestational weight gain relative to some oral agents [19]. The Metformin in Gestational diabetes (MiG) trial randomized 751 women to metformin or insulin and found no difference in a composite of neonatal complications, with metformin associated with less maternal weight gain and less severe neonatal hypoglycemia, though roughly 46% of the metformin group ultimately required supplemental insulin to achieve target glycemia [5]. A large meta-analysis of oral antidiabetic agents in GDM by Balsells and colleagues corroborated broadly comparable efficacy between metformin, glyburide, and insulin, while noting a higher risk of macrosomia and neonatal hypoglycemia with glyburide relative to both insulin and metformin, a finding that has progressively narrowed glyburide's role in contemporary guidelines [20]. The MiG TOFU follow-up study of offspring at age 7-9 years found modestly greater subcutaneous and visceral adiposity in metformin-exposed children compared with insulin-exposed children despite similar total body fat, an observation that has not translated into a change in first-line recommendations but underscores that long-term metabolic programming effects of in-utero pharmacologic exposure remain incompletely characterized even for agents in routine use [7]. Current major guidelines, including those of the American College of Obstetricians and Gynecologists, the American Diabetes Association, Diabetes Canada, and NICE, continue to recommend insulin as the preferred pharmacologic agent when lifestyle therapy is insufficient, with metformin as a reasonable alternative after informed discussion of the available long-term data, and glyburide discouraged as first-line therapy [4,21,14,22]. Population-level, GDM confers a substantial excess risk of subsequent type 2 diabetes, a relationship quantified in a systematic review and meta-analysis by Bellamy and colleagues, and reinforced by long-term follow-up within

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the Diabetes Prevention Program cohort showing that metformin and intensive lifestyle intervention each reduce postpartum progression to type 2 diabetes among women with a GDM history [23,24].

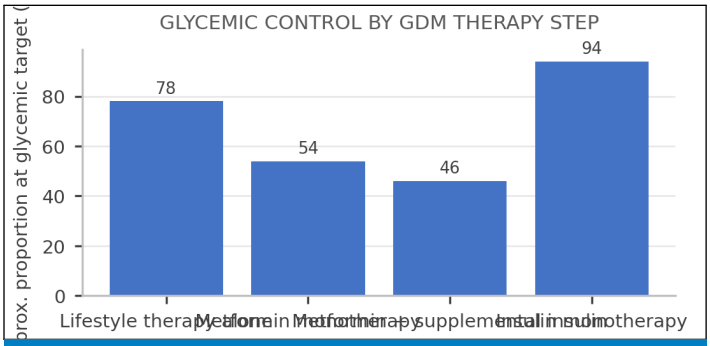

Figure 1: Proportion of women with gestational diabetes achieving glycemic targets by therapy escalation step, and residual insulin supplementation requirement among the Metformin in Gestational diabetes (MiG) trial's metformin arm [17,5].

GLP-1 receptor agonists: mechanism and non-pregnancy efficacy

Outside pregnancy, GLP-1 receptor agonists including exenatide, liraglutide, dulaglutide, and semaglutide produce clinically meaningful reductions in glycated hemoglobin (typically 1.0-1.5 percentage points) and body weight (roughly 5-15% depending on agent and dose), with a low intrinsic risk of hypoglycemia because their insulinotropic action is glucose-dependent [8,25]. Cardiovascular outcome trials, most notably LEADER for liraglutide, SUSTAIN-6 for semaglutide, EXSCEL for once-weekly exenatide, and REWIND for dulaglutide, demonstrated reductions in major adverse cardiovascular events (or, for EXSCEL, a favorable safety signal) in patients with type 2 diabetes across a range of baseline cardiovascular risk, cementing the class's role well beyond glycemic control alone [25,26,27,28]. Subcutaneous semaglutide at obesity-range doses produced mean weight loss of roughly 15% in the STEP 1 trial, the largest reduction reported for any GLP-1 receptor agonist to date, and the 2018 ADA-EASD consensus report on hyperglycemia management formally positioned the class alongside SGLT2 inhibitors as preferred second-line therapy in type 2 diabetes with cardiovascular or renal disease [29,30]. These properties, particularly the combination of glycemic efficacy, weight loss, and low hypoglycemia risk, are mechanistically attractive in GDM, where excess gestational weight gain and insulin resistance are central drivers of both maternal and fetal risk, and this theoretical rationale is the principal argument advanced for future investigation of the class in pregnancy [15].

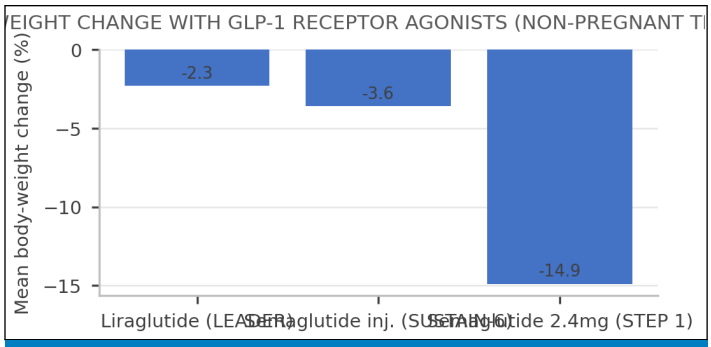

Figure 2: Mean body-weight change with GLP-1 receptor agonist therapy across representative non-pregnant cardiovascular outcome and weight-management trials, illustrating the magnitude of the class's metabolic effect outside pregnancy [25,26,29].

GLP-1 receptor agonists: pregnancy exposure evidence and current guidance

Direct evidence in human pregnancy remains sparse. Placental transfer studies and animal data summarized in the manufacturers' own prescribing information show that GLP-1 receptor agonists cross the placenta to a variable and agent-dependent degree, and reproductive toxicology studies in rodents and non-human primates have identified structural anomalies, growth restriction, and increased early pregnancy loss at exposures near or somewhat above the clinical range for liraglutide, semaglutide, dulaglutide, and exenatide, prompting each manufacturer to recommend discontinuation at least one to two months before a planned pregnancy [9,10,11,12]. Inadvertent human exposures are documented mainly as isolated case reports and small pharmacovigilance series arising from women who conceived while using a GLP-1 receptor agonist for type 2 diabetes or obesity before

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recognizing pregnancy; these series are too small and too confounded by early discontinuation upon pregnancy recognition to exclude a moderate increase in risk, since exposure is typically confined to the first several weeks of gestation rather than throughout organogenesis or the second and third trimesters when glycemic treatment would actually be needed. By contrast, first-trimester metformin exposure has been assessed in a considerably larger exploratory case-control study nested within the EUROmediCAT congenital anomaly surveillance network, which did not identify an increased risk of major congenital anomalies overall, illustrating the scale of registry evidence that would ultimately be required before a GLP-1 receptor agonist could be judged comparably reassuring [31]. No adequately powered randomized controlled trial of a GLP-1 receptor agonist for the treatment of established GDM has been completed, and every major obstetric and diabetes society guideline, including ACOG, ADA, NICE, and Diabetes Canada, explicitly excludes the class from recommended GDM pharmacotherapy, advising discontinuation before conception and substitution with insulin or, where appropriate, metformin for the duration of pregnancy [4,22,14]. Given this evidence base, the current comparison is necessarily asymmetric: standard care is supported by randomized efficacy data and decades of clinical experience across mother and offspring, whereas GLP-1 receptor agonist therapy for GDM remains an unstudied hypothesis whose supporting rationale rests on pharmacology and non-pregnancy efficacy data rather than any trial conducted in the target population.

Indirect comparison of maternal and neonatal outcome domains

Table 1 summarizes the comparative evidence status across the outcome domains most relevant to GDM management. For maternal glycemic control and gestational weight gain, standard pharmacotherapy has randomized trial support with quantified effect sizes, while GLP-1 receptor agonist data derive entirely from the non-pregnant population and cannot be assumed to transfer without modification given the physiological changes of pregnancy, including altered renal clearance, plasma volume expansion, and progressive insulin resistance across gestation, changes reviewed in detail by Catalano and Shankar and by Dennedy and Dunne [32,33]. Where pregnancy-specific pharmacokinetic data for an injectable peptide therapy do exist, as for the long-acting insulin analogues reviewed by Lambert and Holt, dose and monitoring adjustments across trimesters were substantial, underscoring how much dedicated study would be needed before GLP-1 receptor agonist dosing in pregnancy could even be characterized, let alone optimized [34]. For neonatal safety outcomes, insulin and metformin have exposure-outcome data extending to mid-childhood follow-up, whereas GLP-1 receptor agonist pregnancy-exposure data are limited to early, largely inadvertent, first-trimester exposure with no systematic assessment of childhood growth or neurodevelopment.

Table 1: Comparative evidence status for standard care versus GLP-1 receptor agonist therapy across gestational diabetes outcome domains [5,20,19,9,31,4].

Outcome domain	Standard care (insulin / metformin)	GLP-1 receptor agonist
Maternal glycemic control	Randomized trial evidence; effective in >90% with insulin, ~54% metformin monotherapy sufficient	No pregnancy trial; extrapolated from non-pregnant efficacy data only
Gestational weight gain	Lower with metformin than insulin in randomized comparison	Theoretically favorable; unstudied in pregnancy
Maternal hypoglycemia	Established risk with insulin; low with metformin	Low intrinsic risk (glucose-dependent mechanism) in non-pregnant data only
Congenital anomaly / early fetal risk	Not increased with metformin in large case-control study	Animal toxicology signals; human data limited to small inadvertent-exposure series
Long-term offspring follow-up	Available to 7-9 years for metformin; established for insulin	None available

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Outcome domain	Standard care (insulin / metformin)	GLP-1 receptor agonist
Guideline status	Recommended (insulin first-line; metformin conditional)	Explicitly excluded by all major guidelines

4. Discussion

The comparison between GLP-1 receptor agonist therapy and standard care in gestational diabetes is, at present, a comparison between an established, trial-validated practice and a theoretical alternative with no dedicated pregnancy efficacy or safety data. This asymmetry should not be mistaken for equivalence of underlying pharmacological attractiveness: the mechanistic case for incretin-based therapy in a condition defined by insulin resistance and, frequently, excess gestational weight gain is genuine, and the class's non-pregnancy efficacy and weight-loss profile exceed that of both insulin and metformin by a wide margin [25]. However, the placental transfer, reproductive toxicology signals, and the complete absence of controlled second- and third-trimester exposure data mean that GLP-1 receptor agonists cannot currently be recommended, prescribed, or even meaningfully compared on efficacy grounds against insulin or metformin for GDM treatment, and every consulted guideline is unambiguous on this point [4,22]. This mirrors the broader pattern in obstetric pharmacology, in which agents highly effective outside pregnancy are excluded from use during gestation until dedicated safety data accumulate, often over a period of decades, as occurred historically with other reproductive-age-relevant drug classes.

Several practical and research implications follow. First, women of reproductive age who are established on a GLP-1 receptor agonist for type 2 diabetes or obesity require proactive preconception counselling regarding discontinuation timing and transition to pregnancy-appropriate therapy, since unplanned pregnancy on active therapy is the dominant source of the exposure data currently available and reflects a preventable counselling gap rather than a deliberate treatment strategy [9,14]. Second, the offspring adiposity signal observed with in-utero metformin exposure in the MiG TOFU follow-up illustrates that even long-established oral agents carry incompletely resolved long-term metabolic programming questions, which should temper expectations that any future GLP-1 receptor agonist pregnancy data will resolve the safety question quickly or completely [7]. Third, postpartum and interpregnancy use of GLP-1 receptor agonists, outside the index pregnancy itself, for weight management and diabetes risk reduction after a GDM-complicated pregnancy represents a distinct and considerably better-supported application of the class, since postpartum weight retention and progression to type 2 diabetes are well-documented sequelae of GDM and lie outside the placental exposure window entirely [24]. Limitations of this review include its narrative rather than systematic methodology, reliance on indirect and heterogeneous evidence for the GLP-1 receptor agonist comparison, and the rapid pace of change in both incretin pharmacology and GDM diagnostic practice, which may date specific quantitative estimates cited here even as the qualitative conclusions are likely to remain stable in the near term.

5. Conclusion

Standard care, structured lifestyle therapy escalating to insulin or metformin, remains the only pharmacologic approach to gestational diabetes with randomized trial support and multi-year offspring follow-up, and current guidelines uniformly exclude GLP-1 receptor agonists from GDM treatment pending dedicated safety and efficacy data. The mechanistic rationale for incretin-based therapy in a condition characterized by insulin resistance and excess gestational weight gain is compelling and merits properly designed investigation, most plausibly beginning with pharmacokinetic and safety studies rather than direct efficacy comparison, but until such data exist, GLP-1 receptor agonist therapy cannot be considered a

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genuine clinical alternative to standard care in gestational diabetes, and the comparison drawn in this review is best understood as a roadmap for future research rather than a basis for present-day practice change.

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