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# Preconception use of GLP-1 and GLP-1/GIP receptor agonists for obesity treatment

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Obesity is rising among women of reproductive age and significantly contributes to subfertility. If conception occurs, maternal obesity is associated with increased risks for both maternal and neonatal complications, with potential long-term effects on the offspring's health. Current clinical guidelines emphasize the importance of preconception weight optimization in women with obesity to reduce maternal and fetal risks. Amid the rising use of incretin-based anti-obesity medications, particularly among young women, their potential role in preconception care is receiving growing clinical and research interest. With unplanned pregnancies remaining common, incidental exposure during early pregnancy is becoming more likely. In parallel, there is increasing interest in the potential of these agents to support preconception weight loss and enhance fertility outcomes in women with obesity. This narrative review examines the current human evidence on GLP-1 and dual GLP-1/GIP receptor agonists approved for obesity treatment, focusing on their potential role in preconception care and addressing key safety considerations and challenges related to their use during the preconception period, as well as inadvertent exposure in early pregnancy.

## Introduction

Obesity affects over 40 % of females of reproductive age, and this figure is projected to rise in parallel with the global trends in obesity prevalence [1]. According to the data from the National Health and Nutrition Examination Survey (2021–2023), the prevalence of severe (class III) obesity in adults is significantly higher in women (21.1 %) than in men (6.7 %) [2]. This high and rising burden of obesity among reproductive-aged women has far-reaching implications for fertility and for maternal, perinatal and long-term offspring health outcomes.

It is estimated that obesity increases the risk of infertility by 78 %, while being overweight increases it by 27 % [3]. Even in women with regular ovulatory cycles, the probability of spontaneous conception decreases by 4 % for every 1 $kg/m^2$ increase in body mass index (BMI) [4]. Obesity increases the risk of early pregnancy loss and stillbirth and it is strongly linked to gestational complications such as pre-eclampsia, gestational hypertension, gestational diabetes mellitus (GDM) and caesarean delivery [5–8]. Postpartum complications are also more frequent in women with obesity, including venous thromboembolism, wound infections,

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postpartum depression and inability to initiate and sustain breastfeeding [9–11]. Additionally, excessive gestational weight gain (GWG) is common, affecting approximately 50 % of women, and further elevates the risk of postpartum weight retention and future obesity [12,13]. In the long-term, intrauterine exposure to maternal obesity is associated with a threefold increase in the child's risk of developing obesity and an increase in risk for insulin resistance, steatotic liver disease and other metabolic complications [12,14–17]. These trends underscore the pressing need to address obesity in women of reproductive age – not only to improve fertility and pregnancy outcomes, but also to reduce intergenerational transmission of metabolic disease.

Current clinical guidelines consistently emphasize the importance of achieving weight optimization before conception in women with obesity [18–22], as interventions initiated only during pregnancy have not demonstrated significant improvement in perinatal outcomes [23,24]. Most international clinical societies recommend early obesity screening, preconception counselling, and weight loss through lifestyle interventions, with proposed targets of 5–10 % weight loss over six months or achieving a BMI close to normal before conception [18,20–22,25]. Excess GWG should be avoided and in obesity, GWG should be limited to 5–9 kg [18,20–22]. Postpartum weight loss is encouraged, ideally returning to pre-pregnancy BMI within the first year after delivery [20]. Recognizing that lifestyle changes often result in limited sustained weight loss and that surgical obesity treatment delays pregnancy for at least 12–24 months [19,21,25], growing interest is emerging in the potential role of pharmacological agents to support preconception weight management.

Incretin-based anti-obesity medications (AOMs) successfully achieve greater weight loss targets, closing the gap between lifestyle interventions and metabolic surgery [26,27]. Currently, three incretin-based AOMs are approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for chronic obesity treatment: liraglutide, semaglutide and tirzepatide. Several international guidelines, including those from the Endocrine Society, the Canadian Adult Obesity Clinical Practice Guidelines and the European Association for the Study of Obesity recommend the initiation of pharmacotherapy alongside lifestyle interventions in adults with obesity (BMI $\geq$ 30 kg/m$^2$) or overweight (BMI $\geq$ 27 kg/m$^2$) in the presence of obesity-related comorbidities [28–31], although not all national guidelines adopt this threshold. Liraglutide was the first GLP-1 receptor agonist (GLP-1RA) approved by the FDA and EMA for chronic obesity treatment at a dose of 3 mg daily, showing an average weight loss of 8 % in individuals with obesity and 6 % in individuals with obesity and type 2 diabetes (T2D) [32–34]. Semaglutide at a dose of 2.4 mg is the first weekly long-acting GLP-1 RA approved by the FDA and EMA for chronic treatment of obesity, showing an average weight loss of 14.9 % in individuals with obesity and 9.6 % in individuals with obesity and T2D [26,35–37]. Tirzepatide is the first dual GLP-1/GIP RA approved by the FDA and EMA for chronic treatment of obesity [38,39], showing an average of 16 %– 22.5 % weight loss in individuals with obesity and 13.4 %–15.7 % in individuals with obesity and T2D [40,41].

Data from the IQVIA Longitudinal Prescription Database reporting prescriptions from 93.6 % of United States retail pharmacies showed that GLP-1RA dispensing increased dramatically between 2020 and 2023 [42]. The highest increase was seen in young adult females aged 18–25 (659.4 %), with sharp increases seen in the prescriptions of tirzepatide and injectable semaglutide [42]. With approximately 50 % of pregnancies being unplanned, the incidence of preconception use and incidental exposure to these medications during pregnancy is likely to increase [43]. In parallel, a second emerging issue is gaining attention: the intentional use of AOMs during the preconception period as a therapeutic strategy to improve fertility outcomes in women with obesity. These dual trends raise important questions about how to safely and effectively incorporate pharmacotherapy into reproductive care for this growing population.

This review aims to comprehensively evaluate the available human evidence on using GLP-1 and dual GLP-1/GIP RAs approved for obesity treatment in the preconception period. The review focuses on their potential role in preconception weight optimization and fertility improvement, while also addressing safety considerations and challenges related to inadvertent exposure during the preconception phase and early pregnancy.

A literature search was conducted using PubMed database to identify relevant studies investigating the preconception or pregnancy-related use of GLP-1 or dual GLP-1/GIP receptor agonists. The search strategy combined drug-specific terms, including liraglutide, semaglutide, tirzepatide, GLP-1 receptor agonist, dual GLP-1/GIP receptor agonist in combination with reproductive and pregnancy-related keywords, including reproductive, fertility, IVF, PCOS, pregnancy, first trimester, early pregnancy, gestation, pregnancy outcome, gestational weight gain, gestational diabetes, preeclampsia, gestational hypertension, pregnancy complication, miscarriage, spontaneous abortion, stillbirth, congenital abnormality, malformation. Filters were applied to restrict results to humans, the English language, abstracts available, and publication dates from January 2015 to June 2025. The initial search yielded 248 records. After screening, 11 studies were included in the review. In addition, six further studies were identified by an extensive manual search of reference lists. In total, 17 original studies were included: six randomized controlled or mechanistic clinical studies in women with PCOS, six observational or registry-based studies of pregnancy exposure, four case reports and one conference abstract.

## Therapeutic implications of GLP-1 and dual GLP-1/GIP receptor agonist treatment on fertility and maternal health

Current human data on GLP-1 or GLP-1/GIP RAs' effects on fertility and maternal health remain limited and are primarily derived from small-scale or population-specific studies. The impact of GLP-1RA on reproductive health and fertility has been mainly studied in patients with PCOS, with liraglutide being the most used agent.

In a multi-level mechanistic study, Zhao et al. investigated the impact of liraglutide treatment on ovarian inflammation and follicular development in patients with PCOS. Liraglutide significantly decreased ovarian inflammation and improved ovarian microenvironment, leading to improved follicle development [44]. Other mechanistic studies in patients with PCOS and obesity also showed that liraglutide can modulate LEP promoter methylation in granulosa cells, linking liraglutide to epigenetic modulation of leptin in ovarian tissue alongside improvements in natural pregnancy rate [45,46].

A randomized, placebo-controlled trial by Nylander et al. investigated the effect of liraglutide 1.8 mg over 26 weeks on ovarian dysfunction in patients with PCOS and overweight or obesity. Patients treated with liraglutide showed significant weight loss, improved bleeding regularity, increased sex-hormone binding globulin (SHBG), decreased free testosterone and a trend towards lower ovarian and stromal volume [47].

Another randomized, placebo-controlled trial by Elkind-Hirsch et al. evaluated the efficacy of liraglutide 3.0 mg daily on body weight, body composition, metabolic and hormonal parameters in women with PCOS and obesity. Besides significant weight loss and improved insulin sensitivity, liraglutide decreased the free androgen index and improved menstrual regularity. Additionally, during the trial, two participants treated with liraglutide achieved pregnancy and delivered healthy full-term infants [48].

In a prospective randomized open-label study, Salamun et al. reported on the use of liraglutide in the preconception period and its impact on in-vitro fertilization (IVF) treatment success in patients with PCOS, obesity and infertility [49]. In this study, 28 patients were randomized into two groups: one assigned to 1000 mg metformin twice daily (MET group) and the other to 1000 mg metformin twice daily in combination with 1.2 mg liraglutide (COBMI group). Treatment lasted 12 weeks, followed by a 4-week washout period before starting the controlled ovarian stimulation protocol for IVF. Although the group reported no significant difference in weight loss, the pregnancy rate per embryo transfer was significantly higher in the COMBI group (85.7 %) compared to the MET (28.6 %). Overall pregnancy rate over 12 months was also higher (69.2 %) in the COMBI group, compared to 35.7 % in the MET group. Liraglutide treatment combined with metformin significantly reduced HOMA-IR and decreased most androgens, and increased SHBG in both groups. Lastly, no difference between the groups was seen regarding the dose of stimulation, retrieved oocyte number, mature, fertilized and degenerated oocytes and number of day-5 blastocysts. This study provided preliminary evidence on the positive impact of GLP-1 agonism on reproduction outcomes despite comparable weight loss in patients with PCOS and obesity, encouraging further research [49].

A recent observational retrospective study by Imbroane et al. examined the association between preconception GLP-1RA use, defined as GLP-1RA prescription within two years of pregnancy, and adverse obstetric outcomes, such as hypertensive disorders in pregnancy, gestational diabetes, preterm delivery and caesarean delivery [50]. The study included 4267 GLP-1RA-exposed pregnancies and 4267 matched GLP-1RA-unexposed pregnancies (control group). Compared to the control group, the GLP-1RA-exposed group had higher proportions of documented baseline comorbidities, such as overweight/obesity (76.8 % versus 10.7 %), T2D (32.5 % versus 3.7 %), primary hypertension (32.5 % vs 3.7 %), history of gestational diabetes (25.3 % vs 10 %) and history of pre-eclampsia (18.2 % versus 8.5 %). Interestingly, despite this higher proportion of documented basline comorbidities, the GLP-1RA-exposed cohort had lower risk for the development of GDM (OR 0.81; 95 % CI 0.72–0.91), hypertensive disorders in pregnancy (OR 0.84; 95 % CI 0.76–0.94), preterm delivery (OR 0.68; 95 % CI 0.54–0.85) and caesarean delivery (OR 0.89; 95 % CI 0.87–0.97), implying a possible beneficial effect of GLP-1RA treatment on maternal and neonatal outcomes [50].

## Challenges in preconception use of GLP-1 or dual GLP-1/GIP receptor agonists

Substantial gaps have been identified in understanding the safety and teratogenic potential of GLP-1 receptor agonists, underscoring the need for improved documentation of pregnancy and neonatal outcomes in pharmacovigilance databases to support evidence-based clinical decision making [51].

### *Teratogenicity signals in preclinical animal models*

In animal reproductive toxicity studies, both GLP-1 and dual GLP-1/GIP RAs have been associated with adverse pregnancy outcomes in clinically relevant exposures.

Animal studies using liraglutide in rats showed delayed sexual maturation at clinically relevant doses with no impact upon fertility and reproductive capacity [34]. At the same time, exposure during pregnancy led to vascular, renal, skeletal and oropharyngeal malformations in rats, reduced fetal weight and increased incidence of major bone and visceral malformations in rabbits [34,52,53].

Semaglutide administration in pregnant rats resulted in growth restriction and skeletal and visceral malformations in the offspring, decreased GWG and food intake. In cynomolgus monkeys, exposure to semaglutide at doses exceeding the maximum recommended human dose (MRHD) led to early pregnancy losses, congenital malformations and slightly smaller offspring [36].

Tirzepatide administration during organogenesis at 0.5-fold the MRHD increased the incidence of external, visceral and skeletal malformations in rats, accompanied by a reduction in fetal weight, maternal body weight and food intake [38]. In rabbits, even doses as low as 0.01-fold the MRHD caused gastrointestinal side effects that resulted in maternal mortality or miscarriage in a few animals. At the highest tested dose (0.2-fold the MRHD), tirzepatide reduced fetal weight, again associated with decreased maternal weight and food intake [38].

Overall, these preclinical studies demonstrated fetal toxicity while using both GLP-1 and dual GLP-1/GIP RAs in animals, typically associated with reduced maternal food intake and weight loss. Whether these preclinical findings translate to humans remains unclear, highlighting the importance of available clinical data on inadvertent early pregnancy exposure.

### *Human pregnancy safety outcomes*

As potential teratogenicity in humans remains a key safety concern, emerging human data, derived from registry-based population cohorts, multicentre observational studies, and case reports, provide valuable insights into the safety of incretin-based AOMs, both in the preconception period and early pregnancy.

A multicentre observational prospective cohort study by Dao et al., using data from six Teratology Information Services, assessed pregnancy outcomes in 168 women exposed to GLP-1RA during early pregnancy, prescribed for either obesity or diabetes [54]. Exposure was mostly to liraglutide (n = 99), semaglutide (n = 51), dulaglutide (n = 11) and exenatide (n = 7) and treatment was stopped at a median gestational age of 5 weeks. At baseline, most exposed women (86.6 %) had a BMI $\geq 25\ kg/m^2$, and 27.4 % had diabetes. The study compared GLP-1RA exposure to two reference groups: women with diabetes without GLP-1RA exposure and women with overweight/obesity without diabetes. Excluding chromosomal or genetic anomalies, rates of major congenital defects were similar across the GLP-1RA-exposed group (2.6 %) and diabetes reference group (2.3 %), but slightly higher in the overweight/obesity reference group (3.9 %). Live births, pregnancy losses, and pregnancy terminations occurred in 59 %, 23 % and 18 % of the exposed group, respectively – comparable to reference groups. LGA infants occurred in 17.7 % of GLP-1RA-exposed pregnancies, compared to 23,4 % and 6 % in the diabetes and overweight/obesity group, respectively. Rates of small-for-gestational-age infants were similar between the GLP-1RA-exposed and diabetes groups (~8 %), and higher in the overweight/obesity group (14.5 %). No overall increase in pregnancy losses was observed with GLP-1RA exposure and the higher rate of elective terminations most likely reflects unplanned pregnancies and concerns over fetal safety [54].

Another observational retrospective cohort study by Cesta et al. analysed data from 6 large population-based health care databases to assess pregnancy outcomes in 15.148 women with T2D exposed to various glucose-lowering drugs during the periconceptional period [55]. Of these, 50 % used metformin only, 34 % insulin, and smaller proportions used sulfonylureas (9 %), DPP-4 inhibitors (4.5 %), GLP-1RA (6.2 %) and SGLT-2 inhibitors (2.2 %). The overall prevalence of major congenital malformations was 5.28 % in women with diabetes, higher than the 2.7 % seen in the general population. Lower rates of major congenital malformations were observed with no glucose-lowering medication exposure (4.77 %) or metformin alone (5.32 %), while higher rates were associated with exposure to insulin (7.83 %), GLP-1RA (8.23 %) or sulfonylureas (9.71 %). Cardiac malformations followed a similar pattern. Nevertheless, when comparing GLP-1RA exposure to insulin, GLP-1RA exposure showed a comparable adjusted relative risk of major congenital malformations (aRR 0.95; 95 % CI, 0,72–1.26), with no increased risk of cardiac malformations (aRR 0.68; 95 % CI, 0.42–1.12). Additionally, although the participants' mean body mass index was not reported, pregnant women treated with GLP-1RA had the highest prevalence of overweight, obesity and polycystic ovary syndrome. Also, although data on glycemic control were provided only in a smaller subset, women treated with insulin had higher periconceptual HbA1c levels than those treated with metformin or without pharmacotherapy. Therefore, both baseline obesity and glucose control may have also partly contributed to the higher risk of congenital malformations following insulin or GLP-1 RA exposure [55]. Other limitations of this study include lower GLP-1 RA dosing as used in obesity treatment, unclear data regarding the time of GLP-1RA discontinuation, absence of robust maternal glucose data and restriction only to live births, which may potentially underestimate teratogenic risk.

In a recent paper, Parker et al. analysed the regulatory documentation published by EMA and FDA on unplanned pregnancies during clinical development programs for various GLP-1 and dual GLP-1/GIP RA [56].

In the clinical development program for liraglutide, out of the 59 reported pregnancies (39 in the liraglutide group and 20 in the placebo group), 25 healthy children were born (18 with liraglutide and 7 with placebo). The group reported no congenital malformations in pregnancies exposed to liraglutide. Although there was a higher incidence of first-trimester miscarriages in the liraglutide group (29 %) compared to placebo (13 %), six of the ten miscarriages in the liraglutide group had a history of prior miscarriages, ectopic pregnancy, thyroid disease, PCOS and irregular menstrual cycles [56].

In the clinical development program for semaglutide, the group reported 53 unplanned pregnancies, of which 40 were in the semaglutide group, 1 in the exenatide group and 12 in the placebo group. In the semaglutide group, there were 22 healthy children born, seven elective terminations, six miscarriages, one ectopic pregnancy, one congenital malformation, one ongoing pregnancy, while two participants were lost to follow-up. In the placebo group, there were five healthy children born, two elective terminations, one miscarriage, one stillbirth, two congenital malformations, and one lost to follow-up [56].

In the clinical development program for tirzepatide, the group reported 22 pregnancies (6 exposed to tirzepatide, one to semaglutide and 15 with unknown exposure status). In the tirzepatide group, there was one healthy child born, one miscarriage, one ectopic pregnancy, one elective termination and two pregnancies with unknown outcome. In contrast, in the placebo group, there were two ectopic pregnancies, one miscarriage, one threatened abortion, one induced abortion, and eight pregnancies with unknown outcome [56].

The authors' aggregated analysis found that 43 % of pregnancies exposed to the incretin-based AOM resulted in healthy children compared to 34 % in the placebo group. Additionally, spontaneous abortion occurred in 22 % of drug-exposed pregnancies compared to 12 % in the placebo group, nevertheless, the rate of non-viable pregnancies was found to be similar [56].

A recent retrospective, observational study by Kolding et al. investigated the pregnancy outcomes after semaglutide exposure, including all singleton pregnancies surviving the first trimester in the Central Denmark Region [57]. Out of 104.422 pregnancies, 32 were exposed to semaglutide during the first trimester, of which 5 were at obesity treatment doses, 5 at T2D-treatment doses, and 22 in combination with insulin. The semaglutide-exposed group (n = 32) was then compared to the insulin-exposed group (n = 547) and to a non-exposed group (n = 103.843). Patients in the semaglutide-exposed group were older and had higher pre-pregnancy BMI compared to both comparison groups. The authors found no increased risk of major malformations between the groups. The semaglutide-exposed group had higher risks of preterm delivery, large-for-gestational age (LGA), neonatal hypoglycaemia and jaundice compared to the non-exposed group. Nevertheless, when compared to the insulin-exposure group, semaglutide treatment showed comparable risks of congenital malformations, preterm delivery, neonatal hypoglycaemia and jaundice, where the risk of LGA was significantly lower (OR 0.35 CI 95 % 0.12–0.92, p = 0.021) [57].

Morton et al. retrospectively analysed pregnancy outcomes in 13 women exposed to semaglutide treatment during early pregnancy, twelve of whom were treated for T2D and one for obesity prior to conception [58]. Nine patients had obesity and six had an HbA1c of greater than 6.5 %, showing poor glycaemic control prior to conception. Apart from one fetus having significant cardiac abnormalities in the presence

of class II obesity (BMI 37 kg/m$^2$), coexistent hypertension and poor glycaemic control (HbA1c of 12.5 %), no other congenital abnormalities were reported. Five infants were delivered prior to 38 weeks of gestation, with pre-eclampsia in two cases, macrosomia with polyhydramnios, preterm labour and fetal distress in the other three cases. Three neonates also had transient hypoglycaemia [58].

Several case reports have described inadvertent exposure to GLP-1RA in unplanned early pregnancy. Two reports of liraglutide use in pregnant patients with T2D and obesity throughout the first trimester, including one with continuation throughout gestation, resulted in healthy live births without congenital malformations [59,60]. Importantly, maternal-fetal liraglutide transfer was negligible, with no significant transfer seen a few hours after dosing [60]. For semaglutide, reported cases include one woman with significant weight loss prior to conception, who experienced substantial gestational weight regain and delivered a macrosomic infant without congenital malformations, and another woman who developed hyperemesis during pregnancy after applying a single untitrated 2 mg dose of semaglutide, with symptoms resolving in line with the drug's kinetics [61,62]. In all case reports, no structural congenital malformations were reported, but outcomes included transient hypoglycemia, macrosomia and maternal weight gain.

A currently ongoing Pregnancy Registry Study (NCT05503927) by Novo Nordisk will retrospectively investigate the safety of semaglutide 2.4 mg exposure during pregnancy, comparing maternal, fetal and infant outcomes to a reference not-exposed population [63].

In contrast to animal studies, current evidence from the largest available cohort and registry studies provides no signs of increased risk of major congenital malformations following inadvertent early pregnancy exposure to incretin-based AOMs when compared to appropriate reference groups. However, exposure numbers are modest, treatment timing, drug potency and used dosages are heterogeneous. Key confounders such as glycaemic control and obesity are not consistently reported and data on long-term maternal and offspring outcomes are lacking. While these findings are broadly reassuring for unplanned early exposure, they are insufficient to recommend use during pregnancy.

*Contraception and washout guidance: clinical implications of inconclusive safety data*

Effective contraception is recommended for all women of reproductive age receiving incretin-based AOMs. Liraglutide and semaglutide are not considered to impair the efficacy of oral contraceptive agents [34,36]. However, regulatory guidance differs for tirzepatide. The EMA considers the reduced systemic exposure of oral contraceptives following a single dose of tirzepatide to be clinically insignificant and does not recommend dose adjustment [39]. In contrast, the FDA advises women using oral contraceptive agents to employ an additional non-oral contraceptive method for four weeks after treatment initiation and for four weeks following each dose escalation [38]. This precaution is primarily due to concerns that gastrointestinal side effects of the drug may reduce absorption and efficacy of oral contraceptives, rather than the effects of the drug itself on contraceptive action.

According to both EMA and FDA, due to the long half-life and insufficient safety data, semaglutide should be discontinued at least 2 months prior to conception, while according to EMA tirzepatide should be discontinued at least 1 month prior to conception [36,39]. This more prolonged preconception washout for semaglutide than for tirzepatide is justified on pharmacokinetic grounds. Semaglutide exhibits a terminal elimination half-life of approximately 168–183 h (~7 days) in individuals with normal renal function, is > 99 % bound to plasma albumin and undergoes metabolism primarily via proteolytic cleavage and β-oxidation, with only minimal (< 3 %) intact drug renal excretion. Following cessation of once weekly dosing at 2.4 mg, semaglutide remains quantifiable in plasma for approximately 5–7 weeks [64]. A discontinuation interval of 8–9 half-lives (~2 months) ensures reduced systemic exposure to negligible levels and is consistent with current prescribing information [65–67]. In contrast, tirzepatide has a shorter elimination half-life of approximately 128 h (~5.3 days), with most administered radioactivity eliminated within ~480 h (~20 days) and no intact parent compound detected in excreta. This pharmacokinetic profile supports a shorter drug washout of 5 half-lives (~4 weeks) to achieve comparable residual exposure [68]. Although there are no official recommendations regarding the exact time of liraglutide discontinuation, a 4-week washout period prior to conception seems reasonable. The same drug discontinuation timelines are advised in women undergoing assisted reproductive treatments. Lastly, in the case of unplanned spontaneous pregnancy, all incretin-based AOMs should be discontinued immediately.

*Timing and duration of preconception weight loss: balancing metabolic gains with reproductive planning*

In the context of intentional preconceptional use of incretin-based AOMs, determining the optimal initiation and duration of treatment is crucial. These agents typically achieve clinically meaningful weight loss of 5–10 % within 6–20 weeks, with the most rapid weight reduction occurring in the first six months. Maximal weight loss is generally observed at 12 months, followed by a plateau phase around 18 months of treatment [26,27,69]. Importantly, this treatment period – combined with the necessary washout interval prior to conception – may introduce delays in achieving pregnancy. Such delays must be carefully weighed against the potential for age-related decline in fertility, particularly in women of advanced reproductive age. Therefore, close collaboration between obesity medicine specialists and reproductive endocrinologists or gynaecologists is essential to align weight management goals with individual reproductive timelines, assess ovarian reserve and optimize the timing of conception.

## Challenges following preconception use of GLP-1 and dual GLP-1/GIP agonists

*Weight regain and gestational weight gain considerations*

Regardless of the weight loss strategy, physiological adaptations often drive weight regain over time. These include weight loss-induced extracellular matrix remodelling of adipocytes, shifts in immune cell profiles, reduced energy expenditure, neuroendocrine

adaptations and altered gut hormone signalling with hypothalamic feedback adjustments [70]. Another critical challenge following preconceptional use of incretin-based AOMs is therefore the potential for weight regain after treatment discontinuation. In the STEP 4 trial, cessation of semaglutide 2.4 mg after 20 weeks led to an average weight regain of 6.9 % (~6.1 kg) over 48 weeks [71]. Similarly, the SURMOUNT 4 trial reported a 14.0 % (~11.1 kg) regain within 52 weeks following tirzepatide discontinuation after 36 weeks of treatment [72].

In parallel, pregnancy is associated with GWG, a physiologically complex process essential for fetal development, shaped by maternal metabolic adjustments, tissue expansion, placental growth and endocrine function [73]. Post-treatment weight regain may therefore exacerbate GWG, potentially heightening the risk of adverse maternal and fetal outcomes.

A small retrospective study by Maya et al. compared GWG women with preexisting T2D exposed to GLP-1RA prior to conception (n = 47) to unexposed controls (n = 141) [74]. The exposed group had greater GWG (11.3 ± 5.4 kg vs. 8.7 kg ± 7.9 kg) and had a higher proportion of pregnancies exceeding GWG recommendations (61.7 % vs. 41.1 %). The study did not however assess downstream maternal and neonatal outcomes [74].

Complementary evidence from a trial comparing preconception weight loss via standard dietary intervention (SDI) versus a very-low energy diet intervention (VLED) showed significantly greater weight loss in the VLED group (13.0 ± 0.5 kg vs. 3.2 ± 0.6 kg). However, both groups experienced similar pre-pregnancy weight regain (SDI 3 kg; VLED 3.6 kg) and comparable GWG (SDI 10.9 ± 1.0 kg; VLED 10.3 kg ± 1.0 kg) [75]. Notably, the VLED group had significantly fewer adverse pregnancy outcomes, suggesting that a lower pre-pregnancy weight may be beneficial despite subsequent weight regain [75]. These findings underscore the need for further research on post-treatment weight trajectories and GWG in women using incretin-based therapies prior to conception.

In our expert opinion, women of reproductive age who discontinue incretin-based AOMs in preparation for pregnancy require proactive and individualized post-treatment care. Structured monitoring and support are crucial given the high risk of rapid weight regain and its potential to compound GWG. These include behavioural counselling and tailored nutritional guidance, ideally delivered by an obesity medicine specialist within a multidisciplinary team involving reproductive endocrinologists, dietitians and mental health professionals. Such coordinated care ensures continuity from the post-discontinuation phase through conception and pregnancy, minimizing the loss of therapeutic gains. Importantly, women with recent AOM discontinuation should receive ongoing support during pregnancy to mitigate the heightened risk of excessive GWG and its associated maternal and fetal complications. This transitional period presents both a clinical challenge and an opportunity to optimize long-term reproductive and metabolic health.

*Impact on micronutrients*

Despite high caloric intake, individuals with obesity frequently exhibit deficiencies in both water- and fat-soluble vitamins, as well as macro- and trace elements – often presenting as overlapping, complex nutritional gaps. These micronutrient deficiencies may further exacerbate obesity-related pathophysiology, perpetuating a vicious cycle of metabolic dysfunction [76].

Incretin-based AOMs have been consistently shown to reduce caloric intake by 16–39 %. However, few studies have evaluated their effects on macronutrient composition, and available data remain inconsistent [77]. Mechanistically, these agents suppress appetite, delay gastric emptying, and may induce gastrointestinal side effects, decreasing food variety, volume and nutrient absorption. These effects may unmask or worsen preexisting deficiencies, particularly iron, calcium, magnesium, zinc, folic acid, and vitamins such as A, D, E, K, B1, B12 and C [69,76].

Nutritional vigilance is particularly important during treatment with incretin-based AOMs in the preconception period, a time of heightened nutritional vulnerability. Although no specific guidelines address preconception use, a recent joint advisory regarding nutritional support for individuals treated with incretin-based AOMs [69] recommends clinical monitoring and dietary guidance with an emphasis on a diversity of nutrient-dense, minimally processed foods and avoidance of refined carbohydrates, sugar-sweetened beverages, red and processed meats and sweets and savory snacks. Strategies to preserve muscle and bone mass, including adequate protein intake with higher targets (1.2–1.6 g/kg/day) during active weight loss and a structured exercise program, aiming at strength training at least three times weekly plus moderate-intensity aerobic training at least 150 min weekly are also recommended [69].

*Impact on glycaemic control*

Finally, most international societies recommend diabetes screening in the preconception period and universal GDM screening with oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation. In individuals with risk factors, such as obesity, additional early screening for abnormal glucose metabolism using HbA1c or fasting glucose in the first trimester is also recommended [22,78–80]. International guidelines for PCOS recommend offering OGTT to all women planning pregnancy or seeking fertility treatment, and if not performed prior to conception, an OGTT should be provided at the first antenatal visit and repeated between 24 and 28 weeks of gestation [81].

GLP-1 and dual GLP-1/GIP RAs have demonstrated efficacy in reversing prediabetes and delaying the onset of T2D [82,83]. However, as seen in the registration studies STEP 4 and SURMOUNT 4, their discontinuation is often accompanied not only by gradual weight regain as previously described but also a deterioration in various cardiometabolic parameters, including glycaemic control (fasting glucose, HbA1c, fasting insulin), blood pressure, lipid levels and waist circumference [71,72]. Importantly, no studies have evaluated whether preconceptional use or discontinuation of incretin-based AOMs influences the diagnostic accuracy or interpretation of GDM screening in early pregnancy. Given these uncertainties and to avoid a false sense of security during the drug weaning phase, we propose that in selected cases, a targeted interim assessment, such as fasting plasma glucose (FPG), HbA1c, or a

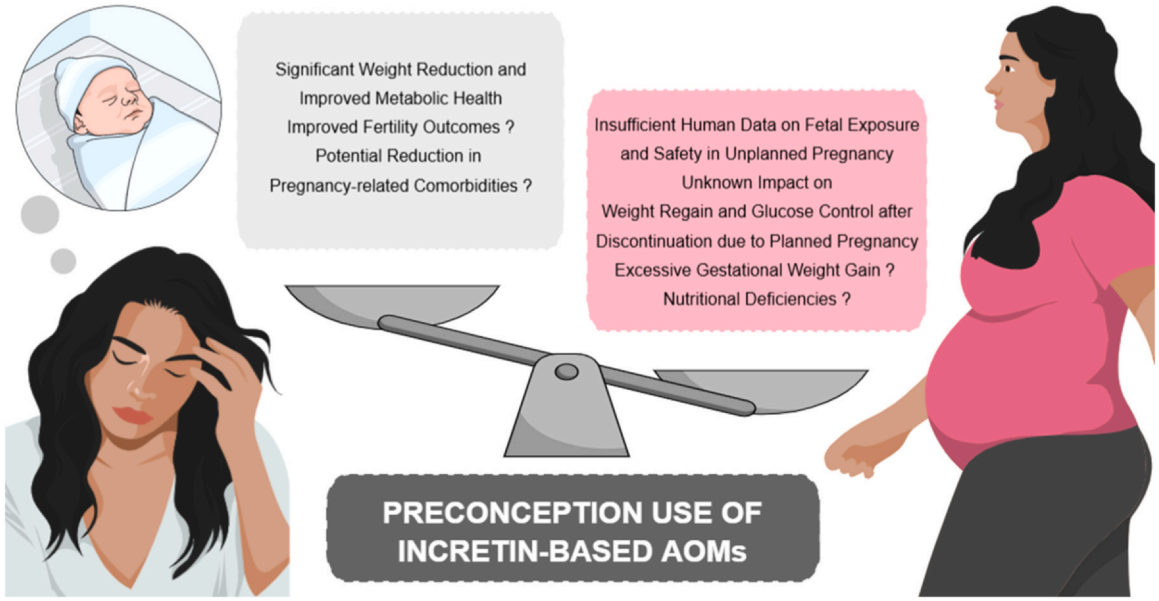


**Fig. 1.** Preconceptional use of Incretin-based AOMs: Balancing Benefits and Potential Risks. AOMs - anti-obesity medications.

brief self-monitoring of blood glucose (SMBG), be performed 4–6 weeks after discontinuation of incretin-based AOMs. Such cases may include women whose initial screening occurred shortly after drug withdrawal, those experiencing substantial weight regain ($\geq 5\,\%$ from the preconception baseline), or those with a personal history of GDM, PCOS, or a strong family history of diabetes.

In the case of intentional preconceptional use of incretin-based AOMs in women with obesity without known prediabetes or diabetes, drug discontinuation should be planned, glycaemic testing should be performed prior to conception, during early pregnancy and between 24 and 28 weeks of gestation. In the setting of an unplanned pregnancy, where incretin exposure may have temporarily improved insulin sensitivity, we suggest glucose testing both at pregnancy confirmation and after drug washout, as testing shortly after drug discontinuation may underestimate the risk of GDM. In the case of normal glycaemic control, an OGTT should be done between 24 and 28 weeks of gestation.

Women with known type 2 diabetes using incretin-based AOMs should regularly discuss family planning and receive preconception counselling. This should also include screening for diabetes-related complications and comorbidities, transitioning off medications not approved for use in pregnancy and optimizing glycaemic control – ideally achieving HbA1c $< 6.5\,\%$ prior to conception, to reduce the risk of adverse neonatal outcomes. During pregnancy, monitoring of fasting, preprandial and postprandial glucose is recommended. Due to altered red blood cell kinetics, HbA1c is usually monitored more frequently with a target of $< 6\,\%$, when safely achievable [84]. The recently published joint clinical practice guidelines from the Endocrine Society and European Society of Endocrinology also recommend discontinuing GLP-1RA in women with preexisting T2D prior to conception rather than between the start and the end of the first trimester [85]. As sudden GLP-1RA discontinuation in preexisting T2D may precipitate hyperglycaemia and cause weight regain, timely transition to and titration of alternative glucose-lowering therapies is considered essential, with both SMBG or continuous glucose monitoring (CGM) considered good alternatives for glucose monitoring during pregnancy. Lastly, the timing of discontinuation should be individualized according to the likelihood of conception, type of GLP-1RA used and risks associated with prolonged drug-free interval [85].

Fig. 1 illustrates the key dilemmas between the potential benefits and the concerns surrounding the preconceptional use of incretin-based AOMs.

## Summary

Obesity is a significant challenge for female reproductive health, negatively influencing fertility, pregnancy outcomes as well as long-term health outcomes for both mother and child. In addition to the known efficacy in treating obesity and diabetes, incretins have multidimensional effects on the reproductive axis, highlighting their potential therapeutic role in preconception care. Nevertheless, despite some recent studies implying that preconception and even early pregnancy exposure to incretin-based AOMs may not be associated with an increased risk of major congenital abnormalities and may even be linked to a reduction in pregnancy-related comorbidities, additional challenges requiring research are their potential impact on maternal nutrients status, weight regain after drug discontinuation, as well as impact on glycaemic control, especially in high-risk patients with obesity, PCOS or prediabetes. Comprehensive and robust are still lacking and should be a priority in future research.

**Research Agenda**

- Prospective, randomized, placebo-controlled trials are needed to evaluate the impact of incretin-based AOMs on fertility outcomes, including their effects on reproductive treatment outcomes, such as oocyte quality or endometrial receptivity in patients with obesity.
- Longitudinal observational studies should investigate the impact of preconceptional or periconceptional use of incretin-based AOMs on both maternal health outcomes and offspring's short- and long-term health, including alterations in macro- and micronutrient intake, weight trajectory and maternal and offspring body composition.
- Large-scale studies are essential to determine whether preconceptional weight loss achieved with these agents can reduce pregnancy-related comorbidities, evaluate the durability of metabolic benefits after treatment discontinuation, define the optimal duration of treatment prior to conception, and identify the ideal timing for discontinuation to maximize maternal metabolic health while minimizing fetal exposure.

**Practice points**

- Women of childbearing age should use a reliable contraceptive method and incretin-based AOMs should be discontinued at least 1 (tirzepatide, liraglutide) or 2 months (semaglutide) prior to planning pregnancy. While oral contraceptive pills remain effective during treatment with semaglutide and liraglutide, patients using tirzepatide are advised to switch or use an additional non-oral contraceptive method for 4 weeks after treatment initiation and for 4 weeks following each dose escalation as a precaution in case of diminished absorption and efficacy due to potential gastrointestinal side effects.
- Discontinuation of incretin-based AOMs often leads to significant weight regain, therefore, women of reproductive age who discontinue incretin-based AOMs in preparation for pregnancy require proactive and individualized post-treatment care. It should include education on weight maintenance strategies and close monthly monitoring by a dedicated obesity specialist coordinating multidisciplinary care.
- Despite preconceptional weight loss benefits, incretin-based AOMs may contribute to, unmask or worsen micronutrient deficiencies. Nutritional status should be assessed and supplemented prior to conception and followed throughout pregnancy.
- In women with obesity without diagnosed prediabetes or diabetes, glucose testing should be performed prior to conception, in early pregnancy, and again between 24 and 28 weeks of gestation. In selected cases of pregnancy after incretin exposure, glucose testing should be done at pregnancy confirmation and repeated after drug washout, as early testing may underestimate the risk of gestational diabetes. If results are normal, an OGTT should still be performed between 24 and 28 weeks of gestation.
- Women with preexisting type 2 diabetes using incretin-based AOMs should receive preconception counselling, including screening for complications, timely discontinuation of medications not approved in pregnancy, monitoring body weight and optimizing glycaemic control with a target HbA1c below 6.5 % before conception. Fasting, preprandial, and postprandial glucose levels (either with SMBG or CGM) and HbA1c (target ideally $< 6$ %) should be monitored regularly during pregnancy.

## Declaration of Competing Interest

A.K. reports receiving lecture honoraria from Eli Lilly, Novo Nordisk, Pfeizer, Novartis, AstraZeneca, Boehringer Ingelheim and Sanofi and being an advisory board member of Novo Nordisk. A.J. has served as a consultant and is on Speakers Bureaus for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Abbott, Novo Nordisk, Medtronic, and Sanofi. M.J. reports receiving lecture honoraria from Novo Nordisk, Eli Lilly, Pfeizer, Amgen, Novartis and Sanofi and being an advisory board member of Novo Nordisk, Eli Lilly, Amgen and Pfeizer.

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