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Consideration of Use of Semaglutide and Tirzepatide Prior to Pregnancy

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Introduction

In reproductive-age females with elevated body mass index (BMI), weight loss is often recommended independent of their reproductive and family planning goals. However, it is clear that lifestyle methods for losing weight often fall short of achieving and maintaining weight loss. As approaches to addressing obesity and weight optimization evolve beyond the simplistic notion of “eat less and move more,” there has been a growing acceptance of weight loss medications as part of comprehensive weight management strategies. It should also be noted that health optimization cannot be solely attributed to reducing BMI or kilograms of body weight. The objective of this paper is not to contribute to the well-established weight stigma in medicine, but rather to highlight a thoughtful approach to the use of weight loss medication in a cohort where the prevalence is expected to rise independent of the indication.

When considering pregnancy and pregnancy health optimization, decreased fertility and increased pregnancy complications have been associated with higher weight.¹ However, the role of weight loss in reversing these associations is

less clear. It is possible that the lack of definitive benefits of weight loss is due to inherent challenges of achieving and sustaining significant weight loss. Pharmacological interventions that assist with weight loss may overcome that obstacle in the future. Related to this efficacy, there is an anticipated rise in the use of anti-obesity medication in reproductive age individuals who aim to optimize their weight for many health and non-health-related reasons. Therefore, as a medical community, we need to be thoughtful in advising this population on how to appropriately use and discontinue these medications in relation to reproductive goals.

Use of Anti-Obesity Medications

The approved anti-obesity medications in Canada include orlistat, naltrexone/bupropion, liraglutide, semaglutide, and tirzepatide, and they have been reviewed recently in relation to pre-pregnancy care.² As pregnancy is not a state of negative energy balance, weight loss medications do not have a role in pregnancy and should be discontinued prior to it. Metformin is not traditionally considered an anti-obesity agent as its effects on weight loss are less clear.²

However, metformin is often first-line adjuvant pharmacotherapy in those with documented insulin resistance, and/or polycystic ovary syndrome in the hope of weight stabilization and anthropometric benefits.³ There is also experience in using metformin during early and late pregnancy. Thus, there are fewer concerns about pregnancy implications in those who conceive when on that medication.⁴ With that in mind, metformin use in this population is less controversial.

The long-acting incretin mimetic medications, including the glucagon-like protein 1 receptor agonist (GLP-1 RA) semaglutide, and the combined GLP-1 RA and gastric inhibitory polypeptide receptor agonist (GIP RA) tirzepatide, have changed the landscape of anti-obesity medications given their observed efficacy in weight reduction. Both GIPs and GLP-1 RAs suppress appetite, slow gastric emptying, and enhance satiety leading to decreased food intake and weight reduction. They also halt the physiologic surge in hunger in response to weight loss that often limits weight loss sustainability.^{5,6} Animal studies suggesting teratogenicity, as well as lack of pregnancy safety data, led to the recommendation to discontinue these medications 1-2 months prior to conception.^{7,8} This paper aims to describe a practical approach to advising individuals who have been prescribed long-acting incretin-based anti-obesity medication, specifically semaglutide and tirzepatide, who are hoping to conceive.

Expectations of Weight Loss with Anti-Obesity Medication Use Prior to Pregnancy

Weight loss outcomes from semaglutide use were studied in a population with body mass index (BMI) >30 but without Type 2 diabetes (T2DM), in the Semaglutide Treatment Effect in People with Obesity (STEP) trials and found a 15.8% average loss after 68 weeks.⁹ Tirzepatide was evaluated in individuals without T2DM and BMI >30 in the SURMOUNT-1 trial, which reported an average change in weight of up to 21% after 68 weeks.⁶ Prescribing information, mechanism of action and dose titration are summarized in **Table 1**.

When considering use of anti-obesity medication in reproductive age patients, it is crucial to clarify expectations and implications of weight loss. Weight loss through lifestyle means has been shown to increase chances of

spontaneous pregnancy, but has not conclusively demonstrated an increase in pregnancy or live birth rates after fertility intervention.¹⁰ There remains a lack of published data on fertility (either unassisted or assisted) after intervention with semaglutide or tirzepatide, although this data is being collected. Pre-gestational weight loss is associated with fewer complications during fertility intervention, and some reduction in certain pregnancy-related health outcomes (e.g., hypertension and cesarian sections).¹⁰ However, there may also be associated risk of early pregnancy losses.¹¹

Expectations of weight regain post-drug cessation were observed in the STEP4 and SURMOUNT-4 trials, where the placebo arm discontinued semaglutide and tirzepatide after 20 or 36 weeks respectively of lead-in treatment with medication. In these studies, the treatment and placebo arm participants continued with monthly counselling, and were prescribed nutritional calorie deficit and weekly exercise requirements, as well as daily diarizing of lifestyle. Despite this, at 8 weeks from randomization to drug continuation vs placebo, the placebo groups did gain weight. However, they remained below their baseline weight.^{12,13} These extension studies observing the sustainability of weight loss while taking semaglutide or tirzepatide also revealed that weight regain continued until the end of observation at 66-88 weeks. Upon trial completion, the participants' weight was still below baseline, but the weight regain had not yet plateaued. In counselling patients who need to discontinue these medications, we can acknowledge that weight regain is expected to occur, but the expected degree and/or speed of the regain is not clear, especially in a real-world scenario.

In patients who intend to conceive and discontinue the medication, the recommended 2-month "wash-out" would lead to potential weight regain immediately prior to and in early pregnancy, the impact of which has not been studied. "Excess" weight regain in early pregnancy post-GLP-1 RA discontinuation has been described in a case report¹⁴ in which the authors proposed that the weight rebound after recent medication use was a potential contributor to observed fetal macrosomia. Regaining weight can lead to an overshoot phenomenon, resulting in excess weight gain, changes in body composition, and adverse surrogate markers of cardiometabolic health.¹⁵ It is not clear if these anticipated weight

changes would pose increased risk during early pregnancy negating the same risks that weight loss was intended to improve. To complicate the decision-making process regarding initiating these medications, consideration should be given to availability of the medication given the rolling shortages, as well as the potential for long-term financial implications of these expensive medications that are rarely reimbursed by insurance when there is no T2DM diagnosis.

Despite the controversial benefits, some individuals will be seeking weight loss prior to fertility therapy for a variety of reasons, including meeting pre-established BMI cut-offs of outpatient fertility clinics. For individuals undergoing in-vitro fertilization (IVF), but not attempting immediate pregnancy, the timing of discontinuation of the medication is nuanced. There is unlikely to be appreciable risk on stimulated oocytes, as pregnancy concerns are related to organogenesis in pregnancy, and not to effects on the oocyte health. Thus, the decision to continue weekly medication through the oocyte stimulation component of IVF (when embryo transfer is delayed) should be done with input from the physicians who will be organizing the fertility interventions. Importantly, consideration should be given to anesthesia plans, as the current recommendation from American Society of Anesthesiologists Consensus-based Guideline suggests holding GLP-1 RA 1 week prior to procedures requiring sedation, irrespective of the medication indication.¹⁶

The concerns regarding the teratogenicity of GLP-1 and GIP RA are based on animal studies in which exposed rodent or rabbit offspring had low weight or bone development changes when the mother had active weight loss.¹⁷ Published literature illustrating the pregnancy effects on humans is limited. Given the long half-life of semaglutide and tirzepatide, even discontinuation when pregnancy is confirmed would imply fetal exposure for at least 4-6 weeks gestation. It has been reassuring that, to date, no fetal defects associated with GLP1 RAs have been reported in case reports,¹⁷ supported by a recent review of pregnancies exposed to non-insulin anti-T2DM medication including 461 individuals who had filled prescriptions of semaglutide.¹⁸ Adequate contraception in those actively treated with anti-obesity medication is crucial given the risk of unplanned pregnancy, especially if ovulation is restored with weight loss. Manufacturers of tirzepatide include a

warning that oral contraceptive pills may not be absorbed properly, necessitating back-up contraception when initiating and titrating the medication.⁷ In the event of conception while taking tirzepatide or semaglutide, the medication should be discontinued, but there is no current recommendation for additional fetal monitoring.

Practical Advice for Pre-Pregnancy Medication Discontinuation

Best practices for discontinuing anti-obesity medications have not been published. After discontinuing GLP-1 or GIP RA medication, there is an expected return of hunger. This may be heightened due to new low weight and a physiological response to return to previous weight set point. It may also be compounded by lower metabolic rate if lean muscle mass loss took place during preceding weight loss. To combat the appetite resurgence, some practitioners hypothesize that gradual reduction of the medication (weaning) may lead to less appreciable appetite resurgence compared to sudden cessation. However, this has not been formally studied. Weaning may inadvertently lead to longer duration of suboptimal dosing, and pregnancy would not be recommended until medication was completely stopped. A preliminary study¹⁹ suggested that using metformin as a “bridge” may assist in halting the degree of weight regain. However, it has not yet been published.

Strategies to support individuals discontinuing incretin mimetics (or any weight loss aid) include:

- Setting expectations: It is important to counsel patients that weight gain has been observed and is expected after medication cessation, based on the given drug’s mechanism of action and large clinical studies.
- Emphasizing non-pharmacologic healthy behaviours to reduce weight regain:
 - Nutritional counselling to optimize whole, satiating food with protein and fibre, and to decrease ultra-processed food and liquid calories
 - Resistance training to increase lean body mass
 - Mental health support to assist with thoughts, and behaviour training that reduces high-risk eating behaviours (this may include involvement of a coach/dietician/behaviour therapist if accessible)

- Gradual dose reduction may ease appetite resurgence but will delay timing of pregnancy
- Trial of metformin use as a “bridge” to slow weight regain (if tolerated)

Conclusion

As there is an anticipated rise in use of semaglutide, tirzepatide, and future versions of long-acting incretin mimetic medications to support weight optimization in reproductive age women, appropriate counselling regarding the risk of pregnancy exposure and management in the peri-partum time is crucial. Discontinuation of these medications is necessary prior to pregnancy but comes with the expectation of weight regain. Non-pharmacologic healthy behaviour optimization should be prioritized during the transition off the medication. Attention should be paid to the implications of rebound weight gain during early pregnancy in order to advise on the future role of the medication in this population.

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Name	Mechanism of Action	Dose	Dosing Titration	Side Effects Management	Safety Concerns/Contraindications	Duration to Stop Prior to Pregnancy	Observed Weight Loss Post Drug Cessation
Semaglutide	GLP-1 Receptor agonist that leads to appetite suppression and delayed gastric emptying	0.25-2.4 mg subcutaneously weekly	<ul style="list-style-type: none"> 0.25 mg/week x 4 weeks, then increased to 0.5 mg/week subcutaneously injected at home If tolerated, the dose can be increased depending on clinical response and tolerability to 1 mg, 1.7 mg or 2.4 mg and then maintained 	<p>Gastrointestinal symptoms, such as:</p> <ul style="list-style-type: none"> nausea vomiting and constipation. <p>Can be managed with over-the-counter medication (eg, anti-nausea or antacid formulations) or reduction in the dose to balance tolerability and clinical effectiveness.</p>	<ul style="list-style-type: none"> Family or personal history of medullary thyroid cancer or multiple endocrine neoplasia type 2 (MEN2) syndrome, pregnancy Not recommended for pregnancy on lactation 	At least 2 months prior to conception ⁸	<p>Change in body weight from baseline was -12% at discontinuation after 20 weeks run in</p> <p>At 1 mo post discontinuation change from baseline up to -10%</p> <p>At 4 mo post discontinuation, change in weight was -9% from baseline¹²</p>
Tirzepatide	GLP/GLP-1 Dual Agonist that suppresses appetite and delays gastric emptying	5-15 mg subcutaneously weekly	<ul style="list-style-type: none"> 2.5 mg/weekly subcutaneous injection and increased to 5 mg after 4 weeks Further titration by 2.5 mg q4 weeks can be increased to achieve desired effects, up to max dose 15 mg/week 			At least 2 months prior to conception ⁷	<p>Change in body weight from baseline was -21% at discontinuation after 36 weeks run-in</p> <p>At 1 mo post discontinuation change in weight was -18% from baseline</p> <p>At 4 mo post discontinuation change in weight was -15% from baseline¹³</p>

Table 1. Semaglutide and tirzepatide prescribing information, mechanism of action, and dose titration^{8,12,7,13}