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# GLP-1 Receptor Agonist Use in Pregnancy

**Irena Druce, MD, FRCPC, MSc**

## Introduction

As of 2018 data, 30–60% of reproductive-aged women in Canada were affected by overweight (body mass index [BMI] 25.9–29.9) and obesity (BMI >30.0), and these rates are increasing.[1] Obesity during pregnancy is associated with higher rates of preeclampsia, gestational diabetes, macrosomia, stillbirth, post-term pregnancy, and increased caesarean delivery rates.[2] Obesity is also associated with higher rates of diabetes, which has well-known consequences for pregnancy, and ovulatory dysfunction, which impacts fertility, such as in polycystic ovarian syndrome (PCOS). Addressing obesity and its associated metabolic impacts could have a profound effect on reproductive and fetal health.[3]

Since the 2000s, incretin-based therapies for diabetes and obesity have become the focus of research and clinical practice. Glucagon-like-peptide 1 (GLP-1), an endogenous incretin hormone secreted by intestinal L-cells in response to food intake, and its agonists, have been available for clinical use in Canada since the introduction of liraglutide in 2011. Recently, pharmacologic agonists of glucose-dependent insulinotropic polypeptide (GIP), an incretin synthesized in the K-cells of the duodenum and jejunum, have also become available. Dual agonism of these hormones is associated with more significant reductions in blood glucose and weight.[4] The currently available incretin-based therapies are listed in **Table 1**, and their physiologic effects are summarized in **Figure 1**.

Active research is underway on new molecules, for example agonists of amylin and glucagon, in various combinations with GLP-1 and GIP, to maximize clinical benefits. These combinations have shown weight loss effects rivalling those of metabolic surgery.[5] Considering their potential, this medication class has taken the world by storm. Canada's Drug Agency (CDA) found that expenditure on injectable semaglutide, under the brand-name Ozempic™, increased from $13.5 million in 2019 to $227 million in 2021, with 20% of the claims being for non-type 2 diabetes use.[6]

The metabolic improvements and weight loss achieved with incretin-based therapies are

| Drug | Administration Route | Administration Frequency | Dose (*mg*) | Effect on A1c | Effect on Weight | Weight Loss Indication | CV Benefit |
|---|---|---|---|---|---|---|---|
| **Exendin-based GLP1 Receptor Agonists** | | | | | | | |
| **Exenatide** | SC | BID | 5–10 | ↓↓ | ↓↓ | No | No |
| **Lixisenatide** | SC | Daily | 10–20 | ↓↓ | ↓ | No | No |
| **Human GLP1-based GLP1 Receptor Agonists** | | | | | | | |
| **Liraglutide** | SC | Daily | 0.6–1.8* | ↓↓ | ↓↓↓ | Yes | Yes |
| **Dulaglutide** | SC | Weekly | 0.75–1.5 | ↓↓ | ↓↓ | No | Yes |
| **Semaglutide** | SC | Weekly | 0.25–2* | ↓↓↓ | ↓↓↓ | Yes | Yes |
| | Oral | Daily | 3–14 | ↓↓↓ | ↓↓↓ | No | Yes |
| **Dual GLP1/G1P Receptor Agonists** | | | | | | | |
| **Tirzepatide** | SC | Weekly | 2.5–15 | ↓↓↓↓ | ↓↓↓↓ | No | No |

**Table 1.** Comparison among incretin-based therapies; *courtesy of Irena Druce, MD, FRCPC, MSc.*

*Doses indicated for weight loss are higher than those listed, all listed dosages are for the indication of glycemic management.

**Abbreviations: BID:** twice daily, **CV:** cardiovascular, **GIP:** glucose-dependent insulinotropic polypeptide, **GLP1:** glucagon-like peptide 1, **SC:** subcutaneous.

associated with improved fertility. While product monographs warn against use in pregnancy and lactation, conception while on these treatments is becoming more common.[3] Considering this increasing reality, this review aims to summarize what is currently known about GLP-1 and GIP agonists and their effects during pregnancy.

## GLP-1 Effects on Reproduction and Fertility

Metabolic dysfunction associated with PCOS and type 2 diabetes results in menstrual irregularities from anovulation and infertility. GLP-1 action has been implicated in pituitary function; it was shown to increase serum luteinizing hormone (LH) in most functional studies, with GLP-1-related increases in gonadotropin-releasing hormone (GnRH) being the prime mechanism. An acute central administration of GLP-1 to female rats during the proestrous phase doubled the amplitude of the pre-ovulatory LH surge. This, in turn, influenced the estradiol and progesterone levels throughout the oestrous cycle and promoted an increased number of mature Graafian follicles.[8]

GLP-1 may also be associated with effects on other reproductive organs. It may have direct effects on the ovary, as GLP-1-receptor knockout mice exhibited a slight delay in the onset of puberty and a decreased number of ovarian follicles.[7] In animal models, insulin resistance has also been shown to affect the endometrium, leading to implantation failure, pregnancy loss, and defective placentation. In diabetic rats, exenatide administration led to decreased histologic degeneration and fibrosis in the endometrium, mainly by decreasing inflammation and antagonizing oxidative stress.[9]

One of the mainstays of PCOS management is weight reduction, which makes GLP-1 and GIP agonists attractive options. Currently none of the available therapies are indicated for PCOS;

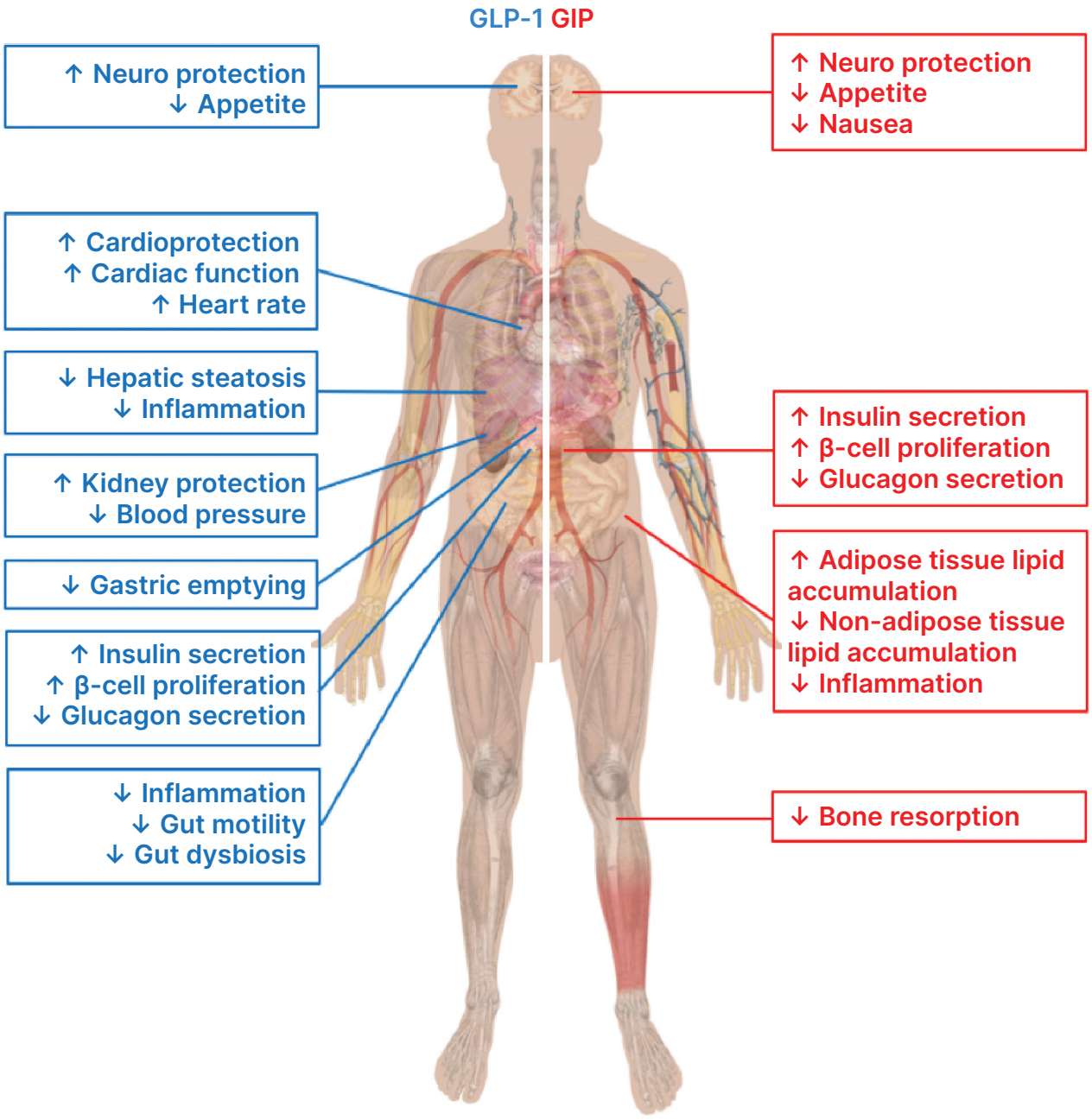


**Figure 1.** Summary of the biological actions of glucagon-like polypeptide 1 (GLP1-) and glucose-dependent insulinotropic peptide (GIP) receptor agonism; *adapted from Hammoud R. et al. Nat Rev Endocrinol. 2023; 169(4):201-16.*

however, numerous small studies have shown their benefits. Treatment of women with PCOS using GLP-1 led to reduced body weight, improved insulin sensitivity, decreased liver and visceral adiposity, and decreased androgen levels. Furthermore, trials comparing GLP-1 receptor agonists with metformin demonstrated improved menstrual regularity and ovulation rates in the GLP-1-treated group.[10] Another study showed that women with PCOS treated with GLP-1 experienced improved spontaneous pregnancy rates, although there was no discussion on the outcomes of the pregnancies or effects on the offspring.[11]

The use of GLP-1 receptor agonists for weight management is also endorsed by The Canadian Adult Obesity Practical Guidelines, citing benefits for many cardiovascular and metabolic parameters, including PCOS.[12]

## GLP-1 in Pregnancy

### Animal Data

Numerous studies in rats and rabbits have assessed the effects of high dose exposure to GLP-1 receptor agonists. At doses 0.8–11 times the levels of human exposure of the drug liraglutide, there was a reduction in fetal growth and early embryonic death. All GLP-1 receptor agonists are too large to pass through the placenta and were not found on the fetal side, indicating that the effects are exerted via impact on maternal food consumption and possibly placental effects.[3]

Mouse studies revealed that treating healthy pregnant mice with semaglutide resulted in lower maternal blood glucose levels. Even when these levels were restored with glucose infusion, the pups had lower birth weights. The placentas maintained their usual mass but had decreased architecture with alterations in placental blood supply, decreased capillary density, and decreased expression of the facilitative glucose transporter GLUT1.[13]

In a mouse model of placental ischemia and maternal hypertension, liraglutide administration resulted in lower blood pressure, improved renal function, and improved placental perfusion, however, the pups were still smaller in size compared to those from control pregnancies.[14]

Other abnormalities noted in animals who were exposed to GLP-1 receptor agonists were delayed ossification, skeletal variants, and visceral abnormalities.[3]

The picture is muddied by studies with contrasting results. When pregnant mice were administered exenin-4, the peptide found in Gila monster venom that shares homology with human GLP-1, and is the basis for drugs such as exenatide and lixisenatide, the pregnant mice gained more weight than controls, and the pups were also heavier prior to weaning.[15]

In the peripartum period, animal studies demonstrated a rapid upregulation of GLP-1 receptors in offspring, which correlated with improved surfactant production and lung function. When GLP-1 was administered to animals during lactation, the concentrations in milk compared to maternal serum were found to be <2.5% for exenatide, 8.3–33% for semaglutide, and 50% for liraglutide, with liraglutide being the smallest GLP-1 receptor agonist.[16]

### Human Pregnancies

Various case reports have described the outcomes of unintentional GLP-1 use in early pregnancy, with exposure lasting up to 17 weeks of gestation. Among the seven pregnancies presented, all deliveries occurred after 37 weeks, with one elective cesarean section mentioned. One birth defect, an atrial septal defect, was noted, which resolved by the age of three years. There was one case of shoulder dystocia due to fetal macrosomia. Whether the increased fetal birth weight was due to drug exposure, or the underlying condition for which the drug was prescribed, cannot be proven.[3]

Another case report described a woman who intentionally used liraglutide throughout her entire pregnancy to manage difficult-to-control diabetes. She had an uncomplicated pregnancy and delivery via elective cesarean section at 39 weeks. The concentration of liraglutide was assessed in maternal blood and the umbilical vein 3.5 hours after the last dose was administered. However, the concentration of drug in the umbilical vein was below the sensitivity of the assay.[17]

A recent observational population-based cohort study looked at trends in the use of antidiabetic medications in pregnancy and the associated risks of congenital malformations compared to insulin. The study examined over 50,000 pregnancies from six countries, with 8.3% (n = 938) exposed to GLP-1 receptor agonists, mainly for the treatment of obesity and PCOS. They concluded that there was no elevated risk of major congenital malformations based on adjusted relative risks. In line with prescribing

practices, the study noted an increased use of GLP-1 receptor agonists during pregnancy in the US over time.[18]

Dao and colleagues conducted an observational, multicenter prospective cohort study based on six databases of the European Network of Teratology Information Services. They assessed three groups of approximately 160 patients; patients exposed to GLP-1 receptor agonists in the first trimester, and patients with diabetes and with overweight and obesity, without any GLP-1 exposure. In the GLP-1-treated group, the median exposure was five weeks and three congenital malformations were noted, though they were thought to be unrelated to the medication. After adjusting for maternal age, parity, and number of medications, the GLP-1 group had the same rate of congenital malformations as the diabetes group (2.6% vs. 2.3%). The highest rate of malformations was noted in the overweight and obesity group at 3.9%.[19]

None of the recent studies discussed the link between GLP-1 exposure and fetal or birth weight. Interestingly, a study looking at obese pregnancies noted that compared to controls, women with obesity had higher levels of endogenous GLP-1, which correlated with large for gestational age (LGA) infants. Higher GLP-1 expression was also noted in the umbilical cord blood of LGA infants.[20] Elevated fasting GLP-1 levels have been noted in obese children and adolescents, although data in adults is conflicting.[21] It is not possible to compare the effects of endogenous GLP-1 to pharmacologic agonists that have been molecularly altered, and clearly more research in this domain is needed.

### Effects on Hormonal Contraception

With very rare exceptions, data on GLP-1 and GIP agonist exposure intrapartum comes from unintended pregnancies while on the medication. Currently, the generally accepted guidance is to discontinue GLP-1 receptor agonists prior to conception (1-2 months before, depending on the agent) and during lactation due to the limited evidence. What may add another level of complexity to the story is that data is emerging which suggests that these medications may impact the effectiveness of oral hormonal contraception, which is the second most commonly used contraceptive option in Canada.[22]

Data from Eli Lilly's clinical trials found that among over 5,000 treated patients, there were six pregnancies in those treated with the dual GLP-1/GIP receptor agonist tirzepatide, five of whom were using hormonal contraception at the time of the study. A review found that the use of the concomitantly administered tirzepatide with an oral hormonal contraceptive showed a statistically significant reduction in area under the plasma drug concentration-time curve, maximum concentration, and time to reach maximum plasma concentration for the contraceptive. Similar assessments of GLP-1 monoagonists did not show a statistically or clinically significant difference in the impact of the agents on oral hormonal contraceptives. The postulated mechanism is that tirzepatide is associated with a faster dose escalation and a greater slowing of gastric emptying, which may impact the absorption of oral medications such as contraceptives.[23]

In view of these findings, the manufacturer of tirzepatide recommends that individuals taking oral contraceptives use a barrier method of contraception for 4 weeks after starting the medication or increasing the dose. Until further data is available, the possible impacts of these novel agents on contraceptive effectiveness need to be communicated to patients as part of our counselling around their use in pregnancy.

## Conclusions

The benefits of GLP-1 receptor agonist therapy continue to expand and there is potential for this medication class to improve fertility and pregnancy outcomes via reductions in weight, blood glucose, and insulin resistance. However, data specifically on the use of these medications in pregnancy is unfortunately still limited. Therefore, all relevant clinical guidelines still recommend cessation of GLP-1 and GIP receptor agonists prior to conception and during lactation.

A fundamental issue is the ongoing exclusion of pregnant women from clinical trials. Relevant agencies are calling for an end to this practice, stating that the active exclusion of pregnant patients from clinical research is unethical. However, as the majority of clinical trials are industry-led, it is unlikely that we will see such a bold step forward in the near future.

Clinicians should be reassured that, despite animal studies demonstrating possible negative impacts of GLP-1 exposure on birth weight and possible increased birth defects, human data (from largely accidental exposure) has thus far been quite reassuring. Hopefully, we will continue to gather post-marketing evidence demonstrating safety. At a minimum, this data

will allow clinicians to counsel and reassure their patients who will inadvertently become pregnant while on incretin therapy. For some practitioners, this knowledge could also bolster clinical courage to consider these therapies in women wishing to conceive while managing obesity, diabetes, and metabolic disease.

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## Financial Disclosures

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## References

1. Statistics Canada. Overweight and Obese Adults, 2018: Statistics Canada; 2018 [updated 2019, cited March 10, 2025]. Available from: https://www150.statcan.gc.ca/n1/pub/82-625-x/2019001/article/00005-eng.htm
2. Mission JF, Marshall NE, Caughey AB. Pregnancy risks associated with obesity. Obstet Gynecol Clin North Am. 2015;42(2):335-353. doi:10.1016/j.ogc.2015.01.008
3. Drummond RF, Seif KE, Reece EA. Glucagon-like peptide-1 receptor agonist use in pregnancy: a review. Am J Obstet Gynecol. 2025;232(1):17-25. doi:10.1016/j.ajog.2024.08.024
4. Drucker DJ, Holst JJ. The expanding incretin universe: from basic biology to clinical translation. Diabetologia. 2023;66(10):1765-1779. doi:10.1007/s00125-023-05906-7
5. Jastreboff AM, Kaplan LM, Frias JP, Wu Q, Du Y, Gurbuz S, et al. Triple-hormone-receptor agonist retatrutide for obesity - a phase 2 trial. N Engl J Med. 2023;389(6):514-526. doi:10.1056/NEJMoa2301972
6. Vaanabouathong C, Crotty C, Le K, Eurich D, Dyrda P. CADTH health technology review: current utilization patterns of glucagon-like peptide-1 receptor agonists. Canadian Journal of Health Technologies. 2022;2(9):1-50.
7. Jensterle M, Janez A, Fliers E, DeVries JH, Vrtacnik-Bokal E, Siegelaar SE. The role of glucagon-like peptide-1 in reproduction: from physiology to therapeutic perspective. Hum Reprod Update. 2019;25(4):504-517. doi:10.1093/humupd/dmz019
8. Outeirino-Iglesias V, Romani-Perez M, Gonzalez-Matias LC, Vigo E, Mallo F. GLP-1 increases preovulatory lh source and the number of mature follicles, as well as synchronizing the onset of puberty in female rats. Endocrinology. 2015;156(11):4226-4237. doi:10.1210/en.2014-1978
9. Artunc-Ulkumen B, Pala HG, Pala EE, Yavasoglu A, Yigitturk G, Erbas O. Exenatide improves ovarian and endometrial injury and preserves ovarian reserve in streptozocin induced diabetic rats. Gynecol Endocrinol. 2015;31(3):196-201. doi:10.3109/09513590.2014.975686

10. Szczesnowicz A, Szeliga A, Niwczyk O, Bala G, Meczekalski B. Do GLP-1 analogs have a place in the treatment of PCOS? New insights and promising therapies. J Clin Med. 2023;12(18):5915. doi:10.3390/jcm12185915
11. Siamashvili M, Davis SN. Update on the effects of GLP-1 receptor agonists for the treatment of polycystic ovary syndrome. Expert Rev Clin Pharmacol. 2021;14(9):1081-1089. doi:10.1080/17512433.2021.1933433
12. Pedersen SD, Manjoo P, Wharton S. Canadian Adult Obesity Clinical Practice Guidelines: Pharmacotherapy for Obesity Management. Available from: https://obesitycanada.ca/guidelines/pharmacotherapy.
13. Qiao L, Lu C, Zang T, Dzyuba B, Shao J. Maternal GLP-1 receptor activation inhibits fetal growth. Am J Physiol Endocrinol Metab. 2024;326(3):E268-E276. doi:10.1152/ajpendo.00361.2023
14. Younes ST, Maeda KJ, Sasser J, Ryan MJ. The glucagon-like peptide 1 receptor agonist liraglutide attenuates placental ischemia-induced hypertension. Am J Physiol Heart Circ Physiol. 2020;318(1):H72-H77. doi:10.1152/ajpheart.00486.2019
15. Graham DL, Madkour HS, Noble BL, Schatschneider C, Stanwood GD. Long-term functional alterations following prenatal GLP-1R activation. Neurotoxicol Teratol. 2021;87:106984. doi:10.1016/j.ntt.2021.106984
16. Price SAL, Nankervis A. Considering the use of GLP-1 receptor agonists in women with obesity prior to pregnancy: a narrative review. Arch Gynecol Obstet. 2025. doi:10.1007/s00404-024-07849-9
17. Ivanisevic M, Herman M, Horvaticek M, Vucic Lovrencic M, Delmis J. Pregnancy outcome and liraglutide levels in serum and umbilical vein blood of a woman with type 2 diabetes. A case report. Gynaecol Perinatol. 2018;27(3-4):70-72.
18. Cesta CE, Rotem R, Bateman BT, Chodick G, Cohen JM, Furu K, et al. Safety of GLP-1 receptor agonists and other second-line antidiabetics in early pregnancy. JAMA Intern Med. 2024;184(2):144-152. doi:10.1001/jamainternmed.2023.6663
19. Dao K, Shechtman S, Weber-Schoendorfer C, Diav-Citrin O, Murad RH, Berlin M, et al. Use of GLP1 receptor agonists in early pregnancy and reproductive safety: a multicentre, observational, prospective cohort study based on the databases of six Teratology Information Services. BMJ Open. 2024;14(4):e083550. doi:10.1136/bmjopen-2023-083550
20. Dumolt JH, Rosario FJ, Kramer AC, Horwitz S, Powell TL, Jansson T. Maternal glucagon-like peptide-1 is positively associated with fetal growth in pregnancies complicated with obesity. Clin Sci (Lond). 2023;137(8):663-678. doi:10.1042/CS20220890
21. Kubota S, Yabe D. Elevation of Fasting GLP-1 Levels in Child and Adolescent Obesity: Friend or Foe? J Clin Endocrinol Metab. 2021;106(9):e3778-e3780. doi:10.1210/clinem/dgab301
22. Chapter 1 Contraception in Canada. J Obstet Gynaecol Can. 2015;37(10 Suppl):S5-S12. doi:10.1016/S1701-2163(16)39370-7
23. Skelley JW, Swearengin K, York AL, Glover LH. The impact of tirzepatide and glucagon-like peptide 1 receptor agonists on oral hormonal contraception. J Am Pharm Assoc (2003). 2024;64(1):204-211 e204. doi:10.1016/j.japh.2023.10.037