Glucagon-like peptide-1 receptor agonist use in pregnancy: a review

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Glucagon-like peptide-1 receptor agonists are peptide analogues that are used to treat type 2 diabetes mellitus and obesity. The first medication in this class, exenatide, was approved in 2005, and these medications, specifically semaglutide, have become more popular in recent years due to their pronounced effects on glycemic control, weight reduction, and cardiovascular health. Due to successful weight loss from these medications, many women previously diagnosed with oligomenorrhea and unable to conceive have experienced unplanned pregnancies while taking the medications. However, there are currently little data for clinicians to use in counseling patients in cases of accidental periconceptional exposure.

In some studies examining small animals exposed to glucagon-like peptide-1 receptor agonists in pregnancy, there has been evidence of adverse outcomes in the offspring, including decreased fetal growth, skeletal and visceral anomalies, and embryonic death. Although there are no prospective studies in humans, case reports, cohort studies, and population-based studies have not shown a pattern of congenital anomalies in infants. A recent large, observational, population-based cohort study examined 938 pregnancies affected by type 2 diabetes mellitus and compared outcomes from periconceptional exposure to glucagon-like peptide-1 receptor agonists and insulin. The authors concluded there was not a significantly increased risk of major congenital malformations in patients taking glucagon-like peptide-1 receptor agonists, although there was no information on maternal glycemic control or diabetic fetopathy. As diabetic embryopathy is directly related to the degree of maternal hyperglycemia and not the diagnosis of diabetes itself, it is not possible to make this conclusion without this information. Furthermore, there is little evidence available regarding fetal growth restriction, embryonic or fetal death, or other potential complications. At this time, patients should be counseled there is not enough evidence to predict any adverse effects, or the lack thereof, of periconceptional exposure of glucagon-like peptide-1 receptor agonists during pregnancy. We recommend that all patients use contraception to prevent unintended pregnancy while taking glucagon-like peptide-1 receptor agonists.

Key words: abortion, diabetic fetopathy, dulaglutide, embryonic death, exenatide, fetal anomalies, fetal death, fetal growth restriction, glucagon-like peptide-1 receptor agonists, glycemic control, hyperglycemia, insulin resistance, liraglutide, lixisenatide, major congenital malformations, miscarriage, obesity, PCOS, periconceptional use, semaglutide, teratogenicity, tirzepatide, type 2 diabetes, unplanned pregnancy, weight loss

Introduction

Obesity, defined as body mass index equal to or over 30 kg/m^2, is one of the most common medical complications in the US and it continues to increase in prevalence.[1] In 2020, 41.9% of US adults were considered obese.[2] Obese patients have higher rates of comorbidities, including cardiovascular disease, diabetes, ovulatory dysfunction, and infertility. Weight loss alone can improve fertility outcomes, and as such, a 5% to 10% weight loss is often recommended.[3] While lifestyle modifications are the mainstays of treatment, many patients choose medical and surgical management. Bariatric surgery has been associated with successful treatment of morbid obesity, with subsequent improvement in the incidence of polycystic ovarian syndrome (PCOS) and ovulatory dysfunction.[4] Glucagon-like peptide-1 receptor agonists (GLP-1RAs), as illustrated in Table 1, have become popular as weight loss medications, in addition to their utility in the management of type 2 diabetes mellitus (T2DM).

About 38 million people (11.6% of the population) in the US are affected by diabetes, and 90% to 95% have T2DM.[16] Similar to the general population, between 10% and 14% of all women in the US are affected by diabetes.[16] While insulin is the "gold standard" therapy for glycemic control during pregnancy, many different antidiabetic medications (ADMs) are frequently used outside of pregnancy (Table 2). Metformin is one of the few noninsulin ADMs that has been used in pregnancy. However its use in gestational diabetes mellitus and T2DM is controversial as it crosses the placenta and there are limited data regarding long term outcomes in offspring. While there are studies demonstrating acceptable glycemic control in pregnancy with minimal risk of maternal hypoglycemia and similar perinatal outcomes compared to insulin, there are concerns regarding long term effects. Animal studies have shown

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TABLE 1
Glucagon-like peptide-1 receptor agonists, doses, and pharmacokinetics[5–15]

Name	Indication	Dose	Half-life	Time to peak	Route
Exenatide IR (Byetta)	T2DM	5 or 10 mcg twice daily	2.4 h	2.1 h	SC
Exenatide ER (Bydureon)	T2DM	2 mg weekly	2 wk	2 wk, 6–7 wk	SC
Dulaglutide (Trulicity)	T2DM	0.75, 1.5, or 4.5 mg weekly	5 d	24–72 h	SC
	T2DM with CVD				
Liraglutide (Victoza)	T2DM	0.6, 1.2, or 1.8 mg daily	13 h	8–12 h	SC
	T2DM with CVD				
Liraglutide (Saxenda)	Obesity	0.6, 1.2, 1.8, 2.4, or 3 mg daily	13 h	8–12 h	SC
	Overweight with weight related comorbid condition				
Lixisenatide (Adlyxin)	T2DM	10 mcg daily for 14 d, then increase to 20 mcg daily	3 h	1–3.5 h	SC
Semaglutide (Ozempic)	T2DM	0.25, 0.50, or 1 mg weekly	1 wk	1–3 d	SC
Semaglutide (Wegovy)	Obesity	0.25 mg weekly for 4 wk, increase up to 2.4 mg weekly	1 wk	1–3 d	SC
	Overweight with weight related comorbid condition				
Semaglutide (Rybelsus)	T2DM	3, 7, or 14 mg daily	1 wk	1 h	PO
Tirzepatide (Mounjaro)	T2DM	2.5 mg weekly for 4 wk, increase to 5 mg weekly, maximum 15 mg weekly	5 d	8–72 h	SC
Tirzepatide (Zepbound)	Obesity	2.5 mg weekly for 4 wk, increase to 5 mg weekly, maximum 15 mg weekly	5 d	8–72 h	SC
	Overweight with comorbidities				

CVD, cardiovascular disease; *ER*, extended release; *IR*, immediate release; *PO*, per os; *SC*, subcutaneous; *T2DM*, type 2 diabetes mellitus.

increased weight, adiposity, and insulin resistance as the offspring age, and there is concern for an association between maternal metformin use and fetal programming leading to metabolic syndrome in offspring.[19–25] While there is debate regarding metformin use in pregnancy, GLP-1RAs are gaining in popularity outside of pregnancy due to their dual effects on glycemic control and weight loss. Between 2019 and 2022, there was an increase in annual Semaglutide users by more than 40-fold in the University of California health system.[26] However, similar to metformin, there are insufficient data regarding short- and long-term effects on offspring.

The safety box warning on the manufacturer of Semaglutide's website states, "*It is not known if [Semaglutide] will harm your unborn baby or pass into your breast milk. You should stop using [Semaglutide] 2 months before you plan to become pregnant.*"[27] Many women who take these medications for T2DM and obesity often have the common comorbidities of PCOS and infertility. GLP-1RA use, presumably through its effect on weight loss, leads to improved fertility, providing an opportunity to evaluate maternal, fetal, and neonatal risks. This review aims to summarize what is known in the literature about GLP-1RAs and pregnancy outcomes.

Mechanism of action

Glucagon-like peptide-1 (GLP-1) is one of the main endogenous incretin hormones that is secreted by enteroendocrine L-cells of the small intestine in response to food intake (Figure).[28] Incretin hormones stimulate release of insulin from pancreatic beta cells. These small peptide hormones are continuously secreted at a low basal rate to maintain a normal blood glucose and can quickly rise to stimulate additional insulin release to control the postprandial blood glucose spike.[29–31] Endogenous GLP-1 also inhibits glucagon release from pancreatic alpha cells and delays gastric emptying.[29] GLP-1 receptors are not only found in the pancreas, but also in the brain, heart, and kidney.[32] In the hypothalamic neurons of the brain, activation of these receptors is associated with early satiety and subsequent weight loss.[33] These medications can decrease heart rate, blood pressure, total cholesterol, low-density lipoprotein, and triglycerides.[31] At the level of the kidney there is decreased albumin excretion.[34] While the exact mechanisms of GLP-1 receptor activation in the heart and kidney are not yet clear, antiinflammatory and antioxidant properties may be involved.[29,31,35]

Due to the effects on glycemic control, satiety, and weight loss, GLP-1RAs were pursued initially as a treatment for T2DM.[32] GLP-1RAs are peptide analogues that have traditionally been developed for subcutaneous

administration due to the necessary metabolism in the subcutaneous space.[36,37] Semaglutide is the only oral GLP-1RA approved by the Food and Drug Administration for the treatment of T2DM.[38] While endogenous GLP-1 has a very short half-life of about 2 minutes, GLP-1RAs are not degraded by the same enzyme (dipeptidyl peptidase-4) and thus experience extended half-lives in the range of hours to days.[39] Therefore, the receptors are activated for a longer period of time, leading to a potentiated effect.[40] The lengthened effect of GLP-1RAs is the main driver of observed effects, including successfully lowering blood glucose levels and controlling T2DM, leading to weight loss and improved cardiovascular health.[41]

In general, drugs with a molecular weight less than 500 to 600 Da cross the placenta freely.[42,43] These medications have high molecular weights, ranging from 3751 to 63,000 Da, and are not expected to cross the placenta and thus minimize the risk of direct fetal exposure.[44–47,5–11] However, specific studies exploring this hypothesis have not been performed.

Clinical effects

Currently, GLP-1RAs are approved for use in patients with obesity and T2DM who have an hemoglobin A1c (HbA1c) ≥1.5% above goal (7%–8% in T2DM), atherosclerotic cardiovascular disease (ASCVD), or chronic renal disease.[48] They can be given in combination with insulin and with or without metformin. On average, HbA1c reduction is between 0.8% and 1.6% within a year.[49] Patients can lose 3 to 10 kg over the course of a year of taking the drug, with some individuals experiencing even higher weight loss.[50] Studies have demonstrated a decrease in atherothrombotic events like cardiovascular death, myocardial infarction, and stroke in patients with known ASCVD.[31]

In this setting of weight loss and HbA1c reduction, many patients' infertility may resolve due to the decreased insulin resistance. A recent meta-analysis of 30 studies looking at weight loss interventions and fertility found that women who were randomized to weight loss interventions were more likely to conceive compared to the control groups (relative risk=1.24, 95% confidence interval [CI] 1.07–1.44).[51] This is likely due to the reduction in insulin resistance and increased tissue sensitivity to insulin because of a decrease in the inflammation associated with obesity.[52]

There is little known about the teratogenicity and other effects of these drugs in humans, and while companies suggest avoiding pregnancy while taking this medication, guidelines do not strictly require contraception for patients while on GLP-1RAs. According to the Guttmacher Institute, almost half of all pregnancies (out of approximately 6 million total) in the US were unplanned.[53] Together, the increasing use of these agents and high rates of unintended pregnancies will lead to a higher prevalence of periconceptional exposure, and it will be important to better understand the potential ramifications.

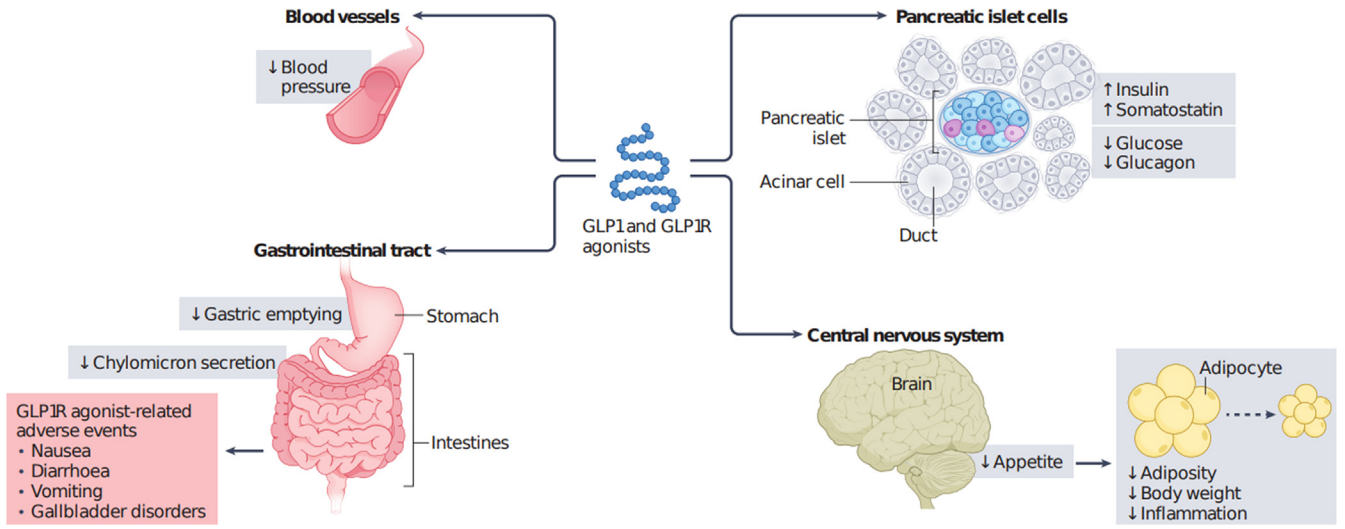
Side effects of GLP-1RAs include gastrointestinal manifestations including nausea and vomiting. More serious side effects can include pancreatitis, gastroparesis, and bowel obstruction.[54] As these medications are studied

TABLE 2
Noninsulin antidiabetic medications[17,18]

Medication type	Brand names	Route of administration	Historical pregnancy risk categories
α-Glucosidase inhibitors	Acarbose	PO	B
	Miglitol		
	Voglibose		
Biguanides	Metformin	PO	B
Dipeptidyl peptidase-4 inhibitors	Alogliptin	PO	B
	Linagliptin		
	Saxagliptin		
	Sitagliptin		
	Vildagliptin		
GLP-1RAs	Dulaglutide	SC	C
	Exenatide/ exenatide ER		
	Liraglutide		
	Lixisenatide		
	Semaglutide		
	Tirzepatide		
Meglitinides	Nateglinide	PO	C
	Repaglinide		
Sodium-glucose cotransporter-2 inhibitors	Canagliflozin	PO	C
	Dapagliflozin		
Sulfonylureas	Gliclazide	PO	B
	Glimepiride		
	Glipizide		
	Glyburide		
Thiazolidinediones	Rosiglitazone	PO	C
	Pioglitazone		

ER, extended release; *GLP-1RA*, glucagon-like peptide-1 receptor agonist; *PO*, per os; *SC*, subcutaneous.

FIGURE
Mechanisms of glucagon-like peptide-1 receptor agonists throughout the body



Adapted from Ussher and Drucker.[28]
Reproduced with permission from Ussher and Drucker.[28]

over longer periods of time in larger populations, new correlations have been noted. A recent study by Hathaway et al observed an association between GLP1-RA use and nonarteritic anterior ischemic optic neuropathy, which can present as sudden vision loss.[55] It will be important to continue to evaluate potential adverse effects of GLP-1RAs as their use becomes even more widespread.

GLP-1RAs in pregnant animals

Muller et al (2023) performed a systematic review of existing evidence on GLP-1RAs during pregnancy and nursing in animals, including 23 studies of mice, rats, and rabbits. The number of animal offspring was not documented.[56] Exposure of mice to GLP-1RAs was associated with decreased fetal weight and growth, delayed ossification, skeletal variants, and visceral anomalies. There was also an increase in embryonic death. These findings were usually associated with a reduction in maternal weight and decreased food consumption. One study looked at whether exendin-4 crossed the placenta.[57] Pregnant mice were injected with the drug and sacrificed 1 day later, and no drug was found on the fetal side. However, when pregnant mice with systemic inflammation were injected with exendin-4, it was found to cross the placenta. The fetal effects of anomalies, growth restriction, and embryonic death were not found.[57] While it is thought that exenatide may not cross the placenta due to its large molecular size (4186 Da) and short half-life, there is no evidence to support this notion.[58]

Studies in rats and rabbits exposed to high doses of liraglutide (0.8−11 times the human exposure) showed fetal malformations at all doses.[59] There was also reduction in fetal growth in doses below expected in humans. At 11 times the human exposure dose, there was an association with early embryonic deaths.[6] Although liraglutide's molecular weight of 3751 Da is well above the threshold of placental transfer of 500 to 600 Da, it is the smallest GLP-1RA. Dulaglutide has the largest molecular weight (63,000 Da), and at high doses (0.5−18 times the human exposure) the effects of decreased fetal weight and skeletal and visceral anomalies were also seen.[47]

Diabetes and congenital malformations

The risk of major congenital malformations in the general population is about 2% to 3%.[60] In pregestational diabetic mothers with inadequately controlled diabetes, that risk rises to 5% to 10%.[61] The most common congenital malformations are cardiovascular, central nervous system (neural tube defects), and gastrointestinal but can include any organ system.[61] However, it is not the diagnosis of diabetes itself that causes these complications, but the presence and degree of hyperglycemia during organogenesis.[61−64] In fact, the risk of congenital malformations rises linearly with the HbA1c. Green et al (1989) found the risk was 3% when HbA1c in the first trimester was less than 9.3%, but 40% when HbA1c was over 14.4%.[62]

In the 1980s, the laboratory of Reece et al proved that hyperglycemia is a teratogen and was instrumental in revealing the underlying biochemical and molecular mechanisms. They showed that oxidative stress resulting in reactive oxygen species causes failure of the yolk sac to develop and function properly, leading to embryopathy.[63] Hyperglycemia in pregnant rodents has been shown to activate a series of molecular pathways resulting in, among other events, excess apoptosis and altered neurogenesis, thus eventuating in neural tube and cardiac

TABLE 3
Case reports/series of pregnancy and GLP-1RAs[71–75,44,45]

Author (yr)	Drug name	Maternal medical comorbidities	Trimester exposure	Presence of birth defects	Pregnancy complications
Williams et al (2009)	Exenatide	T2DM Morbid obesity Oligomenorrhea	Preconception to end of first trimester	None	None
Greco (2015)	Liraglutide	T2DM PCOS	Preconception to end of first trimester	None	Brief neonatal hypoglycemia
Ivanišević et al (2018)	Liraglutide	T2DM	Preconception to end of pregnancy	None	None
Skov et al (2023)	Semaglutide	PCOS	Preconception to 4 wk gestation	None	- Maternal weight gain of 35 kg - Macrosomia - Shoulder dystocia - Brief neonatal hypoglycemia
Doğan et al (2023)	Exenatide	Obesity PCOS	13–17 wk gestation; preconception to 13 wk gestation	Atrial septal defect; none	None; none
Burlina et al (2023)	Dulaglutide	T2DM	Preconception to 15 wk gestation	None	None

GLP-1RA, glucagon-like peptide-1 receptor agonist; *PCOS*, polycystic ovarian syndrome; *T2DM*, type 2 diabetes mellitus.

defects.[61,65–67] Additionally, it has been demonstrated that both epigenetic and environmental factors play a role in diabetic embryopathy.[61] The most common congenital malformation in diabetes is congenital heart disease, and it has been shown that hyperglycemia is associated with altered biochemical pathways that lead to dysregulated gene expression causing abnormal cardiac development.[68]

Pregnancy and GLP-1RAs

The discovery of GLP-1's effect on insulin was first published in 1987.[69] Subsequently, the effects on glucagon, appetite, and weight loss have been discovered, and the interest in receptor agonists as a therapeutic class grew.[33] When the first GLP-1RA was approved in 2005, there was no information regarding safety in pregnancy. However, just 2 years earlier in 2003, Hiles et al performed experiments to evaluate the placental transfer of exenatide and pramlintide in an ex vivo perfusion study.[70] After injecting the drug into the maternal side of the placenta, samples were taken to determine concentrations on the fetal side. They found extremely low ratios of fetal to maternal concentrations of both drugs (pramlintide $\leq$0.006 and exenatide $\leq$0.017) transferred to the fetal side, and hypothesized there would likely be an insignificant amount passed to a fetus. However, due to the nature of the study there was no fetal tissue to test to confirm this finding.

There are 6 published case reports/series describing 7 instances of GLP-1RA use in pregnancy (Table 3).[71–74] The pregnancies were all unplanned and GLP-1RA use occurred during preconception up to a maximum of 17 weeks. Most patients were being treated for T2DM, obesity, and some had a diagnosis of PCOS or oligomenorrhea. In 6 cases, the drug was stopped at diagnosis of pregnancy after counseling patients about the unknown effects of the drug on the fetus. All deliveries occurred after 37 weeks; however, the mode of delivery was not consistently reported in all cases. There was 1 elective cesarean delivery, 1 vaginal delivery, and in 5 cases the mode of delivery was not reported. In those pregnancies in which the GLP-1RA was stopped, there was 1 birth defect noted, an atrial septal defect that closed spontaneously by 3 years of life.[72] Two neonates had transient hypoglycemia at birth.[73,74] There was 1 instance of shoulder dystocia in the setting of fetal macrosomia and maternal weight gain of 35 kg.[74]

Doğan et al (2023) presented a case report of one woman who carried 2 pregnancies while on exenatide.[72] She had a history of obesity and PCOS. In her first pregnancy, her pregnancy status was unknown when she was started on exenatide. She was treated for 4 weeks before it was realized she was pregnant at an estimated gestational age of 17 weeks (taking the drug from 13–17 weeks gestation.) The medication was stopped, and at 37 weeks delivered a female infant with an atrial septal defect which closed spontaneously by 3 years of life. Two years later she had restarted the exenatide and after 6 months, was found to be pregnant at 13 weeks gestation. This pregnancy was overall uncomplicated. Both children were currently healthy at ages 5 and 7 at the time of publishing.

Ivanišević et al (2018) presented a woman who was taking liraglutide prior to and throughout her entire pregnancy.[75] She had a history of T2DM that

TABLE 4
Use of GLP-1RA by country and risks of major congenital malformations (Cesta et al, 2024)[46]

Country	Pregnancies	Prevalence of major congenital malformations	Crude relative risk (95% CI)	Adjusted relative risk (95% CI)
United States	681	7.8%	0.93 (0.67–1.31)	0.85 (0.59–1.22)
Nordic countries	214	7.5%	0.95 (0.57–1.59)	1.02 (0.60–1.73)
Israel	43	14.0%	2.03 (0.89–4.41)	1.69 (0.64–4.44)
Total	938	8.23% (95% CI 5.58–10.88)	1.02 (0.78–1.33)	0.95 (0.72–1.26)

GLP-1RA, glucagon-like peptide-1 receptor agonist.

was challenging to control despite a high dose of insulin, and so she was started on metformin and liraglutide and, after counseling, this was continued during her pregnancy. She had an uncomplicated pregnancy and elective cesarean delivery at 39 weeks. The concentration of liraglutide was measured in maternal blood and the umbilical vein 3.5 hours after the last dose was given, which was on the morning of the cesarean delivery. The umbilical vein concentration was below the sensitivity of the assay and similar to that of a control sample (healthy pregnant patient not exposed to liraglutide). It was still present in the maternal serum at a higher concentration compared to the control sample.

Minis et al (2023) reviewed 6 articles that included 207 patients (3 case reports, 2 randomized controlled trials, and 1 follow-up study) that reported on the use of GLP-1RAs in the preconception period and subsequent fertility rates.[45] They found there were no adverse pregnancy or neonatal outcomes in those studies.[45] Due to limited evidence, their recommendation was to discontinue these medications at least 4 weeks prior to an attempt at conception, or upon a positive pregnancy test. However, there is limited information about possible risks.

Cesta et al (2024) performed an observational population-based cohort study examining the trends and use of second-line oral ADMs and associated risks of major congenital malformations overall and compared to insulin.[46] They examined data from 6 countries that included 51,826 pregnancies affected by diabetes, in which 15,148 were treated with ADMs during the periconceptional period. In women using GLP-1RAs (n=938), the 2 most common comorbidities were obesity and polycystic ovarian syndrome. Periconceptional use of GLP-1RAs increased over time in the US cohort. The authors used databases that reflected diagnosis codes and prescription refills to determine the prevalence of major congenital malformations, crude relative risk, and adjusted relative risk (see Table 4). They reported the adjusted relative risks were comparable, suggesting no elevated risk of major congenital malformations after periconceptional exposure to GLP-1RAs compared to exposure to insulin in patients with T2DM who required medication.

Dao et al (2024) recently published an observational, multicenter, prospective cohort study using information from 6 countries that are part of the European Network of Teratology Information Services.[47] They studied rates of congenital malformations in live births, stillbirths, and abortions in 3 separate groups: any pregnant patients exposed to GLP-1RAs in the first trimester (168 patients), patients with diabetes (156 patients), and patients categorized as overweight or obese (163 patients.) Patients with pregnancies with known chromosomal abnormalities and congenital infections were excluded. There was no information available regarding glycemic control. In the group exposed to GLP-1RAs, the median gestational age at which the medication was stopped was 5 weeks. There were 3 congenital malformations noted in the GLP-1RA group (congenital heart defect, congenital kidney defect, and multiple anomalies) which 3 thought to be unrelated. The rate of congenital malformations were similar between the GLP-1RA group (2.6%) and diabetes group (2.3%) with an adjusted odds ratio of 0.98 (95% CI, 0.16–5.82) after adjusting for maternal age, parity, and number of medications. The rate of congenital malformations was higher in the overweight/obesity group (3.9%) and the adjusted odds ratio was 0.54 (95% CI, 0.11–2.75). While these results are promising and appear to show more evidence of safety of GLP-1RAs in the first trimester, the authors do point out that a congenital malformation rate of 2.3% in the diabetic group is lower than expected, possibly implying undetected bias.

Discussion

Despite the studies discussed above, there are still limited data about the safety of GLP-1RAs in the periconceptional period. Use of GLP-1RAs will likely continue to increase due to their excellent effects on HbA1c control, weight loss, and cardiovascular health. As the critical window of embryonic development and organogenesis occurs in the first trimester when many patients do not know they are pregnant, periconceptional use will also continue to increase.

There are mixed data from animal studies regarding GLP-1RAs causing anomalies, growth restriction, and early fetal demise. Most studies exposed mice, rats, and rabbits to GLP-1RAs throughout gestation, not just periconceptionally. In most animal studies,

placental drug passage was not directly studied. The drug was present in animal breast milk and associated with neonatal growth restriction.

While the 2 large cohort studies described above have investigated teratogenicity, there is limited information about maternal glycemic control, rates of hypertensive disease, or prevalence of preterm birth, all of which are important factors when caring for a pregnant patient with T2DM. There is 1 published case report of GLP-1RA use and a congenital malformation, but there are also case reports without associated anomalies. The recent review by Cesta et al constitutes the largest cohort of GLP-1RA periconceptional use; however, due to the nature of the study there were limitations to the analysis.

The authors compared GLP-1RA use and insulin use in patients with T2DM.[46] However, as the risk of congenital malformations is linked not with the diagnosis of diabetes but to the degree of hyperglycemia, the comparison group should not have been insulin dependent diabetics, but nondiabetics taking GLP-1RAs. The study does show the risk of congenital malformations was higher in patients who took GLP-1RA and insulin for T2DM compared to nondiabetics. Due to the nature of the study, there was limited information about specific patient factors and trends. For instance, while diagnosis codes included major congenital malformations, there was no information on maternal glucose control. Therefore, while some congenital malformations may have reflected drug teratogenicity, some may have reflected the effects of hyperglycemia from poorly controlled diabetes. Importantly, this study only looked at live births. There was no information about spontaneous abortion, stillbirth, or elective termination. Patients may have decided to terminate their pregnancy due to periconceptional exposure to GLP-1RAs with unknown associated risk, sonographic evidence of congenital malformations, or the possibility of the pregnancy worsening their diabetic comorbidities (eg, renal disease). In the study by Dao et al, there was a higher rate of elective abortion in the GLP-1RA group, and the authors cited similar theories.[47] Additionally, poorly controlled T2DM may have resulted in stillbirths of fetuses with congenital malformations, or some severe anomalies may have resulted in stillbirths themselves. Without this information, it is not possible to know the true risk of congenital malformations in this population. Dao et al was able to incorporate this data into their analysis, which is reassuring as they showed no increased risk of congenital malformations in the GLP-1RA group; however, the relatively low rate of anomalies in the diabetic group was surprising as discussed above.

While there does not seem to be a pattern of congenital malformations in live births in population-based cohort studies, concerns regarding the periconceptional use of GLP-1RAs remain. Animal studies have showed fetal death, growth restriction, and anomalies at all doses. There are no human data on the rate of first trimester fetal demise or major congenital anomalies leading some patients to seek pregnancy termination. As such, there is currently insufficient evidence to support their use during pregnancy or to adequately counsel patients about periconceptional exposure. Patients taking GLP-1RAs should be encouraged to use contraception to limit unnecessary exposure to these medications. Furthermore, adequate time off the medication, 2 months according to the product manufacturer of semaglutide, should be considered before attempting pregnancy.

More data about the risks of potential effects on development, teratogenicity, spontaneous abortion, fetal growth, maternal glycemic control, preterm birth, and placental and breast milk drug passage are required. Animal studies exploring the effects on embryological and fetal development will help to direct human investigations. Company and population-based registries have served as important databases to examine the safety of these agents in pregnancy over time. GLP-1RA use in patients with obesity without T2DM could provide a lens through which to study the first trimester effects of the medications in the absence of hyperglycemia. As diabetes and obesity continue to increase in the population, it will be important for providers to be able to counsel patients thoroughly about these medications. ■

GLOSSARY OF TERMS

Glucagon-like peptide-1 receptor agonist. A class of medications that affect the glucagon-like peptide-1 receptors and are used to treat type 2 diabetes mellitus and obesity.

Incretin hormone. A type of peptide secreted from the intestine after food intake that stimulates release of insulin.

Periconceptional use. Use of medication within 90 days before conception through the end of the first trimester.

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