

ORIGINAL ARTICLE

Glucagon-like peptide 1 (GLP-1) receptor agonists' use during pregnancy: Safety data from regulatory clinical trials

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Abstract

Aims: The prevalence of diabetes and obesity continues to rise in women of reproductive age, with significant implications for both mother and foetus. Glucagon-like peptide-1 receptor agonists are effective treatments of diabetes and obesity. However, no Glucagon-like peptide-1 receptor agonists are currently approved for use during pregnancy. We describe the outcomes of unplanned pregnancies during regulatory clinical trials of Glucagon-like peptide-1 receptor agonists submitted to the Food and Drug Administration and European Medicines Agency.

Materials and Methods: A search was conducted of the regulatory documentation published by the European Medicines Agency and the Food and Drug Administration on unplanned pregnancies during regulatory clinical trials of Glucagon-like peptide-1 receptor agonists. Clinical and Medical Reviews published by the Center for Drug Evaluation and Research at the Food and Drug Administration for every Glucagon-like peptide-1 receptor agonist prior to market authorisation were assessed to gather information on unplanned pregnancies that occurred while females were partaking in the clinical development programmes of such drugs.

Results: Evidence in women having planned pregnancies is lacking, and the only evidence thus far relies on pregnancies occurring inadvertently during Glucagon-like peptide-1 receptor agonist trials. The incidence of congenital abnormalities in humans appears relatively low following Glucagon-like peptide-1 receptor agonist use during pregnancy.

Conclusions: Key knowledge gaps must be addressed before the introduction of the Glucagon-like peptide-1 receptor agonist class of drugs for pregnant women. Currently, Glucagon-like peptide-1 receptor agonists should be stopped as soon as the patient becomes aware of a pregnancy. The establishment of patient registries designed to capture data relating to cases of Glucagon-like peptide-1 receptor agonist exposure during pregnancy is a high priority, and where data already exist, the findings need to be published.

KEYWORDS

foetal outcome, GLP-1, GLP-1 receptor agonists, GLP1-RA, pregnancy, pregnancy risk

1 | INTRODUCTION

While Glucagon-like peptide-1 receptor agonists (GLP1-RAs) have been used for decades to treat diabetes, studies previously tended to recruit women of nonreproductive age.^{1–4} Studies investigating obesity recruit more women of child-bearing age. Currently, no GLP1-RA is approved for use during pregnancy or in females trying to become pregnant.⁵ According to the US census data, 39.7% of women aged 20–39 years and within reproductive age have the disease of obesity, so inadvertent use of GLP1-RAs will likely occur during pregnancy.⁶ Questions are raised in clinical practice regarding the potential impact of these medicines on reproductive outcomes. A review of the safety of GLP1-RAs in the context of pregnancy was thus required.

Diabetes and obesity are common during pregnancy, and the prevalence of both conditions is increasing in women of reproductive age.⁷ The importance of the gut–brain axis in both diabetes and obesity and improved mechanistic understanding of the roles of several gut peptides have increased recently. Incretin hormones, such as Glucagon-like peptide-1 (GLP-1), control blood glucose levels by stimulating the secretion of insulin from pancreatic beta cells, suppressing glucagon secretion, and slowing gastric emptying, making GLP-1 an attractive therapeutic target. Endogenous GLP-1 has a half-life of 2–4 minutes, which limits its clinical utility and led to the development of longer-acting, synthetic GLP-1 receptor agonists (GLP1-RA). These have demonstrated significant efficacy in the treatment of diabetes and obesity over the last decade.^{1–4,8–19} GLP1-RAs treat hyperglycaemia while also preserving beta-cell function and improving associated diseases such as hypertension, hyperlipidaemia and obesity.^{9,17,20,21} Endogenous GLP-1 increases threefold after bariatric surgery,²¹ but this does not seem to affect outcomes of pregnancies that occur at least 1 year after bariatric surgery; pregnancies postbariatric surgery reduce the rates of obesity-related pregnancy complications like gestational diabetes and preeclampsia but have higher rates of low birthweight.²²

Currently, seven GLP1-RAs are approved in the EU, the United States and Japan (Table 1). In 2005, exenatide (Astra Zeneca) became the first GLP1-RA approved for use in the treatment of diabetes.²³ This is a synthetic exendin-4 analog with 53% homology to human GLP-1 and a mean half-life in humans of 2–4 h. It is approved for twice-daily administration.²⁴ In 2009, liraglutide (Novo Nordisk,

Bagsvaerd, Denmark) was approved as a once-daily subcutaneous injection either as a monotherapy or in combination with other diabetes medications.^{2,20} It exhibits 97% homology to human GLP-1 with a half-life of 13 h.²⁵ In 2011, the formulation of exenatide incorporated into biodegradable microspheres, which has a half-life of 2 weeks was approved.²¹ Another once-daily GLP1-RA, lixisenatide (Sanofi Aventis, Frankfurt, Germany), was approved in the EU in 2013 and the United States in 2016.²⁶ Despite the short half-life of 2–4 h, lixisenatide is administered once-daily due to its strong binding affinity to the GLP-1 receptor.²⁷ Albiglutide came to market in 2014 in both the United States and EU and was the second once-weekly GLP1-RA approved for the treatment of type 2 diabetes mellitus (T2DM).²⁷ Albiglutide has a half-life of approximately 5 days and is administered initially as a 30 mg subcutaneous once-weekly injection, with potential escalation to 50 mg once weekly.²⁸ In 2014, dulaglutide was approved for the management of T2DM as a 0.75 mg once-weekly injection that can be escalated to 1.5 mg to achieve glycaemic targets.²⁹ Semaglutide was approved in 2017 for the treatment of T2DM and obesity.³⁰ Tirzepatide was approved in 2022 for the management of T2DM and obesity.^{31,32}

In 2015, Greco and colleagues published a case report regarding inadvertent continued use of liraglutide throughout the first trimester of pregnancy in a woman with T2DM and polycystic ovarian syndrome (PCOS).³³ A healthy female child was delivered at 37 gestational weeks. The postpartum period was uneventful except for transient neonatal hypoglycaemia requiring tube feeding for 24 h. No developmental abnormalities were found after 3 months follow-up.³³ Most recently, Skov and colleagues published the case report of a woman with PCOS who used semaglutide 1 mg/week until gestational week 3 + 4.³⁴ A female child was delivered at 41 + 5 weeks gestation, and labor was complicated by shoulder dystocia. The birthweight was high at 5.23 kg, and postnatal examination revealed transient hypoglycaemia, but the child was otherwise healthy and developing normally at 6 months.³⁴

Cesta conducted a cohort study on the use of antidiabetic medications during pregnancy in women with diabetes.³⁵ Data were compiled from Nordic population health registers, the Israeli Maccabi Health Services database and the US MarketScan Database where 938 pregnancies with periconceptional use of GLP1-RAs were identified; 75 children were born with major congenital abnormalities (8.2%). Prevalence of major

TABLE 1 Summary of pharmacokinetic data for GLP1-RAs.

	Exenatide	Liraglutide	Lixisenatide	Albiglutide	Semaglutide	Dulaglutide	Tirzepatide
Administration	SC, BD or QW	SC, QD	SC, QD	SC, QW	SC, QW	SC, QW	SC, QW
Maximum dose	20 ug/day 2 mg/week	1.8 mg/day	20 ug/day	50 mg/week	2.4 mg/week	1.5 mg/week	15 mg/week
Serum t _{1/2}	3.3–4.0 h	13 h	2–4 h	120 h	155–184 h	120 h	120 h
C _{max}	BD—211 pg/mL QW—300 pg/mL	35 ng/mL	187.2 pg/mL	1.74 ug/mL	55.9 nmol/L	114 ng/mL	397 ng/mL
Placental transfer	Low	Low–Moderate	Very low	ND	ND	ND	ND

Abbreviations: BD, twice daily; ND, not determined; QW, once weekly; SC, sub cutaneous.

abnormalities was lower in women exposed to no antidiabetic medications (4.8%) or metformin (5.3%) but similar in women exposed to insulin (7.8%) and sulphonylureas (9.7%). Compared to insulin, GLP1-RA use during pregnancy did not increase the risk of major congenital abnormalities or cardiac malformations. The authors also noted that confounding by obesity and cardiovascular conditions may have resulted in an overestimation of the relative risk of major congenital abnormalities in women exposed to GLP1-RAs in pregnancy.³⁵

Dao conducted a cohort study using data from six centres affiliated with the European Network of Teratology Information Services.³⁶ At such centres, risk assessments of a medication exposure during pregnancy are provided to women and their clinicians at an individual level. Extensive data regarding maternal characteristics, drug exposure and pregnancy outcomes are collected. There was no difference in birth defects or pregnancy loss of 168 pregnancies with first trimester exposure to GLP1-RAs when compared to those of 156 pregnant women with diabetes and 163 pregnant women with a BMI >27 kg/m² and no GLP1-RA exposure. Preterm birth rate was lower in the GLP1-RA cohort (8.0%) compared to cohorts with diabetes (15.1%) and obesity (14.5%). However, there were increased incidence of elective pregnancy termination compared to the diabetes and obesity cohorts.³⁶

Muller conducted a systematic review of the impact of GLP1-RA exposure during pregnancy, and, in addition to the case reports discussed above, they found a study that demonstrated negligible transfer of exenatide through the human placenta.³⁷ Maslin et al. performed a scoping review investigating reproductive outcomes of women without PCOS or diabetes taking GLP1-RAs or orlistat preconceptionally or during pregnancy.⁵ They identified six narrative reviews, two systematic reviews and a protocol for a pregnancy registry for health outcomes of women exposed to semaglutide; they concluded that the lack of primary data necessitates further research.⁵

Based on animal studies, GLP1-RAs have not been classified as direct teratogens (Supporting Information). Thus, the current licensing status is based on the precautionary principle given the lack of supporting safety data in pregnant women. Primary data regarding incidental pregnancies occurring during the clinical development programmes for GLP1-RAs evaluated by the Food and Drug Administration (FDA) have not been investigated previously.

2 | METHODS

Clinical Reviews published by the FDA for every GLP1-RA were assessed for information on pregnancies that occurred in female participants during the clinical development programmes.³⁸ These reviews are conducted at the end of a multistep process for developing and approving new drugs in the United States. Sponsors are required to report to the FDA when pregnancy occurs during clinical trials, and pregnant individuals are followed to term.³⁹ These data are included in the Clinical Reviews, which makes them a uniquely valuable source of data for assessing the safety of GLP1-RA use in pregnancy. When data were not available in the Clinical Reviews, results

posted on [ClinicalTrials.gov](https://clinicaltrials.gov) were examined for studies in the clinical development programmes of the included drugs.

3 | RESULTS

While interventional GLP1-RA studies have strictly excluded participants who are pregnant or intend to become pregnant, several unplanned pregnancies occurred in clinical development programmes. Their outcomes were reported to the FDA and made publicly available in the Clinical reviews published by the FDA prior to market authorisation of the drugs.³⁸ The results are summarised in Table 2.

3.1 | Exenatide

The clinical development programme for exenatide once-weekly suspension (EQWS) included two trials with 307 females, of whom 227 received exenatide and 80 received comparators, including placebo.⁴⁰ A total of two unplanned pregnancies were reported, and both patients were exposed to exenatide. One of the pregnancies occurred in the EQWS 2.0 mg group, where maternal age was 41 years, estimated exposure time was 8 weeks, and the outcome was a healthy child. The other pregnancy occurred in the exenatide 0.005 mg twice-daily group; maternal age was 43 years, and in addition to T2DM, the patient had hyperlipidaemia, elevated ALT, nephropathy and anaemia. The patient required rescue medication for hyperglycaemia during the study. The patient had a positive pregnancy test 1 week after the study concluded, which resulted in a spontaneous abortion 10 days later.⁴⁰ In addition to the clinical development programme for EQWS, we are aware of two other pregnancies where patients were exposed to exenatide in comparator groups of clinical development programmes for other GLP1-RAs. Both pregnancies resulted in elective terminations, though it is not known whether this was due to developmental abnormalities.^{41,42}

3.2 | Liraglutide

The clinical development programmes for liraglutide (brand names Saxenda and Xultophy) included eleven phase two and three trials with 6092 females, of whom 4220 received liraglutide and 1872 received placebo.^{43,44} There were 64 pregnancies; 44 received liraglutide and 20 received placebo.^{43,44} A total of 59 pregnancies (39 with liraglutide 3.0 mg and 20 with placebo) were reported in exposed patients in the completed trials, with 25 healthy children (18 with liraglutide 3.0 mg and seven with placebo) born through the 120-Day Safety Update.⁴³ The overall proportions of patients who became pregnant were similar in the two treatment groups (~1.5% of exposed women in the completed clinical trials), and all 18 babies born to mothers who had been exposed to liraglutide were healthy and had no congenital abnormalities. The incidence of first trimester miscarriage was 29% in the liraglutide groups compared to 13% of pregnant patients in the control groups. No causal relationship was identified. A

TABLE 2 Overview of pregnancy outcomes in GLP1-RA clinical development programmes.

	Total	Healthy	Foetal abnormality	Nonviable pregnancy	Elective termination	Other
Exenatide	4	1	0	1	2	0
Liraglutide	44	19	0	15	4	6 ^a
Lixisenatide	3	1	0	2	0	0
Albiglutide	6	3	1 ^b	0	0	2 ^c
Dulaglutide	7	1	1 ^d	0	0	5 ^e
Semaglutide	41	22	1 ^f	7	7	4 ^g
Tirzepatide	7	1	0	3	1	2 ^h
Total GLP1-RA	112	48	3	28	14	19
Placebo	38	13	2 ⁱ	10	5	8 ^j

^aFour ongoing pregnancies, one lost to follow-up and one abortion unknown whether spontaneous or elective.

^bSubject gave birth to a male who developed neonatal hyperbilirubinaemia with transient tachypnea and had an abscess on the back and nape of the neck.

^cOne loss to follow-up, one abortion unknown whether spontaneous or elective.

^dSubject experienced the following maternal complications: mild hypertension, cholestasis and hyperglycaemia. The infant remained hospitalised for 15 days due to low weight. No other complications were reported.

^eNone of the five pregnancies had reported outcomes.

^fThe infant was diagnosed with a congenital anomaly of a small left ear fold and was positive for sickle cell trait. At 4 months of age, the ear fold resolved. Due to the positive HIV status of the mother, the infant was given AZT and had 2 negative HIV RNA PCRs at birth and at 1–2 months of age.

^gOne ongoing pregnancy, two losses to follow-up and one no reported outcome.

^hBoth pregnancies had no reported outcomes.

ⁱOne child was born with an imperforate anus and a rectovaginal fistula. One child has congenital dacryostenosis and chordee.

^jTwo ongoing pregnancies, four lost to follow-up and two with no reported outcome.

review of concomitant medications, weight change before and after the time of conception, medical history and other adverse events reported did not reveal potential relationships or explanations. Of the ten cases of spontaneous abortion with liraglutide, six women had medical histories of prior miscarriages, thyroid disease (chronic autoimmune thyroiditis and hypothyroidism), PCOS, ectopic pregnancy and irregular menstrual cycles.⁴³

3.3 | Lixisenatide

The clinical development programme for lixisenatide included nineteen phase two and three trials with 6299 females, of whom 3703 received lixisenatide, 22 received liraglutide, 129 received exenatide and 2445 received comparators, including placebo.⁴¹ There were seven total pregnancies reported in the clinical development of lixisenatide. Of these, three received lixisenatide, one received exenatide, one received sitagliptin and two received placebo. There was one healthy child, one spontaneous abortion and one stillbirth in the lixisenatide group. The patient who received exenatide elected to terminate the pregnancy (described above). The pregnancy of the patient who received sitagliptin resulted in a stillbirth. There was one elective termination and one healthy child in the placebo group.⁴¹

3.4 | Albiglutide

The clinical development programme for albiglutide included eight phase three trials with 2533 females, of whom 1242 received albiglutide,

190 received liraglutide and 1101 received comparators, including placebo.⁴⁵ There were six pregnancies reported in the albiglutide group.⁴⁵ Data on the number and outcomes of pregnancy in the comparator group were not reported in the FDA's clinical review, but one spontaneous abortion in the placebo group was reported on [ClinicalTrials.gov](https://clinicaltrials.gov). Of the six pregnancies in the albiglutide group, three had no reported complications, one was terminated early, one was lost to follow-up and one subject gave birth to a male with neonatal hyperbilirubinaemia, transient tachypnea, and an abscess on the back and neck.⁴⁵

3.5 | Dulaglutide

The clinical development programme for dulaglutide included ten trials with 2930 females, of whom 1872 females received dulaglutide, 120 received exenatide and 938 received placebo.⁴⁶ There were nine total pregnancies reported in the clinical development of dulaglutide. Of these, seven received dulaglutide and two received placebo. There was one healthy child and one child born at low birthweight in the dulaglutide group. Among the seven other pregnancies, there were five healthy children and two elective terminations, but the exposure status of the mother was not reported.⁴⁶

3.6 | Semaglutide

The clinical development programmes for semaglutide (brand names Ozempic, Wegovy and Rebelsus) included 20 trials with 9736 females, of whom 5936 received semaglutide, 202 received liraglutide, 177 received

exenatide and 3017 females received placebo.^{42,47,48} There were 53 pregnancies reported; 40 received semaglutide, one received exenatide and 12 received placebo. There were 22 healthy children, six spontaneous abortions, seven elective terminations, two lost to follow-up, one congenital abnormality, one ectopic pregnancy and one ongoing pregnancy in the semaglutide group. The patient who received exenatide elected to terminate the pregnancy. In the placebo group, there were five healthy children, two congenital abnormalities, two elective terminations, one spontaneous abortion, one stillbirth and one lost to follow-up.^{42,47,48}

3.7 | Tirzepatide

The clinical development programme for tirzepatide included 11 phase two and three trials with 4701 females, of whom 3203 received tirzepatide, 244 received semaglutide, 96 received dulaglutide and 1158 females received placebo.⁴⁹ There were 22 pregnancies reported; six received tirzepatide, one received semaglutide and 15 where maternal exposure status is unknown. There was one healthy child, one spontaneous abortion, one ectopic pregnancy, one elective termination and two pregnancies with no outcomes reported in the tirzepatide group. In the placebo group, there were two ectopic pregnancies, one spontaneous abortion, one threatened abortion, one induced abortion and eight pregnancies with no outcomes reported.⁴⁹

3.8 | Aggregated GLP1-RA exposure during pregnancy

There were 32 598 females in the clinical development programmes of GLP1-RAs, 164 of whom had unplanned pregnancies during their participation. At least 111 of the 21 987 females exposed to GLP1-RAs became pregnant (0.51%), and at least 38 of the 10 611 females who received placebo or other non-GLP1-RA comparators became pregnant (0.36%). The exposure status of 15 additional pregnancies was not reported. In the placebo group, there were 13 healthy children (34%), two ongoing pregnancies (5.3%), two congenital abnormalities (5.3%), two stillbirths (5.3%), five spontaneous abortions (13%), three ectopic pregnancies (7.9%) and five elective terminations (13%). Four were lost to follow-up, and two reported no outcomes. In the GLP1-RA exposure group, there were 48 healthy children (43%), five ongoing pregnancies (4.5%), two congenital abnormalities (1.8%), one low birthweight (0.9%), one stillbirth (0.9%), 24 spontaneous abortions (22%), three ectopic pregnancies (2.7%), 14 elective terminations (13%) and two additional abortions, unknown whether spontaneous or elective. There were two maternal complications, one report of pre-eclampsia and one report of oligohydramnios, among the mothers of healthy children. Finally, four were lost to follow-up and seven had no outcomes reported.

4 | DISCUSSION

Existing human evidence does not suggest that inadvertent exposure to GLP1-RAs during pregnancy poses a teratogenic risk to the

developing foetus. Pregnancy or the intention of becoming pregnant was exclusion criterion in the clinical development programmes of all GLP1-RAs, and women of child-bearing age were counselled on the necessity of using appropriate birth control methods during the trials. However, several pregnancies still occurred in these clinical development programmes, and their incidence and outcomes were reported in regulatory documents made public by the FDA. Our analysis found that 43% of pregnancies in the GLP1-RA exposure group resulted in healthy children compared to 34% in the placebo group. The incidence of congenital abnormalities was 5.3% in the placebo group and 2.7% in the GLP1-RA exposure group. Electively terminated pregnancies were 13% in both groups. Spontaneous abortions occurred in 22% of pregnancies in the exposure group and 13% in the placebo group. While the rate of spontaneous abortions was higher in the exposure group, the rate of nonviable pregnancies, including spontaneous abortions, stillbirths and ectopic pregnancies, was very similar. Overall rates of nonviable pregnancies (stillbirth, spontaneous abortion and ectopic pregnancy) were 26.3% in the placebo and 25.2% in the exposure groups. This can provide information to clinicians to counsel women who use GLP1-RAs while inadvertently becoming pregnant.

Obesity and pregestational diabetes are known risk factors for early pregnancy loss, stillbirths and congenital anomalies.⁴⁹ These risks increase with increasing obesity severity. In our small sample size, there do not appear to be major differences in pregnancy outcomes between periconceptual GLP1-RA exposure and nonexposed pregnancies. Our results are relatively consistent with previously published cohort studies.^{35,36} Cesta found that 8.2% of children born from pregnancies with periconceptual GLP1-RA exposure resulted in major congenital abnormalities compared to our findings of 2.7%.³⁵ However, the populations assessed in the Cesta study and in the present study had different comorbidities. For example, everyone in the Cesta study had diabetes whereas only some in the present study did, so conclusions cannot be drawn from the comparison of the results due to confounding.

Initiating interventional clinical trials for GLP1-RAs in expectant mothers is not justifiable on the current risk-benefit analysis. Therefore, the most effective means of further advancing this important clinical question is through the establishment of patient registries to capture data relating accurately and comprehensively to cases where GLP1-RAs have continued to be used, inadvertently, during pregnancy. While registries exist, companies have not published their data on the outcomes of GLP1-RA use in pregnancy, so they are currently of little use to women eligible to join such registries and their healthcare providers.

This study is the first of its kind to extract pregnancy incidence and outcome data from RCTs in the clinical development programmes of GLP1-RAs. While the placebo and exposure groups were likely similar, there were not sufficient data to compare maternal characteristics, comorbidities and other potential confounding variables. Additionally, in most cases, exposure to GLP1-RAs was during the first trimester, so there is a lack of data during later trimesters. Finally, the sample size was not large enough, nor were country-level data available to perform statistical analysis against a country-specific incidence of congenital abnormalities of the background population.

The most effective means of advancing this important clinical question is by establishing patient registries to capture comprehensive data from cases where GLP1-RAs have continued to be used during pregnancy. While registries exist, companies have not published their data on the outcomes of GLP1-RA use in pregnancy, so they offer little guidance to women eligible to join such registries and their clinicians.

5 | CONCLUSIONS

The present study expands upon the growing body of evidence regarding the impact of GLP1-RA use during pregnancy. More studies are required to build a strong justification for widespread, safe use of GLP1-RAs during pregnancy. Companies with patient registries designed to capture data relating to GLP1-RA exposure during pregnancy should publish their data. Until then, GLP1-RAs remain contraindicated in pregnancy.

AUTHOR CONTRIBUTIONS

CHP, CS, CLR and DJB conceived the study, performed data analysis and wrote the manuscript. All authors reviewed the manuscript prior to submission.

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CONFLICT OF INTEREST STATEMENT

CHP, CS and DJB have no conflicts of interest to declare. CIR reports grants from the EU Innovative Medicine Initiative, Irish Research Council, Science Foundation Ireland, Anabio and the Health Research Board. He serves on advisory boards and speakers panels of Novo Nordisk, Roche, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Gila, Irish Life Health, Boehringer Ingelheim, Currax, Zealand Pharma, Keyron, AstraZeneca, Arrowhead Pharma, Amgen and Rhythm Pharma. CIR is the Chair of the Irish Society for Nutrition and Metabolism. CIR provides obesity clinical care in the My Best Weight clinic and Beyond BMI clinic and is a co-owner of these clinics.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16437>.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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