

ORIGINAL ARTICLE

Unintentional periconceptional exposure to glucagon-like peptide-1 receptor agonists and adverse pregnancy outcomes: A nationwide cohort study in Taiwan

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Funding information

Department of Health, Taipei City Government, Grant/Award Number: 11401-62-007

Abstract

Aims: To assess whether periconceptional exposure to glucagon-like peptide-1 receptor agonists (GLP-1 RAs) is associated with adverse outcomes in women with pregestational type 2 diabetes.

Materials and Methods: We linked Taiwan's Birth Certificate Application and National Health Insurance claims (2013–2022) to assemble a nationwide cohort of singleton births to mothers (18–50 years) with pregestational diabetes. Exposure was any GLP-1 RA dispensed during the 90 days before and after the last menstrual period; insulin without GLP-1 RA was the active comparator. Outcomes were major congenital malformations, stillbirth, preterm birth (<37 weeks) and small for gestational age (SGA, <10th percentile). We used 1:4 propensity-score matching and Poisson generalised estimating equation (GEE); sensitivity analyses required ≥ 2 prescriptions and restricted exposure to the first trimester.

Results: We identified 3351 comparison pregnancies (GLP-1 RA 160; insulin 3191); matching yielded 160 versus 606. Risk ratios (GLP-1 RA vs. insulin) were malformations 0.64 (95% confidence interval 0.11–3.83), stillbirth 2.05 (0.82–5.13), preterm birth 1.09 (0.85–1.39) and SGA 0.86 (0.31–2.41). Sensitivity analyses were similar.

Conclusions: Periconceptional GLP-1 RA exposure was not associated with increased risks of malformations, stillbirth, preterm birth or SGA versus insulin use. These preliminary data require confirmation in larger agent-specific studies; until then, intentional GLP-1 RA use in planned pregnancy is not advised.

KEYWORDS

glucagon-like peptide-1 receptor agonists, periconceptional exposure, pregnancy outcomes, type 2 diabetes mellitus

Hsiao-Yun Hu and Chieh-Hsing Liu contributed equally to this study.

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1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is increasingly common among women of reproductive age, driven by earlier disease onset, the global rise in maternal obesity, and persistent socioeconomic disparities.^{1–4} Hyperglycaemia both before and during pregnancy heightens the risk of miscarriage, stillbirth, congenital anomalies, preterm delivery, low birth weight, pre-eclampsia, macrosomia and neonatal morbidity.^{5–8}

Clinical pharmacotherapy during pregnancy has traditionally centred on insulin, with the supplementary use of metformin supported by an expanding evidence base.^{9,10} However, over the past decade, second-line non-insulin agents such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been increasingly prescribed to women of reproductive age for glycaemic control and weight management.^{11,12} Consequently, an expanding cohort of patients may be exposed to these drugs during early gestation, despite the paucity of reproductive safety data.^{13,14}

This concern is amplified by the fact that roughly half of all pregnancies worldwide are unplanned,^{15,16} making it common for inadvertent foetal exposure to occur during organogenesis, often before the pregnancy is recognised.¹⁷ Yet convincing data on the periconceptual safety of GLP-1 RA remain scarce.^{17,18} Although a recent small-scale study and a larger multinational cohort study have provided initial reassuring data,^{17,19} the evidence base remains limited and has primarily focused on malformations. Therefore, further large-scale studies are urgently needed to clarify the safety of these agents across a spectrum of adverse pregnancy outcomes.

Given the increasing use of these drugs and the high rate of unintended pregnancies, clarifying their periconceptual risks is an urgent public health priority. Using data from the National Birth Certificate Application (BCA) and the National Health Insurance (NHI) databases in Taiwan, we conducted a nationwide cohort study to investigate the risks of major adverse pregnancy outcomes, including stillbirth, major congenital malformations, preterm birth and small for gestational age (SGA), following unintentional periconceptual exposure to GLP-1 RA.

2 | MATERIALS AND METHODS

2.1 | Study setting and data sources

We conducted a nationwide, population-based cohort study in Taiwan by linking two national databases: the BCA database (from January 1, 2014, to December 31, 2022) and the NHI claims database (from January 1, 2013, to December 31, 2022). The NHI database is a comprehensive claims repository that covers more than 99% of Taiwan's 23 million residents and contains complete records of outpatient and inpatient visits, diagnostic codes (International Classification of Diseases, 9th and 10th Revisions), procedures and dispensed prescriptions.²⁰ The BCA database provides mandatory registration data for all live births, including maternal demographics, high-risk

behaviours (e.g., smoking), gestational age, birth weight and clinician-reported congenital anomalies. Datasets were linked deterministically using encrypted, unique personal identifiers to ensure anonymity. The study protocol was approved by the Institutional Review Board of Taipei City Hospital (TCHIRB-11303004-E). The requirement for individual informed consent was waived because all data were de-identified before analysis.

2.2 | Study cohort

We identified all pregnancies among women aged 18–50 years that resulted in a singleton birth between January 1, 2014, and December 31, 2022. We excluded records with implausible or missing values, pregnancies in which the infant had a chromosomal abnormality, and pregnancies in which the mother was exposed to a known teratogen during the first trimester (Figure 1 and Table S1, Supporting Information). We restricted the cohort to women with pregestational T2DM, defined as ≥ 3 outpatient visits or ≥ 1 inpatient admission with a T2DM diagnosis in the 12 months before the first day of the last menstrual period (LMP) (Figure 1; Table S1). Stillbirths were omitted from the preterm birth and small-for-gestational-age analyses because their underlying causes and risk profiles differ from those of live births. The end of pregnancy was defined as the delivery date, and the LMP was estimated by subtracting the recorded gestational age from that date (Figure 2).

2.3 | Exposure

Periconceptual exposure was ascertained from dispensed outpatient prescriptions in the NHI claims database. The primary exposure window spanned from 90 days before the first day of the LMP to the end of the first trimester (LMP + 90 days), to accommodate typical supply durations of 1–3 months. For this analysis, pregnancies were classified into two mutually exclusive groups. The GLP-1 RA group included all pregnancies with any dispensing of a GLP-1 RA; concomitant use of other antidiabetic medications (ADMs), including insulin, was permitted (Table S2). The comparator (insulin) group comprised pregnancies with any dispensing of insulin but no exposure to a GLP-1 RA. To reflect real-world prescribing, this comparator group could include co-prescriptions of other non-GLP-1 RA agents, such as metformin, sulfonylureas, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Pregnancies exposed to other ADMs alone (without GLP-1 RAs or insulin), as well as those with no ADM exposure, were excluded from the comparison (Table S3).

2.4 | Outcomes

The study outcomes were (1) major congenital malformations, (2) stillbirth, (3) preterm birth and (4) SGA. Major congenital malformations

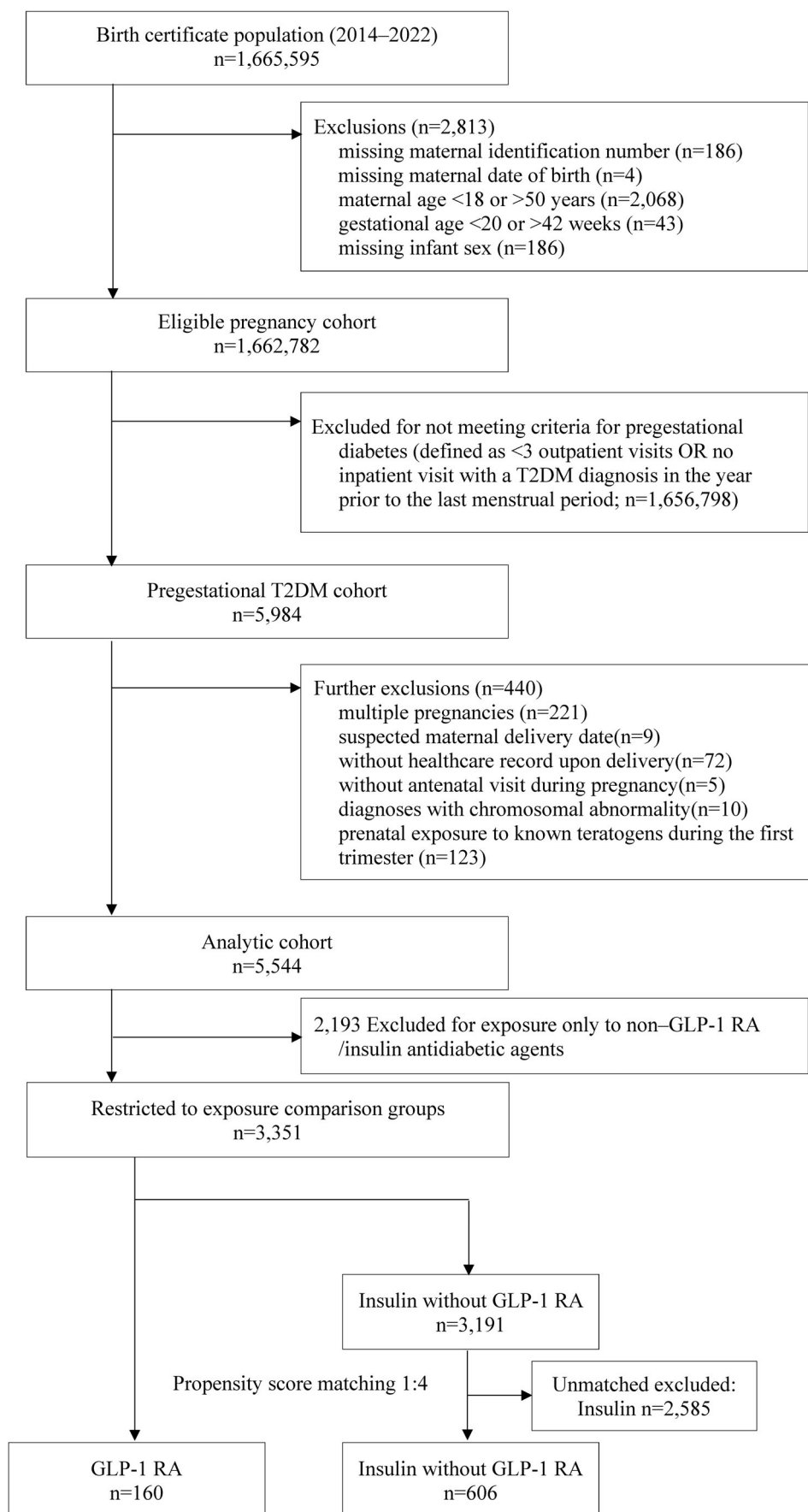


FIGURE 1 Flow chart of study population. T2DM, type 2 diabetes mellitus; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

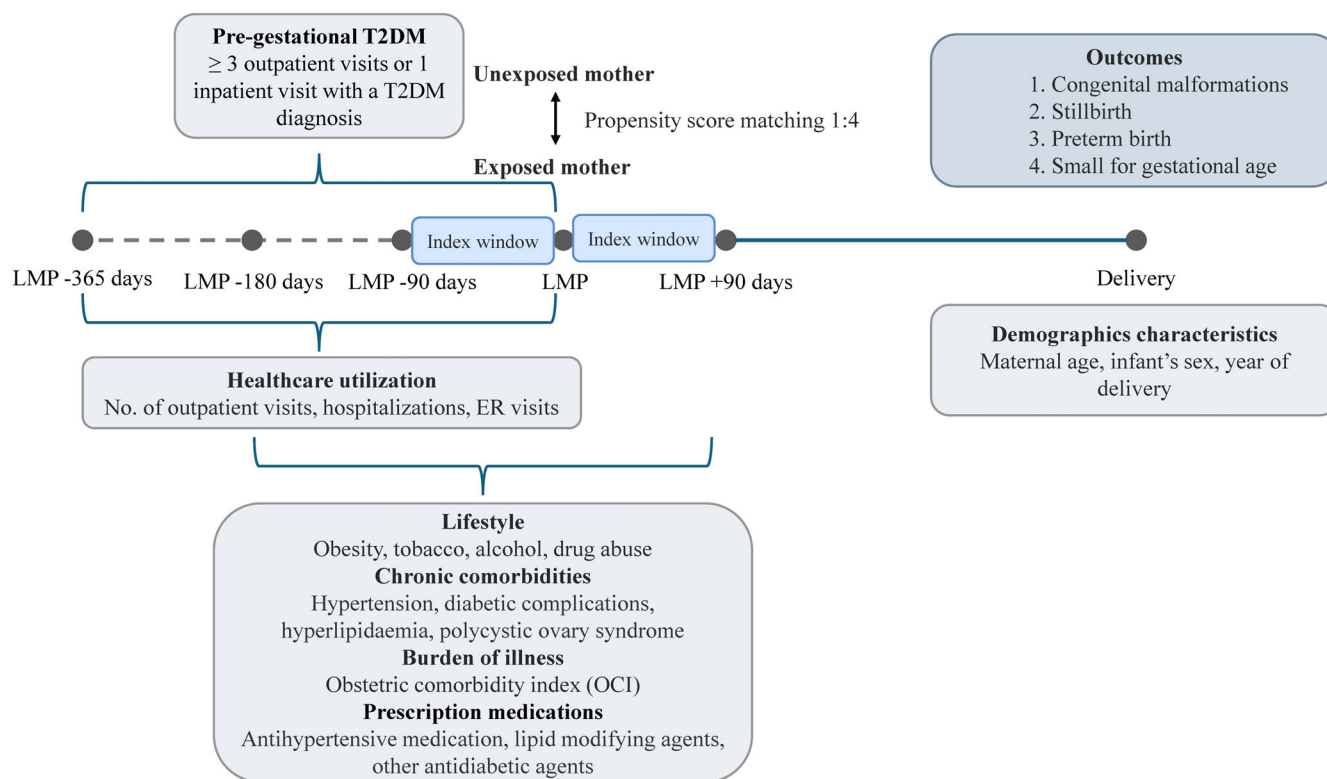


FIGURE 2 Study schema and timelines for periconceptional GLP-1 receptor agonist exposure. GLP-1, glucagon-like peptide-1 receptor agonist; T2DM, type 2 diabetes mellitus; LMP, last menstrual period (first day defined as day 0); ER, emergency room.

were ascertained from the BCA database, documented by the attending clinician within 7 days of delivery, and identified using BCA-specific congenital anomaly codes for 2014–2015 and International Classification of Diseases, Tenth Revision (ICD-10) codes for 2016–2022 (Table S4). Stillbirth was defined as foetal death at or after 20 completed weeks of gestation. Preterm birth was defined as delivery before 37 completed weeks of gestation. SGA was defined as birth weight below the 10th percentile for gestational age and sex, using a Taiwan-specific birth weight-for-gestational-age reference.²¹

2.5 | Covariates

Baseline characteristics were summarised by exposure group. We prespecified a broad set of covariates as potential confounders or proxies of confounding, covering maternal demographics, comorbidities, lifestyle factors, medication use, obstetric morbidity burden and health care utilisation.

Demographics included maternal age, nationality, infant sex and infant year of birth. Maternal comorbidities comprised hypertension, cardiac valvular disease, diabetes-related complications and polycystic ovary syndrome. Lifestyle factors captured via the BCA/NHI linkage included obesity, tobacco and alcohol use and indicators of substance use. Concomitant medication use included antihypertensive agents and lipid-modifying therapies, as well as other ADMs (e.g., metformin, sulfonylureas, SGLT-2 inhibitors and DPP-4 inhibitors), with drug

classes defined using Anatomical Therapeutic Chemical codes (Table S3). Given the distinct fetotoxic risk profile, ACE inhibitors/ARBs were handled separately rather than pooled with other antihypertensives (see Table S3 note). Use of antihypertensive agents and lipid-modifying therapies was assessed from LMP –180 days through LMP +90 days, whereas concomitant ADMs were assessed from LMP –90 days through LMP +90 days to align with the exposure window (Table S3).

To summarise the overall burden of maternal illness, we used the obstetric comorbidity index.²² Maternal comorbidities, lifestyle factors, medication use and obstetric comorbidity index were assessed from 6 months before the LMP (LMP –180 days) through the end of the first trimester (LMP +90 days). Health care utilisation was measured in the 12 months before the LMP (LMP –365 days to LMP) and included counts of outpatient visits, inpatient admissions, and emergency department visits. All variable definitions and coding rules are provided in Data S1 (Table S3).

2.6 | Statistical analysis

We summarised baseline characteristics of pregnancies by exposure status (GLP-1 RA vs. insulin). To control for confounding, we used propensity score (PS) matching to create a balanced cohort. We estimated the PS for exposure to GLP-1 RA using a multivariable logistic regression model that included all prespecified covariates

(demographics, lifestyle factors, maternal comorbidities, the obstetric comorbidity index, health care utilisation, antihypertensive and lipid-modifying therapies, and concomitant ADMs) without further variable selection.

To account for baseline differences between the treatment groups, we used PS matching to balance covariates. Using the estimated PS, we performed 1:4 greedy nearest-neighbour matching without replacement. This is a standard algorithm that sequentially matches each individual in the GLP-1 RA group with four individuals in the insulin group who have the closest PS. To prevent poor matches, we applied a calliper of 0.2 standard deviations of the logit of the PS, a widely recommended width shown in simulation studies to optimally balance bias reduction with sample size preservation.²³ We also required exact matching on maternal age group, infant year of birth and infant sex. We assessed covariate balance before and after matching using standardised mean differences (SMDs), with an absolute SMD >0.10 indicating a meaningful imbalance.²⁴

After matching, we estimated relative risks (RRs) and 95% confidence intervals (CIs) for each outcome using GEE models with a log link and Poisson distribution to account for the correlated nature of the matched pairs. Each outcome was analysed separately: analyses of preterm birth and SGA were restricted to live births, whereas the analysis of stillbirth included all eligible pregnancies. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

To assess the robustness of our primary findings, we conducted several prespecified sensitivity and subgroup analyses. First, to account for more continuous or substantial medication use, we applied a stricter definition of exposure, requiring two or more filled prescriptions during the periconceptional window. Second, to specifically evaluate the impact of postconception exposure, we restricted the exposure window to the first trimester only (from LMP through 90 days thereafter), again defining exposure as one or more prescriptions filled during this period. Third, given the distinct pregnancy risk profile of ACE inhibitors/angiotensin receptor blockers, we added a binary covariate (any dispensed ACE inhibitor/angiotensin receptor blocker within LMP $\pm$ 90 days) to the GEE outcome models in the matched cohort. Fourth, to address secular trends in GLP-1 RA uptake, we added calendar period (2014–2016, 2017–2019, 2020–2022) as a covariate to the post-match GEE outcome models.

3 | RESULTS

3.1 | Cohort assembly

Between January 1, 2014 and December 31, 2022, we identified 1 665 595 pregnancies in the birth certificate database. After excluding 2813 records with invalid or missing data, 1 662 782 pregnancies remained eligible. Of these, 1 656 798 did not meet criteria for pregestational T2DM, leaving 5984 pregnancies with pregestational T2DM. We then excluded 440 pregnancies for prespecified reasons (multiple pregnancy, suspected delivery date, no delivery record, no antenatal care, chromosomal abnormalities or first-trimester exposure

to known teratogens), yielding an analytic cohort of 5544 (Figure 1). Descriptively, periconceptional GLP-1 RA use in this analytic cohort increased across calendar years—from 3/563 (0.53%) in 2014 to 34/665 (5.11%) in 2022—with noticeable upticks after 2016 and 2020 (Figure S1).

3.2 | Exposure groups and matching

Restricting to the periconceptional exposure window (LMP – 90 to LMP + 90), 3351 pregnancies were eligible for the exposure comparison: 160 (4.8%) were exposed to a GLP-1 RA, and 3191 (95.2%) received insulin without GLP-1 RA. Using 1:4 greedy nearest-neighbour propensity PS matching, all 160 GLP-1 RA-exposed pregnancies were matched to 606 insulin comparators (total $n = 766$); 2585 insulin pregnancies were unmatched and excluded from matched analyses (Figure 1).

3.3 | Baseline characteristics

Before matching, patterns of concomitant ADM use differed between groups (Table 1): metformin 62.5% versus 55.0%, sulfonylureas 43.8% versus 31.9%, DPP-4 inhibitors 12.5% versus 28.3%, and SGLT-2 inhibitors 6.9% versus 14.9% in the GLP-1 RA-exposed versus insulin groups, respectively. After matching, baseline characteristics were comparable across groups (Table 1). In addition, we summarised ACE inhibitor/angiotensin receptor blocker dispensing within LMP $\pm$ 90 days; group-specific prevalences and the standardised mean difference are reported in Table S5.

3.4 | Primary outcomes (matched cohort)

In the PS matching cohort ($n = 766$; GLP-1 RA $n = 160$ vs. insulin $n = 606$), major congenital malformations occurred in 1/160 (0.6%) versus 1/606 (0.2%) pregnancies (RR 0.64, 95% CI 0.11–3.83). Stillbirth occurred in 7/160 (4.4%) versus 13/606 (2.1%) pregnancies (RR 2.05, 95% CI 0.82–5.13). Among live births (GLP-1 RA $n = 153$, insulin $n = 593$), preterm birth occurred in 53/153 (34.6%) versus 189/593 (31.9%) (RR 1.09, 95% CI 0.85–1.39), and SGA in 4/153 (2.6%) versus 18/593 (3.0%) (RR 0.86, 95% CI 0.31–2.41). No association reached statistical significance across outcomes; CIs were wider for the rarer endpoints (Figure 3).

3.5 | Sensitivity analyses

Using a stricter exposure definition of ≥ 2 filled prescriptions during the periconceptional window yielded estimates similar to the primary analysis: major congenital malformations 1/92 versus 2/350 (RR 1.90, 95% CI 0.17–20.9); stillbirth 3/92 versus 14/350 (RR 0.82, 95% CI 0.24–2.85); preterm birth 32/89 versus 101/336 (RR 1.20, 95%

CI 0.85–1.69); and SGA 3/89 versus 14/335 (RR 0.80, 95% CI 0.22–2.83). When the exposure was restricted to the first trimester alone, results were likewise consistent with the null: major congenital malformations 0/68 versus 1/260 (risk in exposed = 0; RR not estimable); stillbirth 2/68 versus 7/260 (RR 1.09, 95% CI 0.23–5.26); preterm

birth 26/66 versus 74/253 (RR 1.35, 95% CI 0.95–1.91); and SGA 3/66 versus 9/253 (RR 1.28, 95% CI 0.34–4.86). No sensitivity estimate reached statistical significance, and CIs were wide, reflecting a small number of exposed events (Figure 4). Baseline balance for ACE inhibitor/angiotensin receptor blocker exposure between groups is

TABLE 1 Baseline characteristics of pregnancies in women with pregestational type 2 diabetes, before and after propensity score matching (N = 3351).

Characteristics	Before matching			After matching		
	Exposed (n = 160)	Unexposed (n = 3191)	Standardised difference	Exposed (n = 160)	Unexposed (n = 606)	Standardised difference
Age at delivery, years	35.2 (4.7)	35.5 (5.0)	−0.062	35.2 (4.7)	35.1 (4.9)	0.021
Sex of infant						
Male	79 (49.4)	1663 (52.1)	−0.054	79 (49.4)	296 (48.8)	0.012
Female	81 (50.6)	1528 (47.9)	0.054	81 (50.6)	310 (51.2)	−0.012
Year of delivery						
2014–2016	19 (11.9)	992 (31.1)	−0.481	19 (11.9)	87 (14.4)	−0.074
2017–2019	53 (33.1)	1032 (32.3)	0.017	53 (33.1)	220 (36.3)	−0.067
2020–2022	88 (55.0)	1167 (36.6)	0.376	88 (55.0)	299 (49.3)	0.114
Lifestyle factors						
Obesity	19 (11.9)	164 (5.1)	0.246	19 (11.9)	70 (11.6)	0.009
Tobacco use	1 (0.6)	45 (1.4)	−0.080	1 (0.6)	4 (0.7)	0.012
Alcohol use	0 (0)	10 (0.3)	−0.078	0 (0)	0 (0)	0.000
Drug abuse	0 (0)	3 (0.1)	−0.045	0 (0)	0 (0)	0.000
Chronic comorbidities						
Hypertension	44 (27.5)	803 (25.2)	0.052	44 (27.5)	151 (24.9)	0.059
Diabetic complications	103 (64.4)	1473 (46.2)	0.372	103 (64.4)	379 (62.5)	0.039
Hyperlipidaemia	106 (66.3)	2072 (64.9)	0.029	106 (66.3)	381 (62.9)	0.079
Polycystic ovary syndrome	13 (8.1)	225 (7.1)	0.038	13 (8.1)	60 (9.9)	−0.063
Medication use						
Antihypertensive drug	45 (28.1)	789 (24.7)	0.077	45 (28.1)	159 (26.2)	0.059
Lipid-modifying agents	18 (11.3)	330 (10.4)	0.029	18 (11.3)	54 (8.9)	0.08
Metformin	100 (62.5)	1754 (55.0)	0.153	100 (62.5)	361 (59.6)	0.059
Sulfonylureas	70 (43.8)	1018 (31.9)	0.247	70 (43.8)	257 (42.4)	0.028
DPP-4 inhibitors	20 (12.5)	904 (28.3)	−0.400	20 (12.5)	95 (15.7)	−0.092
SGLT-2 inhibitors	11 (6.9)	474 (14.9)	−0.259	11 (6.9)	32 (5.3)	0.067
Obstetric comorbidity index						
1	48 (30.0)	896 (28.1)	0.042	48 (30.0)	188 (31.0)	−0.022
2	49 (30.6)	1015 (31.8)	−0.026	49 (30.6)	196 (32.3)	−0.037
≥3	63 (39.4)	1280 (40.1)	−0.014	63 (39.4)	222 (36.6)	0.058
Health-care utilisation						
Number of outpatient visits						
0–3	0 (0)	3 (0.1)	−0.045	0 (0)	0 (0)	0.000
>4	160 (100)	3188 (99.9)	0.045	160 (100)	606 (100)	0.000
Number of emergency room visits						
0	121 (75.6)	2393 (75.0)	0.014	121 (75.6)	461 (76.1)	−0.012
1	20 (12.5)	421 (13.2)	−0.021	20 (12.5)	71 (11.7)	0.025
>1	19 (11.9)	377 (11.8)	0.003	19 (11.9)	74 (12.2)	−0.009

(Continues)

TABLE 1 (Continued)

Characteristics	Before matching			After matching		
	Exposed (n = 160)	Unexposed (n = 3191)	Standardised difference	Exposed (n = 160)	Unexposed (n = 606)	Standardised difference
Number of inpatient visits						
0	106 (66.3)	2093 (65.6)	0.015	106 (66.3)	410 (67.7)	−0.030
1	27 (16.9)	637 (20.0)	−0.080	27 (16.9)	112 (18.5)	−0.042
>1	27 (16.9)	461 (14.4)	0.069	27 (16.9)	84 (13.9)	0.083

Note: Data are presented as mean (SD) or n (%). “Exposed” denotes any dispensing of a glucagon-like peptide-1 receptor agonist (GLP-1 RAs) during the periconceptional window (90 days before through 90 days after the last menstrual period [LMP]); “Unexposed” denotes insulin dispensing with no GLP-1 RA in the same window (other non-GLP-1 RA antidiabetic medications permitted). Maternal comorbidities, lifestyle factors, medication use, and the Obstetric Comorbidity Index were assessed from LMP − 180 to LMP + 90 days; concomitant antidiabetic medications (metformin, sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors) were assessed from LMP − 90 to LMP + 90 days; antihypertensive and lipid-modifying therapies from LMP − 180 to LMP + 90 days; and health-care utilisation (outpatient, emergency department, inpatient visits) during the 12 months before LMP (LMP − 365 to LMP). Abbreviations: DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2 inhibitors, sodium-glucose co-transporter 2 inhibitors.

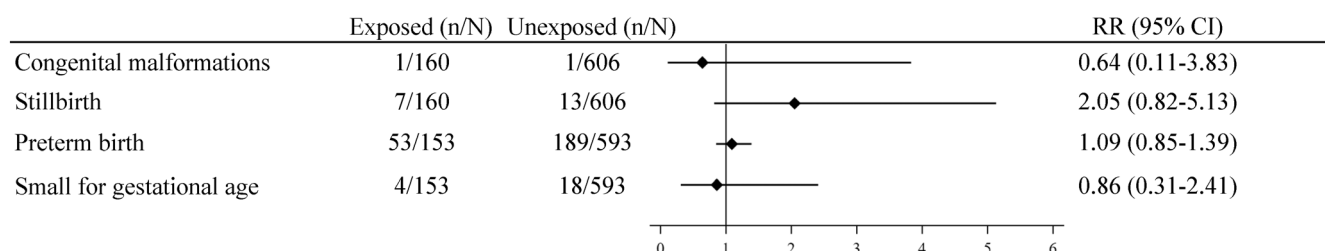


FIGURE 3 Adverse pregnancy outcomes after periconceptional GLP-1 receptor agonist exposure vs. insulin use (propensity-score-matched cohort). Counts are events/total. Points show risk ratios (RRs) with 95% confidence interval from log-link Poisson generalised estimating equations (GEE). GLP-1, glucagon-like peptide-1 receptor agonist.

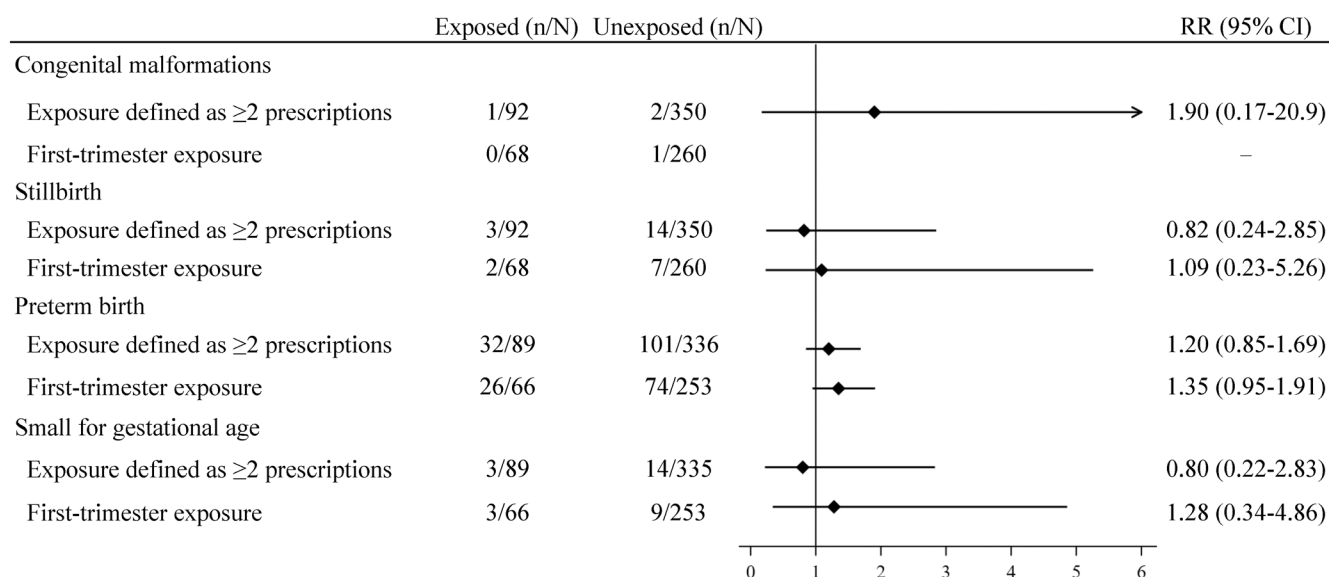


FIGURE 4 Sensitivity analyses of adverse pregnancy outcomes after periconceptional GLP-1 receptor agonist exposure versus insulin use (propensity-score-matched cohort). Two alternative exposure definitions are shown: (1) ≥2 prescriptions within the last menstrual period (LMP) −90 days to the LMP +90 days and (2) first-trimester exposure (LMP to +90 days). Counts are events/total. Points show risk ratios (RRs) with 95% confidence interval from log-link Poisson generalised estimating equations (GEE). GLP-1, glucagon-like peptide-1 receptor agonist.

shown in Table S5. Given the distinct pregnancy risk profile of ACE inhibitors/angiotensin receptor blockers, we additionally included a binary covariate for any ACE inhibitor/angiotensin receptor blocker dispensing within LMP $\pm$ 90 days in the matched GEE outcome models. Estimates across all four outcomes were materially unchanged and remained non-significant (Table S6). Finally, to address potential confounding from secular uptake over 2014–2022, we included the calendar period in the post-match GEE models; effect estimates were materially unchanged (Table S7).

4 | DISCUSSION

In this nationwide cohort of Taiwanese women with pregestational T2DM, we found no evidence of increased risk of major congenital malformations, stillbirth, preterm birth or SGA after periconceptional exposure to GLP-1 RAs (LMP $-$ 90 to LMP $+$ 90 days) compared with insulin. Risk estimates were near null in the matched cohort, with consistent results in sensitivity analyses requiring ≥ 2 prescriptions and those in which exposure was restricted to the first trimester. As periconceptional GLP-1 RA use increased between 2014 and 2022 in this population, the clinical question is no longer only whether harm exists but how best to contextualise potential foetal risks against maternal benefits achieved before conception.

Women with pregestational T2DM carry higher baseline risks for adverse pregnancy outcomes, risks that are at least partly mediated by hyperglycaemia, as poor glycaemic control is associated with increased rates of major congenital malformations and other adverse outcomes.^{25–28} During pregnancy, insulin is considered non-teratogenic and remains the standard therapy, whereas evidence regarding the effect of using non-insulin agents during organogenesis is limited; metformin may be considered according to some guidelines.^{10,29} Prior observational work on preconception glycaemic control often predated contemporary glucose-lowering strategies or focused on postconceptional exposure, and mostly did not adequately address confounding by indication.^{28,30,31} Against this background, our nationwide analysis found no increased risk of major congenital malformations, stillbirth, preterm birth or SGA after periconceptional exposure to GLP-1 RAs compared with insulin.

GLP-1 RA use has risen rapidly in recent years, paralleling uptake in the broader T2DM population and extending beyond diabetes to weight management.^{11,12,32,33} A multicentre, prospective cohort across six Teratology Information Services documented a sharp increase in weight-loss indications for GLP-1 RA in recent years.¹⁹ Given the high rate of unplanned pregnancies, inadvertent exposure to GLP-1 RAs, which are not approved for use in pregnancy, is plausible, and our findings provide initial reassurance for such exposures.

In a multinational cohort spanning the Nordic countries, the United States, and Israel, periconceptional exposure to GLP-1 RAs was not associated with a higher risk of major congenital malformations compared with insulin.¹⁷ Similarly, a multicentre prospective cohort that compared 168 first-trimester GLP-1 RA exposures with two reference groups (women with diabetes treated with non-GLP-1

RA ADMs and overweight/obese women without diabetes) found no excess risk of pregnancy loss in the GLP-1 RA group relative to either comparator.¹⁹ These findings align with our results; moreover, our study extends the evidence by demonstrating no increased risks of SGA or preterm birth following periconceptional GLP-1 RA exposure. In a recent Danish cohort including 32 first-trimester semaglutide exposures, risks of major malformations, preterm birth, large for gestational age, neonatal hypoglycaemia and jaundice were similar to those observed in insulin-exposed pregnancies, although estimates were imprecise given the small sample size.³³

Preclinical data suggest potential growth effects with GLP-1 receptor activation. In late-gestation mouse models, semaglutide reduced foetal weight even after maternal glycemia normalised and impaired placental development (smaller labyrinth zone and lower capillary density).³⁴ Systematic reviews also summarise reduced foetal growth, delayed ossification and skeletal variations with GLP-1 agonists in animals, often accompanied by decreased maternal food intake and weight loss.^{18,35} The discrepancy with our null SGA findings may reflect species and placental transport differences for large peptide drugs in humans, shorter and predominantly periconceptional exposure in our cohort versus sustained gestational dosing in animal studies, and a possible offset of growth effects by improved glycaemic control in clinical practice. Taken together with the preclinical growth signals and the limited, imprecise human evidence, current product labelling and clinical guidance generally advise against the use of GLP-1 receptor agonists during pregnancy and recommend prompt discontinuation once pregnancy is recognised. Until larger, agent-specific human studies across mid- to late gestation with longer-term offspring follow-up are available, preconception counselling should prioritise regimens with established safety, for example, insulin with or without metformin.

Furthermore, our study was primarily designed to evaluate safety signals related to inadvertent early exposures rather than to test therapeutic benefits. Nevertheless, emerging observational data suggest that pre- or early-pregnancy GLP-1 RA exposure in women with pregestational diabetes may be associated with lower odds of hypertensive disorders of pregnancy.³⁶ These signals highlight a risk–benefit tension: any potential maternal advantages from weight reduction and improved glycaemic control before conception must be weighed against uncertain foetal risks if exposure extends into organogenesis. Accordingly, current labelling/guidelines advise against intentional use during pregnancy; potential benefits should be pursued preconception with planned discontinuation and pregnancy-safe regimens during gestation. Future studies should move beyond harm-only frameworks to also assess benefit endpoints (e.g., large-for-gestational-age births and pre-eclampsia) under designs that minimise confounding.

This study leverages a nationwide, population-based cohort created through deterministic linkage of Taiwan's BCA and NHI databases, ensuring near-complete capture of pregnancies and dispensed medications in a system that covers >99% of residents. We used an active-comparator design (insulin) restricted to women with pregestational T2DM to mitigate confounding by indication and emulate real-world treatment choices. Confounding was further addressed through

propensity-score matching with exact constraints on maternal age group, infant year of birth, and infant sex, with balance assessed by standardised mean differences.

Despite our active-comparator design (insulin) and propensity-score matching with exact constraints, residual confounding cannot be excluded. In routine care, women with obesity or cardiometabolic comorbidities are more likely to receive GLP-1 RAs, which could bias risk estimates away from the null relative to insulin. Although we adjusted for a broad set of comorbidities, medications and health care utilisation, we lacked granular measures, such as glycated haemoglobin, prepregnancy BMI or weight trajectory, smoking, and other life-style factors; thus, glycaemic control and adiposity may not have been completely controlled for.

Stillbirth was identified from the birth registration system, which records live births and foetal deaths meeting the statutory threshold of ≥ 20 completed weeks of gestation or birth weight ≥ 500 g; therefore, foetal losses before 20 weeks or neonates with birth weight < 500 g were not included in our analyses. Preterm birth and SGA analyses were restricted to live births by design, as these outcomes are customarily defined among live-born infants and have distinct etiologies compared to those of stillbirth; stillbirth was analysed separately in the fully matched cohort. Although conditioning on live birth can introduce selection bias if exposure alters survival to delivery, our still-birth analysis showed no increased risk, making substantial selection bias unlikely.

Dispensing around the LMP does not ensure ingestion during organogenesis. Moreover, switching to metformin or insulin is possible. We mitigated this by requiring two or more prescriptions and by restricting exposure to the first trimester in sensitivity analyses. This approach yielded similar results, although low-level misclassification may persist. Statistical precision was limited because periconceptual GLP-1 RA exposure was uncommon ($1 = 160$), resulting in wide CIs for rare endpoints and precluding agent-specific analyses. This is a critical limitation, as grouping all GLP-1 RAs may mask important differences. Current human evidence is sparse, limited to small case series that are underpowered to compare risks between agents such as semaglutide, liraglutide, or dulaglutide.^{33,37,38} Furthermore, assuming a uniform “class effect” may be inappropriate, as these drugs vary significantly in molecular structure, half-life, and potential for placental transfer, suggesting that their safety profiles may also differ. Therefore, the inability to provide agent-specific risk estimates remains a key knowledge gap. Finally, generalisability may be constrained by Taiwan's health care system and reimbursement policies, as well as by our periconceptual window (LMP – 90 to LMP + 90). The findings should not be extrapolated to intentional use in planned pregnancy or to second- or third-trimester exposure without further study.

5 | CONCLUSION

In this nationwide cohort of women with pregestational T2DM, in whom infants are known to have higher baseline risks for adverse

outcomes, we found no evidence of increased risk of major congenital malformations, stillbirth, preterm birth, or SGA after periconceptual GLP-1 RA exposure compared with insulin use. Estimates were near the null in PS-matched analyses and remained consistent across sensitivity analyses (≥ 2 prescriptions; restriction to the first trimester). These findings should be interpreted as preliminary; larger agent-specific studies and ongoing surveillance are needed to refine risk estimates as use expands among women of reproductive age. Until more definitive evidence is available, preconception counselling should prioritise established pregnancy-safe therapies, and GLP-1 receptor agonists should not be intentionally used in planned pregnancy.

AUTHOR CONTRIBUTIONS

Yi-Chang Chou: Conceptualization, Resources, Formal analysis, Writing – original draft, Writing – review and editing. Hsiao-Yun Hu: Conceptualization, Resources, Writing – review & editing. Chieh-Hsing Liu: Conceptualization, Resources, Writing – review & editing. Feng-Shiang Cheng: Formal analysis, Methodology. Shih-Han Weng: Formal analysis, Methodology. Chih-Hao Tseng: Formal analysis.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the National Health Insurance Administration (NHIA) and the Health and Welfare Data Science Center (HWDC) for providing access to the databases used in this study. The analyses, interpretations, and conclusions are solely those of the authors and do not represent the official positions of the NHIA or HWDC. This study was supported by the Department of Health, Taipei City Government (11401-62-007).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70334>.

DATA AVAILABILITY STATEMENT

The Taiwan National Health Insurance Administration and Health and Welfare Data Science Center provided the birth certificate application and the population health insurance data used in this study. The corresponding author should be contacted, and only investigators who receive approval of a proposal and sign the data access agreement can get access to data.

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How to cite this article: Chou Y-C, Weng S-H, Cheng F-S, Tseng C-H, Hu H-Y, Liu C-H. Unintentional periconceptional exposure to glucagon-like peptide-1 receptor agonists and adverse pregnancy outcomes: A nationwide cohort study in Taiwan. *Diabetes Obes Metab*. 2026;28(2):1420-1430. doi:[10.1111/dom.70334](https://doi.org/10.1111/dom.70334)