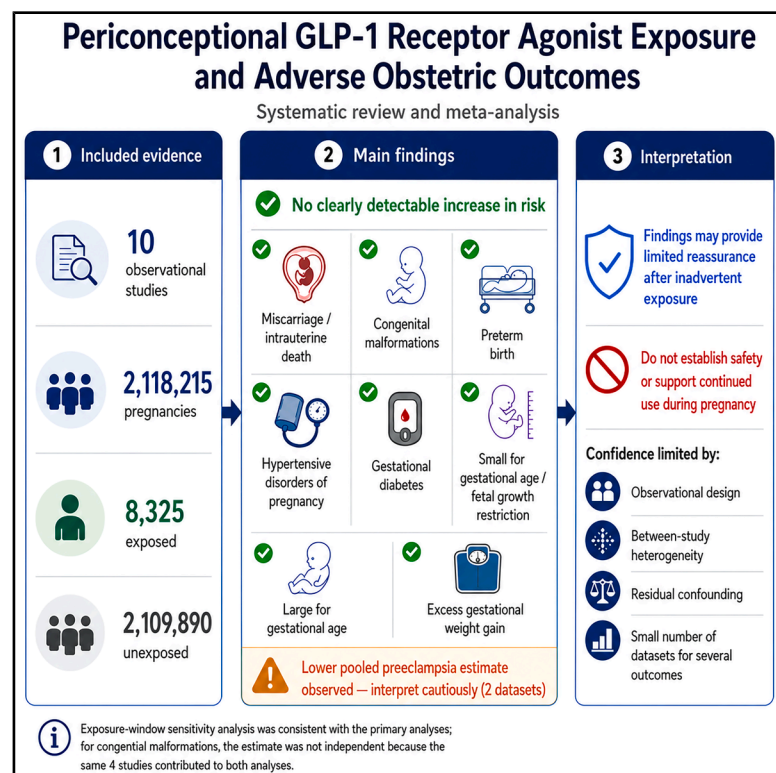


GLP-1 receptor agonist exposure in the periconceptional period and adverse obstetric outcomes: A systematic review and meta-analysis

Graphical abstract



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In brief

This systematic review and meta-analysis found no clearly detectable increase in adverse maternal or perinatal outcomes after periconceptional glucagon-like peptide-1 receptor agonist exposure on the basis of available evidence. However, observational design, heterogeneity, residual confounding, and limited datasets mean that these findings do not establish safety or support continued treatment during pregnancy.

Highlights

- No clearly detectable increase in adverse outcomes after periconceptional exposure
- Meta-analysis included more than 2.1 million pregnancies
- Congenital malformation findings were unchanged in the exposure-window analysis
- Lower pooled preeclampsia estimate requires confirmation



Translation to Population Health

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Meta-analysis/systematic review

GLP-1 receptor agonist exposure in the periconceptional period and adverse obstetric outcomes: A systematic review and meta-analysis

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CONTEXT AND SIGNIFICANCE Glucagon-like peptide-1 receptor agonists are used to treat diabetes and obesity, including by people who may become pregnant. Because these medicines are not recommended during pregnancy and safety data remain limited, it is important to understand outcomes after accidental exposure around conception. The authors combined evidence from observational studies examining outcomes after exposure that occurred before conception or during early pregnancy. They found no clearly detectable increase in miscarriage, congenital malformations, preterm birth, hypertensive disorders, gestational diabetes, or abnormal fetal growth. However, the studies were limited for several outcomes by differences in design, exposure definitions, adjustment methods, and small numbers. Overall, the findings may offer limited reassurance after inadvertent exposure, but they do not establish safety or support continued use during pregnancy.

SUMMARY

Background: This systematic review and meta-analysis assesses whether exposure to glucagon-like peptide-1 receptor agonists (GLP-1 RAs) during pregnancy or the periconceptional period is associated with adverse maternal and perinatal outcomes.

Methods: Medline, Embase, and the Cochrane Library were searched for observational studies comparing pregnancies exposed and unexposed to GLP-1 RAs within 6 months before a positive pregnancy test. Outcomes included miscarriage, intrauterine death, congenital anomalies, preterm birth (PTB), hypertensive disorders of pregnancy (HDP), gestational diabetes mellitus (GDM), fetal growth restriction (FGR), small for gestational age (SGA), large for gestational age (LGA), and excess gestational weight gain. Random-effects meta-analyses and subgroup analyses by indication were performed.

Findings: Ten studies included 2,118,215 women, of whom 8,325 were exposed and 2,109,890 were unexposed. Pooled estimates did not show a clearly detectable increase in miscarriage or intrauterine death, congenital anomalies, preterm birth, HDP, gestational diabetes, abnormal fetal growth, or excess gestational weight gain. A lower pooled estimate for preeclampsia was observed (odds ratio [OR]: 0.87, 95% confidence interval [CI]: 0.78–0.98; $p = 0.02$), but this was based on two datasets and should be interpreted cautiously. Subgroup analyses showed no clearly detectable differences by indication. The exposure-window sensitivity analysis, covering 90 days before conception through the end of the first trimester, used the same four studies as the primary congenital-malformation analysis and therefore was not independent.

Conclusion: Available observational evidence did not identify a clearly detectable increase in adverse maternal or perinatal outcomes following periconceptional exposure to GLP-1 RAs. However, these findings do not establish safety because of heterogeneity, residual confounding, and limited datasets.

Funding: None.

INTRODUCTION

The prevalence of obesity and diabetes has increased markedly worldwide, including among women of reproductive age. In 2022, 43% of adults globally were overweight, and approximately 16% were living with obesity.¹ Among women of reproductive age, the prevalence of obesity is estimated to be approximately 15%–20% globally, with substantially higher rates in some regions. Obesity is a multifactorial condition influenced by biological, sociocultural, environmental, and physiological factors, and women are disproportionately affected, with higher rates of diagnosis and treatment.² In parallel, hyperglycemia in pregnancy (HIP) remains a major contributor to maternal and perinatal morbidity, affecting an estimated 23.3 million live births (15.6%) globally.^{3,4} These epidemiologic trends have made metabolic disease increasingly central to preconception and antenatal care.

Obesity, pre-existing type 2 diabetes mellitus (T2DM), and gestational dysglycemia are associated with increased risks of adverse pregnancy outcomes, including hypertensive disorders of pregnancy (HDP), preeclampsia, fetal overgrowth, preterm birth (PTB), and long-term metabolic disease in offspring.^{5,6} Therefore, optimizing glycemic control and weight before conception is one of the cornerstones of perinatal care. However, treatment strategies in this population are evolving rapidly, particularly with the increasing use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), for glycemic control and weight management, raising important questions regarding periconceptional exposure.^{7,8}

GLP-1 RAs such as liraglutide, semaglutide, and dulaglutide have transformed the management of T2DM and obesity due to their efficacy in improving glycemic control, promoting weight loss, and reducing cardiometabolic risk.^{9,10} Their use among women of reproductive age has also increased substantially. In a large cohort of women aged 18–49 years, GLP-1 RA prescribing rose markedly between 2011 and 2022, with incidence increasing from 13.0 to 88.5 per 1,000 women with type 2 diabetes and from 0 to 14.9 per 1,000 women without type 2 diabetes.¹¹ Notably, only 21.2% of women had concurrent contraception coverage at initiation, and 2.2% had a documented pregnancy within 6 months of starting therapy, stressing the potential for unintended exposure during early pregnancy.¹¹

This is particularly relevant in the context of expanding indications for GLP-1 RAs in obesity management. Recent clinical trials and guideline updates have broadened the use of GLP-1 RAs beyond diabetes to include chronic weight management, leading to a substantial increase in GLP-1 RA prescriptions among individuals without diabetes, including women of reproductive age.^{9–11} This shift has increased the likelihood of periconception and early pregnancy exposure, particularly in the setting of unplanned pregnancies.

Furthermore, attention should be given to first-trimester exposure, when organogenesis occurs, and potential teratogenic risks are greatest. During this critical developmental window, disruptions in cellular differentiation and organ formation may result in structural congenital anomalies.^{12,13} Drug exposures during this period are therefore of particular concern, and even transient exposure prior to pregnancy recognition may be clinically relevant.

Despite their increasing use, GLP-1 RAs are not recommended during pregnancy. Clinical guidelines advise discontinuation prior to conception due to limited human safety data and evidence of reproductive toxicity in animal studies.¹⁴ Regulatory guidance similarly notes insufficient human data and recommends discontinuation of agents such as semaglutide at least 2 months before a planned pregnancy due to prolonged drug half-life.^{15,16}

In addition, human data on GLP-1 RAs exposure in pregnancy remain limited and heterogeneous. The largest prospective multicenter cohort to date, including 168 first-trimester exposures, found no increased risk of major congenital anomalies compared with reference groups (2.6% vs. 2.3%; adjusted odds ratio [OR]: 0.98, 95% confidence interval [CI]: 0.16–5.82).¹⁷ However, sample sizes remain small, and outcomes such as fetal growth, PTB, and longer term child health are insufficiently characterized. Emerging evidence also highlights the complexity of interpreting these data, as underlying maternal metabolic disease, obesity, and treatment discontinuation may independently influence outcomes, making causal inference challenging.¹⁸

Given the rapid increase in GLP-1 RA use and the growing number of pregnancies with unintended exposure, there is a critical need to systematically evaluate the available evidence. This meta-analysis aims to assess the association between maternal exposure to GLP-1 RAs during pregnancy or the periconception period and adverse maternal and neonatal outcomes, including congenital malformations, miscarriage or intrauterine death (IUD), PTB, HDP, gestational diabetes, fetal growth abnormalities, and excess gestational weight gain.

RESULTS

Study selection and characteristics

The literature search identified 1,093 articles, 34 of which were assessed for eligibility for inclusion (Figure 1; Table S2). Ten observational studies were included in the systematic review, and after excluding studies with potentially overlapping cases, 9 were included in the meta-analysis^{17–26} (Table 1). The 10 studies included 2,118,215 women, 8,325 exposed to GLP-1 RAs and 2,109,890 unexposed in the periconceptional period.

The results of the quality assessment of the included studies using the Newcastle-Ottawa Scale (NOS) are presented in

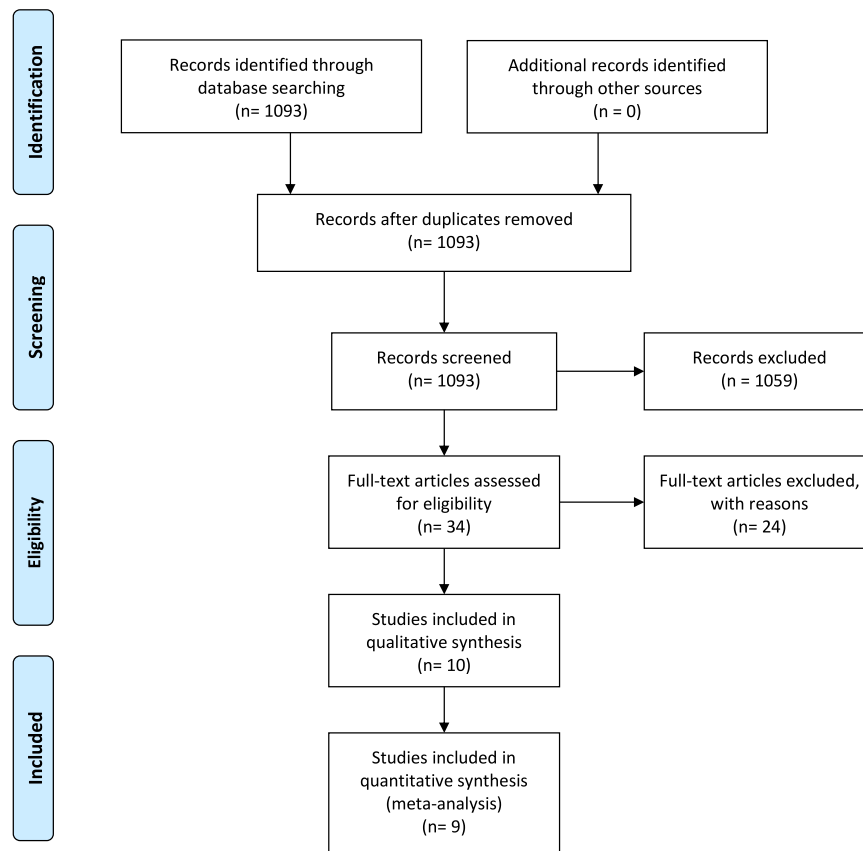


Figure 1. Systematic review flowchart

(OR: 0.87, 95% CI: 0.78–0.98; $p = 0.02$) (Figure 3B; Table 2). However, this finding was based on only two datasets, with one study contributing most of the statistical weight, and should therefore be interpreted cautiously.

Subgroup analyses by indication for GLP-1 RA use

Subgroup analyses by indication for GLP-1 RA use yielded findings consistent with the primary analyses. When considering women taking GLP-1 RAs in the periconceptional period for type 1 or type 2 diabetes, the pooled estimates did not show a clearly detectable difference in the risk of congenital malformations (OR: 0.94, 95% CI: 0.72–1.24; $p = 0.7$), PTB (OR: 1.36, 95% CI: 0.81–2.30; $p = 0.3$), HDP (OR: 0.84, 95% CI: 0.59–1.18; $p = 0.3$), SGA or FGR (OR: 1.28, 95% CI: 0.90–1.82; $p = 0.2$), or LGA (OR: 0.88, 95% CI: 0.67–1.15; $p = 0.3$) between exposed and unexposed individuals (Table 2).

When considering women taking GLP-1 RAs for weight management, the pooled estimates did not show a clearly detectable difference in the risk of HDP (OR: 0.87, 95% CI: 0.63–1.19; $p = 0.4$), SGA or FGR (OR: 0.88, 95% CI: 0.66–1.18; $p = 0.4$), or LGA (OR: 1.14, 95% CI: 0.95–1.37; $p = 0.2$) between exposed and unexposed population (Table 2).

Table S3. Most of the included studies received a moderate score for the selection and comparability of study groups, as well as for outcome ascertainment. The primary weaknesses were the lack of stratification of their analysis by exposure duration and timing, and heterogeneity in how outcomes were defined.

Synthesis of the results

The pooled estimates did not show a clearly detectable increase in the risk of IUD or miscarriage (OR: 1.30, 95% CI: 0.76–2.23; $p = 0.3$) (Figure 2A; Table 2), congenital malformations (OR: 0.92, 95% CI: 0.71–1.19; $p = 0.5$) (Figure 2B; Table 2), PTB (OR: 1.05, 95% CI: 0.80–1.38; $p = 0.8$) (Figure 2C; Table 2), small for gestational age (SGA) or fetal growth restriction (FGR) (OR: 0.99, 95% CI: 0.78–1.25; $p = 0.9$) (Figure 2D; Table 2), or large for gestational age (LGA) (OR: 1.04, 95% CI: 0.90–1.21; $p = 0.6$) (Figure 2E; Table 2) among pregnancies exposed compared with those unexposed to GLP-1 RAs in the periconceptional period.

Similarly, the pooled estimates did not show a clearly detectable increase in HDP (OR: 0.92, 95% CI: 0.76–1.11; $p = 0.4$) (Figure 3A; Table 2), gestational diabetes mellitus (GDM) (OR: 0.94, 95% CI: 0.74–1.21; $p = 0.6$) (Figure 3C; Table 2), or excess gestational weight gain (OR: 0.90, 95% CI: 0.52–1.57; $p = 0.7$) (Figure 3D; Table 2). Substantial between-study heterogeneity was observed for PTB ($I^2 = 85\%$), HDP ($I^2 = 82\%$), gestational diabetes ($I^2 = 79\%$), and excess gestational weight gain ($I^2 = 81\%$). A lower pooled estimate for preeclampsia was observed

Exposure-window sensitivity analyses

Although detailed analyses by treatment duration were not feasible, exposure-window sensitivity analyses were performed using studies that defined exposure as occurring from 90 days before conception through the end of the first trimester (Figure 4; Table 3). Findings were broadly consistent with the primary analyses. For congenital malformations, the sensitivity analysis included the same four studies and participants as the primary analysis and produced the same pooled estimate (OR: 0.92, 95% CI: 0.71–1.19; $I^2 = 0\%$) (Figure 4; Table 3); therefore, this result should not be interpreted as an independent confirmatory analysis.

DISCUSSION

Summary of the main findings

This systematic review and meta-analysis did not identify a clearly detectable increase in adverse maternal or neonatal outcomes following periconceptional exposure to GLP-1 RAs. The pooled estimates did not show clearly detectable increases in PTB, HDP, SGA or FGR, miscarriage or IUD, or congenital

Table 1. General characteristics of the included studies

Author	Year	Country	Study design	Period considered	Drug analyzed	Indication for GLP-1 RA intake	Sub-analysis according to pregestational diabetes & weight management	Timing of exposure	Outcomes observed	Cases (N)
Hviid et al. ¹⁸	2026	Denmark	retrospective nationwide observational cohort study	2009–2023	liraglutide/semaglutide	diabetes, weight management, and hypertension	yes (diabetes and weight management)	within 8 weeks before or after LMP	PTB, PE, SGA, LGA, IUD/ miscarriage	756,636
Chou et al. ¹⁹	2025	Taiwan	retrospective nationwide observational cohort study	2013–2022	any GLP-1 RA	pregestational diabetes	yes (diabetes)	90 days before and after LMP	anomalies, IUD/ miscarriage, PTB, and SGA	766
Hanif et al. ²⁰	2025	United States	retrospective nationwide observational cohort study	2005–2203	any GLP-1 RA	type II GDM	yes (diabetes)	within 1 year before and 1 month after diagnosis of first trimester of pregnancy	PE, GH, anomalies	3,652
Imbroane et al. ²¹	2025	United States	retrospective nationwide observational cohort study	Not reported	any GLP-1 RA	diabetes, obesity, hypertension	not reported	within the 2 years preceding pregnancy	PTB, PE, GH	9,254
Maya et al. ²²	2025	United States	retrospective cohort study	2015–2016	any GLP-1 RA	diabetes, obesity, hypertension	yes (diabetes & weight management)	between 3 years before and 90 days after conception	FGR/SGA, LGA, PTB, HDP, GDM	1,792
Pondugula et al. ²³	2025	United States	retrospective cohort study	2014–2024	any GLP-1 RA	pregestational diabetes, weight management	yes (pregestational diabetes and weight management)	up to 1 year before pregnancy with 64.5% in pregnancy	HDP, PTB, FGR, LGA, GDM, IUD	618
Broe et al. ²⁶	2025	Denmark	retrospective nationwide observational cohort study	2004–2017	liraglutide	not reported	not reported	first trimester exposure	anomalies	570,466
Cesta et al. ²⁴	2024	Finland, Iceland, Israel, Norway, Sweden, and United States	multinational observational population-based cohort	2009–2021	any GLP-1 RA	pregestational diabetes	yes (diabetes)	from 90 days before pregnancy to the end of first trimester	anomalies	6,016
Dao et al. ¹⁷	2024	Germany, Israel, Italy, Switzerland, and the United Kingdom	retrospective nationwide observational cohort study	2009–2022	any GLP-1 RA	pregestational diabetes, weight management	yes (pregestational diabetes and weight management)	exposure during the first trimester	anomalies, IUD/ miscarriage	372
Bartelt et al. ²⁵	2024	United States	retrospective cohort study	2017–2024	any GLP-1 RA	weight management	not reported	90 days before pregnancy	PTB, anomalies	772,295

PE, preeclampsia; PTB, preterm birth; IUD, intrauterine demise; LMP, last menstrual period; GH, gestational hypertension.

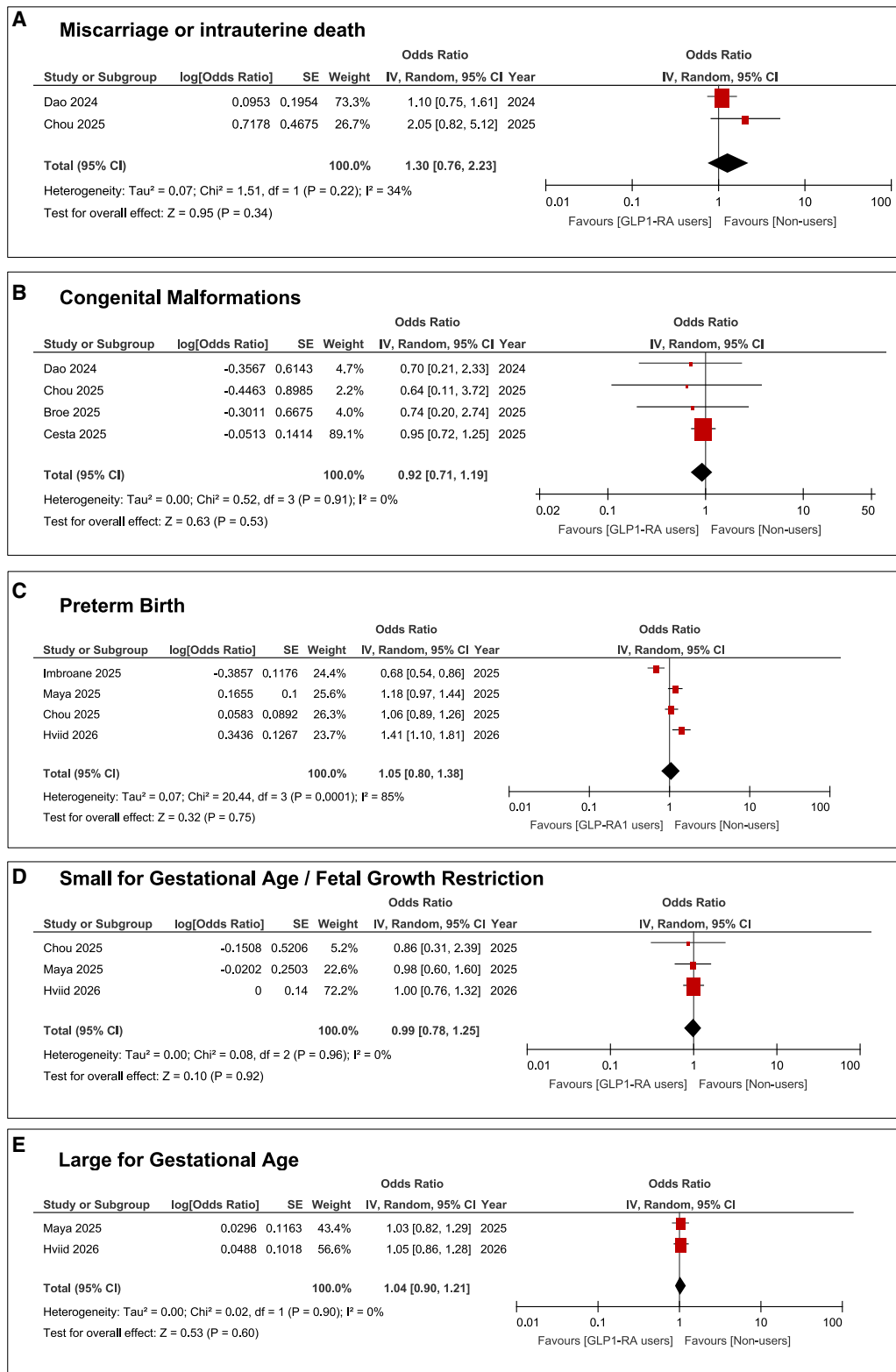


Figure 2. Association between periconceptional glucagon-like peptide-1 receptor agonist exposure and fetal and perinatal outcomes

Forest plots showing the pooled odds ratios for (A) miscarriage or intrauterine death, (B) congenital malformations, (C) preterm birth, (D) small for gestational age or fetal growth restriction, and (E) large for gestational age among pregnancies exposed to glucagon-like peptide-1 receptor agonists

(legend continued on next page)

malformations. However, the absence of a statistically detectable increase should not be interpreted as evidence that these treatments are safe during pregnancy. An exposure-window sensitivity analysis covering the period from 90 days before conception through the end of the first trimester yielded findings consistent with the primary analyses. However, for congenital malformations, the sensitivity analysis included the same four studies as the primary analysis and therefore did not constitute independent confirmatory evidence.

A statistically significant reduction in the risk of preeclampsia was observed; however, this finding should be interpreted with caution. Periconceptional exposure to GLP-1 RAs was associated with an approximately 15% reduction in risk, but the available data did not allow stratification by indication, timing or duration of exposure, or specific agents, thereby limiting causal interpretation.

Given that obesity is associated with a 2- to 4-fold increased risk of preeclampsia and that the condition occurs more frequently in women with type 1 and type 2 diabetes, reaching rates of up to 15%–20% and 10%–14%, respectively, compared with 2%–7% in pregnancies without diabetes, this observed association is more likely explained by differences in baseline metabolic risk rather than a direct pharmacological effect.^{27–30}

In particular, residual confounding, including preconception weight loss, improved glycemic control, and differences in healthcare engagement among GLP-1 RA users, may account for the apparent reduction in risk. Furthermore, the inability to account for exposure timing and duration raises the possibility that this association reflects preconception metabolic optimization rather than drug exposure during pregnancy. Considering these limitations and the observational nature of the available data, any potential protective effect remains unproven, and this finding should be considered hypothesis generating rather than evidence of causality. Furthermore, the pooled estimate was based on only two datasets, one of which contributed nearly 90% of the statistical weight. In addition, multiple outcomes were examined in this review, raising the possibility that this isolated statistically significant finding may have occurred by chance. Notably, recent systematic reviews and meta-analyses have not consistently demonstrated an association between GLP-1 RA exposure and preeclampsia, further supporting cautious interpretation of this finding.^{7,31–33}

Comparison to other studies

The findings presented here are consistent with recent systematic reviews and meta-analyses, which have not demonstrated a clear increase in the risk of major congenital malformations, pregnancy loss, or PTB following periconceptional or early pregnancy exposure to GLP-1 RAs.^{7,31–33} In particular, pooled analyses have reported no statistically significant differences in key outcomes, including miscarriage, preterm delivery, stillbirth, FGR, and major birth defects between exposed and unexposed pregnancies.^{31–33}

Recent evidence has further suggested that GLP-1 RA exposure is not consistently associated with increased maternal, fetal, or neonatal risk, although these findings are based on limited and heterogeneous observational data.^{7,31–33} Some analyses have reported potentially favorable maternal outcomes; however, these observations are likely influenced by residual confounding and differences in baseline metabolic risk and therefore should be interpreted cautiously.

Importantly, most prior meta-analyses have focused predominantly on fetal outcomes, particularly congenital malformations and pregnancy loss, with comparatively limited evaluation of maternal endpoints. In this context, the present study extends the existing literature and provides a more comprehensive assessment across a broader range of maternal and perinatal outcomes, including HDP, gestational diabetes, fetal growth abnormalities, and PTB.

Several outcomes demonstrated substantial statistical heterogeneity, particularly PTB, HDP, gestational diabetes, and excess gestational weight gain. This likely reflects differences in exposure definitions, study populations, treatment indications, outcome ascertainment, and adjustment strategies across studies. Restricting analyses to studies reporting exposure from 90 days before conception through the first trimester reduced heterogeneity for some outcomes, suggesting that variation in exposure definition contributed to between-study variability.

The substantial heterogeneity indicates that these pooled estimates average across clinically and methodologically diverse studies, reducing confidence in the summary effects and limiting their applicability to specific agents, indications, exposure windows, or patient groups.

Strengths of this study

The strengths of this study include a comprehensive and systematic literature search, inclusion of adjusted effect estimates, and evaluation of a wide range of clinically relevant maternal and neonatal outcomes. Furthermore, stratified analyses according to indication for GLP-1 RA use (diabetes vs. weight management) provide further insight into potential sources of confounding. The use of a prespecified exposure-window sensitivity analysis helped assess whether variation in exposure definitions contributed to heterogeneity, although several estimates were based on the same studies as the primary analyses.

Clinical and research implications

GLP-1 RAs have revolutionized the management of type 2 diabetes and obesity by improving glycemic control, promoting weight loss, and reducing cardiometabolic risk.^{9,10} Their use among women of reproductive age has increased considerably, driven by expanding indications for weight management, including in individuals without diabetes.^{6–9,28} This trend increases the likelihood of accidental exposure during the periconceptional and early pregnancy periods, particularly in the

compared with unexposed pregnancies. Pooled estimates were calculated using a random-effects generic inverse-variance approach. Squares represent individual study estimates, with square size proportional to study weight; horizontal lines represent 95% confidence intervals; and diamonds represent pooled estimates. OR, odds ratio; CI, confidence interval; IUD, intrauterine death; SGA, small for gestational age; FGR, fetal growth restriction; LGA, large for gestational age.

Table 2. Risk of adverse obstetric outcomes in pregnancies with periconceptional exposure to GLP-1 receptor agonists, versus unexposed pregnancies

Outcome	No. of datasets (total sample)	Pooled OR (95% CI)	p value	I ² , %
1. Pre-term birth				
All sample	4 (1,079,725)	1.05 (0.80–1.38)	0.8	85
Diabetes	2 (1,067,889)	1.36 (0.81–2.30)	0.3	89
2. Hypertensive disorders of pregnancy				
All sample	4 (1,078,629)	0.92 (0.76–1.11)	0.4	82
Diabetes	2 (1,067,421)	0.84 (0.59–1.18)	0.3	0
Obesity/overweight	2 (1,067,590)	0.87 (0.63–1.19)	0.4	0
3. Preeclampsia				
All sample	2 (1,076,715)	0.87 (0.78–0.98)	0.02	0
4. Gestational diabetes				
All sample	3 (1,078,367)	0.94 (0.74–1.21)	0.6	79
5. SGA				
All sample	3 (1,069,975)	0.99 (0.78–1.25)	0.9	0
Diabetes	3 (1,068,297)	1.28 (0.90–1.82)	0.2	0
Obesity/overweight	2 (1,068,610)	0.88 (0.66–1.18)	0.4	0
6. LGA				
All sample	2 (1,069,229)	1.04 (0.90–1.21)	0.6	0
Diabetes	2 (1,067,551)	0.88 (0.67–1.15)	0.3	0
Obesity/overweight	2 (1,068,610)	1.14 (0.95–1.37)	0.2	0
7. IUD/miscarriage				
All sample	2 (1,138)	1.30 (0.76–2.23)	0.3	34
8. Excess weight gain				
All sample	2 (2,882)	0.90 (0.52–1.57)	0.7	81
9. Congenital malformations				
All sample	4 (577,620)	0.92 (0.71–1.19)	0.5	0
Diabetes	2 (6,782)	0.94 (0.72–1.24)	0.7	0

When possible, all analyses were performed: (1) in the overall sample of women, (2) considering only individuals with diabetes, and (3) considering only individuals with overweight/obesity. All meta-analyses are based upon a generic inverse-variance approach.

OR, odds ratio; CI, confidence interval; SGA, small for gestational age; LGA, large for gestational age; IUD, intrauterine death.

context of unplanned pregnancies, in a setting where evidence on safety across these reproductive stages remains limited and continues to evolve.³⁴

Despite this increasing use, GLP-1 RAs are not recommended during pregnancy and are generally advised to be discontinued prior to conception, in line with current regulatory and clinical guidance. These recommendations are based on limited human safety data and evidence from animal studies demonstrating potential teratogenic effects, including impaired fetal growth, skeletal abnormalities, placental disruption, and embryotoxicity.³⁵

In addition to potential direct effects on embryonic and placental development, GLP-1 RAs may theoretically influence pregnancy outcomes through indirect mechanisms.^{36,37} These include reduced caloric intake and weight loss, which may impact fetal growth, as well as worsening of nausea and vomiting,^{34,37} potentially leading to dehydration and electrolyte imbalance.

In this context, the present findings may provide limited reassurance following inadvertent periconceptional exposure. However, the congenital-malformation estimate from the exposure-window sensitivity analysis, covering 90 days before conception through the end of the first trimester, was based on the same four

studies as the primary analysis and did not provide independent confirmatory evidence. These findings should not be interpreted as establishing safety or supporting continued use during pregnancy, given the limited and observational nature of the available data.

From a clinical perspective, these findings support a balanced approach to counseling women who are inadvertently exposed to GLP-1 RAs prior to or in early pregnancy, allowing for reassurance while maintaining current recommendations to discontinue treatment before conception.

From a research perspective, there remains a critical need for large, well-designed studies with detailed characterization of exposure timing, duration, and indication, as well as robust adjustment for confounding factors. In particular, future research should aim to disentangle the effects of GLP-1 RAs from underlying maternal metabolic risk and preconception optimization, which are likely to play a key role in observed associations.

Conclusions

Available observational evidence did not identify a clearly detectable increase in adverse maternal or neonatal outcomes

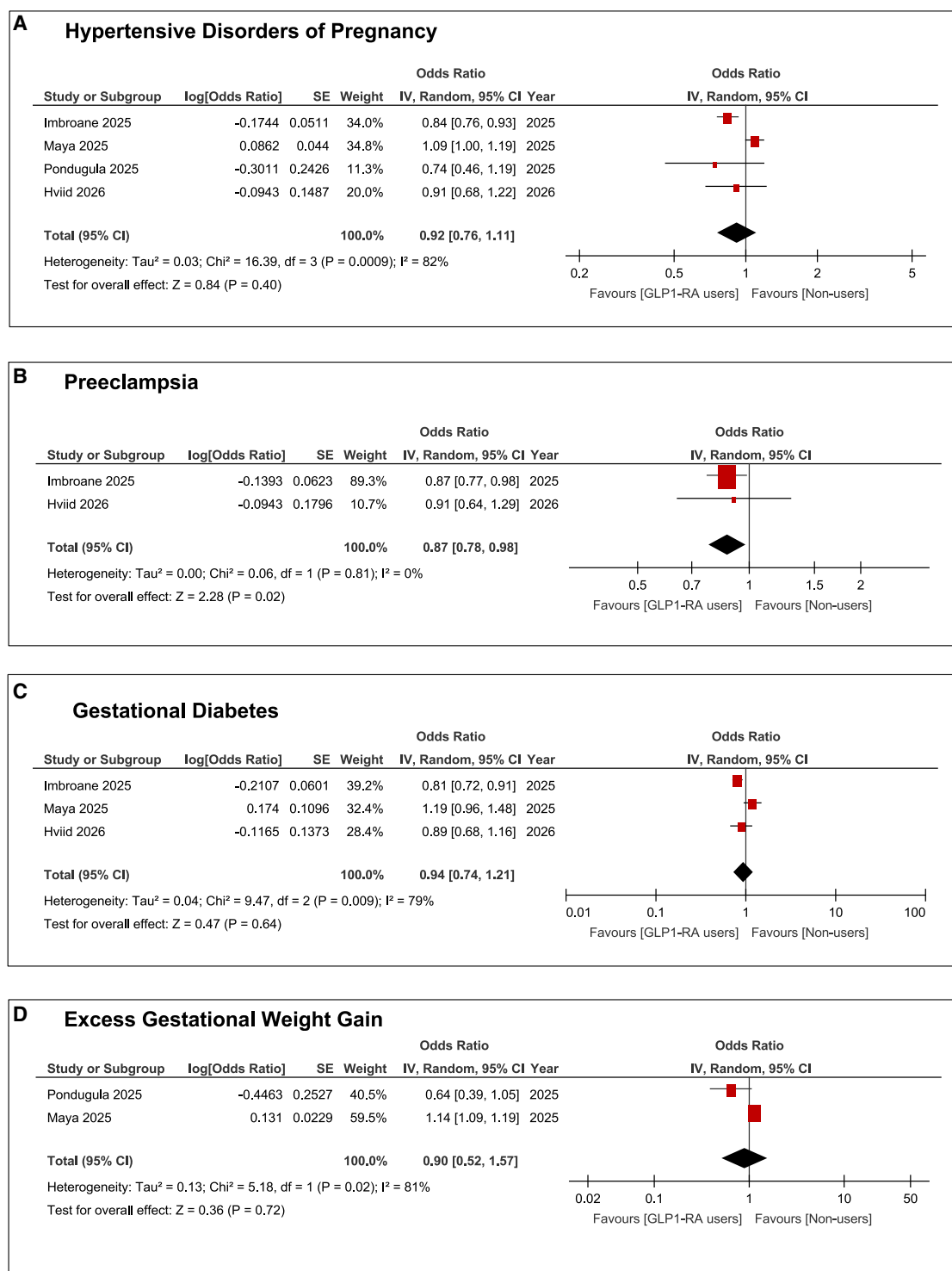


Figure 3. Association between periconceptional glucagon-like peptide-1 receptor agonist exposure and maternal outcomes

Forest plots showing the pooled odds ratios for (A) hypertensive disorders of pregnancy, (B) preeclampsia, (C) gestational diabetes, and (D) excess gestational weight gain among pregnancies exposed to glucagon-like peptide-1 receptor agonists compared with unexposed pregnancies. Pooled estimates were calculated using a random-effects generic inverse-variance approach. Squares represent individual study estimates, with square size proportional to study weight; horizontal lines represent 95% confidence intervals; and diamonds represent pooled estimates. The pooled preeclampsia estimate was based on two datasets and should be interpreted cautiously. OR, odds ratio; CI, confidence interval.

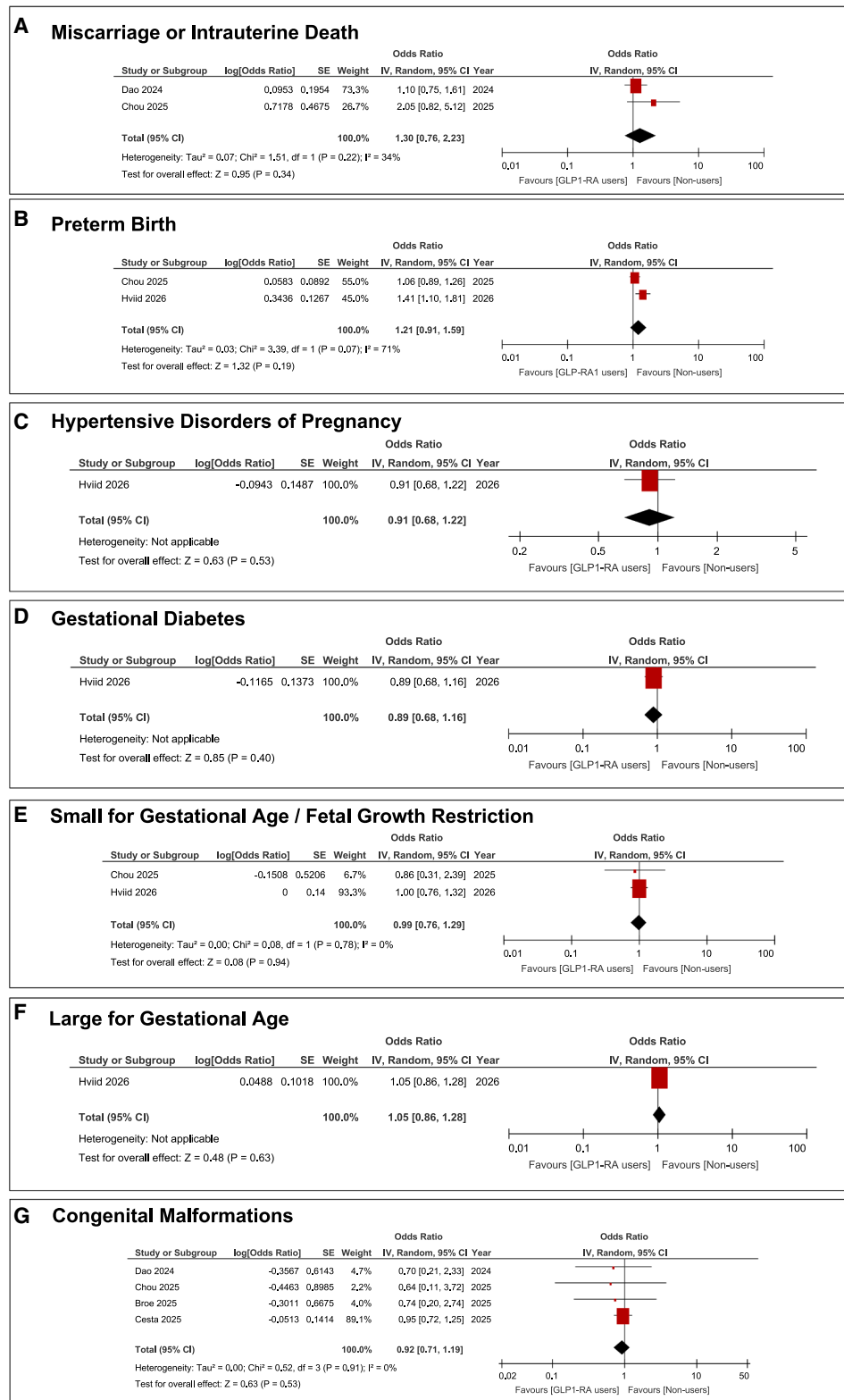


Figure 4. Exposure-window sensitivity analyses of maternal and perinatal outcomes

Forest plots restricted to studies defining exposure from 90 days before conception through the end of the first trimester, showing pooled odds ratios for (A) preterm birth, (B) hypertensive disorders of pregnancy, (C) gestational diabetes, (D) small for gestational age, (E) large for gestational age, (F) miscarriage or (legend continued on next page)

Table 3. Exposure-window sensitivity analyses restricted to studies defining exposure from 90 days before conception through the end of the first trimester: Risk of selected obstetric outcomes among pregnancies exposed to glucagon-like peptide-1 receptor agonists compared with unexposed pregnancies

Outcome	No. of datasets (total sample)	Pooled estimates		
		OR (95% CI)	p value	I ² , %
Preterm birth	2 (1,068,207)	1.21 (0.91–1.59)	0.2	71
Hypertensive disorders of pregnancy	1 (1,067,461)	0.91 (0.68–1.22)	0.5	–
Gestational diabetes	1 (1,067,461)	0.89 (0.68–1.16)	0.4	–
SGA	2 (1,068,207)	0.99 (0.76–1.29)	0.9	0
LGA	1 (1,067,461)	1.05 (0.86–1.28)	0.6	–
IUD/miscarriage	2 (1,138)	1.30 (0.76–2.23)	0.3	34
Congenital malformations	4 (577,620)	0.92 (0.71–1.19)	0.5	0

All meta-analyses were performed using a generic inverse-variance approach.

OR, odds ratio; CI, confidence interval; SGA, small for gestational age; LGA, large for gestational age; IUD, intrauterine death.

For congenital malformations, the same four studies, participants, and pooled data contributed to both the primary analysis in Table 2 and the exposure-window sensitivity analysis in Table 3. This estimate is therefore not independent of the primary analysis.

following periconceptional exposure to GLP-1 RAs. However, these findings do not establish safety, because the evidence is limited by heterogeneity in exposure definitions, residual confounding, and the small number of studies contributing to several outcomes.

The findings may provide limited reassurance following inadvertent exposure before conception or during early pregnancy, but they should not be interpreted as supporting continued treatment during pregnancy. Until more robust evidence is available, current recommendations to discontinue GLP-1 RAs before conception should remain unchanged. Further large-scale studies with detailed assessment of exposure timing, duration, indication, and potential confounders are required.

Limitations of the study

This study has several limitations. The evidence was derived exclusively from observational studies and therefore remains susceptible to residual confounding, despite the inclusion of adjusted estimates. The number of studies contributing to several outcomes was small, limiting statistical power and the precision of the pooled estimates. Substantial between-study heterogeneity was observed for several outcomes, reflecting differences in study populations, indications for treatment, exposure definitions, outcome ascertainment, and adjustment strategies; consequently, confidence in the summary estimates is reduced. Exposure timing, duration, dose, and specific GLP-1 RAs could not be assessed consistently, and concomitant medications were incompletely reported. Definitions of fetal growth outcomes varied, and organ-specific congenital malformations, diabetes subtype, and longer term child outcomes could not be examined. The included studies involved pregnant participants or individuals of reproductive age; however, reporting of age

distributions, sex assigned at birth, gender identity, race or ancestry, ethnicity, and socioeconomic status was inconsistent or unavailable. The methods used to collect these demographic characteristics were also generally not reported. Therefore, the representativeness and generalizability of the findings to specific demographic, geographic, and socioeconomic populations remain uncertain. Eligibility and exclusion criteria, including those relating to breastfeeding or reproductive status before pregnancy, were determined by the individual source studies and were not consistently reported.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Professor Asma Khalil (asma.khalil@stgeorges.nhs.uk).

Materials availability

This study did not generate new unique reagents or other research materials.

Data and code availability

All data analyzed in this systematic review and meta-analysis were derived from previously published studies cited in the article and are summarized in the main and supplemental tables and figures. No original participant-level dataset was generated for this study. No custom code was generated. Meta-analyses were performed using Review Manager (RevMan), version 5.4. Additional information required to reanalyze the data reported in this paper is available from the lead contact upon reasonable request.

AUTHOR CONTRIBUTIONS

F.D'A. and M.E.F. performed the statistical analyses. A.K. oversaw and verified the analyses. F.D'A., M.E.F., L.M., A.S., and A.K. had unrestricted access to all data included in the systematic review and meta-analysis. F.D'A., A.S., and A.K. prepared the first draft of the manuscript. All authors critically reviewed

intrauterine death, and (G) congenital malformations. Pooled estimates were calculated using a random-effects generic inverse-variance approach. Squares represent individual study estimates, with square size proportional to study weight; horizontal lines represent 95% confidence intervals and diamonds represent pooled estimates. For congenital malformations, the same four studies and participants contributed to both the primary and exposure-window sensitivity analyses; therefore, this estimate is not independent of the primary analysis. OR, odds ratio; CI, confidence interval; IUD, intrauterine death; SGA, small for gestational age; LGA, large for gestational age.

Med

Meta-analysis/systematic review



and edited the manuscript. All authors agreed to submit the manuscript, read and approved the final version, and take full responsibility for its content, including the accuracy of the data and the fidelity of the analyses to the registered protocol.

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.medj.2026.101267>.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Systematic review protocol	PROSPERO	CRD420261348316
Software and algorithms		
Review Manager (RevMan)	The Cochrane Collaboration	Version 5.4
Other		
MEDLINE	U.S. National Library of Medicine	Literature database
Embase	Elsevier	Literature database
Cochrane Library	Cochrane	Literature database
Newcastle-Ottawa Scale	Newcastle-Ottawa Scale	Quality/risk-of-bias assessment tool
PRISMA 2020 statement	Page et al. ³⁸	Systematic review reporting guideline

EXPERIMENTAL MODELS AND STUDY PARTICIPANT DETAILS

This systematic review and meta-analysis used aggregate data from previously published observational studies and did not involve direct recruitment or enrollment of participants by the review authors. Eligible studies compared pregnancies with maternal exposure to glucagon-like peptide-1 receptor agonists during the periconceptional or pregnancy period with unexposed pregnancies.

Participant eligibility, demographic characterization, and exclusion criteria were determined by the individual source studies. Because this study used published aggregate data, demographic information was limited to that reported by the original investigators. Maternal age was variably reported across studies. Sex assigned at birth was not consistently reported as a separate variable, although the study populations comprised pregnant individuals. Gender identity, race or ancestry, ethnicity, socioeconomic status, and the methods used to ascertain these characteristics, including whether information was self-reported or clinician-reported, were inconsistently reported or unavailable across the source studies. Consequently, analyses stratified by these demographic characteristics could not be performed.

Pregnancy was the population of interest and was therefore not an exclusion criterion. Other reproductive characteristics, including breastfeeding and pre- or post-menopausal status, were not systematically reported and were not applicable to most pregnancy cohorts included in the analysis.

METHOD DETAILS

Study design and registration

This systematic review and meta-analysis was conducted according to an *a priori* protocol and reported in accordance with the PRISMA 2020 statement.³⁸ The review was prospectively registered in PROSPERO (CRD420261348316).

Literature search

MEDLINE, Embase, and the Cochrane Library were searched electronically using combinations of Medical Subject Headings and keywords relating to glucagon-like peptide-1 receptor agonists and pregnancy outcomes. The principal search terms included “GLP-1 receptor agonist” AND “outcome.” The complete search strategy is provided in Table S1. The final search update was performed on March 26, 2026. The search was restricted to English-language articles. Reference lists of relevant articles and reviews were also hand-searched to identify additional eligible studies.

When more than one publication reported analyses from the same underlying cohort, data were extracted from the publication with the longer follow-up period or, when follow-up was identical, from the publication with the larger sample size, to minimize double counting of participants.

Eligibility criteria

Studies were eligible when they fulfilled the following criteria: (1) cohort study design; (2) available information on glucagon-like peptide-1 receptor agonist exposure during the periconceptional period; (3) explicit definition of at least one prespecified maternal or perinatal outcome; and (4) availability of at least one multivariable-adjusted estimate of the association between glucagon-like peptide-1 receptor agonist exposure and the outcome of interest. For the primary review, periconceptional exposure was defined according to the prespecified eligibility window extending to 6 months before a positive pregnancy test.

The covariates included in each adjustment model were extracted as reported by the original study. Information on underlying comorbidities and concomitant pharmacological treatments during or before pregnancy was extracted where available; absence of this information was not considered an exclusion criterion.

Studies reporting only unadjusted estimates were excluded. Case reports, conference abstracts, and case series with fewer than 10 participants in total or fewer than five participants per comparison group were also excluded.

Study selection and data extraction

Two reviewers (F.D'A. and M.E.F.) independently evaluated eligible articles and extracted study characteristics and effect estimates. Disagreements were resolved through discussion and, when necessary, consultation with a third reviewer (A.K.).

Extracted study characteristics included study design, country, study period, glucagon-like peptide-1 receptor agonist evaluated, indication for treatment, timing of exposure, pregnancy outcomes, sample size, adjustment variables, underlying comorbidities, and concomitant pharmacological treatments when reported.

Outcomes

The prespecified outcomes were:

- Miscarriage, defined as fetal loss before 20 weeks of gestation, or intrauterine death, defined as fetal loss after 20 weeks of gestation.
- Preterm birth, including spontaneous or iatrogenic preterm birth, defined as delivery before 37 completed weeks of gestation.
- Hypertensive disorders of pregnancy, including gestational hypertension and preeclampsia.
- Gestational hypertension, defined as new-onset hypertension, with systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, after 20 weeks of gestation in an individual who was previously normotensive.
- Preeclampsia, defined as new-onset hypertension after 20 weeks of gestation accompanied by proteinuria, maternal organ dysfunction, including renal, hepatic, haematological, or neurological dysfunction, or uteroplacental dysfunction.
- Gestational diabetes mellitus, as defined in the individual source studies.
- Small for gestational age or fetal growth restriction, defined as estimated fetal weight or birthweight below the 10th percentile or according to the Delphi consensus criteria³⁹ for fetal growth restriction.
- Large for gestational age, defined as estimated fetal weight or birthweight above the 95th percentile or birthweight $>4,000$ g.
- Excess gestational weight gain, according to prepregnancy body mass index and the definitions used in the individual source studies.

Risk-of-bias assessment

The methodological quality and risk of bias of the included cohort studies were assessed using the Newcastle-Ottawa Scale.²⁵ The assessment considered three domains: selection of the study groups, comparability of exposed and unexposed groups, and ascertainment of the outcome.

The selection domain assessed representativeness of the exposed cohort, selection of the unexposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at study entry. The comparability domain evaluated whether the study design or statistical analysis adequately addressed potential confounding. The outcome domain assessed outcome ascertainment and the length and adequacy of follow-up.

Each included study was independently assessed by two reviewers (F.D'A. and M.E.F.), with disagreements resolved by consensus and, where necessary, consultation with A.K. Item-level Newcastle-Ottawa Scale assessments and the basis for the judgments are reported in [Table S3](#).

Exposure-window sensitivity analyses

When sufficient data were available, sensitivity analyses were restricted to studies defining glucagon-like peptide-1 receptor agonist exposure as occurring from 90 days before conception through the end of the first trimester. These analyses were undertaken to assess whether use of a more consistent exposure definition affected the pooled estimates and between-study heterogeneity.

Where the same studies and participants contributed to both the primary and exposure-window sensitivity analyses, the sensitivity analyses were not considered independent confirmatory analyses. In particular, the congenital-malformation sensitivity analysis included the same four studies and participants as the corresponding primary analysis.

Subgroup analyses

When sufficient data were available, subgroup meta-analyses were performed according to the indication for glucagon-like peptide-1 receptor agonist treatment. Analyses were conducted separately for participants with preconception diabetes and for participants receiving treatment for weight management or with overweight or obesity.

QUANTIFICATION AND STATISTICAL ANALYSIS

The unit of analysis was the comparison between pregnancies exposed and unexposed to glucagon-like peptide-1 receptor agonists for each prespecified outcome. Only adjusted effect estimates were included in the quantitative synthesis. Pooled estimates were calculated using a random-effects generic inverse-variance approach to account for between-study heterogeneity.^{40,41,42} When a study reported estimates from multiple multivariable models, the estimate from the model with the most extensive adjustment was selected.⁴³ When models adjusted for the same number of covariates, the estimate from the model containing the most clinically relevant confounders was used. When a study reported separate estimates for subgroups, such as individual glucagon-like peptide-1 receptor agonists, but did not provide an overall estimate, the subgroup estimates were combined using a fixed-effect generic inverse-variance model to derive the study-level overall estimate before inclusion in the primary meta-analysis. Effect estimates are reported as odds ratios with 95% confidence intervals. Between-study heterogeneity was quantified using the I^2 statistic. Publication bias was not assessed using funnel plots or Egger's regression test because fewer than 10 studies contributed to each meta-analysis, resulting in insufficient power to distinguish true asymmetry from chance. All meta-analyses were performed using Review Manager (RevMan), version 5.4 (The Cochrane Collaboration, 2020).

ADDITIONAL RESOURCES

The systematic review protocol was prospectively registered with PROSPERO under registration number CRD420261348316. The complete electronic search strategy is provided in [Table S1](#). Details of studies assessed at full text and excluded from the review are provided in [Table S2](#).