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Article

Continuing Semaglutide into the First Trimester of Pregnancy Is Not Associated with Maternal or Newborn Complications in Routine Care

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Abstract

Semaglutide is recommended to be stopped 2 months before planned pregnancy, but maternal-fetal outcomes following continued exposure remain incompletely characterized. We examined 363,778 pregnancies between January 2018 and March 2025 in de-identified electronic health records from a large U.S. federated data network. Of these, 572 pregnancies had a semaglutide prescription within 90 days before the last menstrual period (LMP), after excluding pregnancies involving other glucagon-like peptide-1 (GLP-1) therapies, type 1 diabetes, or multiple gestation. Semaglutide was prescribed in 246 of the 572 pregnancies (43.0%) during the first trimester (0 to 13 weeks), in 54 of the 360 pregnancies (15.0%) that reached the second trimester (14 to 27 weeks), and in 45 of the 345 pregnancies (13.0%) that reached the third trimester (28 weeks to delivery). Of the 246 pregnancies with a semaglutide prescription order in the first trimester, large language model (LLM)-curated review of the clinical notes confirmed use in 225 women (91.5%) and use once the pregnancy was known in 186 women (75.6%). Further, among pregnancies with a recorded semaglutide dose, the most common highest dose increased from 0.25–0.5 mg during the 3 months before pregnancy (47.5%) to 1–1.7 mg in the first trimester (46.2%), while the proportion prescribed 2–2.4 mg increased from 18.8% to 23.4%. Among 572 semaglutide users and 101,159 similar pregnancies without GLP-1 use exactly matched on age group, LMP year, type 2 diabetes, obesity, and PCOS, similar rates of pregnancies reached the second trimester (62.9% vs 66.7%; P=0.08), third trimester (60.3% vs 64.1%; P=0.08), and delivery (61.4% vs 65.5%; P=0.06). Among the 572 semaglutide users, 146 women prescribed semaglutide during the first trimester gave birth ("semaglutide-continued") and 185 women had no semaglutide prescription during pregnancy gave birth ("semaglutide-discontinued"). Comparing these groups did not show any significant differences (q≥0.05) in the risk of preeclampsia/eclampsia, gestational hypertension, new high blood pressure from 20 weeks, gestational diabetes, gallbladder disease, cesarean delivery, or postpartum hemorrhage. Among newborns to the semaglutide-continued versus newborns to the semaglutide-discontinued groups, rates of preterm birth, stillbirth or neonatal death also did not differ. Furthermore, among infants with a recorded 5-minute Apgar score (Appearance, Pulse, Grimace, Activity, and Respiration), the mean scores (8.5 versus 8.6) and the rates of scores less than 7 were both indistinguishable between the semaglutide-continued and the semaglutide-discontinued groups. In a secondary comparison of 858 semaglutide-exposed and 3,995 metformin-exposed pregnancies, defined by a prescription from 90 days before the LMP through the first trimester, pregnancy loss or stillbirth did not differ significantly. Among pregnancies that resulted in a delivery, maternal complications, cesarean delivery, preterm birth, and newborn outcomes, including the 5-minute Apgar score, did not differ significantly between the semaglutide-exposed and metformin-exposed groups. Overall, semaglutide prescribing during pregnancy was not associated with significant differences in maternal or newborn outcomes studied in this routine care setting. These observations motivate the

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need for larger retrospective and prospective studies to rigorously establish the safety of semaglutide exposure during pregnancies with underlying cardiometabolic burden.

Keywords: semaglutide; pregnancy; GLP-1; obesity; diabetes; cardiometabolism; maternal-fetal health; guidelines; real-world evidence

Introduction

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that lowers glucose and cardiovascular events in type 2 diabetes (T2D) and produces weight loss of about 15% in adults with obesity.[1,2] A growing share of users do not have diabetes, including women of reproductive age. In Australian general practice, 90.5% of women aged 18 to 49 years who started a GLP-1 RA in 2022 did not have T2D.[3] Product labeling advises stopping semaglutide at least 2 months before a planned pregnancy because of the potential for fetal harm and a half-life of about 1 week.[4] Many pregnancies are not planned, however. In the same Australian data, overlapping contraception was documented for only 21% of women starting a GLP-1 RA, and 2.2% had a documented pregnancy within 6 months of the first prescription.[3]

Human evidence on semaglutide in early pregnancy is still limited. A multinational cohort of more than 50,000 pregnancies with T2D found no higher risk of major congenital malformations after periconceptional GLP-1 RA use than after insulin,[5] and a prospective study from six teratology information services found no increase in major birth defects or pregnancy loss after first-trimester exposure.[6] The largest study of continuing versus stopping a GLP-1 RA emulated a target trial in US claims data among 3,572 pregnancies with a GLP-1 RA dispensed in the 90 days before the LMP. Continuing the drug into the first trimester was not associated with more nonlive births than stopping it (29.7% versus 27.1%; adjusted RR 1.09).[7] That study focused on nonlive birth, fetal growth, and malformations, and did not examine maternal complications such as preeclampsia or gestational diabetes, or measurements such as blood pressure (BP) during pregnancy.

Discontinuing semaglutide is not risk-free either. In a matched cohort, patients who discontinued a GLP-1 RA before or early in pregnancy gained 3.3 kg more during pregnancy than unexposed patients and had more preterm delivery, gestational diabetes, and hypertensive disorders of pregnancy,[8] although another cohort found no association with hypertensive disorders.[9] For a woman who learns she is pregnant while taking semaglutide, the practical question is what happens if she continues the drug compared with discontinuing it.

Metformin offers a second point of reference. It is prescribed for T2D, for prediabetes, and for polycystic ovary syndrome (PCOS), including to restore ovulation,[10] and it has been tested in randomized trials during pregnancy for gestational diabetes[11] and for T2D.[12] Its users share some of the conditions that bring patients to semaglutide, but the two groups also differ in age, fertility treatment, and metabolic health, so a comparison with metformin carries a greater risk of residual confounding than a comparison among semaglutide users.

We therefore asked two questions in de-identified electronic health record (EHR) data from a large network in the US. First, how often is semaglutide still prescribed once a pregnancy begins, in each trimester and after delivery? Second, among semaglutide users whose pregnancy reached delivery, do maternal complications, clinical measurements, and newborn outcomes differ when semaglutide is continued into the first trimester compared with discontinued before pregnancy, after the groups are balanced on risk before pregnancy? As a secondary comparison, we compared pregnancies exposed to semaglutide around conception with pregnancies exposed to metformin.

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Results

Cohort Eligibility, Derivation, and Baseline Characteristics

The study comprised 363,778 pregnancies with a last menstrual period (LMP) between January 1, 2018, and March 26, 2025, in patients aged 15 to 49 years. Of these pregnancies, 838 (0.23%) had a semaglutide prescription order in the 90 days before the LMP. After exclusion of pregnancies with another GLP-1 RA prescription order, type 1 diabetes, or multiple gestation, and restriction to the first eligible pregnancy per patient, 572 pregnancies in semaglutide users remained. Of these, 246 (43.0%) had a semaglutide prescription order in the first 14 weeks of pregnancy ("semaglutide-continued"), 306 (53.5%) had no semaglutide prescription order at any point in pregnancy ("semaglutide-discontinued"), and 20 (3.5%) had their first prescription order in pregnancy after 14 weeks ("late restart"). The semaglutide-continued and semaglutide-discontinued groups included 146 and 185 deliveries, respectively (**Figure 1**).

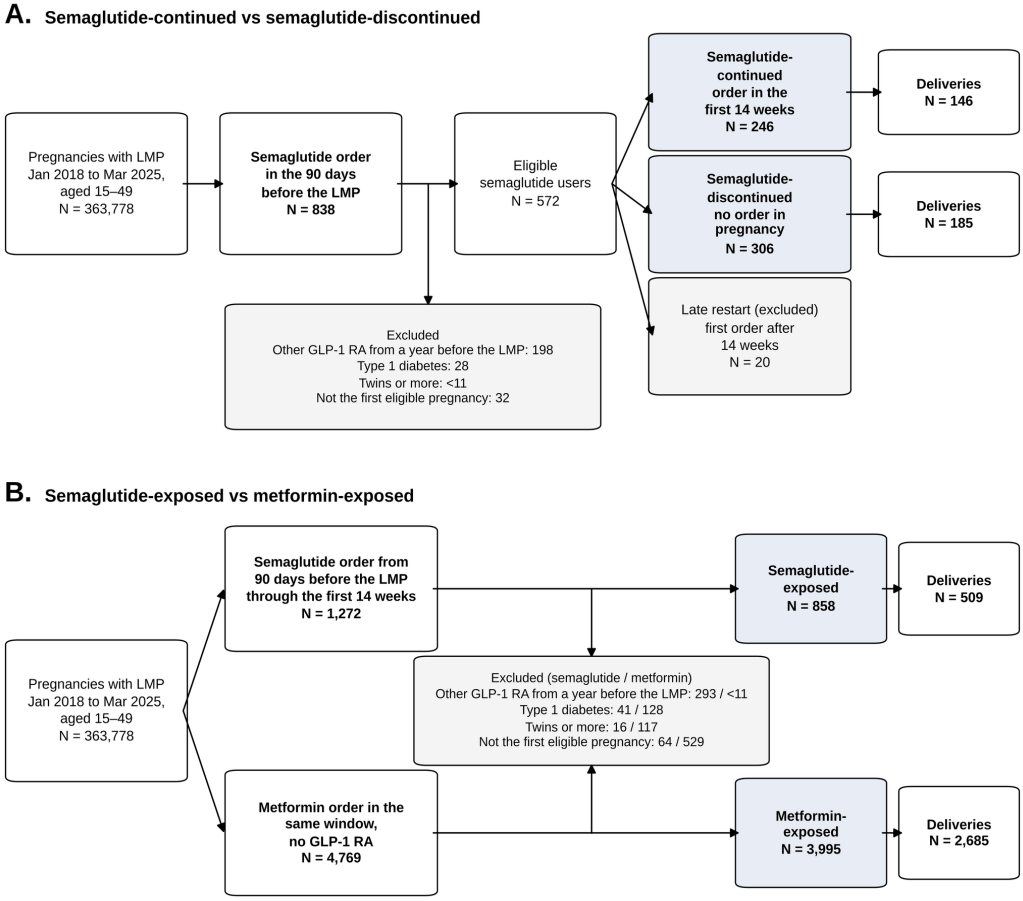


Figure 1. Derivation of the study cohorts. (**A**) Semaglutide-continued versus semaglutide-discontinued: 363,778 pregnancies with an LMP from January 2018 to March 2025 in patients aged 15 to 49 years, 838 with a semaglutide prescription order in the 90 days before the LMP, and, after exclusions, 572 semaglutide users divided into 246 in the semaglutide-continued group (an order in the first 14 weeks), 306 in the semaglutide-discontinued group (no order in pregnancy), and 20 with a late restart (first order after 14 weeks); 146 and 185 pregnancies in the semaglutide-continued and semaglutide-discontinued groups ended in delivery. (**B**) Semaglutide-exposed versus metformin-exposed: 1,272 pregnancies with a semaglutide prescription order and 4,769 with a metformin order from 90 days before the LMP through the first 14 weeks, and, after exclusions, 858 semaglutide-exposed and 3,995 metformin-exposed pregnancies, including 509 and 2,685 deliveries.

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Patients in the semaglutide-continued group more often had T2D (42 [28.8%] versus 18 [9.7%]; P<0.001) and chronic hypertension (37 [25.3%] versus 28 [15.1%]; P=0.02), while infertility or fertility treatment did not differ significantly (25 [17.1%] versus 42 [22.7%]; P=0.21). Most patients in both groups were aged 30 to 39 years (91 [62.3%] and 100 [54.1%]), and the age distribution did not differ (P=0.53; **Table 1**). After overlap weighting, the largest absolute standardized mean difference (SMD) across covariates was 0.09 (**Table 1**, **Figure S1**).

Table 1. Characteristics of the semaglutide-continued and semaglutide-discontinued groups before the LMP. The comparison comprised 146 deliveries with a semaglutide prescription order in the first 14 weeks (semaglutide-continued group) and 185 deliveries with no semaglutide prescription order in pregnancy (semaglutide-discontinued group). Cells show count (column percentage) and the SMD before and after overlap weighting, with rows grouped by characteristic. Cells with counts <11 are reported as <11 per the privacy convention adopted in this study, and SMDs before weighting are not shown for those rows (**Figure 1**, **Figure S1**).

Characteristic	Semaglutide-continued (N=146)	Semaglutide-discontinued (N=185)	SMD before weighting	SMD after weighting
Age (years)				
15–24	<11	18 (9.7%)		−0.02
25–29	35 (24.0%)	48 (25.9%)	−0.05	0.01
30–34	53 (36.3%)	55 (29.7%)	0.14	0.01
35–39	38 (26.0%)	45 (24.3%)	0.04	0.01
40–49	<11	19 (10.3%)		−0.02
Year of LMP				
2018–2020	<11	<11		−0.02
2021–2022	20 (13.7%)	31 (16.8%)	−0.09	0.00
2023–2025	123 (84.2%)	153 (82.7%)	0.04	0.01
BMI before pregnancy (kg/m²)				
<30	20 (13.7%)	22 (11.9%)	0.05	−0.01
30–34.9	29 (19.9%)	52 (28.1%)	−0.19	0.00
35–39.9	38 (26.0%)	59 (31.9%)	−0.13	−0.01
≥40	11 (7.5%)	<11		−0.01
Not recorded	48 (32.9%)	42 (22.7%)	0.23	0.04
HbA1c before pregnancy (%)				
<5.7	32 (21.9%)	43 (23.2%)	−0.03	−0.01
5.7–6.4	14 (9.6%)	13 (7.0%)	0.09	−0.02
6.5–7.9	<11	<11		−0.03
≥8.0	<11	<11		0.00
Not measured	87 (59.6%)	122 (65.9%)	−0.13	0.03
Mean BP in the year before pregnancy (mmHg)				
<130/80	82 (56.2%)	108 (58.4%)	−0.04	0.02
130–139/80–89	50 (34.2%)	62 (33.5%)	0.02	−0.02
≥140/90	<11	12 (6.5%)		−0.01
Not measured	<11	<11		0.04
Encounter days in the 6 months before				
0–2	<11	26 (14.1%)		−0.06
3–5	26 (17.8%)	40 (21.6%)	−0.10	−0.04
6–11	50 (34.2%)	48 (25.9%)	0.18	0.02

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Characteristic	Semaglutide-continued (N=146)	Semaglutide-discontinued (N=185)	SMD before weighting	SMD after weighting
≥12	65 (44.5%)	71 (38.4%)	0.12	0.04
Race				
White	95 (65.1%)	142 (76.8%)		
Black or African American	34 (23.3%)	25 (13.5%)		
Asian	<11	<11		
American Indian or Pacific Islander	<11	<11		
Other or multiple races	<11	<11		
Unknown or not reported	<11	<11		
Ethnicity				
Hispanic or Latino	<11	19 (10.3%)		
Not Hispanic or Latino	114 (78.1%)	117 (63.2%)		
Unknown or not reported	22 (15.1%)	49 (26.5%)		
Medical history				
Type 2 diabetes	42 (28.8%)	18 (9.7%)	0.50	0.09
Chronic hypertension	37 (25.3%)	28 (15.1%)	0.26	0.02
Polycystic ovary syndrome	24 (16.4%)	26 (14.1%)	0.07	0.01
Infertility or fertility treatment	25 (17.1%)	42 (22.7%)	−0.14	−0.02
Smoking	<11	<11		0.00
Gallbladder disease in the 10 years before	<11	19 (10.3%)		−0.03
Obstetric history				
Earlier pregnancy in the records	66 (45.2%)	95 (51.4%)	−0.12	−0.03
Prior cesarean delivery	43 (29.5%)	57 (30.8%)	−0.03	−0.01
Hypertensive disorder in an earlier pregnancy	26 (17.8%)	30 (16.2%)	0.04	0.02
Gestational diabetes in an earlier pregnancy	19 (13.0%)	21 (11.4%)	0.05	0.00
Medication orders in the 3 months before				
Insulin	11 (7.5%)	<11		−0.01
Metformin	24 (16.4%)	26 (14.1%)	0.07	0.00

BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; LMP, last menstrual period; SMD, standardized mean difference.

For the secondary comparison, 1,272 pregnancies had a semaglutide prescription order and 4,769 had a metformin prescription order from 90 days before the LMP through the first 14 weeks, the latter with no GLP-1 RA prescription order from a year before the LMP to the end of pregnancy. After the same exclusions, 858 semaglutide-exposed and 3,995 metformin-exposed pregnancies remained, including 509 and 2,685 deliveries (**Figure 1**). Compared with the metformin-exposed group, the semaglutide-exposed group more often had chronic hypertension (161 [18.8%] versus 362 [9.1%]; P<0.001), T2D (157 [18.3%] versus 541 [13.5%]; P<0.001), and an earlier pregnancy in the records (354 [41.3%] versus 1,172 [29.3%]; P<0.001), and less often had PCOS (120 [14.0%] versus 1,229 [30.8%]; P<0.001) or infertility or fertility treatment (145 [16.9%] versus 1,336 [33.4%]; P<0.001). Most semaglutide-exposed pregnancies began in 2023 to 2025 (693 [80.8%], compared with 1,242 [31.1%] of metformin-exposed pregnancies; P<0.001). After weighting, the largest SMD was 0.07 for all pregnancies and 0.11 for deliveries (**Table S1**, **Figure S1**).

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Most Semaglutide Users Had no Semaglutide Prescription Order After the First Trimester

Among the 572 semaglutide users, a semaglutide prescription order appeared in the first trimester in 246 (43.0%), in the second trimester in 54 of the 360 pregnancies that reached it (15.0%), in the third trimester in 45 of 345 (13.0%), and in the 6 months after delivery in 95 of 280 (33.9%) (**Figure 2A**, **Table S2**). Among the 246 pregnancies in the semaglutide-continued group, the last semaglutide prescription order fell in the first trimester in 194 (78.9%), the second trimester in 17 (6.9%), and the third trimester in 35 (14.2%) (**Table S3**).

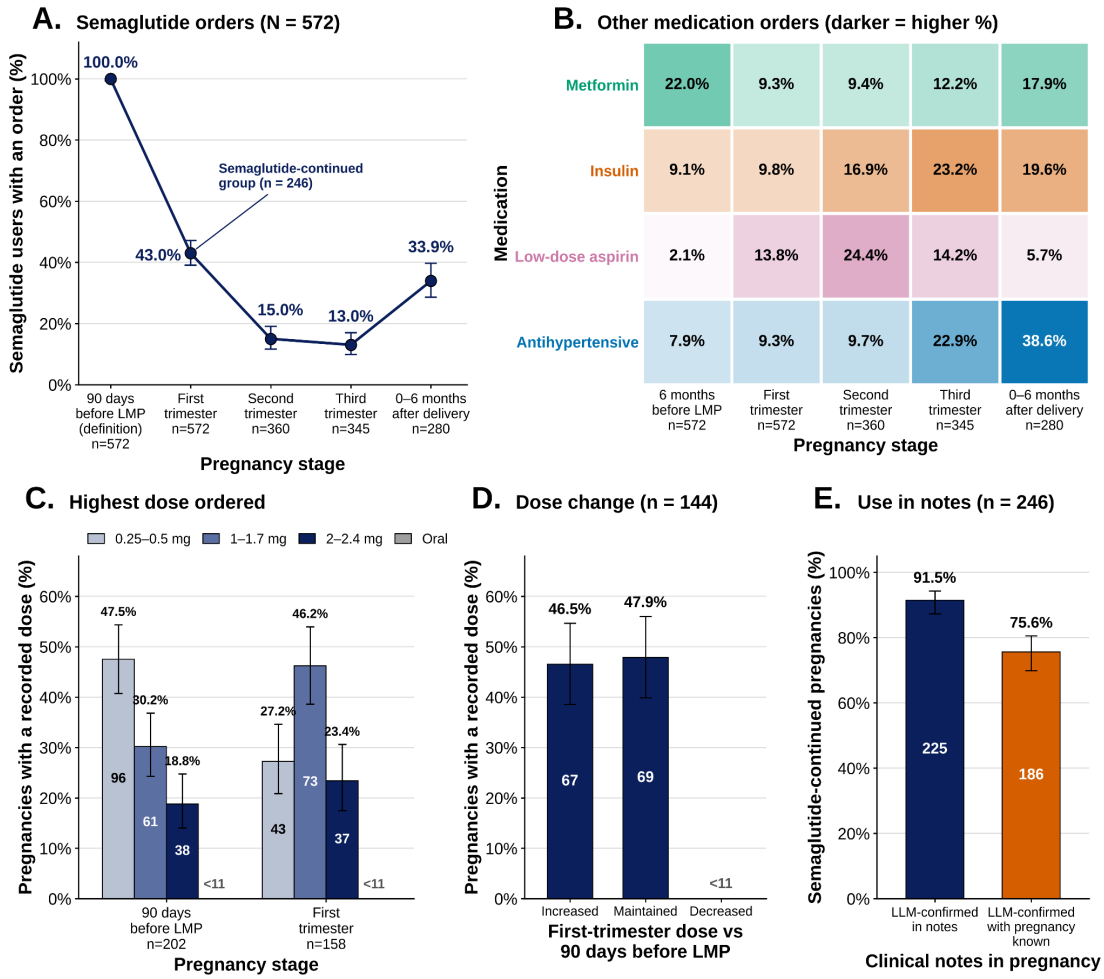


Figure 2. Medication orders and semaglutide dose around pregnancy among semaglutide users. Stages were the first trimester (0 to 13 weeks), the second trimester (14 to 27 weeks), the third trimester (28 weeks to delivery), and the 6 months after delivery. Each stage includes only pregnancies that reached it (n below each column), so the number falls as pregnancies end, and the 6 months after delivery include only deliveries with complete follow-up. (**A**) Percentage of the 572 semaglutide users with a semaglutide prescription order at each stage. All users had an order in the 90 days before the LMP by definition, and the 246 with an order in the first trimester form the semaglutide-continued group. (**B**) Percentage with a prescription order for metformin, insulin, low-dose aspirin, or an antihypertensive medication used in pregnancy at each stage, including the 6 months before the LMP. Each medication has its own color, and darker shading marks a higher percentage. (**C**) Highest semaglutide dose ordered in the 90 days before the LMP and in the first trimester in the semaglutide-continued group, among pregnancies with a recorded dose in that period (n below each period). (**D**) First-trimester dose compared with the 90 days before the LMP among the 144 pregnancies in the semaglutide-continued group with a recorded dose in both periods. Error bars denote 95% Wilson CIs (**Table S2**, **Table S3**). (**E**) Percentage of the 246 semaglutide-continued pregnancies with semaglutide use LLM-confirmed in clinical notes during pregnancy (navy) and LLM-confirmed with the pregnancy known (orange).

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The prevalence of other medication prescription orders changed through pregnancy. Insulin orders rose from 52 of 572 users (9.1%) in the 6 months before the LMP to a peak of 80 of 345 (23.2%) in the third trimester, low-dose aspirin peaked at 88 of 360 (24.4%) in the second trimester, and antihypertensive orders peaked during pregnancy at 79 of 345 (22.9%) in the third trimester and reached 108 of 280 (38.6%) in the 6 months after delivery (**Figure 2B**, **Table S2**).

In the semaglutide-continued group, the highest semaglutide dose ordered was more often 1 mg or more in the first trimester than in the 90 days before the LMP. Among pregnancies with a recorded dose, 0.25–0.5 mg was the highest dose in 96 of 202 (47.5%) before the LMP and 43 of 158 (27.2%) in the first trimester, 1–1.7 mg in 61 (30.2%) and 73 (46.2%), and 2–2.4 mg in 38 (18.8%) and 37 (23.4%); oral semaglutide was ordered in <11 in each period (**Figure 2C**, **Table S3**). Among the 144 pregnancies with a recorded dose in both periods, the first-trimester dose was higher than before the LMP in 67 (46.5%), the same in 69 (47.9%), and lower in <11 (**Figure 2D**, **Table S3**). Semaglutide use was documented in clinical notes for most pregnancies in the semaglutide-continued group. Of the 246 pregnancies with a semaglutide prescription order in the first trimester, large language model (LLM)-curated review of the notes confirmed use in 225 (91.5%) and use once the pregnancy was known in 186 (75.6%) (**Figure 2E**).

Pregnancies of semaglutide users reached each trimester and delivery less often than pregnancies without GLP-1 RA use, but not significantly less often than similar pregnancies. Of the 572 pregnancies in semaglutide users, 360 (62.9%) reached the second trimester, 345 (60.3%) the third trimester, and 351 (61.4%) delivery, compared with 201,650 (77.0%), 197,010 (75.2%), and 199,641 (76.2%) of 261,853 pregnancies without GLP-1 RA use. Among 101,159 similar pregnancies without GLP-1 RA use, matched on age group, LMP year, T2D, obesity, and PCOS, the corresponding rates were 66.7%, 64.1%, and 65.5%. The rates in semaglutide users differed from those in similar pregnancies by −3.8 percentage points (95% CI −8.0 to 0.4; P=0.08) for the second trimester, −3.8 (95% CI −8.1 to 0.5; P=0.08) for the third trimester, and −4.1 (95% CI −8.4 to 0.2; P=0.06) for delivery (**Figure 3**).

Pregnancy loss occurred in 82 of 246 pregnancies in the semaglutide-continued group (33.3%) and 107 of 306 in the semaglutide-discontinued group (35.0%).

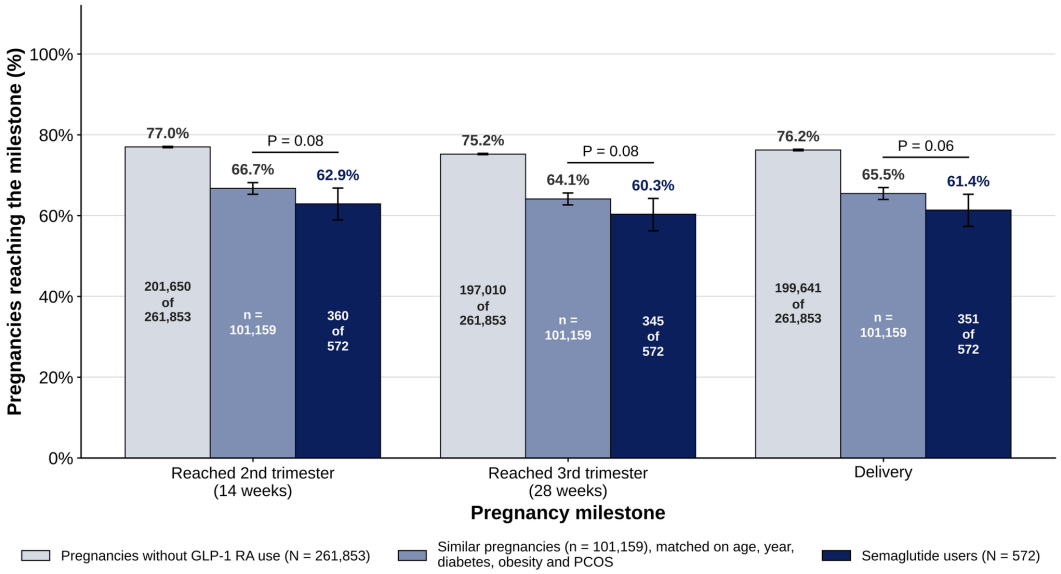


Figure 3. Pregnancies reaching each trimester and delivery among semaglutide users, similar pregnancies, and pregnancies without GLP-1 RA use. Semaglutide users comprised 572 pregnancies with a semaglutide order in the 90 days before the LMP. Pregnancies without GLP-1 RA use comprised 261,853 pregnancies with no semaglutide or other GLP-1 RA order from 365 days before the LMP to the end of pregnancy. Each group had the study exclusions and the first eligible pregnancy per patient. Similar pregnancies were the 101,159 pregnancies without GLP-1 RA use with the same age group, LMP year, type 2 diabetes, obesity, and PCOS

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before pregnancy as a semaglutide user's pregnancy; their percentage is the average, across semaglutide users, of the share reaching each milestone in each user's matched group. Bars show the percentage of all pregnancies in each group reaching the second trimester (14 weeks), the third trimester (28 weeks), and delivery, with counts inside the bars (for similar pregnancies, the number of matched pregnancies). Error bars denote 95% CIs (Wilson for semaglutide users and pregnancies without GLP-1 RA use, and binomial within matched strata for similar pregnancies). P values compare semaglutide users with similar pregnancies.

Continuing Semaglutide into the First Trimester Was not Significantly Associated with Maternal or Newborn Complications

Among 146 deliveries in the semaglutide-continued group and 185 in the semaglutide-discontinued group, no maternal or newborn outcome differed significantly after Benjamini-Hochberg (BH) correction (**Figure 4**, **Table 2**). Preeclampsia or eclampsia occurred in 44 (30.1%) and 36 (19.5%) (adjusted RR 1.60, 95% CI 0.96–2.66; q=0.54), gestational hypertension in 39 (26.7%) and 40 (21.6%) (adjusted RR 0.88, 95% CI 0.55–1.43; q=0.83), and new high BP from readings taken from 20 weeks to delivery in 20 of 62 (32.3%) and 27 of 93 (29.0%) (adjusted RR 1.28, 95% CI 0.73–2.26; q=0.78). Gestational diabetes, assessed in deliveries without diabetes before pregnancy, occurred in 24 of 104 (23.1%) and 31 of 166 (18.7%) (adjusted RR 1.14, 95% CI 0.64–2.02; q=0.83). Cesarean delivery occurred in 74 of 128 (57.8%) and 74 of 176 (42.0%) deliveries with a known mode of delivery (adjusted RR 1.24, 95% CI 0.95–1.62; q=0.54), and postpartum hemorrhage in 12 (8.2%) and 18 (9.7%) (adjusted RR 1.03, 95% CI 0.49–2.16; q=0.94). Gallbladder disease occurred in <11 deliveries in each group (adjusted RR 1.72, 95% CI 0.59–5.05; q=0.78), and heart or kidney complications were too few to estimate (**Figure 4**, **Table 2**).

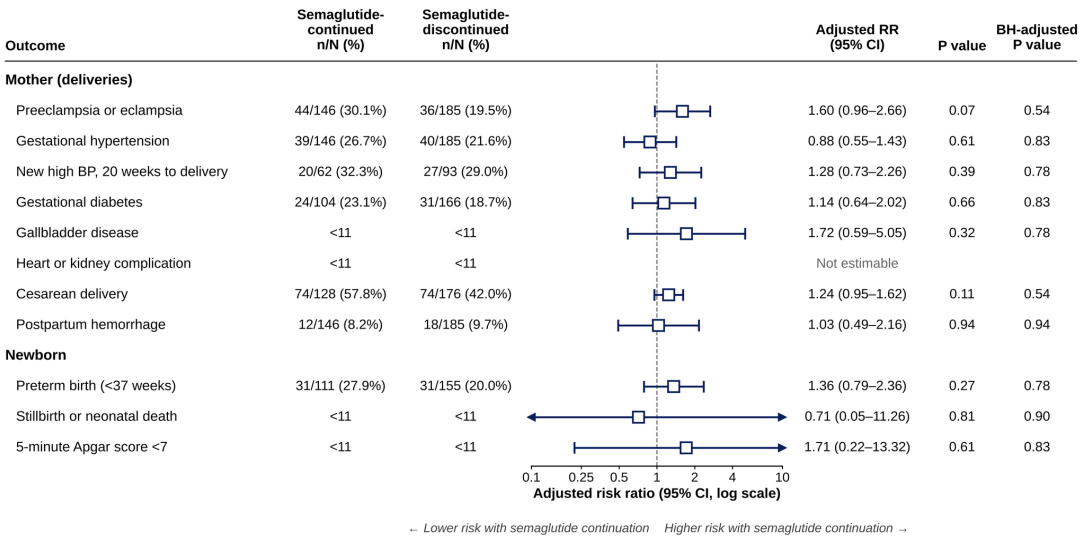


Figure 4. Maternal and newborn outcomes after continuing versus discontinuing semaglutide. Outcomes were assessed in 146 deliveries with a semaglutide prescription order in the first 14 weeks (semaglutide-continued group) and 185 deliveries with no semaglutide prescription order in pregnancy (semaglutide-discontinued group), among semaglutide users with an order in the 90 days before the LMP. Columns give events and denominators in each group, the overlap-weighted RR with its 95% CI, and the raw and BH-adjusted P values; annotations follow the convention defined in Methods. Heart or kidney complications were too few to estimate (**Table 2**).

Table 2. Maternal and newborn outcomes after continuing versus discontinuing semaglutide. The comparison comprised 146 deliveries in the semaglutide-continued group and 185 in the semaglutide-discontinued group; denominators vary by outcome as indicated in each cell. Cells show events/denominator (percentage), crude and overlap-weighted RRs with 95% CIs, and raw and BH-adjusted P values (q). Cells with counts <11 are reported as <11 per the privacy convention adopted in this study, and crude RRs are not shown for those rows (**Figure 4**).

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Outcome	Semaglutide-continued, n/N (%)	Semaglutide-discontinued, n/N (%)	Crude RR (95% CI)	Adjusted RR (95% CI)	P value	q value
		Mother				
Preeclampsia or eclampsia	44/146 (30.1%)	36/185 (19.5%)	1.55 (1.06–2.27)	1.60 (0.96–2.66)	0.07	0.54
Gestational hypertension	39/146 (26.7%)	40/185 (21.6%)	1.24 (0.84–1.81)	0.88 (0.55–1.43)	0.61	0.83
New high BP from readings, 20 weeks to delivery†	20/62 (32.3%)	27/93 (29.0%)	1.11 (0.69–1.80)	1.28 (0.73–2.26)	0.39	0.78
Gestational diabetes*	24/104 (23.1%)	31/166 (18.7%)	1.24 (0.77–1.98)	1.14 (0.64–2.02)	0.66	0.83
Gallbladder disease	<11	<11	Not shown (<11)	1.72 (0.59–5.05)	0.32	0.78
Heart or kidney complication	<11	<11	Not shown (<11)	Not estimable		
Cesarean delivery‡	74/128 (57.8%)	74/176 (42.0%)	1.38 (1.09–1.73)	1.24 (0.95–1.62)	0.11	0.54
Postpartum hemorrhage	12/146 (8.2%)	18/185 (9.7%)	0.84 (0.42–1.70)	1.03 (0.49–2.16)	0.94	0.94
		Newborn				
Preterm birth (<37 weeks)§	31/111 (27.9%)	31/155 (20.0%)	1.40 (0.90–2.16)	1.36 (0.79–2.36)	0.27	0.78
Stillbirth or neonatal death	<11	<11	Not shown (<11)	0.71 (0.05–11.26)	0.81	0.90
5-minute Apgar score <7¶	<11	<11	Not shown (<11)	1.71 (0.22–13.32)	0.61	0.83

*Among deliveries without diabetes before pregnancy. †Among deliveries with at least 1 reading from 20 weeks, no chronic hypertension, and no reading of 140/90 mmHg or higher in the year before the LMP. ‡Among deliveries with a known mode of delivery. §Among deliveries dated by a method other than the estimated gestational length. ¶Among live births with a recorded score.

Among newborns, preterm birth occurred in 31 of 111 (27.9%) in the semaglutide-continued group and 31 of 155 (20.0%) in the semaglutide-discontinued group, among deliveries with a gestational age that was not assumed (adjusted RR 1.36, 95% CI 0.79–2.36; q=0.78). Stillbirth or neonatal death (adjusted RR 0.71, 95% CI 0.05–11.26; q=0.90) and a 5-minute Apgar score below 7 (adjusted RR 1.71, 95% CI 0.22–13.32; q=0.83) each occurred in <11 deliveries per group (**Figure 4**, **Table 2**).

Results were similar when the semaglutide-continued group was limited to women with LLM-confirmed semaglutide in their notes during their pregnancy. Of the 146 women in this group who gave birth, 132 (90.4%) had use confirmed in notes and 108 (74.0%) had use confirmed once the pregnancy was known. Neither subset differed significantly from the 185 women in the semaglutide-discontinued group who gave birth in any maternal or newborn outcome after BH correction (**Figure S2**).

Before pregnancy, mean BMI was 33.5 and 34.0 kg/m² among the 85 and 132 deliveries with a measurement in the semaglutide-continued and semaglutide-discontinued groups, and mean glycated hemoglobin (HbA1c) was 6.0% and 5.6% among 59 and 63 (adjusted difference −0.34 kg/m², 95% CI −1.59 to 0.91, and 0.06 percentage points, 95% CI −0.13 to 0.25; q=0.73 for both). Mean systolic BP from 20 weeks to delivery was 124.9 mmHg in the semaglutide-continued group and 123.3 mmHg in the semaglutide-discontinued group (adjusted difference 1.83 mmHg, 95% CI −0.65 to 4.30; q=0.41),

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and mean systolic BP from 1 to 12 weeks after delivery was 126.2 and 123.4 mmHg (adjusted difference 2.98 mmHg, 95% CI 0.47 to 5.49; q=0.22). HbA1c during pregnancy (5.6% versus 5.3%; q=0.39), mean glucose from 14 weeks to delivery (109.3 versus 115.0 mg/dL; q=0.73), BMI gain during pregnancy (3.4 versus 3.9 kg/m²; q=0.73), BMI 6 to 12 months after delivery relative to before pregnancy (1.1 versus 0.9 kg/m²; q=0.89), and the mean 5-minute Apgar score (8.5 versus 8.6; q=0.79) did not differ (**Table 3**).

Table 3. Clinical measurements during and after pregnancy after continuing versus discontinuing semaglutide. Measurements were assessed among 146 deliveries in the semaglutide-continued group and 185 in the semaglutide-discontinued group, and n gives the number with each measurement. Cells show mean (standard deviation [SD]) and the overlap-weighted difference in means (semaglutide-continued minus semaglutide-discontinued) with its 95% CI and raw and BH-adjusted P values (**Table 2**).

Measure	Semaglutide-continued, n	Semaglutide-continued, mean (SD)	Semaglutide-discontinued, n	Semaglutide-discontinued, mean (SD)	Adjusted difference (95% CI)	P value	q value
HbA1c before pregnancy (%)	59	6.0 (1.1)	63	5.6 (1.1)	0.06 (−0.13 to 0.25)	0.53	0.73
HbA1c during pregnancy (%)	76	5.6 (1.0)	94	5.3 (0.8)	0.14 (−0.03 to 0.32)	0.10	0.39
Mean glucose, 14 weeks to delivery (mg/dL)	84	109.3 (25.4)	112	115.0 (31.2)	−2.24 (−10.29 to 5.81)	0.59	0.73
Mean systolic BP, 20 weeks to delivery (mmHg)	143	124.9 (10.8)	182	123.3 (10.0)	1.83 (−0.65 to 4.30)	0.15	0.41
Mean diastolic BP, 20 weeks to delivery (mmHg)	143	74.8 (7.2)	182	73.4 (6.3)	0.52 (−1.17 to 2.21)	0.55	0.73
Highest systolic BP, 20 weeks to delivery (mmHg)	143	146.7 (19.9)	182	144.2 (18.7)	4.06 (−0.85 to 8.96)	0.11	0.39
BMI before pregnancy (kg/m²)	85	33.5 (4.3)	132	34.0 (3.9)	−0.34 (−1.59 to 0.91)	0.59	0.73
BMI change during pregnancy (kg/m²)	69	3.4 (4.6)	98	3.9 (3.7)	0.34 (−0.92 to 1.61)	0.59	0.73
Mean systolic BP, 1 to 12 weeks after delivery (mmHg)	128	126.2 (10.6)	176	123.4 (10.3)	2.98 (0.47 to 5.49)	0.02	0.22
BMI 6 to 12 months after delivery minus before pregnancy (kg/m²)	52	1.1 (4.4)	64	0.9 (3.6)	0.10 (−1.35 to 1.55)	0.89	0.89
5-minute Apgar score*	75	8.5 (1.1)	99	8.6 (1.1)	−0.05 (−0.34 to 0.24)	0.71	0.79

*Among live births with a recorded score.

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Pregnancy and Perinatal Outcomes with Semaglutide Versus Metformin Exposure

After exclusion of ectopic and molar pregnancies, pregnancy loss or stillbirth occurred in 301 of 828 semaglutide-exposed pregnancies (36.4%) and 1,227 of 3,874 metformin-exposed pregnancies (31.7%) (adjusted RR 1.11, 95% CI 0.99–1.25; q=0.25).

Among 509 semaglutide-exposed and 2,685 metformin-exposed deliveries, gestational hypertension (107 [21.0%] versus 439 [16.4%]; adjusted RR 1.34, 95% CI 1.07–1.68; P=0.01, q=0.12) and new high BP from readings (90 of 256 [35.2%] versus 535 of 1,694 [31.6%]; adjusted RR 1.24, 95% CI 1.02–1.52; P=0.03, q=0.20) were more frequent with semaglutide, but neither remained significant after correction. Preeclampsia or eclampsia (118 [23.2%] versus 467 [17.4%]; adjusted RR 1.19, 95% CI 0.96–1.47; P=0.10, q=0.25) and gallbladder disease (25 [4.9%] versus 74 [2.8%]; adjusted RR 1.59, 95% CI 0.92–2.77; P=0.10, q=0.25) were directionally more frequent with semaglutide but not significant before or after correction. Gestational diabetes (87 of 418 [20.8%] versus 623 of 2,340 [26.6%]; adjusted RR 0.89, 95% CI 0.71–1.11; q=0.44), cesarean delivery, postpartum hemorrhage, heart or kidney complications, preterm birth, stillbirth or neonatal death, and a 5-minute Apgar score below 7 did not differ (**Figure 5**, **Table S5**). BMI gain during pregnancy was slightly greater with semaglutide (3.3 versus 3.1 kg/m²; adjusted difference 0.96 kg/m², 95% CI 0.38 to 1.53; q=0.01), while systolic BP from 20 weeks to delivery (adjusted difference 1.30 mmHg, 95% CI 0.09 to 2.51; q=0.13) and HbA1c during pregnancy (adjusted difference −0.14 percentage points, 95% CI −0.31 to 0.03; q=0.25) did not differ after correction (**Table S6**).

Outcome	Semaglutide-exposed n/N (%)	Metformin-exposed n/N (%)	Adjusted RR (95% CI)	P value	BH-adjusted P value
All pregnancies					
Pregnancy loss or stillbirth	301/828 (36.4%)	1,227/3,874 (31.7%)	1.11 (0.99–1.25)	0.07	0.25
Mother (deliveries)					
Preeclampsia or eclampsia	118/509 (23.2%)	467/2,685 (17.4%)	1.19 (0.96–1.47)	0.10	0.25
Gestational hypertension	107/509 (21.0%)	439/2,685 (16.4%)	1.34 (1.07–1.68)	0.01	0.12
New high BP, 20 weeks to delivery	90/256 (35.2%)	535/1,694 (31.6%)	1.24 (1.02–1.52)	0.03	0.20
Gestational diabetes	87/418 (20.8%)	623/2,340 (26.6%)	0.89 (0.71–1.11)	0.29	0.44
Gallbladder disease	25/509 (4.9%)	74/2,685 (2.8%)	1.59 (0.92–2.77)	0.10	0.25
Heart or kidney complication	<11	57/2,685 (2.1%)	0.88 (0.38–2.04)	0.76	0.76
Cesarean delivery	220/461 (47.7%)	1,082/2,492 (43.4%)	1.02 (0.91–1.15)	0.70	0.76
Postpartum hemorrhage	43/509 (8.4%)	179/2,685 (6.7%)	1.24 (0.83–1.84)	0.29	0.44
Newborn					
Preterm birth (<37 weeks)	99/382 (25.9%)	482/2,235 (21.6%)	1.17 (0.94–1.46)	0.15	0.30
Stillbirth or neonatal death	14/509 (2.8%)	72/2,685 (2.7%)	0.77 (0.39–1.51)	0.45	0.60
5-minute Apgar score <7	11/257 (4.3%)	65/1,361 (4.8%)	1.17 (0.56–2.44)	0.67	0.76

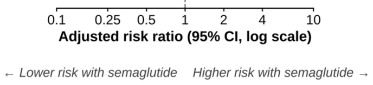


Figure 5. Pregnancy, maternal, and newborn outcomes after semaglutide versus metformin exposure. Pregnancy loss or stillbirth was assessed in 828 semaglutide-exposed and 3,874 metformin-exposed pregnancies, excluding ectopic and molar pregnancies, and the other outcomes in 509 and 2,685 deliveries. The semaglutide-exposed group comprised pregnancies with a semaglutide prescription order from 90 days before the LMP through the first 14 weeks. Columns and annotations follow the convention defined in Methods (**Table S5**).

Gestational hypertension remained more frequent with semaglutide than metformin among deliveries without chronic hypertension, a hypertensive disorder in an earlier pregnancy, or a mean BP of 140/90 mmHg or higher in the year before pregnancy (74 of 342 [21.6%] versus 333 of 2,160 [15.4%]; adjusted RR 1.55, 95% CI 1.19–2.04; q=0.004). Gallbladder disease was more frequent among deliveries without gallbladder disease in the 10 years before (23 of 464 [5.0%] versus 59 of 2,571 [2.3%]; adjusted RR 2.37, 95% CI 1.32–4.26; q=0.004). In deliveries to patients with T2D, preeclampsia or

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eclampsia occurred in 41 of 90 (45.6%) and 91 of 341 (26.7%) (adjusted RR 1.43, 95% CI 1.07–1.92; q=0.08) (**Table S7**).

Discussion

In this study of pregnancies in women using semaglutide before conception, most women stopped the drug before or early in pregnancy, and continuing it into the first trimester was not significantly associated with maternal or newborn complications. Of the 572 pregnancies in semaglutide users, 43% had a semaglutide prescription order in the first trimester and 13% had one in the third. Among deliveries, no outcome differed between the semaglutide-continued and semaglutide-discontinued groups after adjustment, although the estimates for preeclampsia and preterm birth were imprecise and do not rule out a moderate increase. In the secondary comparison, pregnancy loss was similar in semaglutide-exposed and metformin-exposed pregnancies. BMI gain during pregnancy was larger with semaglutide, and among patients without the condition before pregnancy, gestational hypertension and gallbladder disease were more frequent.

The prescription order pattern suggests that most patients and clinicians act on the label once a pregnancy is recognized. In 79% of pregnancies in the semaglutide-continued group, the last semaglutide prescription order fell in the first trimester, much of it likely before the pregnancy was known. Among pregnancies with a recorded dose in both periods, the first-trimester dose was higher than before the LMP in about half and rarely lower, consistent with dose escalation that continued until the pregnancy was recognized. Orders that continued into the third trimester (14%) may reflect deliberate continuation, an unrecognized pregnancy, or a medication list that was not updated, because an order does not confirm that the drug was taken.

These findings extend the target trial emulation by Brown and colleagues, which compared continuation of GLP-1 RA dispensing into the first trimester with non-continuation in US claims data and found little or no difference in nonlive birth (adjusted RR 1.09).[7] That study addressed fetal outcomes; ours addresses maternal complications and clinical measurements with the same contrast between continuing and discontinuing. The absence of a significant difference in gestational diabetes, BP during pregnancy, and weight gain between the semaglutide-continued and semaglutide-discontinued groups is reassuring, but with 146 and 185 deliveries the study can exclude only large effects, and the preeclampsia estimate needs confirmation in larger cohorts. A multinational cohort found no excess of major malformations,[5] and a teratology information service cohort found no excess of malformations or pregnancy loss, after first-trimester GLP-1 RA exposure.[6]

The comparison with metformin points to weight gain and BP. BMI gain during pregnancy was larger with semaglutide, and gestational hypertension remained more frequent among patients with no hypertension before pregnancy. One explanation is residual confounding, because semaglutide users start pregnancy at higher cardiometabolic risk than metformin users despite weighting on BP before pregnancy, chronic hypertension, and hypertensive disorders in earlier pregnancies. Another is that discontinuing semaglutide carries its own risk. Most semaglutide users in this study had no prescription order after the first trimester, and discontinuation of a GLP-1 RA has been associated with more gestational weight gain and more hypertensive disorders than no exposure,[8] although not in every cohort.[9] Weight regain after discontinuation could explain the larger gain against metformin, but not differences between the semaglutide-continued and semaglutide-discontinued groups, whose BMI gain did not differ.

About a third of pregnancies in this study ended in pregnancy loss, more than the 21.6% reported in a national US survey that also counted stillbirth and ectopic pregnancy as loss and left induced abortions out of the denominator.[13] Pregnancies enter EHR data through outcome codes and delivery records, so a loss treated within the health system is captured even when the delivery of a continuing pregnancy would have occurred elsewhere. The population was also older and had more obesity and diabetes than the general population, both of which raise the risk of loss. Because these features apply to every group drawn from the same records, they are less likely to bias the comparisons than the absolute proportions. Consistent with this, pregnancies of semaglutide users

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reached each trimester and delivery less often than pregnancies without GLP-1 RA use, but only about 4 percentage points less often than similar pregnancies with the same age, diabetes, obesity, and PCOS, a difference that was not significant. Gallbladder disease was more frequent with semaglutide than with metformin among patients without prior gallbladder disease, consistent with randomized evidence that GLP-1 RAs raise the risk of gallbladder and biliary disease, most strongly at higher doses and in weight-loss trials.[14]

The study has several strengths. It compared the semaglutide-continued and semaglutide-discontinued groups, drawn from the same population of semaglutide users, weighted the comparison on risk before pregnancy, including BP, HbA1c, BMI, and complications of earlier pregnancies, counted losses rather than live births alone when describing semaglutide use and comparing with metformin, and added clinical measurements that claims data lack. It also has limitations. Exposure was defined by medication orders, which do not confirm dispensing or use. The comparison of the semaglutide-continued and semaglutide-discontinued groups was small, so moderate differences cannot be excluded, and pregnancy loss could not be compared between these groups, because whether semaglutide was discontinued can only be judged in a pregnancy that continues. Outcomes were defined by diagnosis codes; preeclampsia was frequent, consistent with a population with much chronic hypertension, obesity, and diabetes, but misclassification is possible. A third of pregnancies were dated by an estimated gestational length, which blurs exposure timing, and preterm birth was assessed only in deliveries with other dating information. BMI and HbA1c were often unmeasured, and BMI above 40 kg/m² was recorded as 40 kg/m² for de-identification. Covariates did not include dyslipidemia or socioeconomic factors, and residual confounding is likely, particularly against metformin. Obesity and diabetes are likely under-recorded in pregnancies without care before conception, so comparisons may not fully account for differences in risk. Infant records were not linked, so malformations and birthweight could not be assessed. The findings come from patients receiving care in a US academic setting and may not apply elsewhere.

In conclusion, most women using semaglutide before pregnancy discontinued it before or early in pregnancy. Continuing it into the first trimester was not significantly associated with maternal or newborn complications compared with discontinuing it, although the study cannot rule out moderate increases in preeclampsia or preterm birth. These results support discussing contraception and pregnancy plans when semaglutide is started, clear information after an inadvertent exposure, and BP monitoring in pregnancies exposed to semaglutide, while larger studies with infant linkage address malformations and the preeclampsia estimate.

Methods

Data Source

This retrospective cohort study used a de-identified US EHR research database that includes diagnoses, procedures, medication orders, laboratory results, vital signs, flowsheet measurements, encounters, and structured delivery records. Diagnoses were recorded with International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) codes and procedures with Current Procedural Terminology (CPT) codes. Records through December 31, 2025, were used: diagnoses and pregnancy records from January 1, 2008, and other records from January 1, 2017.

Pregnancy Episodes and Outcomes

Pregnancy episodes were built for all female patients from pregnancy-outcome diagnosis codes, pregnancy-outcome procedure codes, and structured delivery records (**Table S8**). Outcome codes within 30 days of each other were grouped into one episode, and a new episode required at least 182 days after a delivery or 56 days after another outcome. A structured delivery record within 14 days of a code-based delivery replaced that delivery, delivery records within 30 days of each other were treated as one birth, and a code-based delivery within 182 days of a delivery record was treated as the same birth. A loss, termination, or ectopic pregnancy code dated within the span of a later

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delivery's pregnancy was not counted as a separate pregnancy. Each episode was classified, in order of priority, as a live birth, stillbirth, termination, pregnancy loss (spontaneous or missed abortion), or ectopic or molar pregnancy, adapting a published algorithm.[15] Pregnancies with a multiple-gestation code from the LMP to 3 days after delivery were classified as multiple gestations.

The LMP was assigned from the first available item in the following order: gestational age in the delivery record; an ICD-10 weeks-of-gestation code within 3 days of delivery; the median of earlier weeks-of-gestation codes, each counted on the first date it appeared; nuchal translucency ultrasound (12 weeks and 3 days), chorionic villus sampling (11 weeks and 3 days), or detailed anatomy ultrasound (20 weeks); and the first positive pregnancy test minus 38 days. An LMP from these items was accepted only if the resulting gestational age fit the outcome (22 to 45 weeks for live births, 20 to 45 weeks for stillbirths, 4 to 19 weeks for losses and ectopic or molar pregnancies, and 4 to 24 weeks for terminations) and fell after any earlier pregnancy. Otherwise, an estimated gestational length based on the outcome was applied: 273 days for live births (245 days with a preterm-labor code), 196 days for stillbirths, 70 days for losses and terminations, and 56 days for ectopic or molar pregnancies, moved earlier when needed to fall at least 25 days before a positive pregnancy test. Deliveries were live births or stillbirths at 20 weeks or later. Pregnancies with an LMP from January 1, 2018, to March 26, 2025, in patients aged 15 to 49 years at the LMP were included.

Medication Exposure

Exposure was defined from medication orders. Semaglutide included injectable and oral formulations under any brand name, and the product and weekly dose were read from the order text. Metformin included single-agent and combination products. Other GLP-1 RAs included tirzepatide, liraglutide, dulaglutide, exenatide, lixisenatide, and fixed-ratio combinations with insulin, taken from orders and medication records. Insulin, low-dose aspirin (any aspirin order), antihypertensive medications used in pregnancy (labetalol, nifedipine, methyldopa, and hydralazine), and fertility medications were taken from medication records (**Table S8**).

Semaglutide Use in Pregnancy and the Comparison of the Semaglutide-Continued and Semaglutide-Discontinued Groups

Semaglutide users were pregnancies with at least 1 semaglutide prescription order in the 90 days before the LMP. A pregnancy was in the semaglutide-continued group when at least 1 semaglutide prescription order fell from the LMP through day 97 (the first 14 weeks), or through the end of pregnancy if earlier, and in the semaglutide-discontinued group when no semaglutide prescription order fell from the LMP to the end of pregnancy. Pregnancies whose first semaglutide prescription order in pregnancy came after day 97 were classified as late restart. Pregnancies with another GLP-1 RA order from 365 days before the LMP to the end of pregnancy, a type 1 diabetes code in the 10 years before the LMP through day 97, or a multiple gestation were excluded, and the first eligible pregnancy per patient was retained. Among all semaglutide users, medication orders were summarized for the 6 months before the LMP, the first trimester (day 0 to 97), the second trimester (day 98 to 195), the third trimester (day 196 to delivery), and the 6 months after delivery, among pregnancies that reached each stage; the 6 months after delivery included only deliveries with complete follow-up by December 31, 2025. In the semaglutide-continued group, the timing of the last semaglutide prescription order and the highest injectable or oral dose ordered in the 90 days before the LMP and in the first trimester were described. Dose percentages were calculated among pregnancies with a recorded dose in each period. The first-trimester dose was classified as increased, maintained, or decreased relative to the 90 days before the LMP among pregnancies with a recorded dose of the same formulation in both periods. Maternal and newborn outcomes and clinical measurements were compared between deliveries in the semaglutide-continued and semaglutide-discontinued groups. Pregnancy loss was described but not compared between the two groups. In the semaglutide-continued group, clinical notes from the LMP to the end of pregnancy were reviewed with large language model (LLM)-curated rules to confirm semaglutide use in two

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categories: use at any point in pregnancy and use once the pregnancy was known. The comparison with the semaglutide-discontinued group was repeated within each category.

Comparison of Semaglutide and Metformin Exposure

The semaglutide-exposed group comprised pregnancies with at least 1 semaglutide prescription order from 90 days before the LMP through day 97 (periconceptional exposure); metformin use was allowed. The metformin-exposed group comprised pregnancies with at least 1 metformin order in the same window and no semaglutide or other GLP-1 RA order from 365 days before the LMP to the end of pregnancy. The same exclusions applied, and the first eligible pregnancy per patient in each group was retained. Pregnancy loss or stillbirth was compared in all pregnancies, and the other outcomes in deliveries. Supplementary analyses repeated the comparison in patients with T2D; for the hypertensive outcomes, in deliveries without chronic hypertension, a hypertensive disorder in an earlier pregnancy, or a mean BP of 140/90 mmHg or higher in the year before the LMP; for gallbladder disease, in deliveries without gallbladder disease in the 10 years before the LMP; and for all outcomes, in semaglutide-exposed pregnancies with a 2 or 2.4 mg injectable dose ordered in the exposure window.

Comparison with Similar Pregnancies

Semaglutide users were compared with pregnancies without GLP-1 RA use, defined as pregnancies with no semaglutide or other GLP-1 RA order from 365 days before the LMP to the end of pregnancy. The same exclusions applied to both groups, and the first eligible pregnancy per patient was retained. A pregnancy reached the second trimester when it ended on or after day 98, the third trimester when it ended on or after day 196, and delivery when it ended in a live birth or stillbirth, each expressed as a share of all pregnancies in the group. Pregnancies without GLP-1 RA use were grouped by age group, LMP year, T2D, obesity (an obesity diagnosis or a BMI code of 30 kg/m² or higher), and PCOS, each measured in the 365 days before the LMP. Each semaglutide user's pregnancy was matched to all pregnancies without GLP-1 RA use in the same group (similar pregnancies). For each semaglutide user, the share of her matched group reaching each milestone was taken, and the rate in similar pregnancies was the average of these shares across semaglutide users. The difference between semaglutide users and similar pregnancies was reported in percentage points, with a 95% CI and P value from a normal approximation.

Outcomes

The outcome assessed in all pregnancies, excluding ectopic and molar pregnancies, was pregnancy loss or stillbirth. Outcomes assessed in deliveries were preeclampsia or eclampsia (preeclampsia, including preeclampsia superimposed on chronic hypertension and the syndrome of hemolysis, elevated liver enzymes, and low platelets, or eclampsia, from 20 weeks to 6 weeks after delivery); gestational hypertension (new hypertension in pregnancy without proteinuria, from 20 weeks to 3 days after delivery); new high BP from readings (a systolic BP of at least 140 mmHg or a diastolic BP of at least 90 mmHg on at least 2 days from 20 weeks to delivery, among deliveries with at least 1 reading from 20 weeks, no chronic hypertension, and no reading of 140/90 mmHg or higher in the year before the LMP); gestational diabetes (from the LMP to 3 days after delivery, among deliveries without diabetes before pregnancy); gallbladder disease (gallstones, cholecystitis, or a liver or biliary disorder of pregnancy, including cholestasis of pregnancy, from the LMP to delivery); heart or kidney complication (acute kidney failure, myocardial infarction, cardiac arrest, ventricular fibrillation, heart failure or peripartum cardiomyopathy, acute pulmonary edema, stroke, or cerebral venous thrombosis, from the LMP to 6 weeks after delivery); cesarean delivery (among deliveries with a known mode of delivery); postpartum hemorrhage (from 1 day before to 42 days after delivery); preterm birth before 37 weeks (among deliveries dated by a method other than the estimated gestational length); stillbirth or neonatal death; and a 5-minute Apgar score below 7

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(among live births with a recorded score). Mode of delivery was taken from the delivery record, then from cesarean or vaginal delivery CPT codes within 3 days of delivery, and then from delivery diagnosis codes. The 5-minute Apgar score was taken from the delivery record, or otherwise from the first score documented in clinical notes within 3 days after delivery. Diagnosis and procedure codes are listed in **Table S8**.

Clinical Measurements

HbA1c before pregnancy was the last value in the 182 days before the LMP, and HbA1c during pregnancy the last value from the LMP to delivery. Mean glucose was calculated from 14 weeks to delivery, and mean systolic BP, mean diastolic BP, and the highest systolic BP from 20 weeks to delivery. Mean systolic BP after delivery was calculated from 1 to 12 weeks after delivery. BMI before pregnancy was the last value in the 182 days before the LMP, BMI change during pregnancy was the last value from 28 weeks to delivery minus BMI before pregnancy, and BMI after delivery was the last value from 6 to 12 months after delivery minus BMI before pregnancy.

Covariates

All covariates were measured before the LMP. Categorical covariates were age (15 to 24, 25 to 29, 30 to 34, 35 to 39, and 40 to 49 years); calendar year of the LMP (2018 to 2020, 2021 to 2022, and 2023 to 2025); BMI (below 30, 30 to 34.9, 35 to 39.9, 40 kg/m² or more, or not recorded), taken from the last measurement in the 182 days before the LMP, then from the pre-pregnancy BMI in the delivery record, and then from a BMI diagnosis code in the 365 days before; HbA1c (below 5.7%, 5.7% to 6.4%, 6.5% to 7.9%, 8.0% or higher, or not measured) in the 182 days before; mean BP in the 365 days before (below 130/80, 130 to 139/80 to 89, 140/90 mmHg or higher, or not measured); and the number of encounter days in the 182 days before (0 to 2, 3 to 5, 6 to 11, or 12 or more). Binary covariates were T2D, chronic hypertension, PCOS, infertility or fertility treatment, and smoking in the 365 days before; insulin orders in the 91 days before; any earlier pregnancy, a hypertensive disorder in an earlier pregnancy, gestational diabetes in an earlier pregnancy, and gallbladder disease in the 10 years before; and a prior cesarean delivery, defined from a uterine-scar code, a cesarean code in an earlier pregnancy, or the delivery record. The comparison of the semaglutide-continued and semaglutide-discontinued groups also included metformin orders in the 91 days before (**Table S8**).

Statistical Analysis

A propensity score for the index group (semaglutide-continued, or semaglutide-exposed) was estimated by ridge-penalized logistic regression on all covariates, and each pregnancy received an overlap weight equal to the probability of belonging to the other group.[16] Propensity scores were estimated separately for the comparison of the semaglutide-continued and semaglutide-discontinued groups, for all pregnancies and for deliveries in the comparison with metformin, and for each supplementary analysis. Covariate balance was assessed with the SMD before and after weighting. Characteristics before weighting were also compared with the chi-square test. Crude and weighted RRs were calculated from the risk in each group, with robust variances that treated the weights as fixed, and adjusted differences in means were calculated for clinical measurements in the same way. All P values were two-sided. P values were corrected for multiple comparisons with the BH method within each analysis: the outcomes of the semaglutide-continued versus semaglutide-discontinued comparison, the outcomes in all pregnancies and deliveries of the comparison with metformin, each supplementary analysis, and each set of clinical measurements. A result was considered significant when its BH-adjusted P value (q) was below 0.05. In forest plots, squares mark the overlap-weighted RR and horizontal lines its 95% CI on a log scale; filled squares and bold text mark q below 0.05, and arrows mark CIs that extend beyond the axis. Error bars in bar and line charts denote 95% Wilson CIs for observed percentages. Event and category counts below 11, including zero, are reported as

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<11 without a percentage. Crude RRs are not shown for outcomes with a count <11, and the SMD before weighting is not shown for covariate levels with a count <11.

Data Availability

The de-identified EHR data were accessed within the nference analytics environment under an expert determination in accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Data beyond what is reported in this manuscript, including the patient-level records, cannot be shared under the terms of that determination. The corresponding author can be contacted for details of the platform.

De-Identification and HIPAA Compliance Certification

Prior to analysis, all EHR data were de-identified under an expert determination consistent with the HIPAA Privacy Rule (45 Code of Federal Regulations §164.514(b)(1)). The de-identification methodology employed a multi-layered transformation approach to both structured and unstructured data fields.[17] In structured data, direct identifiers including patient names and precise geographic locations were excluded entirely, while indirect identifiers underwent specific transformations: patient identifiers, medical record numbers, and accession numbers were replaced with one-way cryptographic hashes using confidential salts to preserve linkage across patient encounters; all dates were shifted backward by patient-specific random offsets (1–31 days) to preserve temporal relationships while obscuring exact event timing; the ZIP codes were truncated to two-digit state-level resolution; and continuous variables including age, height, weight, and BMI were thresholded to prevent identification of extreme values (for example, ages ≥89 years transformed to '89+' and BMI >40 transformed to '40+'). In unstructured clinical text, an ensemble de-identification system that combines attention-based deep learning models with rule-based methods achieved an estimated >99% recall for personally identifiable information detection, with detected identifiers replaced by plausible fictional surrogates.[17] nference established secure data environments within each participating center, specifically designed to enable data access and analysis without requiring Institutional Review Board oversight, approval, or exemption confirmation. Accordingly, informed consent and IRB review were not required for this study.

Data Harmonization

To address heterogeneity in EHR data, clinical variables including medications, anthropometric measurements, and diagnoses were harmonized to standardized concepts. For medications, a standardized drug concept database combining the nSights knowledge graph with RxNorm (https://www.nlm.nih.gov/research/umls/rxnorm/index.html) hierarchies captured ingredient, brand, and dose-specific information.[18] EHR medication records were matched using a hierarchical approach prioritizing RxNorm codes when available, followed by ingredient-level matching, and finally natural language processing and pattern matching on free-text medication orders when structured codes were absent. For anthropometric measurements (height, weight, BMI), a unified vocabulary from SNOMED (https://www.snomed.org/, https://athena.ohdsi.org) and LOINC (https://loinc.org/) terminologies was created, and EHR measurement descriptions were matched using standardized text matching with abbreviation expansion and synonym resolution; ambiguous mappings were resolved using OpenAI GPT-4o (https://platform.openai.com/docs/models/gpt-4o) with summary statistics as context, followed by manual verification. For diagnoses, a hierarchical disease concept database from the nSights knowledge graph was used, and EHR diagnosis descriptions and codes were matched by identifying the most specific common child concept in the hierarchy.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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Code Availability: The analysis code is not publicly available. The corresponding author should be contacted for additional details.

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Conflicts of Interest: The authors are employees of nference, inc., which conducts research collaborations with various biopharmaceutical companies whose therapeutic products are included in this study. None of these companies, nor any other nference collaborator, funded, supported, or had any role in the independent study design, data acquisition, analysis, interpretation, manuscript preparation, or the decision to submit this work for publication. All analyses were conducted by the authors using de-identified electronic health record data. The authors declare no additional competing interests.

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