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Early Pregnancy Use of Anti-CGRP Monoclonal Antibodies and Propranolol and Spontaneous Abortion Risk

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IMPORTANCE Migraine affects individuals of reproductive age, but treatment options during pregnancy are limited due to safety concerns. Anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) are effective for migraine prevention; however, CGRP is important in placental development.

OBJECTIVE To determine whether early pregnancy exposure to anti-CGRP mAbs or propranolol is associated with spontaneous abortion compared with no exposure.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used data from the AM-PREGNANT cohort, derived from the Merative MarketScan Commercial Database, from 2018 to 2021. Participants were followed up through 20 weeks' gestation or until spontaneous abortion or censoring. Among 7 991 200 pregnancies identified in the AM-PREGNANT cohort, 7119 individuals contributing 7579 singleton pregnancies met the predefined eligibility criteria, including age 15 to 45 years, continuous insurance enrollment, last menstrual period (LMP) on or after November 1, 2018, pregnancy end or 20-week censoring by December 31, 2021, and pregestational migraine, defined as a migraine diagnosis or triptan or ergot prescription within 6 months before LMP. Data were analyzed in early 2026.

EXPOSURES Anti-CGRP mAbs (erenumab, fremanezumab, galcanezumab, eptinezumab) or propranolol, defined as 1 or more filled prescription or injection procedure claim during follow-up and modeled as time-varying.

MAIN OUTCOME AND MEASURES Spontaneous abortion occurring at 20 weeks' or less gestation. Multivariable Cox proportional hazards models adjusted for comorbidities and concomitant medications estimated the risk of spontaneous abortion.

RESULTS Among 7579 pregnancies in 7119 individuals (mean [SD] age, 31.6 [5.5] years), 1862 spontaneous abortions occurred. There were 100 spontaneous abortions (28.6%) during anti-CGRP mAb-exposed person-time, compared with 37 events among propranolol-exposed person-time without anti-CGRP mAbs (12.8%). Compared with unexposed individuals, anti-CGRP mAbs exposure was associated with an increased risk of spontaneous abortion (adjusted hazard ratio [aHR], 1.42; 95% CI, 1.12-1.80), which remained similar in bias-adjusted analyses (HR, 1.33; 95% simulation interval [SI], 1.23-1.45). Propranolol exposure was not associated with increased risk (aHR, 1.02; 95% CI, 0.71-1.47; bias-adjusted HR, 1.00; 95% SI, 0.96-1.03).

CONCLUSION AND RELEVANCE In this study, early pregnancy exposure to anti-CGRP mAb was associated with a higher risk of spontaneous abortion, while no association was observed with propranolol. These findings support further evaluation of anti-CGRP mAb safety and emphasize counseling for individuals of childbearing potential.

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Multimedia

Supplemental content

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Migraine is one of the most common neurologic disorders worldwide and disproportionately affects individuals of reproductive age.[1,2] Calcitonin gene-related peptide (CGRP) pathway therapies have transformed migraine prevention since 2018, particularly for patients who do not respond to or cannot tolerate traditional oral medications. However, migraine management during pregnancy remains challenging due to safety concerns for the pregnant person and fetus.

Anti-CGRP monoclonal antibodies (mAbs) are typically prescribed after failure of multiple preventive therapies, and therefore, may be used more frequently in patients with severe or treatment-refractory migraine.[3] Although recent guidelines support first-line use in selected cases,[4,5] access restrictions remain common.[6] Thus, pregnancies exposed to anti-CGRP mAbs may involve individuals with greater disease severity, higher health care utilization, and more extensive medication exposure.

Safety concerns during pregnancy stem from CGRP's role in vascular regulation, implantation, placental development, and uteroplacental blood flow,[7-9] and have led to recommendations to discontinue anti-CGRP mAbs 5 to 6 months before conception due to their 1-month half-life.[5,10-12] Evidence on their safety in early pregnancy remains limited. A recent analysis did not identify a clear association with spontaneous abortion, although drug-specific signals based on a small number have been reported.[12,13] Therefore, current guidance for individuals of reproductive age relies largely on indirect evidence, including animal studies and limited observational data. Although migraine itself has not been consistently associated with spontaneous abortion, some studies suggest migraine medication use may increase risk.[14] Interpretation is complicated by confounding by indication, as patients receiving anti-CGRP mAbs may have more severe or refractory disease.[3] Accordingly, we evaluated the association between early pregnancy exposure to anti-CGRP mAbs or propranolol and spontaneous abortion compared with no exposure.

Key Points

Question Is exposure to anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies during early pregnancy associated with spontaneous abortion in individuals with migraine?

Findings In this cohort study of 7579 pregnancies, anti-CGRP monoclonal antibody exposure was associated with an increased risk of spontaneous abortion compared with unexposed person-time, while propranolol exposure was not.

Meaning These results demonstrate that early pregnancy exposure to anti-CGRP monoclonal antibodies may be associated with an increased risk of spontaneous abortion, supporting further evaluation of their safety during pregnancy and informing treatment decisions for individuals of childbearing potential.

Methods

Ethics

Ethics approval was obtained from the Sainte-Justine Hospital Ethics Committee (2024-6976). Informed consent was waived, as the study used deidentified administrative health claims data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Data Source

We conducted a cohort study using the American Pregnancy Mother-Child cohort (AM-PREGNANT), described elsewhere.[15] AM-PREGNANT is derived from the Merative MarketScan Commercial Database, a US administrative health insurance claims database and includes data on more than 2 million pregnancies in the US from 2003 through 2021.[16] Diagnoses and procedures were identified using codes from the *International Classification of Diseases, Ninth and Tenth Revisions* (*ICD-9/10*), and *Current Procedural Terminology*. All diagnosis and procedure codes used are provided in eTable 1 in Supplement 1.

Study Population

Within AM-PREGNANT, we identified all eligible singleton pregnancies meeting the predefined eligibility criteria during the study period. The study size was determined by the number of eligible pregnancies available within the database. Eligible pregnancies occurred among individuals aged 15 to 45 years with continuous health insurance coverage for 6 months or more before their last menstrual period (LMP) and through the end of follow-up. Pregnancies were followed up from LMP until the earliest of spontaneous abortion, induced abortion, 20 weeks' gestation, or December 31, 2021. Pregnancies ending in induced abortion and pregnancies continuing beyond 20 weeks' gestation were censored at those time points. Only pregnancies with complete follow-up before December 31, 2021, were included (**Figure 1**). The study design, assessment windows, exposure ascertainment, and follow-up timeline are illustrated in **Figure 2**.

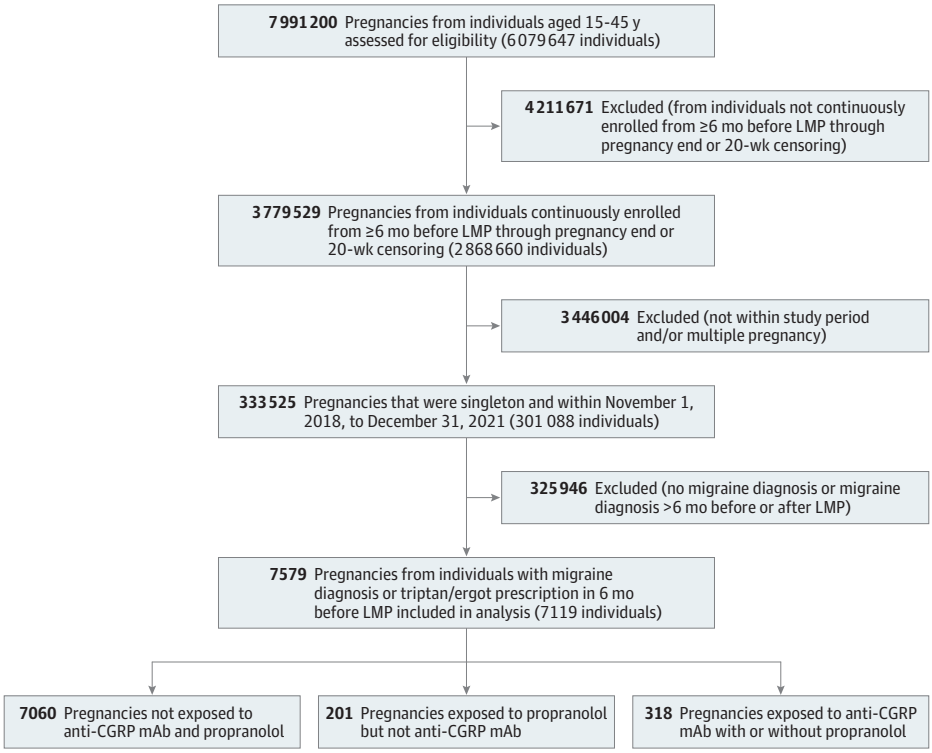
As anti-CGRP mAbs became available in May 2018, we restricted our analysis to pregnancies with LMP on or after November 1, 2018, allowing for 6 months or more of potential prepregnancy exposure following market introduction. LMP was estimated in AM-PREGNANT using previously validated algorithms based on gestational age and pregnancy outcomes.[15] When gestational age codes were unavailable, the algorithm assigned outcome-specific gestational ages to estimate the LMP, including 8 weeks for pregnancies ending in spontaneous abortion. These algorithms were used to estimate pregnancy start dates; spontaneous abortion events for the study outcome were subsequently ascertained using a separate validated claims-based algorithm, as described below. Although pregnancy dating and spontaneous abortion ascertainment were performed using separate algorithms, both relied on the same underlying administrative claims data.

Pregestational migraine was identified using a modified algorithm from Bonafede et al[17] based on diagnoses and migraine-specific medication dispensations occurring within the 6 months before LMP. Inclusions required meeting at least 1 of the following criteria: (1) 1 or more inpatient or emergency department (ED) migraine diagnosis; (2) 2 or more outpatient migraine diagnoses 7 to 180 days apart (excluding ED

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Figure 1. Flowchart of Study Cohort Selection



Selection of pregnancies included in the study cohort from the AM-PREGNANT cohort derived from the Merative MarketScan Commercial Database, including exclusions applied at each stage of cohort assembly. CGRP indicates calcitonin gene-related peptide; LMP, last menstrual period; mAbs, monoclonal antibodies.

visits); (3) 1 or more outpatient migraine diagnosis and 1 or more triptan or ergot prescription, 7 to 180 days apart; or (4) 2 or more triptan or ergot prescriptions, 7 to 180 days apart.

Exposure

Anti-CGRP mAb exposure (erenumab, fremanezumab, galcanezumab, eptinezumab) and propranolol exposure were identified from filled prescription or injection procedure claims using National Drug Codes and Healthcare Common Procedure Coding System J-codes. A time-varying exposure framework classified each day of follow-up as anti-CGRP mAbs (with or without concomitant propranolol), propranolol without anti-CGRP mAbs, or no exposure to either drug. Other concomitant medications were permitted in all groups.

Given the 27- to 31-day half-lives of anti-CGRP mAbs, dispensings during the 6 months before LMP were assessed for exposure extending into pregnancy. A grace period of 5 half-lives was applied; thus, exposure continued for 135 to 155 days after dispensing or infusion.[18] Propranolol exposure was defined using the recorded days' supply plus approximately 1 additional day. Pre-LMP dispensing contributed exposure only when the resulting exposure period overlapped pregnancy. Propranolol was included as a commonly used migraine preventive in pregnancy to provide context for the anti-CGRP mAb findings.

Outcome

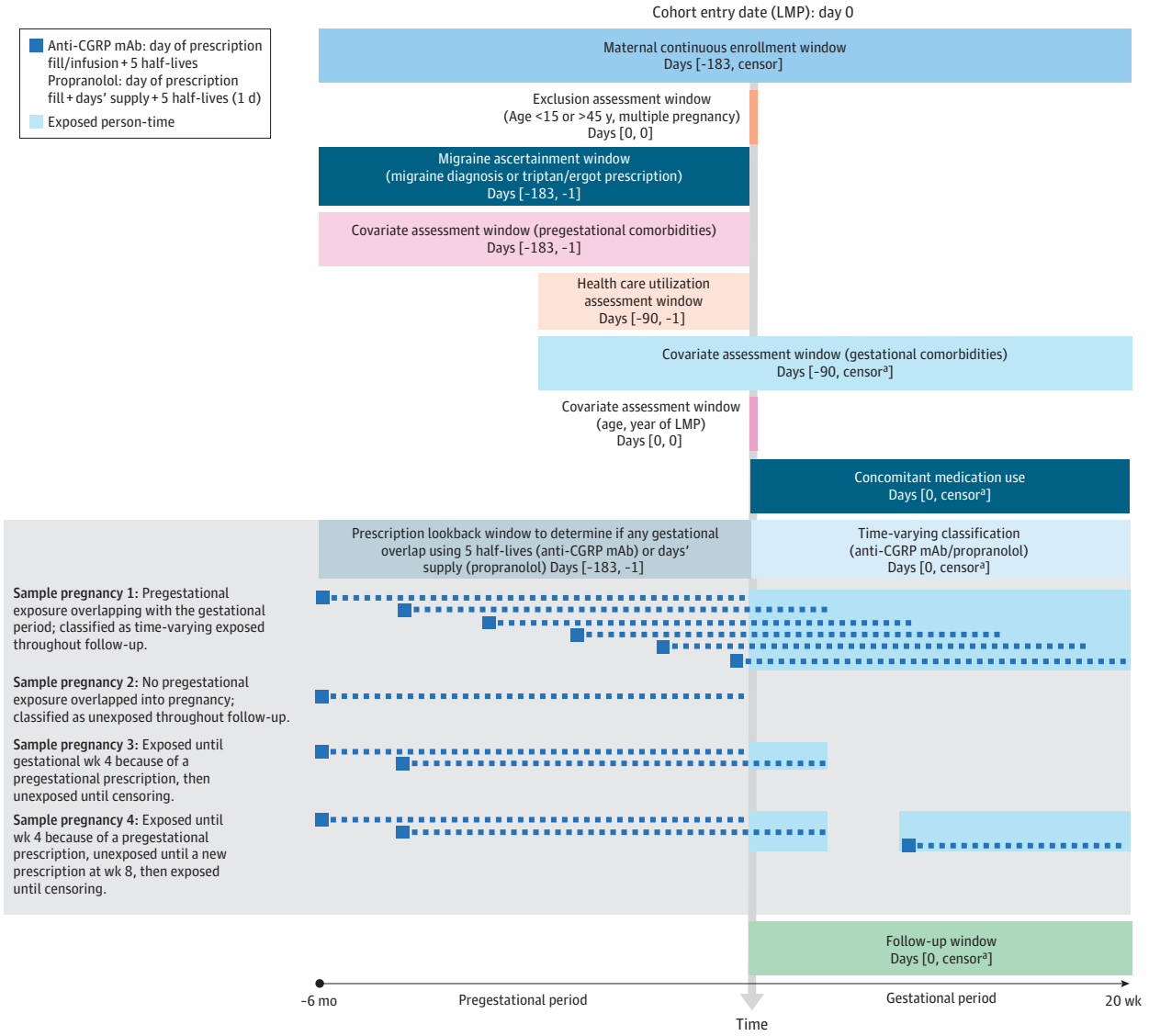
The primary outcome was spontaneous abortion, identified using validated claims-based algorithms.[19,20] Cases required 1 or more inpatient or outpatient spontaneous abortion codes and were excluded if codes for stillbirth or termination occurred within 5 days before or after a spontaneous abortion code.[19] The algorithm has a positive predictive value of 86.4% (95% CI, 75.0%-94.0%).[19] *ICD-9* codes followed Zhu et al[19] and *ICD-10* codes were adapted from Chomistek et al.[20]

Potential Confounders or Effect Modifiers

Age at LMP was included as a continuous covariate. Year of LMP was included as a binary variable. Pregestational comorbidities (kidney disease, hypertension, depression, epilepsy, diabetes, hyperthyroidism, hypothyroidism, and autoimmune and inflammatory diseases) were identified as present or absent (based on diagnostic codes) in the 6 months before LMP. Gestational comorbidities, including drug abuse, alcohol abuse, tobacco use, obesity, underweight, and any diagnosed infectious and parasitic disease, were identified from 90 days before LMP through the end of follow-up. These variables were treated as time-fixed covariates. Concomitant medications used during follow-up were modeled as binary covariates. Medications included acute migraine medications (triptans, ergots, nonsteroidal anti-inflammatory drugs [NSAIDs], ondansetron, metoclopramide, ubrogepant, and rimegepant [8 tablets per month]), preventive migraine medications (β-blockers, onabotulinumtoxinA, antihypertensives, antiepileptics, serotonin and norepinephrine reuptake inhibitor antidepressants, tricyclic antidepressants, atogepant, and rimegepant [16 tablets per month]), other antidepressants, and macrolide antibiotics (eTable 2 in Supplement 1). Gepants, which also

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Figure 2. Schematic of Study Design and Timeline for Exposure and Covariate Assessment



Schematic depicting the pregnancy cohort timeline, including the lookback period for assessment of baseline covariates and comorbidities, continuous insurance enrollment, exposure ascertainment and classification of anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs), and propranolol, time-varying exposure windows, and follow-up for spontaneous abortion from the last menstrual period (LMP) through 20 weeks' gestation.

[a]Censored at spontaneous abortion, induced abortion, or 20 weeks' gestation.

target the CGRP pathway but differ pharmacologically from the long-active anti-CGRP mAbs, were permitted as concomitant medications and accounted for in the adjusted models. We also created a composite health care utilization measure for the 90 days before LMP by summing outpatient visits, inpatient hospitalizations, and neurology visits (inpatient and outpatient), with inpatient encounters weighted twice to reflect greater health care intensity and likely higher disease severity.[21]

Statistical Analysis

For descriptive analyses, pregnancies were classified according to any exposure during follow-up as anti-CGRP mAb, propranolol without anti-CGRP mAbs, or unexposed. Multivariable Cox proportional hazards models were used to estimate adjusted hazard ratios (aHRs) and 95% CIs for spontaneous abortion, using unexposed person-time as the reference. Models adjusted for age, year of LMP, comorbidities, and individual medications. Model assumptions and within-pregnant-persons correlations are described in eMethods 1 in Supplement 1. We estimated adjusted risks by 20 weeks using regression standardization under hypothetical scenarios of universal anti-CGRP mAb exposure and no exposure; we calculated the risk difference between scenarios, with 95% CIs obtained via bootstrap resampling.[22] Analyses were conducted using R version 4.4.3 (R Foundation for Statistical Computing).

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Sensitivity Analyses

We varied the anti-CGRP exposure window from 3 to 6 half-lives. We also restricted propranolol exposure to individuals with evidence of migraine treatment (triptan, ergot, or anti-CGRP mAb) and whose propranolol prescription occurred more than 14 days after a health care encounter with a migraine diagnostic code to reduce potential misclassification of propranolol prescriptions for indications other than migraine. We further extended propranolol exposure windows to 135 days to assess potential exposure-window misclassification. Anti-CGRP mAb exposure and spontaneous abortion were summarized by individual agent. We additionally conducted a logistic regression using binary rather than time-varying exposures.

Lastly, we conducted a probabilistic bias analysis to assess residual confounding by migraine severity (eMethods 2 in Supplement 1).[23] Chronic migraine was used as a proxy for severity, as migraine severity is difficult to measure directly in administrative data. We used external estimates of chronic migraine prevalence among anti-CGRP mAb users and standard-of-care preventive users (0.69 and 0.216, respectively) for the anti-CGRP analysis.[14] For propranolol, we assumed a chronic migraine prevalence of 0.216 among exposed individuals, using the standard-of-care estimate as a proxy, and 0.0523 among unexposed individuals, based on a population-based estimate among individuals with migraine.[24] The association between migraine medication use and spontaneous abortion (HR, 1.14; 95% CI, 0.96-1.36) was used as a proxy estimate for the association between migraine severity and spontaneous abortion.[25] Monte Carlo simulation with 10 000 iterations generated bias-adjusted estimates.

Results

The study included 7579 pregnancies among 7119 individuals. There were 1862 spontaneous abortions (24.6%), including 100 (28.6%) during anti-CGRP mAb-exposed person-time and 37 (12.8%) during propranolol-exposed person-time, without anti-CGRP mAbs. Overall, 350 pregnancies (4.6%) contributed anti-CGRP mAb-exposed person-time, either through a filled prescription during pregnancy or because treatment initiated before LMP resulted in continued biologic exposure into pregnancy due to the long half-lives of these agents. In comparison, 283 (3.7%) contributed propranolol-exposed person-time without anti-CGRP mAbs. Anti-CGRP mAb exposure increased over calendar time, whereas propranolol exposure remained relatively stable (**Table 1**). Among anti-CGRP-exposed pregnancies, 172 (49.1%) had exposure before and during pregnancy, 147 (42%) before pregnancy only, and 31 (8.9%) during pregnancy only.

Anti-CGRP mAb users had greater health care utilization in the 3 months before pregnancy onset and more frequent markers of migraine severity, including use of triptans, NSAIDs, ondansetron, and antiepileptics, as well as higher prevalence of depression and concomitant antidepressant use (Table 1). Propranolol users had more preexisting hypertension (18.4%).

Anti-CGRP mAb exposure was associated with an increased risk of spontaneous abortion (aHR, 1.42; 95% CI, 1.12-1.80) compared with unexposed person-time (**Table 2**). Propranolol exposure was not associated with spontaneous abortion (aHR, 1.02; 95% CI, 0.71-1.47) (Table 2). eFigure 1 in Supplement 1 shows Kaplan-Meier survival curves for spontaneous abortion by exposure group through 20 weeks' gestation.

Under a hypothetical scenario in which all pregnancies had anti-CGRP mAb exposure during pregnancy, the adjusted risk of spontaneous abortion by 20 weeks' gestation was 28.7%, compared with 24.5% under no anti-CGRP mAb exposure. This corresponded to an adjusted risk difference of 4.2 percentage points (95% CI, 2.4-9.6).

In sensitivity analyses, estimates were similar when anti-CGRP mAb exposure was defined using 3 to 6 half-lives (aHR range, 1.38-1.50) (eFigure 2 in Supplement 1) and when propranolol exposure was restricted or extended to 135 days (eTables 3 and 4 in Supplement 1). The quantitative bias analysis yielded HRs of 1.33 (95% simulation interval [SI], 1.23-1.45) for anti-CGRP and 1.00 (95% SI, 0.96-1.03) for propranolol (Table 2). Descriptive data on the number of pregnancies contributing exposed person-time and the number and proportion of spontaneous abortions by individual anti-CGRP mAb are presented in eTable 5 in Supplement 1. Results were consistent with logistic regression using binary exposures (adjusted odds ratio, [aOR], 1.67; 95% CI, 1.18-2.35 for anti-CGRP mAbs and aOR, 0.76; 95% CI, 0.51-1.11 for propranolol) (eTable 6 in Supplement 1).

Discussion

In this population-based cohort study of 7579 pregnancies in people with migraine, anti-CGRP mAb–exposed person-time (with or without propranolol) was associated with a higher risk of clinically detected spontaneous abortion than unexposed pregnancies, whereas propranolol exposure was not. A quantitative bias analysis accounting for residual confounding by migraine severity modestly attenuated the association, which remained elevated under the specified assumptions.

Our findings extend the limited human evidence on anti-CGRP mAbs in pregnancy.[12] Prior pharmacovigilance studies have not identified a consistent association with adverse pregnancy outcomes, although exploratory drug-specific signals have been reported based on small numbers and may be affected by reporting bias.[13] Preclinical studies of erenumab in cynomolgus monkeys did not identify treatment-related effects on embryofetal development or fetal or infant loss, although exposure began after implantation, limiting assessment of early pregnancy loss.[26] Given CGRP's role in uteroplacental vascular adaptation and placental development, an association with spontaneous abortion is biologically plausible.

Anti-CGRP mAb users had greater health care utilization, depression, and concomitant medication use, suggesting greater disease burden and treatment complexity.[27] Because claims data do not capture migraine frequency or migraine severity directly, residual confounding by indication remains possible despite adjustment for available indicators of disease

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Table 1. Characteristics of Pregnant People Stratified by Any Use of Migraine Preventive Treatment Exposure During Follow-Up (N = 7579)

Variables	No. (%)		
	Unexposed (n = 6946)	Propranolol (n = 283)[a]	Anti-CGRP mAbs (n = 350)[a]
Age, mean (SD), y	31.66 (5.49)	31.13 (5.68)	32.11 (5.80)
Pregestational comorbidities			
Kidney disease	35 (0.5)	2 (0.7)	0 (0.0)
Hypertension	567 (8.2)	52 (18.4)	26 (7.4)
Depression	1765 (25.4)	95 (33.6)	127 (36.3)
Epilepsy	210 (3.0)	8 (2.8)	7 (2.0)
Diabetes	168 (2.4)	10 (3.5)	10 (2.9)
Hyperthyroidism	87 (1.3)	7 (2.5)	6 (1.7)
Hypothyroidism	664 (9.6)	31 (11.0)	38 (10.9)
Autoimmune and inflammatory diseases	231 (3.3)	10 (3.5)	20 (5.7)
Health care encounters, 90 d before LMP, mean (SD)	6.07 (7.55)	6.20 (8.13)	7.88 (12.00)
Gestational comorbidities			
Obesity	1529 (22.0)	65 (23.0)	89 (25.4)
Underweight	79 (1.1)	4 (1.4)	3 (0.9)
Tobacco use	53 (0.8)	3 (1.1)	2 (0.6)
Drug abuse	155 (2.2)	8 (2.8)	8 (2.3)
Alcohol abuse	138 (2.0)	8 (2.8)	7 (2.0)
Infection	5414 (77.9)	216 (76.3)	273 (78.0)
Acute migraine drugs			
Triptans	1493 (21.5)	74 (26.1)	100 (28.6)
Ergots	7 (0.1)	0	0
NSAIDs	672 (9.7)	42 (14.8)	62 (17.7)
Ondansetron	1652 (23.8)	79 (27.9)	122 (34.9)
Metoclopramide	674 (9.7)	35 (12.4)	44 (12.6)
Ubrogepant	21 (0.3)	0	5 (1.4)
Rimegepant (8 tablets/mo)	14 (0.2)	3 (1.1)	10 (2.9)
Preventive migraine drugs			
β-Blockers (metoprolol, nadolol, atenolol)	126 (1.8)	4 (1.4)	17 (4.9)
OnabotulinumtoxinA	5 (0.1)	0	2 (0.6)
Antihypertensives (candesartan, lisinopril)	26 (0.4)	3 (1.1)	4 (1.1)
Antiepileptics (topiramate, valproate)	237 (3.4)	11 (3.9)	19 (5.4)
SNRI antidepressants (venlafaxine, duloxetine)	214 (3.1)	15 (5.3)	26 (7.4)
Tricyclic antidepressants (amitriptyline, nortriptyline)	217 (3.1)	19 (6.7)	30 (8.6)
Atogepant	0	0	0
Rimegepant (16 tablets/mo)	0	0	0
Other medications			
Other antidepressants	1267 (18.2)	92 (32.5)	95 (27.1)
Macrolide antibiotics (clarithromycin, azithromycin)	468 (6.7)	16 (5.7)	27 (7.7)
Year of LMP, No./total No. (%)			
2018 (n = 630)	589/630 (93.5)	30/630 (4.8)	11/630 (1.7)
2019 (n = 3243)	3036/3243 (93.6)	100/3243 (3.1)	107/3243 (3.3)
2020 (n = 3164)	2835/3164 (89.6)	129/3164 (4.1)	200/3164 (6.3)
2021 (n = 542)	486/542 (89.7)	24/542 (4.4)	32/542 (5.9)

Abbreviations: CGRP, calcitonin gene-related peptide; LMP, last menstrual period; mAbs, monoclonal antibodies; NSAIDs, nonsteroidal anti-inflammatory drugs; SNRI, serotonin and norepinephrine reuptake inhibitors.

[a] Propranolol indicates propranolol (but no anti-CGRP mAb); anti-CGRP mAbs indicates CGRP mAb (with or without propranolol).

burden and treatment history and restriction to individuals with pregestational migraine. The 6-month lookback period also limited characterization of long-term migraine treatment history and distinction between new and prevalent users.

Our quantitative bias analysis evaluated residual confounding by migraine severity using chronic migraine as a proxy and external estimates of chronic migraine prevalence and its association with spontaneous abortion. Under the specified assumptions, the estimates were modestly attenuated but remained elevated. However, these results depend on the validity of the external estimates and assumptions, and cannot exclude residual confounding as an explanation for some of

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Table 2. Crude and Adjusted Hazard Ratios for the Association Between Time-Varying Current Migraine Preventive Treatment Use and Risk of Spontaneous Abortion

Exposure[a]	No. of pregnancies contributing person-time[b]	Person-years	Spontaneous abortion events	Hazard ratio (95% CI)		
				Crude	Adjusted[c]	Bias-adjusted[d]
Unexposed	7344	2357.1	1725	1 [Reference]	1 [Reference]	
Propranolol	290	47.8	37	1.03 (0.71-1.51)	1.02 (0.71-1.47)	1.00 (0.96-1.03)
Anti-CGRP mAbs	350	88.2	100	1.51 (1.17-1.94)	1.42 (1.12-1.80)	1.33 (1.23-1.45)

Abbreviations: CGRP, calcitonin gene-related peptide; mAbs, monoclonal antibodies.

[a] Propranolol indicates propranolol (but no anti-CGRP mAb); anti-CGRP mAbs indicates CGRP mAb (with or without propranolol).

[b] Number of unique pregnancies that contributed any person-time to the corresponding exposure category during follow-up. As exposure was modeled as time varying, a pregnancy could contribute person-time to more than 1 exposure category.

[c] Adjusted for age, year of last menstrual period, pregestational comorbidities, gestational comorbidities, acute migraine drugs, preventive migraine drugs, other medications, and health care utilization.

[d] Bias-adjusted estimates were obtained from probabilistic bias analysis; intervals represent 95% simulation intervals.

the association. Restricting the cohort to individuals with migraine, nevertheless, reduced confounding by migraine diagnosis itself.

In addition, the most recent data available to the study team extended only through 2021. As anti-CGRP mAbs had only recently been introduced into clinical practice, the number of exposed pregnancies was limited. Inclusion of more recent calendar years would likely have increased the number of exposed pregnancies, resulting in greater statistical precision and allowing for a more robust evaluation of the association between anti-CGRP mAb exposure and spontaneous abortion.

Strengths and Limitations

This study has several strengths. To our knowledge, it is the first large population-based study to evaluate anti-CGRP mAb exposure and spontaneous abortion. By leveraging a large US commercial claims database, we examined medication exposures and pregnancy outcomes in a large real-world population. The use of routine clinical data captured real-world exposures, including unintended early pregnancy exposure. However, because MarketScan captures a commercially insured US population, findings may not be generalizable to uninsured or publicly insured individuals. Inclusion of propranolol provided clinically relevant context for interpreting the association with anti-CGRP mAbs, although it was not intended as an active comparator. In addition, exposures were modeled as time-varying, allowing individuals to contribute person-time according to their current medication exposure status and reflect changes in treatment patterns during pregnancy rather than assuming a fixed-treatment assignment.

Several sources of potential misclassification should also be considered. First, our outcome definition captured only clinically recognized spontaneous abortions recorded in administrative health data. Early pregnancy losses that occur before clinical detection are not captured in such data sources. Estimates of miscarriage incidence vary depending on the populations studied and the method of outcome ascertainment. Among clinically recognized pregnancies, approximately 15% to 25% end in miscarriage.[28] However, the incidence of miscarriage differs depending on the gestational week, with a lower incidence the further along in pregnancy.[29] In our study, the observed proportion of clinically detected spontaneous abortion by 20 weeks' gestation was 28.6% among pregnancies exposed to anti-CGRP mAbs. After adjustment, the estimated absolute increase in risk associated with anti-CGRP mAb exposure was 4.2 percentage points.

Nevertheless, our study likely underascertained very early pregnancy losses that were not clinically detected. Among the 1862 spontaneous abortions identified by our outcome algorithm, 1097 (58.9%) had no observed gestational age code and were assigned an 8-week gestational age by the AM-PREGNANT pregnancy-dating algorithm for the purpose of estimating the LMP. Because the spontaneous abortion event dates identified by our outcome algorithm could differ from the pregnancy outcome dates used by the AM-PREGNANT dating algorithm, the interval between the imputed LMP and the spontaneous abortion event date ranged from 57 to 63 days. Thus, the estimated gestational timing of a substantial proportion of spontaneous abortions was based on imputed pregnancy dating.

Exposure misclassification is possible because prescription dispensing records do not confirm medication use, and residual medication use may occur after the defined exposure window. However, exposure was ascertained independently of spontaneous abortion status, and results were robust to varying the anti-CGRP mAb exposure window and extending the propranolol window to 135 days. As anti-CGRP mAbs have long half-lives, our estimates primarily reflect residual or ongoing exposure around conception and early pregnancy rather than treatment initiated during pregnancy.

Treatment context may also differ between exposure groups. Anti-CGRP mAbs are generally recommended to be discontinued 5 to 6 months before conception due to limited evidence regarding their safety during pregnancy; therefore, exposure during early pregnancy may reflect prerecognition exposure or unintended pregnancy, whereas propranolol may be intentionally continued when clinically indicated.[5,10-12] Pregnancy intention was unavailable in claims data and may therefore contribute to residual confounding. Nearly half of pregnancies ending in spontaneous abortion have been reported to be unintended, highlighting the potential for inadvertent anti-CGRP mAb exposure and for pregnancy intention to contribute to residual confounding.[30] In addition, prevalent users were included and incomplete characterization of prepregnancy treatment history may have contributed to residual confounding. These differences in treatment context may in-

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troduce systematic differences between exposure groups that are difficult to fully capture in administrative data.

However, effect estimates from the time-varying exposure analysis were slightly lower than those from the binary exposure analysis, likely reflecting reduced exposure misclassification in the time-varying approach, which accounts for changes in exposure status during pregnancy and incorporates the medication's long half-life, unlike the binary ever/never classification. This approach assumes that the biologically relevant period of increased risk is adequately captured by the defined exposure window, which is based on treatment duration and residual pharmacologic effects. If early exposure initiates processes that increase the risk of spontaneous abortion beyond this window, the binary exposure analysis may better capture such effects, albeit with reduced temporal specificity and greater exposure misclassification.

Misclassification of migraine diagnoses in administrative health data could also affect case ascertainment. Migraine may be underdiagnosed in administrative data.[31] However, our cohort definition was designed to prioritize specificity, reducing false-positive migraine classification and confounding by migraine diagnosis.[32]

Conclusions

In conclusion, in this study, anti-CGRP mAb exposure was associated with an elevated risk of clinically detected spontaneous abortion. Given the increasing use of anti-CGRP mAbs for migraine prevention among individuals of reproductive age, further research is needed to evaluate their safety during pregnancy, including studies examining spontaneous abortion, fetal outcomes, and longer-term offspring outcomes. Until more evidence is available, clinicians should consider the limited evidence on pregnancy safety when discussing anti-CGRP mAb treatment with individuals who may become pregnant.

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