*Brief Communication*

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# Case series on monoclonal antibodies targeting calcitonin gene-related peptide in migraine patients during pregnancy: Enhancing safety data

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**Iker Elosua-Bayes[1], Alicia Alpuente[1,2], Laura Melgarejo[1], Edoardo Caronna[1,2], Marta Torres-Ferrús[1,2], and Patricia Pozo-Rosich[1,2]**

## Abstract

**Background:** Monoclonal antibodies targeting calcitonin gene-related peptide (CGRP-mAbs) are approved for adult migraine prevention but pose safety concerns in pregnancy. We assess the safety of CGRP-mAbs in the periconceptional period through a case series and literature review.

**Methods:** Six migraine-diagnosed women received CGRP-mAbs; treatment ceased upon pregnancy. We collected data and conducted safety assessments. To provide a comprehensive context, we performed a literature review.

**Results:** The series includes three erenumab, two fremanezumab and one galcanezumab case. A fremanezumab recipient experienced miscarriage; severe perinatal asphyxia linked to dystocia occurred with erenumab (140 mg). Database reviews revealed 63 spontaneous abortions, eight premature births, and seven birth defects among 286 World Health Organization and 65 European Medicines Agency cases. These rates align with untreated population rates.

**Conclusions:** CGRP-mAbs use in the periconceptional period does not lead to clinically significant increase in pregnancy-related pathology or adverse effects on newborns within our case series and the literature reviewed.

## Keywords

adverse drug reaction, CGRP monoclonal antibodies, migraine, pregnancy, safety

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## Introduction

Migraine is the most prevalent neurological disease, ranking as the third leading cause of disability-adjusted life years in the population aged 15–49 years, particularly affecting women of fertile age (1).

Calcitonin gene-related peptide (CGRP) is a peptide consisting of 37 amino acids with an ubiquitous expression in our organism. During an acute migraine attack, activation of the trigeminovascular system leads to an increase of CGRP levels, resulting in vasodilation and inflammation (1). CGRP is also crucial in utero-placental development. Elevated CGRP levels during pregnancy contribute to decidualization, implantation, angiogenesis and placental trophoblast proliferation, and its dysregulation may lead to complications such as pre-eclampsia, preterm birth and fetal growth restriction (2).

CGRP therapies are the first target-driven drugs for preventive treatment of migraine. As a new-class drug, their

[1]Headache and Neurological Pain Research Group, Vall d'Hebron Research Institute, Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain
[2]Headache and Craniofacial pain Unit, Neurology Department, Vall d'Hebron University Hospital, Barcelona, Spain

**Corresponding author:**
Patricia Pozo-Rosich, Headache and Craniofacial pain Unit, Neurology Department, Vall d'Hebron University Hospital, 119–129 Passeig de la Vall d'Hebron. Barcelona, 08035, Spain.
Email: patricia.pozo@vallhebron.cat

safety during gestation has not been demonstrated. Additionally, these treatments present an elimination half-life of 27–31 days and can only be considered as eliminated from circulation after five half-lives, close to five months in the case that concerns us (2). Therefore, CGRP-mAbs use for migraine prevention during pregnancy is not approved by the US Food and Drug Adminstration or European Medicines Agency (EMA) and should not be prescribed to women seeking pregnancy.

These case-reports aim to provide data to keep assessing the safety of CGRP-mAbs during the periconceptional period and to put it in context by conducting a narrative review on their safety during pregnancy.

## Methods

### *Case series*

We present six clinical cases of women with migraine who unexpectedly became pregnant while undergoing treatment with CGRP-MAbs at our Headache Clinic. Treatment was duly suspended in each participant as soon as pregnancy was reported.

Patients were followed prospectively and when appropriate, were referred to high-risk-pregnancy consultations. We collected sociodemographic data as well as data regarding pregnancy.

All variables were collected from the medical history of the patients:

(a) Sociodemographic variables: demographic and clinical variables include age, gender and ethnicity, as well as previous medical history.
(b) Migraine and previous treatments: including data regarding migraine classification, headache days per month and previous preventive treatment.
(c) Gestational and birth parameters: data pertaining to the last menstrual period, gestational details and birth parameters are collected through trimestral echographies and anthropometric measures performed according to the standard of care.

Despite follow-up throughout and after pregnancy in our outpatient consultation, the above data are not available in all patients, as some patients carried out gestational studies at private clinics.

### *Literature review*

In January 2024, we conducted a comprehensive literature review on PubMed to explore clinical outcomes related to pregnancy and CGRP-mAbs. Utilizing the search terms "pregnancy" in combination with "calcitonin gene-related peptide monoclonal antibodies", "eptinezumab", "fremanezumab", "galcanezumab" or "erenumab", published from the year 2017 onwards, we identified 26, 11, 18, 16 and 22 papers, respectively. After removing duplicates, we found 31 titles, of which only five contained relevant clinical data, specifically gestational and birth parameters. The selection process comprised two phases: initial evaluation of titles and abstracts followed by a thorough reading of full articles. Two independent investigators (IE-B and AA) conducted the study selection, resolving any disagreements through dialogue. We included prospective observational studies and case reports, while articles with incomplete information and preclinical data were deemed ineligible. There were no language or date restrictions. Additionally, we scrutinized the reference lists of included articles and incorporated any additional papers identified by the authors that fulfilled the outlined criteria and may have been initially overlooked (Figure 1). Furthermore, we included the assessment reports from the EMA for erenumab, fremanezumab and galcanezumab in our analysis and additional analysis cases from the World Health Organization.

## Results

### *Results from our case series and case reports in the literature*

The results from the six cases we report alongside the previously published cases (3–5) are displayed in Table 1.

### *Results from the literature review*

Noseda et al. (6) report 137 adverse drug reactions (ADRs) to erenumab, galcanezumab, fremanezumab, and eptinezumab during pregnancy out of 286 safety reports collected. No specific toxicity is reported for mothers. Regarding the fetus, six cases of fetal growth restriction and prematurity are associated with erenumab, two cases of prematurity with galcanezumab, and seven heterogenous birth defects are recorded (four with erenumab, two with galcanezumab

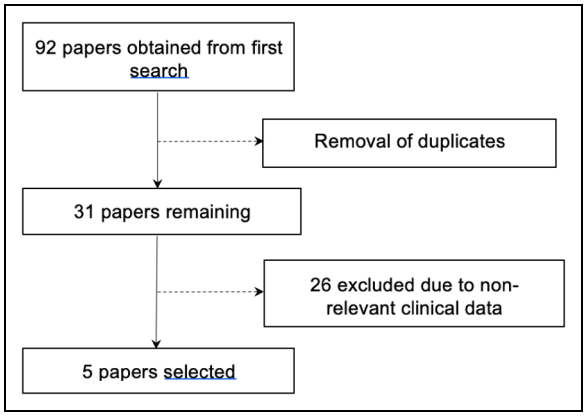


**Figure 1.** Data collection flow diagram.

**Table 1.** Baseline characteristics of the series of cases presented in this article, as well as follow-up results during pregnancy.

| | Diag-nosis | Age | CGRP-mAb | Previous births (live births) | Migraine days per month (pre-pregnancy/ first TM/third TM) | Time of last dose relative to LMP (weeks) | 1 TM echography | 2 TM echography | 3 TM echography | Birth | Gestational age (weeks + days) | Weight at birth (kg) | Complications |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient 1 | HFEM | 32 | Erenumab 140 | 0 (0) | 8/4/ 0 | −3 | – | – | – | Vaginal | 39 + 3 | 2.940 | – |
| Patient 2 | CM | 35 | Erenumab 140 | 0 (0) | 12/18/15 | 0 | CRL: 57 mm NT: 1.2 mm UD: Normal Anatomy: Normal | BPD: 43.3 mm CP: 166.4 mm AP: 157.1 mm FL: 30.6 mm | EFW: 1600 G DU: Normal Anterior placenta | Cesarean section | 41 + 2 | 3.300 | Severe perinatal asphyxia Moderate hypoxic ischemic encephalopathy Acute ischemic stroke |
| Patient 3 | CM | 32 | Erenumab 140 | 0 (0) | 4/0/1 | −1 | CRL: 74.1 mm NT: 1.8 mm UD: Normal Anatomy: Normal | BPD: 48.6 mm CP: 180.1 mm AP: 157.1 mm FL: 34.8 mm | EFW: 2038 G DU: Normal Anterior placenta | Vaginal | – | – | – |
| Patient 4 | CM | 38 | Fremanezumab 675 | 1 (1) | 1/2/1 | −4 | CRL: 60 mm NT: 1.71 mm UD: Normal Anatomy: Normal | BPD: 43.7 mm CP: 167.9 mm AP: 149.9 mm FL: 33.6 mm | EFW: 1320 G DU: Normal Marginal posterior placenta | Cesarean section | 39 + 0 | 3.610 | – |
| Patient 5 | CM | 39 | Fremanezumab 675 | 0 (0) | 4/4/– | −12 | – | – | – | Differed abortion | – | – | Differed abortion during first TM |
| Patient 6 | CM | 37 | Galcanezumab 120 | 1 (1) | 8/4/5 | 1 | CRL: 62 mm NT: 1.22 mm UD: Normal Anatomy: Normal | – | EFW: 3000 G DU: Normal Posterior placenta | Cesarean section | 38 + 3 | – | – |
| Patient 7 [3] | CM | 37 | Erenumab 70 | 0 (0) | 7/10/4 | 3 | – | – | – | Vaginal | 38 + 5 | 3.300 | Breastfeeding jaundice |
| Patient 8 [4] | HFEM | 31 | Erenumab 70 | 0 (0) | 2/2/2 | Throughout pregnancy | – | Anatomy: Normal | – | Vaginal | 38 + 4 | 2.950 | – |

*(continued)*

**Table 1.** (continued)

| | Diag-nosis | Age | CGRP-mAb | Previous births (live births) | Migraine days per month (pre-pregnancy/ first TM/third TM) | Time of last dose relative to LMP (weeks) | 1 TM echography | 2 TM echography | 3 TM echography | Birth | Gestational age (weeks + days) | Weight at birth (kg) | Complications |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient 9 [5] | HFEM | 33 | Erenumab 70 | 1 (1) | 1/1/– | –4 | – | – | – | Miscarriage | – | – | Gestational trophoblastic neoplasia |
| Patient 10 [5] | CM | 37 | Erenumab 70 | 1 (1) | 5 /12/ 0 | 1 | – | – | Small cisterna magna | Cesarean section | 40 + 0 | – | – |
| Patient 11 [5] | HFEM | 41 | Erenumab 140 | 3 (2) | 2/2/2 | 4 | – | – | – | Vaginal | 39 + 0 | – | – |

AP = abdominal perimeter; BPD = biparetal diameter; CM = chronic migraine; CP = cephalic perimeter; CRL = craneal–rump length; EFW = estimated fetal weigth; FL = femur length; HFEM = high frequency episodic migraine; LMP = last menstrual period; NT = nuchal translucency; TM = trimester; UD = uterine doppler.
Patients 7–11 were obtained from the literature review, accordingly cited.

and one with fremanezumab). Sixty-three spontaneous abortions are reported.

The EMA assessment report for galcanezumab describes one case report of preeclampsia leading to preterm birth out of 21 patients (7). No significant ADRs are reported for fremanezumab (8). As for erenumab, two spontaneous abortions and one preterm birth are reported out of 29 cases of maternal exposure and one birth complication requiring intensive care unit admission for four days (reason unknown) (9).

## Discussion

### *Maternal ADRs*

In terms of maternal impact, among the case reports gathered in our study, three reported migraine worsening during the first trimester, with posterior improvement. This observation aligns with the general trend in the population, where migraine improvement during pregnancy is commonly recognized (1). Within our series, case 2 experienced intrahepatic cholestasis of pregnancy (ICP) during the third trimester. No association between CGRP-mAbs and this condition has been identified, and considering it is the sole case of ICP reported in the literature in relation to CGRP-mAbs, it does not appear to be linked to erenumab. Examining the broader database, lack of efficacy of treatment is the most frequently reported ADR, followed by migraine and limited nausea and vomiting (6). The comorbidity of migraine with psychiatric pathology or mood disorders is well documented, of special importance in pregnant women (1), in which treatment discontinuation before gestation may lead to higher levels of anxiety and consequently an increase of migraine attacks. We hypothesize that, if future studies support the safety of periconceptional use of CGRP-mAbs, treatment discontinuation upon pregnancy confirmation could be considered, eliminating the need for suspension months before conception in women of childbearing age.

### *Fetal ADRs*

Regarding the fetus, we report a case of cardiorespiratory arrest following dystocia during birth. Despite requiring invasive ventilation and a four-day stay in the intensive care unit, the child exhibited no defects to date and displayed normal psychomotor development. It is noteworthy that the fetus showed no alterations on follow-up ultrasounds throughout pregnancy, and this complication appears to be related to the dystocia rather than previous erenumab use. No pathophysiological explanation has been identified linking erenumab use to cardiorespiratory arrest in the newborn. The literature review reports spontaneous abortion as the most frequent ADR, followed by preterm delivery (6). As for the heterogeneous birth defects reported in Vigibase (2.4%) (6), it does not provide information regarding if the exposure occurred in the first, second or third gestational trimester, making it hard to relate drug-exposure to these events. It is important to note that, all in all, these events did not occur at a higher incidence than in general population because up to one-third of pregnancies present at least one adverse pregnancy outcome (6,10).

### *Preclinical data*

When considering preclinical data, none of these treatments have demonstrated deleterious effects on either the mother or the fetus at clinical doses. Bussiere et al. (11) conducted a non-clinical safety evaluation of erenumab, examining its impact on pregnant cynomolgus monkeys. Their study concludes that the administration of erenumab does not affect body weights, gestation length, pregnancy or postpartum outcomes in pregnant cynomolgus monkeys. Notably, erenumab-treated monkeys exhibit a similar rate of fetal/infant losses and preterm births in comparison to the control group (11). Additionally, we highlight that despite their prolonged elimination half-life, CGRP-mAbs are large immunoglobulin G antibodies, requiring the neonatal Fc receptor and permeability of the cytotrophoblast to cross the placenta, which appears after the first trimester of pregnancy (12). The physiology of this process reinforces our hypothesis of a possible treatment suspension once pregnancy is reported because these molecules cannot cross de blood–placental barrier in the first twelve weeks.

These results suggest a potential safety profile for the use of CGRP-mAbs during the periconceptional period; however, they must be interpreted cautiously because of several limitations. Firstly, our study presents a series of only six cases of CGRP-mAbs use during the periconceptional period. As case reports, they lack the statistical power to definitively demonstrate the safety of these drugs in the target population. Second, the lack of information on dosage or treatment duration from the cases reported in Vigibase prevents extrapolation of this data to the broader population. Third, it is important to acknowledge the possibility of publication bias on this topic. ADRs may be overestimated if there is underreporting of cases of CGRP-mAbs exposure without negative outcomes, or conversely, if there is overreporting of such cases.

## Conclusions

In conclusion, our study suggests that the use of CGRP-mAbs during the periconceptional period may not pose significant adverse drug reaction related to the treatment. However, constant clinical observation is warranted to consolidate these findings. The observed tendency of migraine attacks to improve during pregnancy, coupled with the potential safety profile of periconceptional CGRP-mAbs use, could pave the way for a shorter safety period for drug suspension, potentially mitigating the risk of disease exacerbation during this critical period for women.

## Clinical implications

- CGRP-mAbs use in the periconceptional period does not lead to clinically significant increase in pregnancy-related pathology or adverse effects on newborns.
- Migraine improvement during pregnancy, coupled with the potential safety profile of periconceptional CGRP-mAbs use, could lead to a shorter safety period for drug suspension, mitigating the risk of disease exacerbation.

## Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: IEB and LM report no disclosures. AA has received honoraria from Allergan-Abbvie, Novartis, and Lilly. EC has received honoraria as a speaker for Chiesi and Novartis. MTF has received honoraria as a consultant or speaker for Allergan-Abbvie, Almirall, Chiesi, Eli Lilly, Novartis and Teva. PP-R has received honoraria as a consultant and speaker for Abbvie, Almirall, Amgen, Biohaven, Chiesi, Eli Lilly, Lundbeck, Medscape, Novartis and Teva. Her research group has received research grants from Allergan, Novartis and Teva, and has received funding for clinical trials from Alder, Abbvie, Amgen, Electrocore, Eli Lilly, Lundbeck, Novartis and Teva. She is the Honorary Secretary of the International Headache Society. She is on the editorial board of *Revista de Neurologia*, and an associate editor for *Cephalalgia*, *Headache*, *Neurologia*, *Frontiers of Neurology* and *The Journal of Headache and Pain*. She is a member of the Clinical Trials Guidelines Committee and Scientific Committee of the International Headache Society. She has edited the Guidelines for the Diagnosis and Treatment of Headache of the Spanish Neurological Society. She is the founder of www.midolordecabeza.org. PP-R does not own stocks in any pharmaceutical company.

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## Ethical statement

The study follows the Declaration of Helsinki, all data were collected retrospectively and patients were treated according to the standards of clinical practice.

## ORCID iDs

Iker Elosua-Bayes https://orcid.org/0009-0005-1730-2448
Alicia Alpuente https://orcid.org/0000-0001-5296-9401
Edoardo Caronna https://orcid.org/0000-0001-5525-0267
Marta Torres-Ferrús https://orcid.org/0000-0003-2856-4134
Patricia Pozo-Rosich https://orcid.org/0000-0003-0796-4702

## References

1. Charles A. The pathophysiology of migraine: implications for clinical management. *Lancet Neurol* 2018; 17: 174–182.
2. Al-Hassany L, Goadsby PJ, Danser AHJ, et al. Calcitonin gene-related peptide-targeting drugs for migraine: how pharmacology might inform treatment decisions. *Lancet Neurol* 2022; 21: 284–294.
3. Fofi L, Egeo G, Aurilia C, et al. Erenumab during pregnancy: a case report in a patient with chronic migraine. *Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol* 2021; 42: 2145–2146.
4. Vig SJ, Garza J and Tao Y. The use of erenumab for migraine prophylaxis during pregnancy: a case report and narrative review. *Headache* 2022; 62: 1256–1263.
5. Bonifácio GV, de Carvalho SC, Oliveira R, et al. Gestational exposure to erenumab-the outcome of three pregnancies. *Headache* 2022; 62: 1218–1221.
6. Noseda R, Bedussi F, Gobbi C, et al. Safety profile of monoclonal antibodies targeting the calcitonin gene-related peptide system in pregnancy: updated analysis in VigiBase®. *Cephalalgia* 2023; 43: 33310242311 58083.
7. European Medicines Agency: EMA/708631/2018 – Assessment report: Emgality.
8. European Medicines Agency: EMA/118499/2019 – Assessment report: Ajovy.
9. European Medicines Agency: EMA/CHMP/413393/2018 – Assessment report: Aimovig.
10. Crump C, Sundquist J, McLaughlin MA, et al. Adverse pregnancy outcomes and long term risk of ischemic heart disease in mothers: national cohort and co-sibling study. *BMJ* 2023; 380: e072112.
11. Bussiere JL, Davies R, Dean C, et al. Nonclinical safety evaluation of erenumab, a CGRP receptor inhibitor for the prevention of migraine. *Regul Toxicol Pharmacol* 2019; 106: 224–238.
12. Simister NE, Story CM, Chen HL, et al. An IgG-transporting fc receptor expressed in the syncytiotrophoblast of human placenta. *Eur J Immunol* 1996; 26: 1527–1531.