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Calcium Channel Blocker Exposure in Late Pregnancy and the Risk of Neonatal Seizures

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Abstract

Objective—To assess whether maternal calcium channel blocker exposure during late pregnancy is independently associated with infant neonatal seizures after carefully controlling for confounding factors.

Methods—Data were derived from the Medicaid Analytic eXtract for the years 2000–2007 and included 2,529,636 completed pregnancies. We compared the risk of neonatal seizures among infants who were born to women who took calcium channel blockers in the final month of pregnancy to the risk in infants born to women who did not use calcium channel blockers. Confounding was addressed through the use of propensity-score matching.

Results—Twenty two thousand nine hundred eight (0.91%) of pregnancies were exposed to calcium channel blockers during the final month of pregnancy. Neonatal seizures occurred in 53 (0.23%) infants born to mothers exposed to calcium channel blocker and 4,609 (0.18%) infants of unexposed women (unadjusted odds ratio (OR) 1.26, 95% confidence interval (CI) 0.96 to 1.65). After accounting for confounders, there was no increase in risk of neonatal seizures associated

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with calcium channel blocker exposure (OR 0.95, 95% CI 0.70 to 1.30). This null finding was robust across multiple sensitivity analysis.

Conclusion—In this large, carefully controlled, population-based cohort study, there was no significant increase in the risk of neonatal seizures in infants attributable to maternal calcium channel blocker exposure in late pregnancy. The results suggest that calcium channel blockers can be used by obstetricians in late pregnancy without excess concern about this neonatal complication.

Introduction

Calcium channel blockers are commonly used medications in pregnancy for the treatment of hypertension and, off-label, for preterm labor tocolysis.(1–5) These medications are generally thought to have a favorable safety profile in pregnancy. However, a recent large study performed within the AHRQ-funded HMO Research Network’s Center for Education and Research on Therapeutics (HMO CERTs) program observed that third-trimester exposure to calcium channel blockers prescribed to mothers in the outpatient setting was associated with a markedly increased risk of neonatal seizures in term infants (relative risk (RR) 3.6, 95% confidence interval (CI) 1.3 to 10.4).(6) As the authors of this study point out, there may be biological plausibility for this association as calcium channel blockers can cross the placenta and can cause a decrease in intracellular calcium.(6) Indeed, hypocalcemia is part of the differential diagnosis for the underlying etiology of neonatal seizures.(7–9) Further, seizures have been observed with calcium channel blocker toxicity in other settings.(10)

The risk reported previously (6) was found in a study that assessed the association between calcium channel blocker exposure and a large number of adverse perinatal outcomes (~60), increasing the possibility that the observed risk is a chance finding. The study also did not adjust for differences between pregnant patients exposed to calcium channel blockers and those who were unexposed, which might confound the observed association including maternal indications for calcium channel blockers (e.g., hypertensive disorders), comorbid conditions (e.g., diabetes), or demographic characteristics (e.g., age).

Confirmation of a risk of neonatal seizures associated with maternal calcium channel blocker exposure would have important public health implications. Calcium channel blocker exposure in the third trimester occurs in between one and two percent of pregnancies in the United States,(1, 5) or 40,000–80,000 patients per year, and neonatal seizures are associated with adverse developmental outcomes in the affected infants.(11)

The objective of this study was therefore to assess whether calcium channel blocker exposure during late pregnancy is independently associated with neonatal seizures using a large cohort of Medicaid pregnancies with linked maternal and infant records.

Materials and Methods

Study data were derived from the Medicaid Analytic eXtract (MAX), a healthcare utilization database which contains Medicaid healthcare claims. Medicaid is an insurance program for

low-income individuals in the United States that is jointly sponsored by state and federal governments. During the study period, Medicaid covered approximately 40% of births in the United States.(12) The database includes information on beneficiary demographic characteristics, claims for inpatient admissions and outpatient visits (including all recorded diagnoses and procedures), and claims for all filled prescriptions for outpatient medications. The use of this de-identified database for research was approved by the Partners Institutional Review Board (Boston, MA).

A cohort for the study of drug safety in pregnancy was created using MAX data from 46 US states and the District of Columbia from 2000 to 2007. The details of the cohort creation have previously been described in detail by Palmsten et al. (13) and the cohort has been used extensively for drug safety and utilization studies in pregnancy.(5, 14–19) Briefly, women age 12 to 55 years with completed pregnancies were linked to their live-born infants. Approximately 14.2 million deliveries to women with one or more months of Medicaid enrollment were identified. (13) Of these, about 6.1 million deliveries were linked to a liveborn infant prior to imposing any eligibility restriction.(13) A validated algorithm was used to define the time of the last menstrual period (LMP) prior to the pregnancy, as the MAX database does not include direct information about the gestation age at delivery or LMP.(20) In this algorithm, the LMP is assigned to be 245 days prior to the infants date of birth if the maternal or infant diagnostic codes indicate preterm delivery and otherwise 270 days prior to delivery(13, 20). This approach has been demonstrated in one administrative database to accurately classify gestational age within 2 weeks of the clinical gestational age at birth in 99% of term deliveries (13, 20). Given that the exposure of interest was calcium channel blocker consumption in late pregnancy, we restricted the cohort to women who were continuously eligible for Medicaid from 5 months after the LMP through one month postpartum (n=3,365,825). We required that women in the cohort be without restricted benefits, private insurance, or certain capitated managed care programs that underreport claims to MAX. Linked infants were required to meet the same eligibility criteria as their mothers for at least 3 months following birth (unless they died). Finally, we restricted our analysis to term deliveries (Figure 1). This was done because the previous analysis that described the association between calcium channel blocker exposure and neonatal seizures was restricted to term deliveries.(6) Further rationale for this approach is provided by the fact that while our data allow us to define that preterm birth occurred, they do not include information on exact gestational age. Extreme prematurity is a well recognized risk factor for neonatal seizures. An inability to control for gestational age within the stratum of preterm deliveries could therefore be an important source of residual confounding in our analysis if we did not exclude preterm infants.

The primary exposure was maternal consumption of a calcium channel blocker during the final 30 days of pregnancy. This was defined based on filled prescriptions for calcium channel blockers with days supply that overlap with the month prior to delivery. This would correspond to exposure that occurred between 33 and 40+ weeks gestation (depending on when delivery for an individual woman in the cohort occurred). Calcium channel blockers considered included both dihydropyridines and non-dihydropyridines. For a complete listing of the calcium channel blockers included in the analysis see Table 1. Non-exposed patients included those parturients without a calcium channel blocker dispensing whose days supply

overlaps the final 30 days of pregnancy. While the paper that previously identified the association between calcium channel blocker exposure and neonatal seizures examined calcium channel blocker exposure at any point in the 3rd trimester,(6) given the mechanism proposed to account for the association between calcium channel blockers and neonatal seizures (intracellular calcium depletion in neonate following placental transfer of calcium channel blockers) exposure at a time point proximate to delivery was considered to be a more etiologically relevant exposure window and was selected as the exposure window for the primary analysis in our study. However, in order to replicate more exactly the approach taken previously,(6) we also examined exposure at any time during the third trimester (see Sensitivity Analyses).

The study outcome was defined by the presence of one or more diagnostic codes indicating neonatal seizure in the infants record from date of birth to day of life 90. While neonatal seizures are expected to occur shortly after delivery, we allow for codes up to day of life 90 in case there is a delay in the posting of claims for the condition. The diagnostic code of interest was 779.0x from the International Classification of Diseases, 9th revision.

Following IRB approval, a member of our study team (A.M.) validated by electronic chart review 50 randomly selected cases in which an infant had a diagnosis code indicating neonatal seizures (779.0x) from an academic medical center between the years 2000 and 2007. Neonatal seizures were defined as documentation of seizure activity in the newborn by a clinician or suspected seizure that resulted in treatment with phenobarbital or/and an electroencephalography (EEG) that showed abnormal activity. Of the 50 cases reviewed, 43 cases met these criteria resulting in a positive predictive value of the diagnostic code of 86% (95% CI 74% to 93%).

Covariates

We considered four groups of potential confounders in our analysis: maternal demographic characteristics, maternal medical and obstetrical conditions, medication exposures, and measures of healthcare utilization. The covariates were selected for consideration because they may be risk factors for the outcome of interest or proxies for these risk factors. The maternal demographic characteristics assessed included maternal age at the time of delivery (grouped as 19, 20–24, 25–29, 30–34, 35–39, 40 years), race/ethnicity (grouped as white, black (non-Hispanic), Hispanic, Asian/Pacific Islander, other, unknown), and year of delivery. Maternal medical and obstetrical conditions were defined based on one or more diagnostic code recorded in the outpatient or inpatient records from 5 months after LMP to delivery. The conditions assessed included pre-existing hypertension, gestational hypertension, mild preeclampsia, severe preeclampsia, pre-existing diabetes, gestational diabetes, chronic renal disease, threatened premature labor, illicit drug use, alcohol abuse, tobacco use, and multiple gestation. Maternal medications which may act as markers for maternal comorbidities or cause a neonatal withdrawal syndrome that results in neonatal seizures were also assessed based on one or more filled prescription from 5 months after LMP to delivery. These included benzodiazepines, barbiturates, opioids, oral hypoglycemics, insulin, and antidepressants. Finally, two measures of healthcare utilization, which might be markers of general maternal comorbidity were also assessed from the period

prior to ascertainment of calcium channel blocker exposure: the number of distinct non-calcium channel blocker prescription drugs dispensed and the number of physician visits.

We described the baseline characteristics of the cohort, stratified by exposure to calcium channel blockers in the final 30 days of pregnancy. We also determined the frequency of neonatal seizures in the infants of exposed and unexposed women and calculated unadjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between exposure and the outcome.

To account for the differences in measured covariates between the exposed and unexposed groups, we used a propensity score (PS) based method. The PS was estimated using a logistic regression model predicting exposure to calcium channel blockers during the final 30 days of pregnancy with all of the covariates described above included in the model without further selection.

Women exposed to calcium channel blockers were then matched to those unexposed on the basis of PS in a fixed 1 to 3 ratio using a nearest neighbor algorithm, with a maximum caliper of 0.05. The distribution of covariates in the matched cohort was then described and the absolute difference in the frequency of each covariate in the exposed and unexposed groups determined. The number of neonatal seizures in the exposed and unexposed in the matched cohort was determined and the OR and 95% CI again calculated.

Sensitivity analyses

We conducted a number of sensitivity analyses to test the robustness of our findings. First, we explored three alternative definitions of exposure to calcium channel blockers: (1) days supply that overlaps any time during the 3rd trimester (which was the exposure window that was assessed previously (6)) defined as 90 days prior to delivery through delivery for term infants, (2) days supply that overlaps the date of delivery, and (3) requiring more than one dispensing of calcium channel blocker during the 3rd trimester with days supply that overlaps the final 30 days of pregnancy (on the assumption that if a prescription for calcium channel blockers is filled more than once, it is more likely that the medication was taken, reducing the potential for exposure misclassification). We also considered two alternative definitions of outcome: (1) defining the diagnosis of neonatal seizure based on claims recorded on more than one date in the infant inpatient or outpatient record from day of birth to day of life 90 (as requiring a diagnostic code on more than one date has been shown to increase the specificity the outcome definition in some circumstances) and (2) defining the presence of neonatal seizures based on codes in either the infant or maternal record (as the infant's diagnosis codes are sometimes applied to the maternal claims). Because the same woman may be included in the cohort more than once, we also performed an analysis in which we only included the first pregnancy for each woman. Finally, we performed an analysis in which all covariates were defined prior to the exposure window. In the primary analysis, we assessed covariates until delivery to increase the chance of detecting confounding conditions. However, it is possible that this approach could lead to adjusting for conditions that occur as a consequence of calcium channel blocker exposure which would lead us to adjust for an intermediate variable (and potentially bias the estimate of the causal effect of calcium channel blockers on the risk of neonatal seizures).

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

The cohort consisted of 2,529,636 completed term-pregnancies, of which 22,908 (0.91%) were exposed to calcium channel blockers during the final month of pregnancy. The most commonly used calcium channel blocker was nifedipine ($n = 21449$), other calcium channel blockers used included amlodipine besylate ($n = 523$), verapamil hydrochloride ($n = 424$), and diltiazem hydrochloride ($n = 339$).

There were important baseline differences in patients who were exposed and unexposed to calcium channel blockers during the final month of pregnancy (Table 2). Calcium channel blocker-exposed patients tended to be older, were more often white, had a higher prevalence of most of the comorbidities/obstetric conditions examined including hypertensive disorders, pre-existing and gestational diabetes, illicit drug use, tobacco use, and multiple gestations. Nearly three-quarter of the calcium channel blocker-exposed patients had a diagnosis indicating threatened premature labor (compared to about one-fifth of those unexposed). Each of the maternal medications considered, including benzodiazepines, barbiturates, opioids, oral hypoglycemics, insulin, and antidepressants, were more commonly used in the calcium channel blocker-exposed. They also tended to have a higher number of non-calcium channel blocker medications dispensed and physician visits during the baseline period. After PS matching, these differences were no longer present, with the absolute difference in the frequency of all measures between exposed and unexposed less than 2% (Table 2).

Neonatal seizures occurred in the infants of 53 (0.23%) of the calcium channel blocker-exposed women and 4,609 (0.18%) of unexposed women (Table 3). The unadjusted OR for neonatal seizures associated with calcium channel blocker exposure was 1.26 (95% CI, 0.96 – 1.65). After accounting for measured confounders using PS matching, there was no increase in the risk of neonatal seizures in infants associated with maternal calcium channel blocker exposure during the last 30 days of pregnancy (OR 0.95, 95% CI 0.70 – 1.30).

The results across a range of sensitivity analyses were consistent with those from the main analysis, owing to the width of the confidence intervals (Table 4). None of these analyses demonstrated a statistically significant association between calcium channel blocker exposure and neonatal seizures and point estimates were all close to the null. In no instance did the upper bound of the CI for these analyses cross the risk estimate of 3.6 reported in the paper that previously posited this association (6)

Discussion

In this large cohort of approximately 2.5 million pregnancies, with 22,908 exposed to calcium channel blockers during the final month of pregnancy, we did not observe an increase in the risk of neonatal seizures in infants associated with maternal exposure to calcium channel blockers. This is reassuring information for obstetricians and their patients given the frequency with which these medications are used in late pregnancy.(5)

Our findings contrast with those of a prior study based on data from the HMO Research Network's Center for Education and Research on Therapeutics program that observed a more than 3-fold increase in the risk of neonatal seizures associated with 3rd trimester calcium channel blocker exposure.(6) That study screened for the association between beta blocker and calcium channel blocker exposure and a large number of important adverse perinatal outcomes. However, several limitations associated with the paper's finding need to be taken into consideration. First, the risk observed emerged from an analysis that tested for associations between calcium channel blocker exposure during pregnancy and over 60 outcomes, making the finding highly vulnerable to a type I error or false positive. Second, the CI around that estimate was also very wide, spanning from 1.3 to 10.4; indeed the lower bound of this interval is close to the null. Our ability to evaluate a cohort that was over 20 times larger allowed for much more precise assessment of the potential risks of calcium channel blockers. Finally, the prior study did not account for differences between calcium channel blocker exposed and unexposed with respect to confounding conditions. Studies of medication safety, in particular, need to account for confounding by indication, i.e. conditions that are indications for exposure that are also associated with the outcome of interest. In our study, we did observe some attenuation of the risk estimate with adjustment through PS matching, suggesting the importance of assessing and adjusting for confounders when examining this association.

While not the focus of our study, it is notable that 73.5% of the patients who received calcium channel blockers have diagnostic codes indicating threatened preterm delivery. Our database does not have direct information on the indications for which medications are prescribed, but the high prevalence of this condition in those exposed to calcium channel blockers strongly suggests that these medications are being commonly used "off-label" for maintenance tocolysis. This practice is concerning in light of the lack of evidence to support this approach(21–23) and suggests the need for educational initiatives aimed at improving rational prescribing around this issue.

Our study must be interpreted in light of the limitations inherent in its design. The definition of calcium channel blocker exposure is based on filled outpatient prescriptions. While this means that our study is not subject to recall bias, it does potentially result in some exposure misclassification if a patient filled the prescription but did not take the medication as prescribed. While such misclassification is not expected to be substantial, we performed a sensitivity analysis in which a patient was only classified as exposed if they filled 2 or more calcium channel blocker prescriptions on the assumption that requiring refilling the prescription would make misclassification based on not consuming the medication less likely. The results did not substantially change in this analysis, accounting for the precision of the estimate. Another potential limitation is that our ascertainment of neonatal seizures is based on the recording of diagnostic codes in the neonatal record. However, the positive predictive value of the claims for neonatal seizures was 70% in the Davis study and even higher in our chart based validation of claims (86%) (although this should be interpreted with the caveat that this is based on retrospective chart review and based on practices at a single academic center). Given the high positive predictive value, it is likely that this code is being applied with specificity. Nevertheless, we performed a sensitivity analysis in which we defined the outcome based on the presence of claims for neonatal seizures recorded on

more than one date (which is expected to further increase specificity of the code for the diagnosis). This was again consistent with the main analysis and did not suggest increased risk of neonatal seizures associated with calcium channel blocker exposure. While the prevalence of neonatal seizures in our cohort is comparable to what has been observed in other population-based studies,(24–28) suggesting the sensitivity of the codes for identifying the condition is high, we did not validate sensitivity. However, as long as the outcome is defined with high specificity and misclassification is non-differential between exposed and unexposed then relative risk estimates will be unbiased, even in the face of limited sensitivity. An additional limitation is that LMP and gestational age are not directly recorded in the MAX database, but have to be calculated based in the classification of the delivery as term or preterm as defined by codes in the infant or maternal records. This may lead to some misclassification of term deliveries. Given the association between low birthweight and the risk of neonatal seizures and the association between calcium channel blocker exposure and many risk factors for preterm delivery, we would expect such misclassification to bias, if anything, towards finding an association between calcium channel blocker exposure and neonatal seizures. It is also important to note that our data does not have information on inpatient administration of calcium channel blockers and cannot speak to the potential effects of its use. However, we would note that the study that identified a possible association between calcium channel blocker exposure and neonatal seizures also only examined outpatient calcium channel blocker use(6). Finally, while our database is one of the largest of its kind for studying medication safety in pregnancy, based on the CI from our main analysis (which ranged from 0.70 – 1.30), we cannot exclude the possibility that calcium channel blockers are associated with as much as a 30% increase in the risk of neonatal seizures.

In conclusion, in this large, carefully controlled cohort study of late pregnancy exposure to calcium channel blockers, we failed to observe an association with increased risks for neonatal seizures in the offspring. Our results suggest obstetricians can continue to use these medications without undue concern about this potentially serious adverse medication effect.

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References

1. Andrade SE, Raebel MA, Brown J, Lane K, Livingston J, Boudreau D, et al. Outpatient use of cardiovascular drugs during pregnancy. *Pharmacoepidemiology and Drug Safety*. 2008; 17(3):240–7. [PubMed: 18200619]
2. Seely EW, Ecker J. Clinical practice. Chronic hypertension in pregnancy. *N Engl J Med*. 2011; 365(5):439–46. [PubMed: 21812673]
3. Nassar AH, Aoun J, Usta IM. Calcium channel blockers for the management of preterm birth: a review. *Am J Perinatol*. 2011; 28(1):57–66. [PubMed: 20640972]

4. King JF, Flenady V, Papatsonis D, Dekker G, Carbonne B. Calcium channel blockers for inhibiting preterm labour; a systematic review of the evidence and a protocol for administration of nifedipine. *Aust N Z J Obstet Gynaecol.* 2003; 43(3):192–8. [PubMed: 14712983]
5. Bateman BT, Hernandez-Diaz S, Huybrechts KF, Palmsten K, Mogun H, Ecker JL, et al. Patterns of outpatient antihypertensive medication use during pregnancy in a Medicaid population. *Hypertension.* 2012; 60(4):913–20. [PubMed: 22966012]
6. Davis RL, Eastman D, McPhillips H, Raebel MA, Andrade SE, Smith D, et al. Risks of congenital malformations and perinatal events among infants exposed to calcium channel and beta-blockers during pregnancy. *Pharmacoepidemiol Drug Saf.* 2011; 20(2):138–45. [PubMed: 21254284]
7. Yildiz EP, Tatli B, Ekici B, Eraslan E, Aydinli N, Caliskan M, et al. Evaluation of etiologic and prognostic factors in neonatal convulsions. *Pediatr Neurol.* 2012; 47(3):186–92. [PubMed: 22883283]
8. Borkenhagen JF, Connor EL, Stafstrom CE. Neonatal hypocalcemic seizures due to excessive maternal calcium ingestion. *Pediatr Neurol.* 2013; 48(6):469–71. [PubMed: 23668874]
9. Thomas TC, Smith JM, White PC, Adhikari S. Transient neonatal hypocalcemia: presentation and outcomes. *Pediatrics.* 2012; 129(6):e1461–7. [PubMed: 22614771]
10. Isbister GK. Delayed asystolic cardiac arrest after diltiazem overdose; resuscitation with high dose intravenous calcium. *Emerg Med J.* 2002; 19(4):355–7. [PubMed: 12101159]
11. Uria-Avellanal C, Marlow N, Rennie JM. Outcome following neonatal seizures. *Semin Fetal Neonatal Med.* 2013; 18(4):224–32. [PubMed: 23466296]
12. Garcia, G. [Accessed January 15, 2015] Maternal and Child Health (MCH) Update: States Increase Eligibility for Children's Health in 2007. Electronic citation. Available at: <http://www.nga.org/files/live/sites/NGA/files/pdf/0811MCHUPDATE.PDF?jsessionid=7B47A647247DD4E5CB9B709C8F9797AE>
13. Palmsten K, Huybrechts KF, Mogun H, Kowal MK, Williams PL, Michels KB, et al. Harnessing the Medicaid Analytic eXtract (MAX) to Evaluate Medications in Pregnancy: Design Considerations. *PLoS One.* 2013; 8(6):e67405. [PubMed: 23840692]
14. Bateman BT, Hernandez-Diaz S, Huybrechts KF, Palmsten K, Mogun H, Ecker JL, et al. Outpatient calcium-channel blockers and the risk of postpartum haemorrhage: a cohort study. *BJOG.* 2013; 120(13):1668–76. discussion 76–7. [PubMed: 24020971]
15. Huybrechts KF, Palmsten K, Mogun H, Kowal M, Avorn J, Setoguchi-Iwata S, et al. National trends in antidepressant medication treatment among publicly insured pregnant women. *Gen Hosp Psychiatry.* 2013; 35(3):265–71. [PubMed: 23374897]
16. Palmsten K, Hernandez-Diaz S, Huybrechts KF, Williams PL, Michels KB, Achtyes ED, et al. Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. *BMJ.* 2013; 347:f4877. [PubMed: 23965506]
17. Palmsten K, Huybrechts KF, Michels KB, Williams PL, Mogun H, Setoguchi S, et al. Antidepressant use and risk for preeclampsia. *Epidemiology.* 2013; 24(5):682–91. [PubMed: 23873072]
18. Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. *Obstet Gynecol.* 2014; 123(5):997–1002. [PubMed: 24785852]
19. Huybrechts KF, Palmsten K, Avorn J, Cohen LS, Holmes LB, Franklin JM, et al. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med.* 2014; 370(25):2397–407. [PubMed: 24941178]
20. Margulis AV, Setoguchi S, Mittleman MA, Glynn RJ, Dormuth CR, Hernandez-Diaz S. Algorithms to estimate the beginning of pregnancy in administrative databases. *Pharmacoepidemiol Drug Saf.* 2013; 22(1):16–24. [PubMed: 22550030]
21. Carr DB, Clark AL, Kernek K, Spinnato JA. Maintenance oral nifedipine for preterm labor: a randomized clinical trial. *Am J Obstet Gynecol.* 1999; 181(4):822–7. [PubMed: 10521736]
22. Lyell DJ, Pullen KM, Mannan J, Chitkara U, Druzin ML, Caughey AB, et al. Maintenance nifedipine tocolysis compared with placebo: a randomized controlled trial. *Obstet Gynecol.* 2008; 112(6):1221–6. [PubMed: 19037029]

23. Roos C, Spaanderman ME, Schuit E, Bloemenkamp KW, Bolte AC, Cornette J, et al. Effect of maintenance tocolysis with nifedipine in threatened preterm labor on perinatal outcomes: a randomized controlled trial. *JAMA*. 2013; 309(1):41–7. [PubMed: 23280223]
24. Lanska MJ, Lanska DJ, Baumann RJ, Kryscio RJ. A population-based study of neonatal seizures in Fayette County, Kentucky. *Neurology*. 1995; 45(4):724–32. [PubMed: 7723962]
25. Lanska MJ, Lanska DJ. Neonatal seizures in the United States: results of the National Hospital Discharge Survey, 1980–1991. *Neuroepidemiology*. 1996; 15(3):117–25. [PubMed: 8700303]
26. Saliba RM, Annegers JF, Waller DK, Tyson JE, Mizrahi EM. Incidence of neonatal seizures in Harris County, Texas, 1992–1994. *Am J Epidemiol*. 1999; 150(7):763–9. [PubMed: 10512430]
27. Ronen GM, Penney S, Andrews W. The epidemiology of clinical neonatal seizures in Newfoundland: a population-based study. *J Pediatr*. 1999; 134(1):71–5. [PubMed: 9880452]
28. Glass HC, Pham TN, Danielsen B, Towner D, Glidden D, Wu YW. Antenatal and intrapartum risk factors for seizures in term newborns: a population-based study, California 1998–2002. *J Pediatr*. 2009; 154(1):24–8 e1. [PubMed: 18760807]

Figure 1.
Analytic cohort selection, Medicaid Analytic eExtract 2000–2007.

Table 1

Specific calcium channel blocker exposure during the final month of pregnancy

	Count
Amlodipine besylate	523
Benazepril hydrochloride/Amlodipine besylate	42
Diltiazem hydrochloride	339
Felodipine	70
Isradipine	<11
Nicardipine hydrochloride	52
Nifedipine	21449
Nimodipine	<11
Nisoldipine	43
Trandolapril/Verapamil hydrochloride	<11
Verapamil hydrochloride	424

* Exact counts cannot be disclosed for cell sizes <11 in keeping with the data use agreement

Table 2

Baseline characteristics of the cohort, stratified by calcium channel blocker exposure, before and after propensity-score matching

	Unadjusted		Propensity-score matched		Absolute difference (%)
	CCB Exposed	CCB Unexposed	CCB Exposed	CCB Unexposed	
Total	22908	2506728	22906	68718	
Age					
19					-0.5
20-24	4296 (18.8)	516623 (20.6)	4295 (18.8)	13255 (19.3)	-0.8
25-29	9452 (41.3)	1044266 (41.7)	9452 (41.3)	28932 (42.1)	0
30-34	5198 (22.7)	556450 (22.2)	5197 (22.7)	15573 (22.7)	0.8
35-39	2511 (11)	251653 (10)	2511 (11)	7019 (10.2)	0.4
40	1138 (5)	110121 (4.4)	1138 (5)	3160 (4.6)	0.2
Race					
White, Non-Hispanic	13880 (60.6)	1252023 (50)	13878 (60.6)	42447 (61.8)	-1.2
Black, Non-Hispanic	5335 (23.3)	637750 (25.4)	5335 (23.3)	15498 (22.6)	0.7
Hispanic	1919 (8.4)	337634 (13.5)	1919 (8.4)	5703 (8.3)	0.1
Asian	315 (1.4)	80370 (3.2)	315 (1.4)	950 (1.4)	0
Other	759 (3.3)	135285 (5.4)	759 (3.3)	2124 (3.1)	0.2
Unknown	700 (3.1)	63666 (2.5)	700 (3.1)	1996 (2.9)	0.2
Maternal medical/obstetrical conditions					
Pre-existing hypertension	3115 (13.6)	71482 (2.9)	3115 (13.6)	8485 (12.3)	1.3
Gestational hypertension	2480 (10.8)	109449 (4.4)	2480 (10.8)	6949 (10.1)	0.7
Mild preeclampsia	1643 (7.2)	86456 (3.4)	1643 (7.2)	4481 (6.5)	0.7
Severe preeclampsia	898 (3.9)	27715 (1.1)	898 (3.9)	2144 (3.1)	0.8
Gestational diabetes	3063 (13.4)	196530 (7.8)	3063 (13.4)	8392 (12.2)	1.2
Pre-existing diabetes	1764 (7.7)	84345 (3.4)	1764 (7.7)	4540 (6.6)	1.1
Chronic renal disease	429 (1.9)	22672 (0.9)	429 (1.9)	1114 (1.6)	0.3
Threatened preterm labor	16834 (73.5)	468378 (18.7)	16832 (73.5)	51704 (75.2)	-1.8
Illicit drug use	664 (2.9)	61901 (2.5)	664 (2.9)	1944 (2.8)	0.1
Alcohol abuse	93 (0.4)	9943 (0.4)	93 (0.4)	247 (0.4)	0.1

	Unadjusted		Propensity-score matched		Absolute difference (%)
	CCB Exposed	CCB Unexposed	CCB Exposed	CCB Unexposed	
Tobacco use	2094 (9.1)	165073 (6.6)	2094 (9.1)	6323 (9.2)	-0.1
Multiple gestation	735 (3.2)	18887 (0.8)	735 (3.2)	2046 (3)	0.2
Maternal medication use					
Benzodiazepines	353 (1.5)	12668 (0.5)	353 (1.5)	849 (1.2)	0.3
Barbiturates	376 (1.6)	16757 (0.7)	376 (1.6)	1061 (1.5)	0.1
Opioids	4993 (21.8)	260279 (10.4)	4993 (21.8)	14847 (21.6)	0.2
Oral hypoglycemics	388 (1.7)	12602 (0.5)	388 (1.7)	866 (1.3)	0.4
Insulin	1212 (5.3)	38436 (1.5)	1212 (5.3)	2950 (4.3)	1
Antidepressants	1865 (8.1)	90847 (3.6)	1865 (8.1)	5362 (7.8)	0.3

* Also included in the propensity score are number of physician visits and number of distinct non-CCB prescriptions during the baseline period, and year of delivery

Table 3

Odds ratios for neonatal seizures in infants of mothers exposed to calcium channel blockers in the final month of pregnancy as compared with those whose mothers were unexposed

	CCB–Exposed	CCB–Unexposed	Odds ratio (95% CI)
Exposure final 30 days of pregnancy			
Unadjusted	53/22908	4609/2506728	1.26 (0.96 – 1.65)
Propensity-score matched	53/22906	167/68718	0.95 (0.70 – 1.30)

Table 4

Sensitivity analyses showing odds ratios for neonatal seizures in infants of mothers exposed to calcium channel blockers as compared with those whose mothers were unexposed, with varying definitions of exposure and outcome.

		CCB exposed	CCB unexposed	Odds ratio (95% CI)
CCB exposure anytime during 3rd trimester	Unadjusted	82/32238	4580/2497398	1.39 (1.12 – 1.73)
	Propensity-score matched	82/32231	227/96693	1.08 (0.84 – 1.40)
CCB exposure overlapping delivery	Unadjusted	14/7148	4648/2522488	1.07 (0.63 – 1.80)
	Propensity-score matched	14/7148	54/21444	0.78 (0.43 – 1.40)
>1 dispensing of CCB during 3rd trimester	Unadjusted	27/8279	4635/2521357	1.78 (1.22 – 2.6)
	Propensity-score matched	27/8279	64/24837	1.27 (0.81 – 1.99)
Outcome defined using both infant and maternal claims	Unadjusted	58/22908	5065/2506728	1.25 (0.97 – 1.63)
	Propensity-score matched	58/22906	183/68718	0.95 (0.71 – 1.28)
Outcome defined by claim recorded on more than one separate dates	Unadjusted	36/22908	2707/2506728	1.46 (1.05 – 2.02)
	Propensity-score matched	36/22906	96/68718	1.13 (0.77 – 1.65)
For women included in the cohort >1 time, restrict to first pregnancy	Unadjusted	47/19398	4091/2167321	1.29 (0.96 – 1.71)
	Propensity-score matched	47/19397	129/58191	1.09 (0.78 – 1.53)
Covariates defined prior to exposure window	Unadjusted	53/22908	4609/2506728	1.26 (0.96 – 1.65)
	Propensity-score matched	53/22905	185/68715	0.86 (0.63 – 1.17)