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Risks of congenital malformations and perinatal events among infants exposed to calcium channel and beta-blockers during pregnancy

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Abstract

Purpose—Calcium channel blockers and beta-blockers are widely used during pregnancy, but data on their safety for the developing infant is scarce. We used population-based data from 5 HMOs to study risks for perinatal complications and congenital defects among infants exposed in-utero.

Methods—We studied women older than 15 years delivering an infant between 1/1/96 to 12/31/00, who had been continuously enrolled with prescription drug coverage for $\geq$ one year prior to delivery. Information on prescription drug dispensings, inpatient and outpatient diagnoses and procedures was obtained from automated databases at each HMO.

Results—There were 584 full-term infants exposed during pregnancy to beta-blockers and 804 full-term infants exposed to calcium-channel blockers, and over 75,000 unexposed mother-infant pairs with $\geq$ 30 days follow-up. Infants exposed to beta-blockers in the third trimester of

pregnancy had over three-fold increased risk for hypoglycemia (RR 3.1; 95% CI 2.2, 4.2) and an approximately two-fold increased risk for feeding problems (RR 1.8; 95% CI 1.3, 2.5). Infants exposed to calcium-channel blockers in the third trimester had an increased risk for seizures (RR 3.6 95% CI 1.3, 10.4). Chart review confirmed the majority of the exposed seizure and hypoglycemia cases. There were no increased risks for congenital anomalies among either group of infants, except for the category of upper alimentary tract anomalies; this increased risk was based on only two exposed cases.

Conclusions—Infants whose mothers receive beta-blockers are at increased risk for neonatal hypoglycemia, while those whose mothers take calcium-channel blockers are at increased risk for neonatal seizures.

Keywords

calcium channel blockers; beta-blockers; pregnancy; perinatal; malformation; anomalies; prescription drug; drug safety

INTRODUCTION

Each year there are over four million births in the United States. While most pregnancies proceed to term, medical problems requiring care are common. According to a recent study of prescription drug use during pregnancy, almost two-thirds of all women delivering a live infant had been prescribed at least one drug (other than a vitamin or mineral supplement) during pregnancy¹. Hypertension is the most common medical complication of pregnancy, and occurs in up to 2–3% of pregnancies². The sequelae of hypertension during pregnancy include placental abruption, premature delivery, intrauterine growth retardation, and intrauterine death.

Calcium channel blockers (CCB) and beta-blockers (BB) are effective for the treatment of hypertension during pregnancy. They are commonly used for hypertension (and other purposes) - by approximately 1.6% of women delivering a full-term infant, and 7% of women delivering a preterm infant - and are felt to be safe for the developing fetus^{3–7}. The benefits of their use extend to both the mother and the infant, and serve to reduce the morbidity that would otherwise result from uncontrolled hypertension.

However, many of the cardiovascular drugs that are prescribed for a pregnant woman have the potential to cross the placenta and exert a pharmacologic or even teratogenic effect upon the fetus. Some antihypertensive agents such as angiotensin-converting enzyme inhibitors have been shown to have a demonstrated fetotoxic effect^{8–10}. Use of ACE inhibitors has been found to increase the risk for both cardiovascular and central nervous system anomalies after first trimester exposure, or for a group of conditions including oligohydramnios, renal dysplasia, anuria, and renal failure after third trimester exposure⁸. Calcium channel blockers have not shown an increase in teratogenic risk in humans, although studies of high doses of calcium channel blockers administered to pregnant rats and rabbits have found an increased prevalence of cardiovascular and skeletal malformations (including digital and limb defects)^{11–18}. Among beta-blockers, intrauterine growth restriction, bradycardia and hypoglycemia have been found in a number of studies that evaluated their use for treatment of hypertension during pregnancy^{19,20}. However, a number of other studies have failed to demonstrate an elevated risk for these outcomes, and overall beta blockers as a class are considered safe for the developing fetus, particularly in light of its positive impact on maternal health during pregnancy^{4,21}.

Although use of such cardiovascular medications is widespread during pregnancy, in-depth data on their safety profile for the developing fetus remains relatively scarce. We have

recently published a study from a cohort of more than 100,000 births from 1996–2000 in 5 large health maintenance organizations that assessed the safety of selective serotonin reuptake inhibitor and tricyclic antidepressant use during pregnancy²². To address the safety of commonly used cardiovascular medications during pregnancy, we used this same population-based dataset to study the risks for perinatal complications and congenital defects among infants exposed in-utero to beta-blockers and calcium channel blockers.

METHODS

Setting

This study was carried out within the HMO Research Network's Center for Education and Research on Therapeutics (HMO CERTs) program. As this study's design is the same as the one published previously on antidepressant use during pregnancy²², only a summary of the methods will be presented here.

The CERTs program is a AHRQ-funded national initiative to increase awareness of the benefits and risks of therapeutics through education and research²³. Five integrated health care delivery systems from the HMO CERTs, with a combined population over 3 million members, participated in this study: Group Health Cooperative (Seattle, Washington); Harvard Pilgrim Health Care (Boston, Massachusetts); Henry Ford Health System (Detroit, Michigan); Kaiser Permanente Colorado (Denver, Colorado); and Kaiser Permanente Northwest (Portland, Oregon). The health plans serve diverse populations, with the percent of African American members ranging from 2% to 24%, the percent of Hispanics ranging from < 1% to 16%, and the percent of Asian Americans ranging from <1% to 5% of health plan membership.

Each HMO's Institutional Review Board approved this study.

Study design

This retrospective study was conducted using computerized health system databases, which include information on member enrollment, outpatient drug dispensing, and inpatient and outpatient diagnoses and procedures. We identified female members older than 15 years of age who were admitted to a community or HMO-owned hospital between January 1, 1996 and December 31, 2000 for delivery of an infant and who were continuously enrolled with prescription drug coverage for at least one year prior to admission. The maternal–infant linkage was accomplished using unique identifiers that have been previously used for epidemiologic studies of maternal–child pairs in these health systems. We limited our study to those infants that had a requisite follow-up of either 365 days for the evaluation of congenital anomalies, or 30 days for the evaluation of perinatal outcomes. There were a total of 99,419 pregnancies in the 5 participating HMOs, of which 87,407 were able to be linked to infants with at least 30 days of follow-up, a linkage rate of 88%.

As data were not available on the length of gestation in the automated databases, we evaluated prescription drug use with the assumption of a gestational age of 270 days for full term deliveries, including three 90-day trimesters of pregnancy. This same technique was used with our previously published studies using this database^{1,22,24,25}.

Exposure assessment

We obtained information on outpatient use of antihypertensive medications from the pharmacy database files at each HMO. (During the time period covered by this study, the automated databases did not capture inpatient use of medications). Medications were categorized into either beta-blocker or calcium channel blockers; other antihypertensive

medications were not evaluated because of relatively low usage. For comparison, we chose infants born to mothers who were not prescribed these specific medications at any time during pregnancy.

Outcomes

For assessment of congenital anomalies, we limited our analysis to infants with at least 365 days of follow-up. Inpatient (including birth hospitalization), outpatient, and emergency department databases were evaluated for diagnoses of any congenital anomalies of interest that were made in the first year of life. To assess perinatal events, we analyzed infants with at least 30 days of post-delivery follow-up and looked at diagnoses made during the birth hospitalization or in the outpatient setting, emergency department, or additional hospitalizations up through day 30 after birth.

In line with the screening nature of this study, we assessed outcomes via assigned ICD9 codes. We then performed medical record review for three categories of perinatal events where elevated risks were found after the initial analysis was completed: (i) newborn endocrine and metabolic disturbances, including hypoglycemia, following third trimester beta-blocker exposure; (ii) convulsions in the newborn following third trimester calcium-channel blocker exposure; and (iii) hematologic disorders of the newborn following third trimester calcium channel blocker exposure. Funding limitations precluded performing chart reviews to estimate the proportion of missed cases (false negatives).

Statistical analysis

We compared the risk among exposed infants to the risk among unexposed infants for each outcome, stratified by health system, maternal age, and birth season. Relative risks and confidence intervals unadjusted for multiple testing were calculated using stratified cumulative incidence tables. Statistical significance was defined as where the confidence interval excluded 1.0 and $p < 0.05$. Relative risk estimates were only calculated for outcomes where there was at least one event among the exposed infants. All analyses were conducted using STATA v8. We studied risks for infants exposed during the first trimester of pregnancy to evaluate risk for congenital anomalies, and exposure during the third trimester to evaluate risk for perinatal events. Finally, we studied infants exposed at any time during the first through third trimesters of pregnancy to evaluate risk for preterm delivery.

RESULTS

After excluding mother-infant pairs for whom 30 days of post-delivery follow-up were not available, we identified a total of 584 fullterm infants exposed to beta-blockers at any time during pregnancy, and 804 fullterm infants exposed to calcium channel blockers at any time during pregnancy. There were over 75,000 mother-infant pairs unexposed to either BB or CCB with at least 30 days follow-up. After excluding infants for whom 365 days of follow-up were not available, we identified a total of 390 fullterm infants exposed to BBs at any time during pregnancy and 505 exposed to CCBs. The group with 365 days of follow-up was used to assess risk for congenital anomalies, while the group with 30 days of follow-up was used to assess risk for perinatal events.

The risks for congenital anomalies and perinatal events for infants exposed during pregnancy are shown in Tables 1 and 2. Of the fullterm infants exposed to BBs during pregnancy, a total of 188 infants were exposed during the first trimester and had 365 days of follow-up, and 405 infants were exposed during the third trimester and had 30 days of follow-up. Of the fullterm infants exposed to CCBs during pregnancy, 40 infants were exposed during the first trimester and had 365 days of follow-up, and 721 infants were

exposed during the third trimester and had 30 days of follow-up. BB use during first trimester was not statistically significantly associated with an increased risk for congenital anomalies overall, or for any specific type of congenital anomaly. CCB use in the first trimester was associated with an increased risk for congenital anomalies of the upper alimentary tract, but this increased risk was based on only two exposed cases. The point estimate of the risk for one or more malformation was not elevated for CCBs (RR 0.96; 95% CI 0.47, 1.97) or BBs (RR 0.97; 95% CI 0.68, 1.40).

With regards to conditions arising in the perinatal period there were elevated risks for endocrine disturbances including hypoglycemia, respiratory distress, feeding problems, and jaundice among infants exposed to BBs in the third trimester (Table 2). Among infants exposed to calcium channel blockers, there were increased risks for hematological disorders, jaundice, and neonatal convulsions (RR 3.61 95% CI 1.26, 10.37).

Chart review was performed on a total number of 119 infants. Among 68 charts requested for infants with hypoglycemia, 57 were abstracted (11 charts were not able to be obtained); of these, 44 were confirmed to have had the diagnosis of hypoglycemia in the birth hospital record (a confirmation rate of 77%). Of the 44 confirmed cases, 40 had at least one blood sugar <50 mg/dl recorded in the laboratory files. Fourteen of the 44 were born to mothers with either gestational diabetes (11) or pre-existing diabetes mellitus (3); the other 30 mothers had no evidence of preexisting diabetes. All 10 infants with convulsion had their medical records reviewed. A total of seven cases of convulsions were confirmed on record review, and three were not confirmed. Of the seven confirmed convulsions, six had a calcium level obtained, and one of the six had neonatal hypocalcemia (<7 mg/dl).

Finally, for the 41 infants with hematologic disorders, 40 medical records were obtained and 30 of the 40 cases were confirmed by record review. However, the diagnoses were not consistent among this group: 14 had polycythemia neonatorum, 14 had a newborn hemolytic disorder, 3 had neonatal hemorrhage, 4 had disseminated intravascular coagulation, 4 had thrombocytopenia, 2 had congenital anemia, and 9 had other conditions.

DISCUSSION

In this study of a cohort of approximately 100,000 pregnancies and over 1100 infants exposed to either beta blockers or calcium channel blockers, we found an apparent increase in risk for seizures among infants whose mothers were taking calcium channel blockers during pregnancy, and an increase risk for hypoglycemia among infants whose mothers were taking beta-blockers during pregnancy. It is important to note that these risks were measured only in the perinatal period; there was no attempt to measure risk for the longer term, or the long-term sequelae of either neonatal seizures or hypoglycemia.

There was no increase in risk for congenital anomalies among infants exposed to either calcium channel blockers or beta blockers. Additionally, for one category of risk that we did see in the screening phase of the analysis, hematologic disorders, we did not find evidence of any consistent serious disorder associated with this exposure.

Beta-blockers can cross the placenta and can exert physiologic effects in the infant, including an increase in the levels of insulin and a decrease in glucagon^{26,27}. Both of these actions lead to the potential for hypoglycemia in the infant. Hypoglycemia is a common metabolic problem among newborns, and in the majority of cases it is self-resolving and without long-term sequelae. A recent systematic review of neonatal hypoglycemia and subsequent neurodevelopment found substantial variation in studies that have studied this relationship²⁸. If prolonged or severe, hypoglycemia can result in severe neurologic consequences as shown in one study of over 600 infants²⁹. In particular, prolonged

hypoglycemia (noted on at least 5 or more separate days) strongly influenced mental and motor neurodevelopment, and was associated with a 13 and 14 point reduction in mental and motor development, respectively, at 18 months of age. Additionally, the risk for cerebral palsy or developmental delay was increased 3.5 fold among infants with prolonged neonatal hypoglycemia. One drawback of our study is that it did not provide information on the duration of the hypoglycemia, and so we are not able to know if beta-blockers are associated with prolonged and/or severe hypoglycemia.

Like beta blockers, calcium channel blockers also can cross the placenta, and can lead to decreased intracellular calcium in the infant^{30,31}. In both adults and children, calcium antagonist toxicity is associated with seizures³². In addition, hypocalcemia is a known cause of neonatal seizures, and the work-up of neonatal seizures typically includes checking a serum calcium level³³. Neonatal seizures due to hypocalcemia are typically associated with endocrinologic abnormalities of either the newborn or the mother, such as parathyroid diseases or diabetes. Hypocalcemia is also seen in infants of diabetic mothers, and is more common, and more severe, with more severe maternal diabetes and glucose abnormalities³⁴.

Neonatal seizures can be particularly serious, and may be associated with poor neurodevelopmental outcomes for the infant dependent upon the etiology of seizures³³. Most neonatal seizures are caused by acute problems, such as meningitis or hypoxic-ischemic encephalopathy which, in and of themselves, are associated with poor neurodevelopmental outcomes. According to the 'Summary Proceedings from the Neurology Group on Neonatal Seizures', seizures are the most important sign of acute neonatal encephalopathy³⁵ and are an independent, and major, risk factor for death or subsequent neurologic disability. While neonatal seizures are often part of a group of symptoms indicating an underlying disease process, it is also felt that neonatal seizures may contribute, by themselves, to adverse neurodevelopmental outcomes. We did not collect information on the persistence of the seizures seen in this study and therefore cannot comment on their long-term effect.

Our study has a number of strengths. First, we collected information on prescribing during pregnancy from administrative datasets, and so this information was immune from recall bias that might arise from exposure assessments from parental interviews. Second, the cohort study design allowed us to assess the absolute risks resulting from medication exposures during pregnancy. Further, compared with case-control studies which typically have a more complete description of one or a few conditions, we evaluated a wide range of outcomes, both teratogenic and perinatal, providing a relatively complete picture of the safety of BB and CCB use during pregnancy.

An important limitation to our study is that we were not able to disentangle the effect of the drug from that of the underlying condition. Indeed, many of the conditions for which either BB or CCB are given may themselves place the infant under stress and increase the risk for some of the conditions studied here. Equally importantly is the potential for misclassification of one or more outcomes, which would likely bias our findings towards the null and would limit our ability to detect a real signal. Additionally, the administrative datasets that we used provided information on prescriptions, but not on whether the medication was actually taken by the mother. In a prior study, we found that 59% of pregnant women filled their prescriptions for antidepressants on two or more occasions, but we do not have similar data for the numbers of women refilling prescriptions for BB or CCB²². As such, care must be taken not to over-interpret our findings of the overall safety of BB and CCB use during pregnancy.

An additional limitation to our study is that the results might be subject to diagnostic bias, whereby clinicians might be more likely to note conditions in the infant suspected to be associated with the medications if they knew the mother had been exposed. Finally, our study lacked information on potential confounders, such as the women's exposure to alcohol, cigarette smoking, and other substance abuse.

A new initiative known as the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) has been recently launched, and is a collaboration among the U.S. Food and Drug Administration and researchers at 10 managed care organizations and Vanderbilt University³⁶. Collectively, these 11 sites have health care information on over 1 million births covering the time period 2001–2007. Additional years' data will be added over time. This initiative will address many of the limitations noted above, and is anticipated to have sufficient power to address questions such as the safety of medication use during critical periods of exposure for the infant.

The association seen here between calcium channel blockers and neonatal seizures has not been reported previously, while the association between beta blockers and hypoglycemia has, although not from a population-based perspective. These findings may impact care of the newborn whose mother was on either medication prior to delivery, and these rare potential side-effects must be weighed against the risks of hypertension in pregnancy, which can be dangerous both to the mother and the infant. Given the recent increased attention directed towards increasing data gathered on drug safety during pregnancy³⁷, this study illustrates two drugs that might merit further evaluation in even larger population settings.

Take-Home Messages

- Fullterm infants with third trimester exposure to BBs were at increased risk for respiratory distress syndrome, endocrine and metabolic disturbances including hypoglycemia, perinatal jaundice, digestive system disorders and feeding problems.
- Third trimester exposure to CCB was associated with an increased risk for neonatal convulsions and for perinatal jaundice.
- Over three-quarters of the diagnoses of hypoglycemia and neonatal convulsions were confirmed after medical record review
- Exposure to BBs did not increase risk for congenital anomalies. Exposure to CCBs raised the risk for one category of anomalies but this was based on only two exposed cases.

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Table 1

Number and relative risks of congenital malformations among fullterm infants exposed to cardiovascular medications during the first trimester of pregnancy, compared to unexposed fullterm infants. All infants were followed for outcomes for 365 days after delivery.

Outcome	Beta Blockers			Calcium Channel Blockers		
	Exposed (n=188)	Not Exposed (n=49,648)	Relative Risk (95 CI)	Exposed (n=40)	Not Exposed (n=49,796)	Relative Risk (95 CI)
One or more malformation of interest	13.30% (25)	13.71% (6806)	0.97 (0.81,1.16)	15.00% (6)	13.71% (6825)	0.96 (0.47,1.97)
Central nervous system malformation in fetus	0.00% (0)	0.00% (2)		0.00% (0)	0.00% (2)	
Chromosomal abnorm in fetus	0.00% (0)	0.00% (0)		0.00% (0)	0.00% (0)	
Hereditary disease in family possibly affecting fetus	0.00% (0)	0.00% (0)		0.00% (0)	0.00% (0)	
Suspected damage to fetus from viral disease in mother	0.00% (0)	0.00% (0)		0.00% (0)	0.00% (0)	
Suspected damage to fetus from other disease in mother	0.00% (0)	0.00% (0)		0.00% (0)	0.00% (0)	
Suspected damage to fetus from drugs	0.00% (0)	0.00% (0)		0.00% (0)	0.00% (0)	
Decreased fetal movements	0.00% (0)	0.00% (0)		0.00% (0)	0.00% (0)	
Other known or suspected fetal abnormality, NEC	0.00% (0)	0.01% (6)		0.00% (0)	0.00% (0)	
Known or suspected fetal abnormality affecting mgmt of mother / unspecified	0.00% (0)	0.03% (15)		0.00% (0)	0.03% (15)	
Known/suspected fetal anomaly affecting mgmt of mother	0.00% (0)	0.05% (24)		0.00% (0)	0.05% (24)	
Intrauterine death	0.00% (0)	0.00% (0)		0.00% (0)	0.00% (0)	
Anencephalus and similar anomalies	0.00% (0)	0.01% (4)		0.00% (0)	0.01% (4)	
Spina bifida	0.00% (0)	0.06% (29)		0.00% (0)	0.06% (29)	
Other congenital anomalies of nervous system	0.53% (1)	0.46% (228)	1.08 (0.15,7.62)	0.00% (0)	0.46% (229)	
Congenital anomalies of eye	1.06% (2)	1.30% (647)	1.00 (0.25,3.99)	0.00% (0)	1.30% (649)	
Congenital anomalies of ear, face and neck	1.06% (2)	0.42% (209)	2.42 (0.60,9.74)	0.00% (0)	0.42% (211)	
Bulbus cordis anomalies and anomalies of cardiac septal closure	1.60% (3)	1.37% (679)	1.09 (0.35,3.35)	2.50% (1)	1.37% (681)	1.02 (0.16,6.36)
Other congenital anomalies of heart	2.13% (4)	1.01% (502)	1.94 (0.73,5.15)	0.00% (0)	1.02% (506)	
Other congenital anomalies of circulatory system	1.06% (2)	0.83% (410)	1.16 (0.29,4.62)	0.00% (0)	0.83% (412)	
Congenital anomalies of respiratory system	0.00% (0)	0.52% (257)		2.50% (1)	0.51% (256)	5.08 (0.73,35.23)
Cleft palate and cleft lip	0.00% (0)	0.19% (93)		0.00% (0)	0.19% (93)	
Other congenital anomalies of upper alimentary tract	1.60% (3)	0.85% (421)	1.92 (0.62,5.92)	5.00% (2)	0.85% (422)	7.20 (1.89,27.51)*
Other congenital anomalies of digestive system	0.00% (0)	0.28% (139)		0.00% (0)	0.28% (139)	
Congenital anomalies of genital organs	1.60% (3)	2.35% (1165)	0.69 (0.22,2.12)	0.00% (0)	2.35% (1168)	
Congenital anomalies of urinary system	0.53% (1)	0.94% (469)	0.54 (0.08,3.82)	0.00% (0)	0.94% (470)	

Outcome	Beta Blockers			Calcium Channel Blockers		
	Exposed (n=188)	Not Exposed (n=49,648)	Relative Risk (95 CI)	Exposed (n=40)	Not Exposed (n=49,796)	Relative Risk (95 CI)
Certain congenital musculoskeletal deformities	1.60% (3)	2.53% (1256)	0.60 (0.19,1.83)	0.00% (0)	2.53% (1259)	
Other congenital anomalies of limbs	1.06% (2)	1.69% (837)	0.63 (0.16,2.51)	2.50% (1)	1.68% (838)	0.62 (0.07,5.23)
Other congenital musculoskeletal anomalies	0.53% (1)	1.37% (680)	0.40 (0.06,2.83)	0.00% (0)	1.37% (681)	
Congenital anomalies of the integument	2.13% (4)	1.24% (616)	1.84 (0.70,4.86)	2.50% (1)	1.24% (619)	2.71 (0.39,18.80)
Chromosomal anomalies	0.00% (0)	0.19% (92)		0.00% (0)	0.18% (92)	
Other and unspecified congenital anomalies	0.53% (1)	0.61% (301)	0.83 (0.12,5.89)	0.00% (0)	0.61% (302)	

Table 2

Number and relative risks of perinatal events among fullterm infants exposed to cardiovascular during the third trimester of pregnancy, compared to unexposed fullterm infants. All infants were followed for outcomes for 30 days after delivery.

Outcome	Beta Blockers			Calcium Channel Blockers		
	Exposed (n=405)	Not Exposed (n=75,688)	Relative Risk (95 CI)	Exposed (n=721)	Not Exposed (n=75,372)	Relative Risk (95 CI)
One or more perinatal event of interest	45.68% (185)	34.26% (25934)	1.30 (1.17,1.45)*	36.89% (266)	34.30% (25853)	1.06 (0.96,1.17)
Fetal-maternal hemorrhage	0.00% (0)	0.00% (0)		0.00% (0)	0.00% (0)	
Fetal distress	0.00% (0)	0.06% (47)		0.14% (1)	0.06% (46)	5.76 (0.83,39.82)
Poor fetal growth	0.00% (0)	0.01% (8)		0.00% (0)	0.01% (8)	
Excessive fetal growth	0.00% (0)	0.01% (11)		0.00% (0)	0.01% (11)	
Other placental conditions	0.00% (0)	0.00% (1)		0.00% (0)	0.00% (1)	
Other specified fetal and placental problems	0.00% (0)	0.01% (7)		0.00% (0)	0.01% (7)	
Unspecified fetal and placental problems	0.00% (0)	0.00% (2)		0.00% (0)	0.00% (2)	
Polyhydramnios	0.00% (0)	0.01% (4)		0.00% (0)	0.01% (4)	
Oligohydramnios	0.00% (0)	0.01% (5)		0.00% (0)	0.01% (5)	
Premature rupture of membranes	0.00% (0)	0.01% (8)		0.00% (0)	0.01% (8)	
Polyhydramnios and oligohydramnios	0.49% (2)	0.03% (22)	17.54 (4.02,76.60)*	0.00% (0)	0.03% (24)	
Complications of placenta, cord and membranes	0.99% (4)	1.01% (766)	0.98 (0.37,2.61)	0.97% (7)	1.01% (763)	1.12 (0.53,2.38)
Complications of delivery, including malpresentation and malformation	4.20% (17)	3.28% (2486)	1.39 (0.87,2.20)	1.11% (8)	3.31% (2495)	1.10 (0.55,2.21)
Disorders related to gestational age and birthweight	6.67% (27)	4.83% (3654)	1.28 (0.89,1.84)	6.52% (47)	4.82% (3634)	0.63 (0.48,0.84)*
Birth trauma	2.72% (11)	2.11% (1598)	1.24 (0.69,2.24)	1.94% (14)	2.12% (1595)	0.83 (0.49,1.42)
Intrauterine hypoxia and asphyxia	2.47% (10)	2.11% (1597)	1.19 (0.65,2.20)	0.55% (4)	2.13% (1603)	0.73 (0.27,2.00)
Respiratory distress syndrome and other respiratory conditions	9.63% (39)	7.10% (5373)	1.41 (1.05,1.90)*	6.66% (48)	7.12% (5364)	1.07 (0.81,1.42)
Neonatal hemorrhage and hemolytic diseases of the newborn	2.96% (12)	2.12% (1602)	1.33 (0.76,2.32)	2.77% (20)	2.11% (1594)	1.00 (0.64,1.56)
Other causes of perinatal jaundice	21.23% (86)	13.88% (10506)	1.46 (1.21,1.77)*	20.53% (148)	13.86% (10444)	1.41 (1.22,1.64)*
Endocrine and metabolic disturbances specific to newborn, including neonatal hypoglycemia (775.6)	8.40% (34)	2.34% (1771)	3.05 (2.20,4.21)*	3.47% (25)	2.36% (1780)	1.06 (0.72,1.58)
Hematological disorders of the newborn, including hemorrhagic diseases, polycythemia, thrombocytopenia, and anemia	0.99% (4)	0.39% (292)	2.12 (0.79,5.67)	1.39% (10)	0.38% (286)	2.62 (1.36,5.06)*
Disorders of the digestive system	0.99% (4)	0.23% (177)	4.04 (1.50,10.90)*	0.14% (1)	0.24% (180)	0.39 (0.05,2.86)
Disorders of temperature regulation, including hypothermia	2.72% (11)	1.84% (1392)	1.29 (0.71,2.31)	1.11% (8)	1.85% (1395)	0.63 (0.31,1.27)
Convulsions in the newborn	0.25% (1)	0.26% (199)	0.91 (0.13,6.44)	0.55% (4)	0.26% (196)	3.61 (1.26,10.37)*

Outcome	Beta Blockers			Calcium Channel Blockers		
	Exposed (n=405)	Not Exposed (n=75,688)	Relative Risk (95 CI)	Exposed (n=721)	Not Exposed (n=75,372)	Relative Risk (95 CI)
Feeding problems in the newborn	8.64% (35)	4.57% (3461)	1.82 (1.32,2.51)*	2.91% (21)	4.61% (3475)	1.12 (0.73,1.71)
Drug reactions specific to the newborn	0.00% (0)	0.00% (3)		0.00% (0)	0.00% (3)	
Other conditions	8.64% (35)	5.35% (4051)	1.57 (1.14,2.16)*	3.47% (25)	5.39% (4061)	1.10 (0.75,1.62)
Observation and evaluation of newborns for suspected condition not found	4.69% (19)	2.62% (1983)	1.99 (1.28,3.09)*	0.83% (6)	2.65% (1996)	0.48 (0.22,1.05)