# Late Pregnancy β Blocker Exposure and Risks of Neonatal Hypoglycemia and Bradycardia

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abstract

**BACKGROUND AND OBJECTIVES:** β blockers are widely used in the treatment of hypertensive disorders during pregnancy. These medications cross the placenta and may cause physiologic changes in neonates exposed in utero. We sought to define the risks of neonatal hypoglycemia and bradycardia associated with maternal exposure to β blockers at the time of delivery in a large, nationwide cohort of Medicaid beneficiaries.

**METHODS:** We used a cohort of 2 292 116 completed pregnancies linked to liveborn infants of Medicaid-enrolled women from 2003 to 2007. We examined the risks of neonatal hypoglycemia and neonatal bradycardia associated with maternal exposure to β blockers at the time of delivery. Propensity score matching was used to control for potential confounders including maternal demographics, obstetric and medical conditions, and exposure to other medications.

**RESULTS:** There were 10 585 (0.5%) pregnancies exposed to β blockers at the time of delivery. The risk of neonatal hypoglycemia was 4.3% in the β blocker–exposed neonates versus 1.2% in the unexposed; the risk of neonatal bradycardia was 1.6% in the exposed versus 0.5% in the unexposed. After controlling for confounders, risk remained elevated for both neonatal hypoglycemia and bradycardia among exposed pregnancies versus unexposed (adjusted odds ratio, 1.68, 95% confidence interval, 1.50–1.89 and adjusted odds ratio, 1.29, 95% confidence interval, 1.07–1.55, respectively).

**CONCLUSION** Our findings suggest that neonates born to mothers exposed to β blockers in late pregnancy, including labetalol, are at elevated risk for neonatal hypoglycemia and bradycardia.

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**WHAT'S KNOWN ON THIS SUBJECT:** β blockers are commonly used to treat hypertensive disorders during pregnancy. β blockers can cross the placenta and may cause physiologic changes in neonates exposed in utero.

**WHAT THIS STUDY ADDS:** β blockers, including labetalol, cause an elevated risk for both neonatal hypoglycemia and bradycardia among neonates exposed during late pregnancy compared with unexposed pregnancies.

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Hypertensive disorders complicate between 5% and 10% of all pregnancies[1] and are associated with significant maternal and fetal morbidity.[1–4] Although the threshold for treating hypertension in pregnancy and the risks and benefits of treatment remain controversial,[5–7] ~5% of pregnant women in the United States are treated with antihypertensive medications as outpatients each year.[8,9] β blockers are some of the most widely used agents for the treatment of hypertension in pregnancy,[8,9] and labetalol is now considered a first-line medication for the treatment of hypertension in pregnancy.[10]

Although generally considered safe for use in pregnancy, β blockers can cross the placenta and have the potential to cause physiologic changes in neonates exposed in utero.[11] Sympathetic blockade in the exposed neonates leads to 2 potential risks after delivery, neonatal hypoglycemia and neonatal bradycardia, and previous studies have suggested an association between late pregnancy β blocker exposure and these outcomes.[7,11]

The magnitude of these risks and how they may vary as a function of type of β blocker remain poorly defined. In particular, there are very few data on whether these risks extend to the combined α–β blocker labetalol.[12] Understanding these risks is important because both of these outcomes, particularly prolonged neonatal hypoglycemia, have been tied to adverse fetal outcomes, including neurologic injury.[11,13,14] If these drugs confer excess risk for these outcomes, neonates exposed in utero may benefit from more intensive monitoring after delivery.

We therefore sought to define the risks of neonatal hypoglycemia and bradycardia associated with maternal exposure to β blockers at the time of delivery in a large, nationwide cohort of Medicaid beneficiaries.

## METHODS

### Cohort

The cohort was defined using data from the Medicaid Analytic eXtract (MAX), a healthcare use database including Medicaid beneficiaries. MAX contains information regarding beneficiary demographic characteristics, inpatient admissions and outpatient clinic visits (including diagnosis and procedure claims), and dispensed prescriptions for outpatient medications. The use of this de-identified database for research was approved by the institutional review board of the Partners Healthcare System (Boston, MA).

A cohort for the study of medication safety in pregnancy was developed by using MAX data from 46 US states and the District of Columbia from 2000 to 2007, as previously described by Palmsten et al.[15] The last menstrual period (LMP) before the pregnancy was defined using a validated algorithm based on maternal and infant diagnostic codes.[15,16] This cohort has been used extensively for drug safety and use studies in pregnancy.[9,17–23]

Before 2003, there was not a distinct diagnostic code indicating neonatal bradycardia, so we restricted the analysis to births occurring from 2003 to 2007. We restricted the cohort to women who were continuously eligible for Medicaid from 5 months after the LMP through 1 month postpartum. We required that women in the cohort be without restricted benefits, private insurance, or certain capitated managed care programs that underreported claims to MAX during this period of eligibility. To capture the outcomes of interest in the linked infants, we required that they meet the same eligibility criteria as the mothers for at least 1 month after birth (unless they died).

### Exposure

Because the posited mechanism for β blockers causing neonatal hypoglycemia and bradycardia is direct placental transfer around the time of delivery, the primary exposure was maternal consumption of β blockers at the time of delivery, defined based on dispensed prescriptions with day's supply sufficient to cover the date of delivery. We considered prescriptions that were filled between 5 months after the LMP and the day of delivery and accumulated the days supply for consecutive prescriptions of the same medication, if a new dispensing occurred before the expected end date for the last prescription. The primary analysis included all β blockers, including combined α–β blockers, and combination medications that included a β blocker (see Supplemental Table 5). The reference group consisted of patients without β blocker exposure at the time of delivery. In secondary analyses, we examined the effect of exposure at the time of delivery to the most commonly used individual β blockers (labetalol, metoprolol, and atenolol) compared with nonexposure to any β blocker.

### Outcomes

The outcomes of interest were defined by the presence of ≥1 diagnostic codes from the *International Classification of Diseases, Ninth Revision* (ICD-9) indicating the presence of neonatal hypoglycemia or bradycardia in the infant records from the day of birth to day of life 30. We identified recordings of the diagnostic codes for 1 month after delivery to allow for potential lags in the posting of claims.

To determine the positive predictive value of the diagnostic codes used to define the outcome in our study, after IRB approval, a member of our study team (A.M.) validated by electronic and paper chart review 50

randomly selected cases in which an infant had a diagnosis code indicating neonatal bradycardia (ICD-9 Clinical Modification 779.81) and 50 with a code indicating neonatal hypoglycemia (ICD-9 Clinical Modification 775.6X) recorded in the electronic medical record between 2003 and 2007 at a single academic medical center. Patients identified with the code who did not have a medical record associated with an inpatient admission during the first 30 days of life at the institution were excluded and replaced with additional randomly selected cases. The presence of neonatal bradycardia was defined as documentation of bradycardia in the newborn by a clinician in the medical record, heart rate of ≤100, and/or treatment with rate control medications or resuscitative measures. Of the 50 cases reviewed, 47 cases met these criteria, resulting in a positive predictive value of the diagnostic code of 94% (95% confidence interval [CI], 83%– 99%).

Neonatal hypoglycemia was defined as documentation of hypoglycemia in the newborn by a clinician in the medical record, a glucose level ≤45 mg/dL, and/or treatment with intravenous glucose or a prescribed increased frequency of feeding. Of the 50 cases reviewed, 48 cases met these criteria, resulting in a positive predictive value of the diagnostic code of 96% (95% CI, 87%–99%).

### Covariates

We extracted 5 groups of potential confounders of the planned analysis: demographic characteristics, medical conditions, obstetrical conditions, maternal medications, and measures of healthcare use. The demographic characteristics assessed included maternal age at delivery, maternal race/ethnicity, and calendar year of delivery. Maternal medical conditions were defined based on the presence of diagnostic codes recorded in the patients' inpatient or outpatient codes from 5 months after the estimated LMP to delivery; we considered the major indications for β blockade, along with conditions that were likely to be associated with both the exposure and outcome. Obstetrical conditions were defined in the same manner. Preterm delivery was adjusted for in the analysis because it may be a proxy for the severity of conditions that are indications for β blockers and is not expected to be a causal intermediate in the relationship between β blockers and the outcome. The assessment of maternal medication use included oral glucose-lowering medication or insulin use during the final month of pregnancy and was used as a marker for the severity of maternal gestational and preexisting diabetes. Finally, we defined 2 measures of healthcare use assessed from 5 to 6 months after LMP that might serve as markers for patients' overall burden of comorbidity and/or access to healthcare, the number of distinct non–β blocker prescriptions and the number of physician visits for any reason.

### Statistical Analysis

We described the baseline characteristics for the analytic cohort stratified by β blocker exposure at the time of delivery, calculated the frequency of neonatal hypoglycemia and neonatal bradycardia stratified by β blocker exposure status, and determined unadjusted odds ratios (OR) and 95% CIs for the association between exposure and the outcome.

To account for differences with respect to potentially confounding variables between pregnancies exposed and unexposed to β blockers at the time of delivery, we used propensity scores (PS). The PS was estimated using a logistic regression model in which exposure was the dependent variable and was estimated on the basis of all the covariates defined above without additional selection.

Women exposed to β blockers were then matched to those unexposed on the basis of the PS in a fixed 1:3 ratio using a nearest neighbor algorithm, with a maximum caliper of 0.05. After matching, we determined the distribution of all covariates in the exposed and unexposed, and the absolute difference in the frequency of each covariate was calculated. The numbers of outcomes occurring among exposed and unexposed pregnancies in the matched cohort were determined and the ORs and 95% CIs were again calculated. This analysis was repeated for the 3 most commonly used β blockers (labetalol, metoprolol, and atenolol) with the PS re-estimated for each of these analyses.

### Sensitivity Analyses

In the first sensitivity analysis, we employed an active comparator design, because this may make the exposed and unexposed more comparable with respect to unmeasured confounders. We selected as our active comparator methyldopa that was the most commonly used antihypertensive medication in our cohort and that has not, to our knowledge, been associated with the outcomes of interest. Second, we defined a high dimensional PS (hd-PS) to adjust for empirically defined covariates in addition to the investigator-specified covariates; hd-PS has been shown to improve control of confounding in some circumstances.[24] Third, we conducted a sensitivity analysis in which we restricted to pregnancies complicated by preexisting diabetes or gestational diabetes. Infants born to mothers with diabetes are frequently screened for hypoglycemia. By imposing this restriction, we can reasonably assume that most infants will be screened, which reduces the likelihood

**TABLE 1** Baseline Characteristics Stratified by Exposure to β Blockers, Before and After PS Matching

| | Full Cohort | | Matched Cohort | | |
|---|---|---|---|---|---|
| | β Blocker Exposed | β Blocker Unexposed | β Blocker Exposed | β Blocker Unexposed | Absolute Difference |
| Total | 10 585 | 2 281 531 | 10 561 | 31 683 | |
| Age (y) | | | | | |
| ≤19 | 894 (8.5) | 440 708 (19.3) | 894 (8.5) | 2906 (9.2) | −0.7 |
| 20–24 | 2921 (27.6) | 938 225 (41.1) | 2920 (27.7) | 9088 (28.7) | −1 |
| 25–29 | 2787 (26.3) | 527 668 (23.1) | 2784 (26.4) | 8505 (26.8) | −0.5 |
| 30–34 | 2069 (19.6) | 240 599 (10.6) | 2060 (19.5) | 5948 (18.8) | 0.7 |
| 35–39 | 1400 (13.2) | 107 070 (4.7) | 1392 (13.2) | 3882 (12.3) | 0.9 |
| ≥40 | 514 (4.9) | 27261 (1.2) | 511 (4.8) | 1354 (4.3) | 0.6 |
| Race | | | | | |
| White | 6347 (60) | 1 121 952 (49.2) | 6328 (59.9) | 19 374 (61.2) | −1.2 |
| Black | 2658 (25.1) | 574 024 (25.2) | 2654 (25.1) | 8028 (25.3) | −0.2 |
| Hispanic | 746 (7.1) | 296 576 (13) | 746 (7.1) | 2099 (6.6) | 0.4 |
| Asian | 189 (1.8) | 75 534 (3.3) | 188 (1.8) | 445 (1.4) | 0.4 |
| Other | 395 (3.7) | 147 696 (6.5) | 395 (3.7) | 1059 (3.3) | 0.4 |
| Unknown | 250 (2.4) | 65 749 (2.9) | 250 (2.4) | 678 (2.1) | 0.2 |
| Medical/obstetrical conditions | | | | | |
| Preexisting hypertension | 6309 (59.6) | 76 218 (3.3) | 6285 (59.5) | 19 251 (60.8) | −1.3 |
| Gestational hypertension | 4022 (38) | 110 315 (4.8) | 4006 (37.9) | 12 670 (40) | −2.1 |
| Mild preeclampsia | 2626 (24.8) | 92 618 (4.1) | 2615 (24.8) | 8018 (25.3) | −0.5 |
| Severe preeclampsia | 2474 (23.4) | 42 122 (1.9) | 2464 (23.3) | 6828 (21.6) | 1.8 |
| Migraine | 387 (3.7) | 18 859 (0.8) | 383 (3.6) | 1251 (4) | −0.3 |
| Cardiac arrhythmia | 973 (9.2) | 16 524 (0.7) | 953 (9) | 2848 (9) | 0 |
| Ischemic heart disease | 48 (0.5) | 591 (0) | 45 (0.4) | 88 (0.3) | 0.2 |
| Anxiety | 308 (2.9) | 21 456 (0.9) | 304 (2.9) | 912 (2.9) | 0 |
| Congestive heart failure | 279 (2.6) | 3025 (0.1) | 268 (2.5) | 554 (1.8) | 0.8 |
| Multiple gestation | 259 (2.5) | 34 670 (1.5) | 258 (2.4) | 761 (2.4) | 0 |
| Preterm delivery | 3107 (29.4) | 263 861 (11.6) | 3089 (29.3) | 8573 (27.1) | 2.2 |
| Preexisting diabetes | 1466 (13.9) | 85 451 (3.8) | 1458 (13.8) | 4063 (12.8) | 1 |
| Gestational diabetes | 2175 (20.6) | 190 371 (8.3) | 2161 (20.5) | 6281 (19.8) | 0.6 |

Also included in the PS model: alcohol abuse, illicit drug use, tobacco use, chronic renal disease, essential tremor, number of distinct non–β blocker prescription drugs and physician visits during baseline period, calendar year, and maternal exposure to insulin or oral hypoglycemics in the final month of pregnancy.

that our results are vulnerable to surveillance bias (which would occur if infants born to mothers treated with β blockers were screened more often for hypoglycemia). Fourth, we restricted to term deliveries to examine whether there was effect modification by term delivery. Fifth, we excluded patients with β blockers dispensed from 5 months after the LMP to delivery who did not have a β blocker with days supply overlapping delivery from the reference group to minimize the potential for misclassification of the unexposed. Sixth, we excluded neonates with preterm delivery, who were small for gestational age, had low birth weight, or experienced intrauterine hypoxemia/birth asphyxia. Although these conditions cannot be determinants of treatment and may, in fact, in some instances be intermediates on the causal pathway from β blocker exposure to the outcomes, they may also be proxies for the severity of the underlying indication. Finally, we explored 3 alternative definitions of outcome: (1) requiring recording of the outcomes of interest in the infant claims from day of birth to day of life 30 ≥2 times (which may increase the specificity of the outcomes definition in some cases); (2) defining the outcome based on inpatient claims only (which most closely matches the outcomes defined in our validation study); and (3) defining the presence of the outcomes using diagnoses recorded in both maternal and infant claims (as claims for the infant are sometimes instead applied to the maternal claims).

All analyses were performed by using SAS 9.3 (SAS Institute, Inc, Cary, NC).

## RESULTS

The cohort included 2 292 116 completed pregnancies linked to liveborn infants, of which 10 585 (0.5%) pregnancies were exposed to β blockers at the time of delivery. Labetalol was the most commonly used β blocker ($n$ = 6748), followed by metoprolol ($n$ = 1485) and atenolol ($n$ = 1121).

β blocker–exposed patients were more likely to be older, white, and have diagnoses that represent indications for the medication. They were also more likely to have preexisting or gestational diabetes and to deliver preterm. After matching on the basis of the PS, these differences were no longer present, with the absolute difference in the prevalence of all measured confounders <3% (Table 1).

**TABLE 2** The Association Between β Blockers (Overall) and the Risks of Neonatal Hypoglycemia and Neonatal Bradycardia

| | β Blocker Exposed | | β Blocker Nonexposed | | OR (95% CI) |
|---|---|---|---|---|---|
| | Outcomes | Total | Outcomes | Total | |
| Neonatal hypoglycemia | | | | | |
| Unadjusted | 460 | 10 585 | 27 228 | 2 281 531 | 3.76 (3.42–4.13) |
| PS-matched | 459 | 10 561 | 834 | 31 683 | 1.68 (1.50–1.89) |
| Neonatal bradycardia | | | | | |
| Unadjusted | 165 | 10 585 | 11 659 | 2 281 531 | 3.08 (2.64–3.6) |
| PS-matched | 165 | 10 561 | 385 | 31 683 | 1.29 (1.07–1.55) |

**TABLE 3** The Association Between Exposure to Specific β Blockers and the Risks of Neonatal Hypoglycemia and Neonatal Bradycardia

| | Exposed | | Nonexposed | | OR (95% CI) |
|---|---|---|---|---|---|
| | Outcomes | Total | Outcomes | Total | |
| Labetalol | | | | | |
| Neonatal hypoglycemia | | | | | |
| Unadjusted | 345 | 6748 | 27 228 | 2 281 531 | 4.46 (4.00–4.98) |
| Propensity-score matched | 344 | 6730 | 593 | 20 190 | 1.78 (1.55–2.04) |
| Neonatal bradycardia | | | | | |
| Unadjusted | 124 | 6748 | 11 659 | 2 281 531 | 3.65 (3.05–4.36) |
| Propensity-score matched | 123 | 6730 | 276 | 20 190 | 1.34 (1.08–1.67) |
| Metoprolol | | | | | |
| Neonatal hypoglycemia | | | | | |
| Unadjusted | 49 | 1485 | 27 228 | 2 281 531 | 2.83 (2.13–3.76) |
| Propensity-score matched | 49 | 1484 | 91 | 4452 | 1.64 (1.15–2.33) |
| Neonatal bradycardia | | | | | |
| Unadjusted | 12 | 1485 | 11 659 | 2 281 531 | 1.60 (0.91–2.81) |
| Propensity-score matched | 12 | 1484 | 61 | 4452 | 0.59 (0.32–1.09) |
| Atenolol | | | | | |
| Neonatal hypoglycemia | | | | | |
| Unadjusted | 30 | 1121 | 27 228 | 2 281 531 | 2.28 (1.59–3.28) |
| Propensity-score matched | 30 | 1121 | 59 | 3363 | 1.54 (0.99–2.4) |
| Neonatal bradycardia | | | | | |
| Unadjusted | 12 | 1121 | 11 659 | 2 281 531 | 2.11 (1.2–3.73) |
| Propensity-score matched | 12 | 1121 | 31 | 3363 | 1.16 (0.60–2.27) |

Neonatal hypoglycemia occurred in 4.3% of offspring of pregnancies exposed to β blockers compared with 1.2% of pregnancies that were unexposed, such that the OR associated with β blocker exposure was 3.76 (95% CI, 3.42–4.13) (Table 2). After matching, the risk of neonatal hypoglycemia was substantially attenuated but remained elevated (OR, 1.68; 95% CI, 1.50–1.89).

Neonatal bradycardia occurred in 1.6% of the infants born to mothers exposed to β blockers and in 0.5% of those born to mothers who were unexposed (OR, 3.08; 95% CI, 2.64–3.60). In the PS-matched cohort, the risk of neonatal bradycardia also remained, albeit attenuated by approximately threefold from the crude estimate (OR, 1.29; 95% CI, 1.07–1.55).

We examined separately the 3 most commonly prescribed β blockers (Table 3). The risk estimates for neonatal hypoglycemia in the PS-matched cohorts were similarly increased in association with exposure to each of the agents, including labetalol (OR, 1.78; 95% CI, 1.55– 2.04), metoprolol (OR, 1.64; 95% CI, 1.15–2.33), and atenolol (OR, 1.54; 95% CI, 0.99–2.40). Risk estimates for neonatal bradycardia across the specific β blockers in the PS-matched cohorts were less consistent, although the CIs for some estimates were wide: labetalol (OR, 1.34; 95% 1.08–1.67), metoprolol (OR, 0.59; 95% CI, 0.32–1.09), and atenolol (OR, 1.16; 95% CI, 0.60– 2.27).

Results across each of the sensitivity analyses conducted were similar to those from the main analysis, although for some analyses, in the setting of widened CI, the lower bound of the 95% CI intersected the null (Table 4).

## DISCUSSION

In this large cohort study that included ∼2.2 million pregnancies, over 10 000 of which were exposed to β blockers around the time of delivery, we observed an ∼70% increase in the risk of neonatal hypoglycemia and a 30% increase in the risk of neonatal bradycardia in infants born to mothers taking

**TABLE 4** Sensitivity Analyses Showing the Association Between β Blocker Exposure and the Risks of Neonatal Hypoglycemia and Neonatal Bradycardia

| | Neonatal Hypogylcemia, OR (95% CI) | Neonatal Bradycardia, OR (95% CI) |
|---|---|---|
| Reference methyldopa[a] | | |
| Unadjusted | 1.57 (1.34–1.83) | 1.28 (1–1.63) |
| PS-matched | 1.67 (1.39–2.01) | 1.21 (0.91–1.6) |
| hd-PS adjustment | | |
| Unadjusted | 3.76 (3.42–4.13) | 3.08 (2.64–3.6) |
| PS-matched | 1.44 (1.28–1.63) | 1.09 (0.90–1.32) |
| Restricted: patients with diabetes[b] | | |
| Unadjusted | 2.83 (2.39–3.36) | N/A |
| PS-matched | 1.50 (1.22–1.84) | N/A |
| Restricted: term deliveries | | |
| Unadjusted | 3.10 (2.64–3.65) | 2.07 (1.4–3.04) |
| PS-matched | 1.69 (1.38–2.06) | 1.35 (0.85–2.14) |
| Excluding patients from reference group with β blocker exposure | | |
| Unadjusted | 3.77 (3.43–4.15) | 3.10 (2.65–3.61) |
| PS-matched | 1.69 (1.51–1.90) | 1.27 (1.06–1.53) |
| Excluded neonates with preterm delivery, small for gestational age, low birth weight, or intrauterine hypoxemia/birth asphyxia | | |
| Unadjusted | 2.98 (2.50–3.55) | 2.05 (1.35–3.12) |
| PS-matched | 1.53 (1.24–1.90) | 1.61 (0.96–2.71) |
| Two codes in the infant record | | |
| Unadjusted | 3.73 (3.2–4.34) | 3.29 (2.39–4.53) |
| PS-matched | 1.70 (1.41–2.06) | 1.34 (0.92–1.97) |
| Codes from inpatient claims only | | |
| Unadjusted | 3.66 (3.29–4.06) | 3.21 (2.72–3.80) |
| PS-matched | 1.79 (1.57–2.04) | 1.30 (1.07–1.59) |
| Codes in the infant or maternal record | | |
| Unadjusted | 3.76 (3.44–4.12) | 3.00 (2.58–3.49) |
| PS-matched | 1.67 (1.49–1.86) | 1.25 (1.05–1.5) |

N/A, not applicable.

[a] 1:1 (given similar numbers in unmatched cohorts in both groups).

[b] Restricted: patient with preexisting or gestational diabetes.

these medications after adjusting for relevant confounders. In addition, we found that these risks were present for the most commonly used medication in the class, the combined α–β blocker labetalol. These results suggest that infants born to mothers exposed to β blockers should be monitored for these conditions and potentially screened for hypoglycemia after birth.

Our findings confirm and extend those of previous studies. A recent meta-analysis of randomized controlled clinical trials examining treatment of mild to moderate hypertension in pregnancy suggested that treatment with oral β blockers was associated with an increased risk of neonatal bradycardia (risk ratio [RR], 1.93; 95% CI, 1.05–3.53).[25] Although data from RCTs on the risk of neonatal hypoglycemia associated with β blockers is inconclusive, with a wide CI in the pooled estimate (RR, 0.81; 95% CI, 0.44–1.49) and unclear exposure status for the participant around the time of delivery,[25] a recent observational study reported a threefold increased risk in association with third-trimester exposure (RR, 3.1; 95% CI, 2.2–4.2).[11] These findings have physiologic plausibility, because β blockers are known to cross the placenta and have the potential to cause sympathetic blockade in exposed infants.

It has not previously been clear whether these risks extend to the combined α–β blocker labetalol, which is recommended as a first-line therapy for the treatment of hypertension in pregnancy.[12] Our findings suggest that labetalol exposure is associated with a1.3-fold increase in the risk of neonatal bradycardia and a 1.8-fold increased risk for hypoglycemia. Clinicians should therefore be alert to the possibility of these outcomes in infants exposed in utero to this commonly used antihypertensive.

Although the literature on the effects of neonatal hypoglycemia on long-term neurodevelopment is limited and conflicting,[26] brain imaging studies suggest that the developing brain may be vulnerable to hypoglycemia.[13,14] This motivates the prompt recognition and treatment of this condition to avoid the potential for neurologic injury. Guidelines do not generally include maternal use of β blockers as an indication for routine blood glucose monitoring in asymptomatic infants.[27] Our findings suggest that such monitoring may be indicated, particularly as it is possible that the β blocker transmitted in utero to an infant may mask its symptoms. Defining the value of such monitoring will be an important focus for future clinical studies.

Our study has several important strengths. Its large size makes it possible to generate relatively precise risk estimates both for β blockers overall and for specific medications. It assesses drug exposure in an objective fashion that is free from recall bias. Finally, it captures a wide range of potential confounders and controls for them with PS-based methods.

The study also has some limitations inherent in its design. First, the outcomes are defined based on the presence of diagnostic codes for the conditions of interest recorded in the infant claims, introducing the possibility of outcome misclassification. However, our chart-based validation suggests that these diagnoses are recorded with

very high accuracy in claims data (>90% for both conditions) and any misclassification of outcome (assuming it is nondifferential with respect to exposure status) will be expected to bias the outcome to the null. Second, although we attempted to rigorously define and adjust for all measured clinical factors that might confound the association between β blocker exposure and the outcome, the possibility exists that the reported associations may be biased by unknown or unmeasured confounders. To minimize this limitation, we performed a sensitivity analysis using an active comparator design. In this analysis, the patients in the reference group are expected to closely match those in the exposed group with respect to unmeasured conditions.[28] The findings from this analysis were very similar to those of the main study, suggesting the observed associations are not likely to be due to residual confounding. We do not have information about whether infants were screened for the presence of hypoglycemia. If infants born to women exposed to β blockers were more closely monitored for this condition, it could lead to surveillance bias. However, when we restricted the analysis to offspring of diabetic mothers (who are routinely screened for hypogylcemia), the increased risk of hypoglycemia associated with the use of β blockers persisted and was of a similar magnitude to that of the main analysis. Finally, the strength of the association between β blocker exposure and neonatal bradycardia was weaker than the association with hypoglycemia. In many of the sensitivity analyses, the CI for the bradycardia estimate crosses the null. This association therefore needs to be interpreted with some caution.

## CONCLUSIONS

Infants born to mothers exposed to β blockers, including labetalol, around the time of delivery are at heightened risk for neonatal bradycardia and hypoglycemia. Our results support increased surveillance of these infants, including routine glucose monitoring, so that these conditions can be promptly recognized and treated.


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## ABBREVIATIONS

CI: confidence interval
hd-PS: high-dimensional propensity score
ICD-9: *International Classification of Diseases, Ninth Revision*
LMP: last menstrual period
MAX: Medicaid Analytic eXtract
OR: odds ratio
PS: propensity score
RR: risk ratio


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