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Association between labetalol use for hypertension in pregnancy and adverse infant outcomes

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ABSTRACT

Objective: Labetalol and methyldopa are the two antihypertensive drugs most frequently used to control blood pressure for hypertensive disorders of pregnancy. The objective of this study was to assess if labetalol is associated with poor infant outcomes.
Study design: Retrospective population-based cohort study using the linked maternal/infant databases in the Province of Saskatchewan. Women with a diagnosis of a hypertensive disorder of pregnancy who delivered a singleton in Saskatchewan from January 1, 1990 to December 31, 2005 and who were dispensed only labetalol or only methyldopa were included in the study. Occurrences of small for gestational age (SGA) < 10th percentile, SGA < 3rd percentile, preterm birth, stillbirth, hospitalization for respiratory distress syndrome (RDS), sepsis, and seizure during infancy, and infant death were compared. Multiple logistic regression analysis was performed to adjust for potential confounding.
Results: A total of 1223 eligible women were included in the final analysis. Among them, 300 received labetalol only and 923 received methyldopa only during pregnancy. For women with chronic hypertension, the rate of hospitalization for RDS, sepsis, and seizure during infancy was significantly higher for infants born to mothers who were dispensed labetalol only as compared with infants born to mothers who were dispensed methyldopa only (adjusted odds ratio (OR) 1.51, 95% confidence interval (CI) 1.02–2.22).
Conclusion: Compared with methyldopa, the use of labetalol for chronic hypertension of pregnancy may be associated with increased rate of hospitalization during infancy.

1. Introduction

Hypertensive disorders of pregnancy remain a leading cause of maternal, fetal and neonatal morbidity and mortality in industrialized countries, including Canada [1–4]. Although there is general consensus on the need to control blood pressure with antihypertensive medication in non-pregnant patients, whether and how to control blood pressure for hypertensive disorders of pregnancy has not been clearly defined, especially in mild or moderate cases of hypertension [5,6].

Labetalol and methyldopa are generally towards the top of the list of antihypertensive drugs during pregnancy recommended by most professional associations/societies [7–10]. Several studies, however, have found an association between exposure to beta-blockers in pregnancy and low birth weight infants [6,11,12]. Given the combined beta and alpha blocking effects of labetalol, we hypothesized that exposure to labetalol in pregnancy may be associated with higher rates of adverse perinatal outcomes compared with other antihypertensives. The objective of the present study was to compare perinatal outcomes in infants born

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to mothers with pregnancy exposure to labetalol and methyldopa, two of the most frequently recommended antihypertensive drugs during pregnancy.

2. Methods

A retrospective population-based cohort was formed using the linked maternal/infant databases in the Canadian Province of Saskatchewan. The cohort included all women with a diagnosis of a hypertensive disorder in pregnancy who were eligible for coverage by the Saskatchewan prescription drug plan (out-patient prescriptions) and who delivered a singleton in Saskatchewan from January 1, 1990 to December 31, 2005. They were identified through ICD-9/ICD-10-CA codes recorded in the database. Women with co-morbidities (i.e., diabetes, renal disease, and/or cardiac disease) were excluded from the analyses to minimize confounding, as these conditions are independently associated with increased risks of adverse perinatal outcomes [13]. The study population was comprised of women with diagnoses of a hypertensive disorder during pregnancy who were dispensed either labetalol or methyldopa. Information on labetalol and methyldopa use in pregnancy was ascertained for each study participant using number of days between date of drug dispensing and date of infant birth.

Outcomes of interest included: small-for-gestational age (SGA, defined as birth weight being less than the 10th percentile of the population-based Canadian reference recommended by Kramer et al. [14]); severe SGA (birth weight less than 3rd percentile); preterm birth (live infants delivered at less than 37 completed weeks of gestation); stillbirth (stillbirth with a birth weight above 500 grams or gestational age more than 20 weeks); offspring hospitalization during infancy; and infant death (death of a live-born infant within the first year of life). For hospitalization, we counted only first hospitalization with a ICD-9 or ICD-10 code diagnostic code for respiratory distress syndrome (or RDS, a syndrome in premature infants caused by developmental insufficiency of surfactant production and structural immaturity in the lungs), sepsis (a potentially fatal whole-body inflammation (a systemic inflammatory response syndrome) caused by severe infection), or seizures (changes in the brain's electrical activity which can cause dramatic, noticeable symptoms including violent shaking and loss of control) during the first year of life, because we thought hospitalizations for many other causes (e.g. accidents) may not be related to antihypertensive drugs uses during pregnancy.

We first described maternal characteristics and occurrence of adverse perinatal outcomes between the two study groups, women who received labetalol only and women who received methyldopa only during pregnancy. Multiple logistic regression analyses were then performed to assess the independent association between the type of antihypertensive drugs and adverse perinatal outcomes, with methyldopa only as the reference. Potential confounding variables included in the regression models were: maternal age (<25 years, 25–29 years, and ≥30 years; <25 years as the reference); year of childbirth; Saskatchewan assistance plan coverage (no versus yes; no as the reference); parity (1 versus ≥2; 1 as reference); and type of hypertensive disorders in pregnancy (chronic hypertension [including chronic hypertension with superimposed preeclampsia], gestational hypertension, and preeclampsia/eclampsia; gestational hypertension as the reference). Confounding variables and their categorizations included in the regression model were selected a priori by an expert panel based on literature review. Those variables that are possibly associated with both drug selection and the examined outcomes were considered, but we were restricted by factors that cannot be controlled by ourselves. Some important variables were not available in the database. A full model consisting of all independent variables was used in the analysis.

As there are major differences in the clinical indications and duration of treatment of hypertensive disorders of pregnancy we performed two pre-planned analyses as follows. First we compared perinatal outcomes between the two study groups in women with a diagnosis of chronic hypertension and in those women with a diagnosis of gestational hypertension or preeclampsia/eclampsia separately. Second, women with chronic hypertension may be treated with antihypertensive medications for longer durations during pregnancy and the initiation time of treatment may be associated with clinical outcomes. As such, we performed an additional multiple logistic regression analysis for women with a diagnosis of chronic hypertension to adjust for timing of initiation of antihypertensive treatment (pre-conception, first trimester, second trimester, and third trimester) as it reflects duration of therapy. Supplementary analysis restricted to first pregnancies was also performed.

3. Results

A total of 1223 women were included in the final analysis. Among them, 300 received labetalol only and 923 received methyldopa only during pregnancy. Table 1 describes the baseline characteristics of the two study groups. Women who were dispensed labetalol only tended to be of older age, to initiate treatment in later gestation, to be diagnosed with gestational hypertension/preeclampsia, and to be delivered in more recent years, but were less likely to depend on government assistance.

Table 2 compares odds ratios of various adverse perinatal outcomes between the two study groups. None of the differences between the two study groups reached statistical significance.

Table 3 compares outcomes between the two study groups in women with a diagnosis of chronic hypertension and in those women with a diagnosis of gestational hypertension or pre-eclampsia/eclampsia separately. For women with chronic hypertension, the odds of hospitalization for RDS, sepsis, and seizures during infancy was significantly higher (odds ratio (OR) 1.51, 95% confidence interval (CI) 1.03–2.22) in infants born to mothers who were dispensed labetalol only, compared with infants born to mothers who were dispensed methyldopa only. For women with gestational hypertension or preeclampsia/eclampsia, no difference in the incidence of adverse perinatal outcomes was observed between the two study groups.

Table 1
Distribution of maternal characteristics between women who received labetalol and methyldopa, 1990–2005.

Characteristics	Labetalol only No. (%)	Methyldopa only No. (%)	Total
Age group (years)			
<25	62 (20.67)	217 (23.51)	279
25–29	96 (32.00)	285 (30.88)	381
≥30	142 (47.33)	421 (45.61)	563
Year of birth			
1990–1994	23 (7.67)	160 (17.33)	183
1995–1999	47 (15.67)	311 (33.69)	358
2000–2005	230 (76.67)	452 (48.97)	682
Saskatchewan Assistance Plan coverage			
No	284 (94.67)	846 (91.66)	1130
Yes	16 (5.33)	77 (8.34)	93
Parity			
1	167 (55.67)	496 (53.74)	663
≥2	133 (44.33)	427 (46.26)	560
Type of hypertensive disorder			
Chronic hypertension	116 (38.67)	414 (44.85)	530
Gestational hypertension	155 (51.67)	469 (50.81)	624
Preeclampsia	29 (9.67)	40 (4.33)	69