

Long-Acting β_2 -Agonists and Risk of Hypertensive Disorders of Pregnancy: A Cohort Study



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What is already known about this topic? Long-acting β_2 -agonists (LABAs) added to inhaled corticosteroids are the second most widely used controller therapy in asthma. Some studies have linked LABA use in pregnancy with an increased risk of gestational hypertension, eclampsia, and preeclampsia.

What does this article add to our knowledge? We studied a cohort of 8,900 pregnancies (over 20 weeks' gestation) in women with asthma in Quebec, Canada. Risks of hypertensive disorders of pregnancy were not increased with LABA use at midpregnancy.

How does this study impact current management guidelines? This study confirms current asthma guidelines that pregnant women with asthma should likely continue their inhaled corticosteroids and prescribed LABA medication, if needed.

BACKGROUND: Maternal asthma has been found to be associated with an increased risk of hypertensive disorders of pregnancy (HDP), that is, gestational hypertension, preeclampsia, and eclampsia. There is limited data, however, regarding the relationship between the use of long-acting beta-agonists (LABAs) during pregnancy and these outcomes. **OBJECTIVE:** To investigate whether exposure to a LABA in addition to an inhaled corticosteroid increases the risk of HDP

or preeclampsia/eclampsia, as compared with nonexposure to LABAs, in pregnant women with asthma.

METHODS: A cohort of 8,936 pregnancies in women with asthma who delivered between 1998 and 2010 was reconstructed using Quebec (Canada) health administrative databases. Cox proportional hazard regression models, adjusted for potential confounders, were used for statistical analyses. The primary exposure was LABA use (yes/no) measured on the first day of the 20th week of pregnancy. HDP were identified on the basis of recorded diagnoses and on prescriptions of antihypertensive drugs filled on or after the first day of week 20 of gestation. **RESULTS:** There were 567 (6.3%) cases of HDP and 256 (2.9%) cases of preeclampsia/eclampsia in the cohort, and the rates of both disorders were similar in women exposed or not exposed to LABAs. LABA use was not associated with increased risks of HDP (adjusted hazard ratio, 0.96; 95% CI, 0.69-1.33) or preeclampsia/eclampsia (adjusted hazard ratio, 0.89; 95% CI, 0.53-1.50).

CONCLUSIONS: The results of this study provide evidence suggesting the safety of LABAs for the treatment of asthma in pregnancy, in terms of the risks of HDP and preeclampsia/eclampsia. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:555-61)

Key words: Asthma; Pregnancy; Long-acting β_2 -agonists (LABAs); Hypertensive disorders of pregnancy; Preeclampsia; Eclampsia; Gestational hypertension; Administrative databases

It is estimated that up to 13% of pregnancies may be affected by asthma, making it one of the most common chronic conditions of pregnancy.^{1,2} Because it is important to control asthma symptoms for the health of the mother and the baby, the current treatment guidelines recommend that women with asthma should continue active treatment during pregnancy.³ Hypertensive disorders of pregnancy (HDP) include gestational hypertension, preeclampsia, and eclampsia that resolve postpartum.

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Abbreviations used

<i>aHR</i> - Adjusted hazard ratio
<i>HDP</i> - Hypertensive disorders of pregnancy
<i>ICD-9</i> - International Classification of Diseases, Ninth Revision
<i>HR</i> - Hazard ratio
<i>ICD-10</i> - International Classification of Diseases, Tenth Revision
<i>ICS</i> - Inhaled corticosteroid
<i>LABA</i> - Long-acting β_2 -agonist
<i>MED-ECHO</i> - Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière
<i>QAPD</i> - Quebec Asthma and Pregnancy Database
<i>RAMQ</i> - Régie de l'Assurance Maladie du Québec
<i>SABA</i> - Short-acting β_2 -agonist

They are frequent complications that affect 6% to 10% of pregnancies.⁴ These disorders can have a significant, negative impact on the fetus, the infant, and the mother, and may result in preterm birth, low birth weight, and maternal cardiovascular complications.⁵⁻⁷

Maternal asthma and HDP were found to be associated in several studies.^{2,8-17} Most of these studies have reported significantly increased risk of HDP, with relative risk estimates ranging from 1.15 to 2.21.^{2,9-11,13,15-17} Moreover, in a previous study conducted by our team, we found that the risk of HDP was increased by 18%, albeit not significantly, among women with uncontrolled asthma compared with women with controlled asthma.¹⁸ Several research groups, including ourselves, have examined the impact of asthma medications such as inhaled corticosteroids (ICSs), the first-line asthma-controller medication, on the risk of HDP but none of the studies reported a significant increase in the risk of HDP.¹⁹⁻²¹ Of these 3 studies, 2 used a comparison group formed of women with asthma and 1 used a comparison group formed of women without asthma. The possible impact of exposure to short-acting β_2 -agonists (SABAs) during pregnancy was also investigated,^{14,22-27} and the results of an earlier study by our group showed that exposure to a SABA was associated with a reduced risk of HDP.²⁷ Of the 7 studies on the impact of SABA exposure, 3 used a comparison group formed of pregnant women without asthma, 2 used 2 comparison groups formed of women with and without asthma, and 2 used a comparison group formed of women with asthma.

Long-acting β_2 -agonists (LABAs) are the second most widely used controller medications in asthma. However, scarce data exist regarding the impact of LABAs on the risk of HDP. In a previous study, we assessed the impact of exposure to LABA on perinatal outcomes, and we found that the percentage of preeclampsia/eclampsia was greater in women exposed to a LABA (4.2%) than in unexposed women (2.9%).²⁸ However, we cannot make firm conclusions on the basis of that study because it was not specifically designed to evaluate the association between exposure to a LABA and the risk of preeclampsia/eclampsia, and consequently it was not possible to determine whether the exposure occurred before or after the diagnosis of preeclampsia/eclampsia. In addition, a recent Swedish cohort study reported that the risk of preeclampsia was significantly increased, by 28%, in women exposed to a LABA after the first trimester of pregnancy compared with all other women who gave birth in that cohort.²⁹ However, because the reference group included women without

asthma, it is not possible to distinguish the effects of exposure to a LABA from the effect of asthma per se.

Because few studies have specifically evaluated the impact of exposure to a LABA on the risk of HDP, we performed a large retrospective cohort study to investigate whether exposure to a LABA during pregnancy increases the risk of HDP in women with asthma compared with that in unexposed women with asthma.

METHODS

Data sources

To conduct our study, we used the Quebec Asthma and Pregnancy Database (QAPD), which was built by linking 2 administrative health databases from the province of Quebec (Canada): the MED-ECHO (Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière) and the RAMQ (Régie de l'Assurance Maladie du Québec) databases. The MED-ECHO database contains data on acute care hospitalizations (eg, the date of admission, the primary and secondary diagnoses coded according to the *International Classification of Disease, Ninth Revision* [ICD-9] before 2006 or the *International Classification of Disease, Tenth Revision* [ICD-10] since 2006, duration of hospital stay, and treatments received during hospitalization) and covers all residents of Quebec. The RAMQ database contains data on medical services (eg, the type of medical care received; date of medical service; site [outpatient clinic, emergency department, or inpatient clinic]; ICD-9 diagnosis codes; and the treating physician's specialty) provided to all residents of Quebec as well as data on prescription medications (eg, the date of filling; name, dose, dosage form, quantity, and duration of the prescription; new or refill prescriptions; and encrypted identification and the prescribing physician's specialty) dispensed in community pharmacies for residents covered by RAMQ's Public Drug Insurance Plan (about 43% of the residents of Quebec). The prescription data and the medical diagnosis for asthma recorded in the RAMQ database have been evaluated and were deemed to be highly reliable. The accuracy of the data was 69.1% for the quantity and 72.1% for the duration of prescriptions, although not specific to asthma, and the positive predictive value and the negative predictive value of the diagnosis of asthma recorded in the RAMQ database were found to be 0.67 to 0.75 and 0.96 to 0.99, respectively, whether they were made by family or respiratory physicians.^{30,31}

The QAPD includes all women who delivered between January 1990 and March 2010, and who had at least 1 asthma diagnosis recorded in the RAMQ database or the MED-ECHO database up to 2 years before 1 or more of their deliveries, plus a 4 times greater random sample of women without asthma diagnosis 2 years before any of their deliveries and who delivered in the same period of time as the women with asthma diagnosis. We retrospectively determined the date of the first day of the last menstrual period and the date of delivery for each pregnancy using the date of birth of the offspring and the gestational age at birth that was recorded in the MED-ECHO database. The algorithms used to determine these dates were previously evaluated and were highly valid.³² We had access to data related to the hospitalizations and medical services dispensed between January 1988 and March 2010 for all the pregnant women and their infants. The QAPD was previously used to study the associations between asthma, asthma medications, and maternal or infant outcomes.³³⁻³⁵

This study was approved by the Ethics Committee of the Hôpital du Sacré-Coeur de Montréal. The Commission d'Accès à

l'Information du Quebec authorized the linkage of data from the MED-ECHO and RAMQ databases.

STROBE statement was followed throughout.

Study design and study population

We conducted a retrospective population-based cohort study based on a cohort of women selected from the QAPD. We defined the cohort entry date as the first day of week 20 of gestation (134 days after the last menstrual period) because pregnancies that terminated before week 20 were not included in the database. The cohort inclusion criteria were as follows: (1) a pregnancy with a recorded singleton delivery between January 1, 1998, and March 31, 2010, that was recorded in the MED-ECHO database; (2) gestation period of 20 to 45 weeks; (3) maternal age of 15 to 45 years at cohort entry; (4) coverage by RAMQ's Public Drug Insurance Plan from at least 1 year before cohort entry until delivery; and (5) maternal asthma during pregnancy. Using a previously validated definition, asthma was defined as at least 1 asthma diagnosis (*ICD-9* code 493, except 493.2, or *ICD-10* code J45) recorded during a hospitalization, or at least 2 medical claims with an asthma diagnosis within 2 consecutive years between 1988 and cohort entry.³⁶ In addition, the women were to have at least 1 medical claim for asthma recorded in the RAMQ database or the MED-ECHO database within the 2 years preceding cohort entry to consider that asthma was present during pregnancy.

The exclusion criteria were as follows: (1) a previous delivery in the 6 months before the beginning of the pregnancy under study; (2) documented chronic hypertension (based on relevant diagnoses or filled prescriptions) less than 1 year before cohort entry; (3) diagnosis of gestational hypertension, preeclampsia, or eclampsia between the beginning of pregnancy and cohort entry; (4) diagnosis of kidney disease, cystic fibrosis, polycystic ovarian syndrome, antiphospholipid syndrome, or systemic lupus erythematosus less than 1 year before cohort entry; (5) filled prescription for a disease-modifying antirheumatic drug less than 1 year before cohort entry; (6) filled prescription for rarely prescribed antiasthmatic drugs during pregnancy (oxtriphylline, aminophylline, theophylline, montelukast, zafirlukast, nedocromil, cromoglycate, or ketotifen); and (7) filled prescription for a LABA but not an ICS during pregnancy, because a LABA should not be used without an ICS in pregnancy. The criteria 4 to 6 were excluded because these conditions were rare in the cohort and could not be adjusted for in the regression model. The list of diagnosis codes and medications used for the exclusion criteria is available upon request. A woman could contribute multiple pregnancies in the cohort.

Outcomes

The primary outcome was HDP, which included gestational hypertension, preeclampsia, or eclampsia. The secondary outcome was preeclampsia or eclampsia (hereafter preeclampsia/eclampsia). In clinical practice, *gestational hypertension* was defined as hypertension (systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg) that develops for the first time at gestational week 20 or later.³⁷ *Preeclampsia* was defined as gestational hypertension with 1 or more of the following: new proteinuria, or at least 1 adverse condition, or at least 1 severe complication.³⁷ *Eclampsia* is a severe form of preeclampsia characterized by convulsions.

For this study, gestational hypertension was operationally defined as either (1) a diagnosis of gestational or chronic hypertension (*ICD-9* codes 642.3, 642.9, or 401-405 or *ICD-10* codes O13 or O16) on or after cohort entry, or (2) a prescription for an

antihypertensive medication recommended during pregnancy (amlodipine, hydralazine, labetalol, methyldopa, metoprolol, nifedipine, oxprenolol, or pindolol) that was filled on or after cohort entry, without a prescription filled before this time. Of note, only 16 women (cases) had a prescription for an antihypertensive medication without having a hypertension diagnosis and only 1 woman had a prescription for an antihypertensive medication outside this list and was therefore not identified as a case. Preeclampsia and eclampsia were defined as a diagnosis of preeclampsia (*ICD-9* codes 642.4, 642.5, or 642.7 or *ICD-10* codes O11 or O14) or eclampsia (*ICD-9* code 642.6 or *ICD-10* code O15) recorded in the RAMQ database or the MED-ECHO database after cohort entry.

Exposure

The exposure of interest was the use of a LABA (salmeterol and formoterol), and was evaluated as a dichotomous variable (yes/no). Exposure to a LABA was first measured at cohort entry, and was based on the mean daily dose calculated in the previous 30 days. We also considered exposure to a LABA as a dichotomous time-dependent variable (yes/no) by measuring the occurrence of LABA prescriptions within the 30 days before the date on which HDP or preeclampsia/eclampsia was identified (by prescription or diagnosis) for the cases and on the corresponding date for the matched control.

Potential confounders

After conducting a literature search, we identified the reported risk factors for HDP and preeclampsia/eclampsia and we considered them as potential confounders of the relationship between exposure to a LABA and the occurrence of HDP. We classified these variables into 4 categories.

Maternal sociodemographic variables included the age of the mother at cohort entry, the socioeconomic status of the mother based on the receipt of last-resort financial assistance up to 1 year before cohort entry, and the area of residence (rural or urban) at cohort entry.

Pregnancy-related variables included a proxy of parity (delivery in the 10 years preceding the current pregnancy) and the season of birth (winter, spring, summer, and autumn).

Maternal health variables included a diagnosis of urinary tract infections (yes/no) between the beginning of pregnancy and cohort entry, a diagnosis of infertility (yes/no), a diagnosis of depression/anxiety or a filled prescription for an antidepressant/anxiolytic medication (yes/no), a diagnosis of migraine (yes/no), a diagnosis of cardiac disease or a filled prescription for a cardiac disease-related medication (yes/no), a diagnosis of diabetes mellitus or a prescription filled for an antidiabetic medication (yes/no) up to 1 year before cohort entry, as well as the history of gestational diabetes and history of HDP (yes/no) up to 10 years before the index pregnancy based on the specific diagnostic codes.

Asthma-related variables included asthma severity (mild, moderate, or severe, as defined by Firoozi et al,³⁸ based on ICS daily doses, use of other controller therapy, SABA weekly use, and markers of exacerbations [an emergency department visit for asthma, a hospital admission for asthma, or a filled prescription of an oral corticosteroid]) and 1 or more visit to a respiratory physician (yes/no) up to 1 year before cohort entry and recognized markers of uncontrolled asthma, namely, 1 or more hospitalization or emergency department visit for asthma (yes/no), SABA use (<4 or ≥4 doses/wk assessed by an algorithm developed by our team and based on filled prescriptions and dose equivalences³⁹), and filling a prescription for a short-course (≤10 days) of oral corticosteroids between the beginning of pregnancy and cohort entry.

TABLE I. Pregnancy characteristics for the entire cohort and according to LABA use at cohort entry date*

Characteristic	Entire cohort	LABA use on the cohort entry date*	
		No	Yes
No. of pregnancies	8,936	8,279	657
Age (y) at cohort entry			
Mean $\pm$ SD	26.2 $\pm$ 5.4	26.0 $\pm$ 5.7	27.0 $\pm$ 5.6
15-<18	343 (3.8)	331 (4.0)	12 (1.8)
18-<35	7,788 (87.2)	7,215 (87.2)	573 (87.2)
35-45	805 (9.0)	733 (8.8)	72 (11.0)
Gestational age at delivery (wk), mean $\pm$ SD	38.6 $\pm$ 2.1	38.6 $\pm$ 2.2	38.6 $\pm$ 2.0
Rural area of residence at cohort entry	1,691 (18.9)	1,570 (19.0)	121 (18.4)
Season of birth			
Winter	2,235 (25.0)	2,072 (25.0)	163 (24.8)
Spring	2,144 (24.0)	1,980 (23.9)	164 (25.0)
Summer	2,345 (26.2)	2,147 (26.0)	198 (30.1)
Autumn	2,212 (24.7)	2,080 (25.1)	132 (20.1)
Delivery up to 10 y before the current pregnancy	1,459 (16.3)	1,309 (15.8)	150 (22.8)
Up to 1 y before cohort entry			
Receipt of last-resort financial assistance	4,393 (49.2)	4,080 (49.3)	313 (47.6)
≥ 1 diagnosis or 1 filled prescription for cardiac disease	687 (7.7)	633 (7.6)	54 (8.2)
≥ 1 diagnosis or 1 filled prescription for diabetes mellitus	297 (3.3)	268 (3.2)	29 (4.4)
≥ 1 diagnosis of infertility	389 (4.3)	359 (4.3)	30 (4.6)
≥ 1 diagnosis of migraine	319 (3.6)	301 (3.6)	18 (2.7)
≥ 1 diagnosis of depression/anxiety	1,366 (15.3)	1,266 (15.3)	100 (15.2)
Asthma severity			
Mild	7,847 (87.8)	7,441 (89.9)	406 (61.8)
Moderate	943 (10.6)	720 (8.7)	223 (33.9)
Severe	146 (1.6)	118 (1.4)	28 (4.3)
≥ 1 visit to a respiratory physician	928 (10.4)	758 (9.2)	170 (25.9)
Between the beginning of pregnancy and cohort entry			
≥ 1 diagnosis for urinary infections	409 (4.6)	378 (4.6)	31 (4.7)
≥ 1 ED visit or hospitalization for asthma	810 (9.1)	713 (8.6)	97 (14.8)
≥ 1 short-course prescription of oral corticosteroids	493 (5.5)	415 (5.0)	78 (11.9)
SABA doses/wk			
<4	6,673 (73.6)	6,209 (75.0)	364 (55.4)
≥ 4	2,363 (26.4)	2,070 (25.0)	293 (44.6)
Diagnoses within 10 y of the current pregnancy			
Gestational diabetes	115 (1.3)	103 (1.2)	12 (1.8)
HDP	67 (0.7)	55 (0.7)	12 (1.8)

ED, Emergency department.

Results are presented as n (%) or mean $\pm$ SD.

*The cohort entry date is defined as the first day of week 20 of pregnancy.

Statistical analyses

We calculated descriptive statistics to describe the characteristics of the pregnancies as a function of exposure to a LABA recorded at cohort entry. We also estimated the proportions of women in the entire cohort who were diagnosed with HDP or preeclampsia/eclampsia according to exposure to a LABA at cohort entry.

Crude hazard ratios (HRs), adjusted hazard ratios (aHRs) for all potential confounders listed previously, and 95% CIs were estimated for HDP and preeclampsia/eclampsia according to the exposure to a LABA at cohort entry using Cox proportional hazard regression model with clustered data analysis⁴⁰ because some women contributed more than 1 pregnancy to the analysis. We also used the Cox regression model to analyze the association between time-dependent exposure to LABA after cohort entry and the 2 outcomes of interest. Finally, we performed Cox regression analysis stratified by exposure

to a SABA between the beginning of pregnancy and cohort entry because these drugs were reported to be associated with a reduced risk of HDP.²⁷

All analyses were performed using SAS v9.3 software (SAS Institute, Cary, NC).

RESULTS

After applying the inclusion and exclusion criteria, the cohort comprised 8936 pregnancies in 7853 women who had asthma during pregnancy. Overall, 952 women (12.1%) contributed 2 to 6 pregnancies to the analysis. A LABA was used in 657 pregnancies (7.4%) at cohort entry and in 811 (9.1%), 795 (8.9%), and 768 pregnancies (8.6%), in the first, second, and third trimester, respectively.

TABLE II. Proportion of women with HDP and preeclampsia/eclampsia in the entire cohort and according to LABA use at cohort entry date*

Outcome	No. of pregnancies	No. of cases (%)
HDP		
Entire cohort	8,936	567 (6.3)
According to LABA use at cohort entry*		
Yes	657	41 (6.2)
No	8,279	526 (6.3)
Preeclampsia/eclampsia		
Entire cohort	8,936	256 (2.9)
According to LABA use at cohort entry*		
Yes	657	16 (2.4)
No	8,279	240 (2.9)

*The cohort entry date was defined as the first day of week 20 of pregnancy.

TABLE III. Associations between LABA use at cohort entry date* and HDP or preeclampsia/eclampsia

Outcome	Crude HR	aHR
HDP		
LABA use at cohort entry* (vs no)	0.99 (0.72-1.36)	0.96 (0.69-1.33)
Preeclampsia/eclampsia		
LABA use at cohort entry* (vs no)	0.85 (0.51-1.41)	0.89 (0.53-1.50)

ED, Emergency department.

Values in parentheses are 95% CIs.

The association was adjusted for potential confounders: age at CE (categorized 15-18, 18-34, 34-45 y), rural area of residence at CE (yes/no), season of birth (winter, spring, summer, autumn) delivery up to 10 y before the current pregnancy (yes/no), events up to 1 y before CE (yes/no: receipt of last-resort financial assistance, ≥ 1 diagnosis or 1 filled prescription for cardiac disease, ≥ 1 diagnosis or 1 filled prescription for diabetes mellitus, ≥ 1 diagnosis of infertility, ≥ 1 diagnosis of migraine, ≥ 1 diagnosis of depression/anxiety), asthma severity (mild, moderate, or severe), events between the beginning of pregnancy and cohort entry, and diagnoses (yes/no: ≥ 1 diagnosis of urinary infections, ≥ 1 ED visit or hospitalization for asthma, ≥ 1 short-course prescription of oral corticosteroids, ≥ 4 SABA doses/wk vs < 4 doses/wk) and events up to 10 y before the current pregnancy (gestational diabetes yes/no, HDP [vs no]).

*The cohort entry (CE) date was defined as the first day of week 20 of pregnancy.

The characteristics of the pregnancies included in the cohort according to exposure to a LABA at cohort entry are presented in Table I. The mean age of the mothers was 26 years and the mean gestational age at delivery was 38.6 weeks. Most women lived in an urban area and 49% received last-resort financial assistance. Depression/anxiety, cardiac disease, and diabetes mellitus were recorded in 15%, 7.7%, and 3.3% of women, respectively, up to 1 year before cohort entry. Most of the women in the cohort had mild asthma. Women exposed to a LABA were more likely than unexposed women to have a history of HDP. Exposed women were also more likely to have severe asthma and to have visited a respiratory physician up to 1 year before cohort entry. Moreover, exposed women were more likely to be hospitalized or to visit an emergency department for asthma, to use oral corticosteroids, and to use high doses of SABA between the beginning of pregnancy and cohort entry.

As presented in Table II, there were 567 (6.3%) cases of HDP and 256 (2.9%) cases of preeclampsia/eclampsia in the entire cohort. The rates of these outcomes were similar between women exposed to a LABA and unexposed women.

TABLE IV. Associations between LABA use and HDP or preeclampsia/eclampsia in the entire cohort and in women stratified by SABA use between the beginning of pregnancy and cohort entry date*

Exposure	HDP	Preeclampsia/eclampsia
Entire cohort (n = 8,936)		
LABA use at cohort entry* (vs no)	0.96 (0.69-1.33)	0.89 (0.53-1.50)
LABA time-dependent use† (yes vs no)	1.02 (0.74-1.41)	0.95 (0.57-1.58)
SABA not used between the beginning of pregnancy and cohort entry (n = 3,777)		
LABA use at cohort entry (vs no)	1.06 (0.57-1.97)	0.89 (0.31-2.61)
LABA time-dependent use† (yes vs no)	1.24 (0.68-2.26)	1.29 (0.49-3.40)
SABA used between the beginning of pregnancy and cohort entry (n = 5,159)		
LABA use at cohort entry (vs no)	0.96 (0.65-1.40)	0.89 (0.49-1.62)
LABA time-dependent use† (yes vs no)	0.99 (0.68-1.43)	0.85 (0.47-1.55)

HRs (95% CI) were adjusted for the following variables: rural area of residence at cohort entry, season of birth, and delivery up to 10 y before the current pregnancy; up to 1 y before cohort entry—receipt of last-resort financial assistance, cardiac disease, diabetes mellitus, infertility, migraine, depression/anxiety, asthma severity, and visits to a respiratory physician; between the beginning of pregnancy and cohort entry—urinary infections, ED visits or hospitalizations for asthma, short-course prescription for an oral corticosteroid, and weekly SABA use; up to 10 y before the current pregnancy—histories of gestational diabetes mellitus or gestational hypertension.

*The cohort entry date was defined as the first day of week 20 of pregnancy.

†The time-dependent exposure was assessed within the 30 days before the date on which HDP or preeclampsia/eclampsia was identified (by prescription or diagnosis) for the cases and on the corresponding date for the matched control.

Table III presents the crude HRs and aHRs for the association between LABA exposure and the outcomes of interest. LABA use on the cohort entry date was not associated with increased risks of HDP (aHR, 0.96; 95% CI, 0.69-1.33) or preeclampsia/eclampsia (aHR, 0.89; 95% CI, 0.53-1.50). When we analyzed LABA use as a time-dependent exposure (Table IV), we also observed no association with HDP (aHR, 1.02; 95% CI, 0.74-1.41) and preeclampsia/eclampsia (aHR, 0.95; 95% CI, 0.57-1.58). In addition, we found no significant associations when the analysis was stratified by the use of a SABA. As expected, nulliparity, diabetes mellitus, history of gestational diabetes, and history of HDP were significant risk factors for HDP and preeclampsia/eclampsia.

DISCUSSION

Our findings suggest that the risks of HDP or preeclampsia/eclampsia are not increased in women with asthma who reach week 20 of gestation and who use a LABA in the second or third trimester.

In our literature searches, we found only 1 study that specifically investigated the association between LABA use during pregnancy and the risk of preeclampsia. The Källén study, which was based on Swedish births and prescribed drugs registers in the

period 2009 to 2011, identified 10,553 pregnant women who had filled prescriptions for antiasthmatic medications during the second and third trimesters. The authors reported that the risk of preeclampsia was significantly increased among women exposed to a LABA after the first trimester of pregnancy (odds ratio, 1.28; 95% CI, 1.12-1.38), compared with all other women who gave birth, after controlling for year of delivery, maternal age, parity, smoking in early pregnancy, and pre-pregnancy body mass index.²⁹ This adjusted odds ratio should, however, be interpreted cautiously because women using antiasthmatic drugs were compared with a general population of pregnant women, which prevented the authors from distinguishing the impact of antiasthmatic medications from that of asthma. In fact, including women without asthma in the reference group could overestimate the impact of the antiasthma medications. Unlike the Swedish study, we restricted the cohort to women with asthma, and we found no significant association between exposure to a LABA and HDP or preeclampsia/eclampsia after adjusting for the independent effects of several potential confounders.

It is noteworthy that although we included a large number of pregnancies in women with asthma, only 7% of women were exposed to a LABA on the cohort entry date. Moreover, only 23% of 1089 pregnancies in women with moderate-to-severe asthma (ie, those who might most need these drugs) were exposed to a LABA at this time. This could reflect a cessation of these medications after learning about the pregnancy because women are worried about the potential harm that antiasthma medications could have on the fetus, resulting in reluctance to using LABAs during pregnancy. Nevertheless, there is strong evidence that poor control of asthma during pregnancy and resulting asthma exacerbations is more harmful to the mother and the fetus than the medications used to treat asthma.³⁵

Our study showed that some maternal characteristics were associated with the risk of HDP (see Table E1 in Appendix I in this article's Online Repository at www.jaci-inpractice.org). As expected, we found that nulliparity was strongly associated with HDP or preeclampsia/eclampsia. We also found that diabetes mellitus and a history of gestational diabetes were strongly associated with HDP or preeclampsia/eclampsia. Moreover, we found a very strong association between the history of HDP and HDP or preeclampsia/eclampsia.

There are several advantages of using administrative databases in this study, namely, the possibility to analyze a large number of pregnant women with asthma who developed HDP, the avoidance of recall bias due to prospective recording of prescriptions and diagnoses independently of the outcome, and the ability to account for several potential confounding variables, such as maternal chronic conditions as well as objective and validated markers of asthma severity and control. In addition, the definitions of asthma and pregnancy-related variables such as the duration of gestation that were used in this study were formally validated and were highly valid. Another strength of this study is that we have set the cohort entry date at the first day of week 20 of gestation to avoid collider bias. Indeed, pregnancies terminating before week 20 are not included in the QAPD because this database includes only those pregnancies that ended with a delivery in a hospital, which are of 20 weeks of gestation or more by definition (pregnancies that terminate before week 20 are considered as abortions in the province of Quebec). If there is an unmeasured variable (eg, obesity) associated with both pregnancy termination and HDP, LABA exposure before week 20 is associated with pregnancy

termination before week 20, and LABA is measured before week 20, the association between LABA and HDP could have been biased by the unmeasured variable, that is, the collider. A collider bias⁴¹ would occur in this case because the analysis is restricted to pregnancies with 20 weeks of gestation or more (for more information, please refer to Appendix II and Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

There are also some limitations that should be considered when interpreting the results. First, the use of medications is based on filled prescriptions, not their actual use, which could cause a nondifferential information bias, underestimating the association between LABA exposure and HDP or preeclampsia/eclampsia.⁴² Second, our definition of HDP has not been formally validated, so we possibly underestimated the associations owing to nondifferential misclassification of the outcome. Nevertheless, the prevalence of HDP in our cohort is consistent with the previously reported prevalence,⁴ supporting the validity of our outcome definition. Third, some risk factors for HDP such as body mass index, smoking habits, and ethnicity are not recorded in the administrative databases and not adjusting for these variables might have led to residual confounding if they are also associated with the use of a LABA. This possible bias can overestimate or underestimate the associations under study because it depends on the strength and direction of the association between the potential confounder and the exposure and outcome. Fourth, the indication for antiasthmatic medications may introduce residual confounding because LABAs are more likely to be prescribed in addition to ICSs to patients with severe or difficult-to-control asthma. If present, such bias could overestimate the impact of LABA use on HDP. However, despite this possible bias, we did not observe an increased risk of HDP among women exposed to a LABA, providing evidence of the safety of these medications. Finally, women with a low socioeconomic status are over-represented in our study cohort because the RAMQ database is limited to residents of Quebec with public drug insurance, limiting the generalizability of our results.

In summary, these new findings on exposure to a LABA during pregnancy are reassuring because our results suggest that their use does not increase the risk of HDP or preeclampsia/eclampsia in women with asthma who reach week 20 of gestation. Women treated with LABA added to ICSs and their physicians could be tempted to step down the therapy after learning about the pregnancy because of concerns about the use of LABA. However, our findings provide additional data on the safety of this association. Therefore, these results should encourage women to continue using their prescribed medications to control their asthma symptoms once they know that they are pregnant, as recommended by the current asthma guidelines. This approach should help reduce the risk of complications of uncontrolled asthma in the mother or the infant.³⁵

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APPENDIX I

TABLE E1. Associations between LABA use at cohort entry date* and HDP or preeclampsia/eclampsia

Exposure and potential confounders	HDP		Preeclampsia/eclampsia	
	Crude HR	aHR	Crude HR	aHR
LABA use at cohort entry* (vs no)	0.99 (0.72-1.36)	0.96 (0.69-1.33)	0.85 (0.51-1.41)	0.89 (0.53-1.50)
Age at cohort entry (y) (vs 18-34)				
15-18	0.91 (0.59-1.41)	0.90 (0.58-1.40)	0.96 (0.51-1.81)	0.91 (0.48-1.73)
34-45	1.31 (0.99-1.72)	1.25 (0.94-1.65)	1.23 (0.82-1.85)	1.16 (0.76-1.76)
Rural area of residence at cohort entry (vs urban)	0.97 (0.78-1.20)	0.96 (0.78-1.19)	0.72 (0.50-1.02)	0.73 (0.51-1.05)
Season of birth (vs winter)				
Spring	0.98 (0.78-1.24)	1.00 (0.79-1.26)	1.21 (0.86-1.70)	1.21 (0.86-1.71)
Summer	1.00 (0.80-1.25)	1.01 (0.81-1.26)	1.12 (0.80-1.58)	1.13 (0.80-1.60)
Autumn	0.89 (0.71-1.13)	0.89 (0.70-1.12)	0.86 (0.59-1.24)	0.84 (0.58-1.22)
Delivery up to 10 y before the current pregnancy (vs no)	0.63 (0.48-0.82)	0.43 (0.31-0.61)	0.46 (0.29-0.72)	0.35 (0.20-0.61)
Events up to 1 y before cohort entry				
Receipt of last-resort financial assistance	1.01 (0.86-1.20)	1.01 (0.86-1.20)	1.03 (0.81-1.32)	1.02 (0.79-1.31)
≥1 diagnosis or 1 filled prescription for cardiac disease	1.28 (0.96-1.70)	1.20 (0.89-1.60)	0.98 (0.61-1.58)	0.90 (0.55-1.46)
≥1 diagnosis or 1 filled prescription for diabetes mellitus	2.69 (1.91-3.78)	2.19 (1.47-3.27)	2.67 (1.63-4.39)	2.56 (1.44-4.54)
≥1 diagnosis of infertility	1.49 (1.05-2.11)	1.33 (0.94-1.9)	1.15 (0.65-2.06)	1.02 (0.57-1.84)
≥1 diagnosis of migraine	0.79 (0.47-1.32)	0.74 (0.45-1.23)	0.35 (0.11-1.08)	0.32 (0.10-1.02)
≥1 diagnosis of depression/anxiety	1.04 (0.82-1.31)	0.98 (0.77-1.24)	1.39 (1.02-1.90)	1.35 (0.98-1.86)
Asthma severity				
Moderate (vs mild)	1.20 (0.93-1.54)	1.26 (0.93-1.71)	0.76 (0.49-1.19)	0.79 (0.47-1.34)
Severe (vs mild)	1.10 (0.60-2.02)	1.20 (0.63-2.25)	1.16 (0.48-2.78)	1.25 (0.50-3.12)
≥1 visit to a respiratory physician	0.85 (0.64-1.13)	0.76 (0.57-1.02)	0.89 (0.59-1.36)	0.85 (0.56-1.30)
Between the beginning of pregnancy and cohort entry				
≥1 diagnosis of urinary infections	1.14 (0.79-1.66)	1.11 (0.76-1.62)	1.13 (0.65-1.98)	1.10 (0.63-1.93)
≥1 ED visit or hospitalization for asthma	1.10 (0.83-1.45)	1.03 (0.75-1.42)	0.94 (0.61-1.46)	0.90 (0.57-1.43)
≥1 short-course prescription of oral corticosteroids	1.24 (0.90-1.72)	1.13 (0.75-1.71)	1.07 (0.64-1.81)	1.19 (0.66-2.16)
≥4 SABA doses/wk (vs < 4 doses/wk)	0.96 (0.79-1.16)	0.87 (0.70-1.08)	0.89 (0.67-1.19)	0.93 (0.67-1.29)
Diagnoses up to 10 y before the current pregnancy				
Gestational diabetes (vs no)	2.38 (1.35-4.21)	2.11 (1.07-4.17)	1.50 (0.56-4.06)	1.84 (0.60-5.69)
HDP (vs no)	4.63 (2.63-8.15)	7.15 (3.82-13.36)	2.74 (1.01-7.43)	5.52 (1.94-15.65)

ED, Emergency department.

Values in parentheses are 95% CIs.

*The cohort entry date was defined as the first day of week 20 of pregnancy. This association was all potential confounders presented in this table.

APPENDIX II. COLLIDER BIAS

A collider is a variable that is the result of 2 different causal pathways. When one of the variables causing the collider is the exposure of interest and the other one is an unmeasured variable that is associated with the outcome of interest, restricting the analysis to one category of the collider will induce a false association between the exposure and the outcome. This will lead to a biased estimate of the association between the exposure and outcome of interest: the collider bias.^{E1}

The QAPD includes only those pregnancies that were terminated by a delivery in a hospital in the province of Quebec, and by definition a delivery is a pregnancy that terminated on or after the 20th week of gestation. Consequently, all pregnancies that terminated before week 20 were not included in the QAPD. LABA exposure before week 20 could be associated with early pregnancy termination (arrow 1 in Figure E1). In addition, there could be an unmeasured confounder that is associated with early pregnancy termination (arrow 2) and HDP (arrow 3). If these associations are present, the variable termination of pregnancy (<20 weeks vs ≥20 weeks) would be a collider. The available database restricts the analysis only to those pregnancies that reached the 20th week of gestation (Figure E1, B), and this could create a false association between LABA exposure before week 20 and the unmeasured confounder (arrow 4). This would lead to a biased estimate of the association between LABA exposure and HDP. The magnitude and direction of the collider bias will depend on the strength and the direction of the associations between the unmeasured confounder and the variable pregnancy termination (collider) and HDP. For example, if obesity is associated with a higher risk of early pregnancy termination and HDP, the exclusion of pregnancies that terminated before week 20 would create a false association between obesity and LABA use before week 20: women exposed to LABA before week 20 who delivered after week 20 will be less likely to be obese. This will bias the association between LABA and HDP toward the null.

To avoid this collider bias, we changed the objective of the study as to specifically evaluate the association between

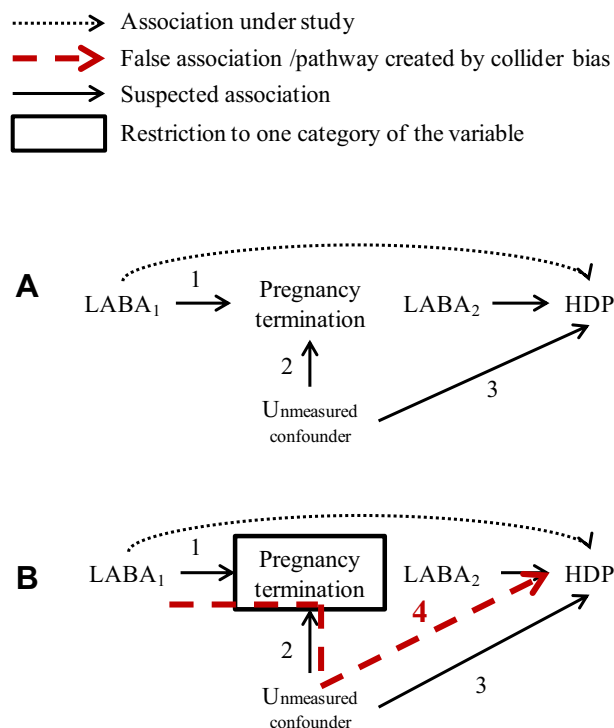


FIGURE E1. Directed acyclic graph (DAG) of the association between exposure to LABA and HDP. **A**, Initial DAG. **B**, DAG showing the biased association when restricting to one category of the collider (ie, pregnancy termination). *LABA₁*, Exposure to LABAs before 20 weeks of gestation; *LABA₂*, LABA exposure on week 20 and up to delivery.

LABA exposure starting from week 20 of gestation and HDP.

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