

# Long-Acting $\beta_2$ -Agonists and Risk of Hypertensive Disorders of Pregnancy: A Cohort Study



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**What is already known about this topic?** Long-acting  $\beta_2$ -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  $\beta_2$ -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.<sup>1,2</sup> 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.<sup>3</sup> 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 $\beta_2$ -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 $\beta_2$ -agonist

They are frequent complications that affect 6% to 10% of pregnancies.<sup>4</sup> 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.<sup>5-7</sup>

Maternal asthma and HDP were found to be associated in several studies.<sup>2,8-17</sup> Most of these studies have reported significantly increased risk of HDP, with relative risk estimates ranging from 1.15 to 2.21.<sup>2,9-11,13,15-17</sup> 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.<sup>18</sup> 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.<sup>19-21</sup> 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  $\beta_2$ -agonists (SABAs) during pregnancy was also investigated,<sup>14,22-27</sup> and the results of an earlier study by our group showed that exposure to a SABA was associated with a reduced risk of HDP.<sup>27</sup> 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  $\beta_2$ -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%).<sup>28</sup> 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.<sup>29</sup> 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.<sup>30,31</sup>

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.<sup>32</sup> 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.<sup>33-35</sup>

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

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