Methods

Data Source

The Régie de l'assurance-maladie du Québec (RAMQ) database provides information on medical services dispensed to all residents of Quebec and prescribed medications filled in community pharmacies for 3.3 million (about 42%) residents of the province insured by the RAMQ drug-insurance plan.[1] The other database—Maintenance et Exploitation des données pour l'étude de la clientèle hospitalière (MED-ECHO)—contains information on all hospitalizations in the province. Data recorded in the RAMQ prescription-medication database have been formally evaluated and found to be comprehensive and valid[2], as were some medical diagnoses recorded in the MED-ECHO database[3] and the medical diagnoses for asthma recorded in the RAMQ medical-services database.[4] These databases have been often used in the past for epidemiologic research in the field of asthma.[5-9]

Using gestational age at birth and offspring date of birth, we retrospectively identified the date of the first day of the last menstrual period and the date of delivery for each pregnancy. For each pregnancy included in the cohort, we obtained data on all prescriptions filled by the mother from the RAMQ in the year preceding and during pregnancy; date of filling, name, dose, dosage form, quantity, and duration of the prescription; and encrypted identification and specialty of the prescribing physician. We also obtained data from the RAMQ on all inpatient and ambulatory medical services dispensed to the mother, nature of the medical act, date, site of medical practice (outpatient clinic, emergency department [ED], hospitalization), diagnosis code,

encrypted identification, and specialty of the treating physician. The RAMQ also provided the date of birth, periods of social-assistance coverage, and area of residence (by period) of the mothers during follow-up. MED-ECHO provided data on all maternal acute-care hospitalizations occurring in the year preceding and during pregnancy, including principal diagnosis, secondary diagnoses, date of admission, and length of hospitalization, in addition to the length of gestation and birth weight from the delivery hospitalization. Pregnancy-related variables such as birth weight, gestational age, and date of delivery—recorded directly in the RAMQ and MED-ECHO databases and based on our own algorithms—were formally evaluated and deemed to be highly valid.[10]

Potential Confounding Variables

Twenty risk factors of LBW, PB and SGA identified in the literature were considered as potential confounding variables and divided into four categories. *Maternal characteristics*, which include age at beginning of pregnancy (<18, 18–34, >34 years), receiving social assistance benefits in the year before or during pregnancy (yes/no), and urban residency at delivery (yes/no). *Maternal comorbidities*, which include diabetes mellitus (yes/no), chronic hypertension (yes/no), epilepsy (yes/no), cystic fibrosis of the pancreas (yes/no), cyanotic congenital heart disease (yes/no), collagen vascular diseases (yes/no), antiphospholipid syndrome (yes/no). *Pregnancy-related variables*, which include gestational diabetes (yes/no), pregnancy-induced hypertension (yes/ no), eclampsia/preeclampsia (yes/no), infections during pregnancy (urinary-genital infections, malaria, trypanosomiasis, cytomegalovirus, toxoplasmosis, rubella, herpes virus: yes, if at least one condition is present; no, otherwise), use of beta-blockers

during pregnancy (yes/no), anemia (yes/no), vaginal bleeding (yes/no), uterine defects (yes/no), placental conditions (single umbilical artery, velamentous umbilical cord insertion, bilobate placenta, suboptimal implantation site, placenta previa, placental anomalies, and cord anomalies: yes, if at least one condition present; no, otherwise), placenta abruption (yes/no). *Asthma related variables*, which includes the severity of asthma in the year before conception measured with an algorithm that we developed and validated, and that categorizes asthma on three levels: mild, moderate, or severe.[11] This algorithm is based on the daily ICS dose used and the use of add-on therapy (long-acting B_2-agonists (LABAs), leukotriene-receptor antagonists (LTRAs), or theophylline) over a one year period. In terms of other asthma medications, we assessed, during pregnancy, average use of short-acting B_2-agonists (SABAs) (0, >0–3, >3 doses per week), use of LTRAs (yes/no), use of oral corticosteroids (yes/no), and use of intranasal corticosteroids (yes/no). Weekly SABA use was measured with an algorithm that we developed and used in past studies.[12, 13] We also assessed whether the women had a hospitalization (yes/no) or an ED visit for asthma (yes/no) during pregnancy. The following variables were finally not considered as potential confounders because their prevalence within our cohort was too small (less than five exposed cases) or all exposed pregnancies were cases: hemoglobinopathy, collagen vascular diseases and use of warfarin during pregnancy for all three outcomes, cyanotic congenital heart disease for LBW and SGA, and fetal–maternal hemorrhage for SGA. Other determinants of the outcomes, such as maternal weight, parity, illicit-drug consumption, and maternal nutrition, were not available in the databases. A detailed description of the

algorithms and of the ICD-9 and ICD-10 codes used for each condition is available upon request.

Statistical Analysis

The generalized-estimation-equation (GEE) models used can estimate the effect of independent variables—including the main exposures and confounding variables—on several types of outcomes, namely dichotomous outcomes such as the presence or the absence of SGA, LBW, or preterm delivery with a logit function as well as take into account the fact that a woman could contribute more than one pregnancy to the analysis by estimating the correlation between consecutive pregnancies.[14] The reduced models were obtained by a backward selection strategy that started with ICS doses, LABA use, and all potential confounding variables and kept in the model ICS doses, LABA use, and variables that were found to act as confounders (a change of at least 10% in at least one OR associated with ICSs or LABAs after the variable was removed from the model) or those that were significantly associated with the outcome (p value <.05).[15]

Results

Sensitivity Analysis for LABA Exposure by Trimester

As reported in Table E1, a secondary analysis looking at number (1, 2, or 3) of trimesters exposed to LABA showed inconclusive results.

Table E1. Adjusted ORs of LBW, PB, and SGA according to the daily ICS* dose and categories of LABA use

	LBW	PB	SGA
		OR (95% CI)	
Daily ICS dose (µg/day)			
None	Reference	Reference	Reference
0–62.5	0.74 (0.58–0.94)	0.77 (0.61–0.96)	0.90 (0.75–1.08)
>62.5–125	1.09 (0.86–1.40)	1.08 (0.86–1.35)	1.14 (0.95–1.38)
>125–250	1.27 (0.93–1.72)	1.22 (0.91–1.65)	1.13 (0.88–1.45)
>250–500	1.29 (0.91–1.85)	1.29 (0.91–1.83)	1.33 (0.96–1.84)
>500	1,76 (0.99–3.13)	1.48 (0.77–2.86)	1.63 (1.01–2.65)
LABA			
None	Reference	Reference	Reference
One trimester	0.72 (0.43–1.21)	0.76 (0.48–1.21)	1.25 (0.89–1.77)
Two trimesters	0.98 (0.57–1.69)	1.06 (0.65–1.73)	0.74 (0.46–1.21)
Three trimesters	0.73 (0.43–1.24)	0.78 (0.46–1.32)	0.69 (0.45–1.05)

ICS, inhaled corticosteroid; LABA, long-acting B_2-agonist; LBW, low birth weight; OR, odds ratio; PB, preterm birth; SGA, small for gestational age; 95% CI, 95% confidence interval

*(fluticasone equivalent, µg/d)

For LBW and PB, a trend for a protective effect (OR: 0.72 to 0.78) was seen for LABA exposure during one or three trimesters, while no effect (OR: 0.98 and 1.06) was

observed for exposure during 2 trimesters. For SGA, a trend for a protective effect was seen for exposure during 2 or 3 trimesters.

The confounders and variables retained in each GEE model presented in Table E1 Adjusted ORs of LBW, prematurity and SGA according to the daily ICS dose and categories of LABA use are:

- LBW model: maternal age, receipt of social assistance, rural/urban residence, antiphospholipid syndrome, gestational diabetes, eclampsia/preeclampsia, vaginal bleeding, fetal–maternal hemorrhage, placental conditions, placenta abruption, ≥1 emergency-department (ED) visit for asthma
- PB model: maternal age, receipt of social assistance, eclampsia/preeclampsia, vaginal bleeding, fetal–maternal hemorrhage, placental conditions, placenta abruption, severity of asthma prior to pregnancy
- SGA model: maternal age, receipt of social assistance, rural/urban residence, gestational diabetes, eclampsia/preeclampsia, anemia, placental conditions, severity of asthma prior to pregnancy

Sensitivity Analysis for Smoking

As reported in Table E2, a sensitivity analysis was conducted to evaluate the impact of differential smoking prevalence for those exposed or not to ICSs or LABAs on the association between ICS or LABA use and LBW, PB, and SGA.

Table E2. Sensitivity Analysis for Smoking

AOR	**OR_{CD}**	**P_{C1}**	**P_{C0}**	**$OR_{adjusted}$**

LBW

Daily ICS* dose (µg/day)					
0–62.5	0.70	2.9	0.48	0.55	0.75
>62.5–125	1.03	2.9	0.48	0.55	1.10
>125–250	1.18	2.9	0.48	0.55	1.26
>250–500	1.20	2.9	0.48	0.55	1.28
>500	1.57	2.9	0.48	0.55	1.67
LABA	0.81	2.9	0.48	0.55	0.86

PB

Daily ICS* dose (µg/day)					
0–62.5	0.77	1.4	0.48	0.55	0.79
>62.5–125	1.08	1.4	0.48	0.55	1.10
>125–250	1.23	1.4	0.48	0.55	1.26
>250–500	1.28	1.4	0.48	0.55	1.31
>500	1.45	1.4	0.48	0.55	1.48
LABA	0.84	1.4	0.48	0.55	0.86

SGA

Daily ICS* dose (µg/day)					
0–62.5	0.91	2.6	0.48	0.55	0.96
>62.5–125	1.15	2.6	0.48	0.55	1.22
>125–250	1.12	2.6	0.48	0.55	1.19
>250–500	1.26	2.6	0.48	0.55	1.33
>500	1.50	2.6	0.48	0.55	1.59

LABA	0.92	2.6	0.48	0.55	0.97

AOR, apparent (observed) OR; ICS, inhaled corticosteroid; LABA, long-acting B_2-agonist; LBW, low birth weight; OR, odds ratio; $OR_{CD,}$ confounder–disease association; PB, preterm birth; $PC_{1,}$ prevalence of confounder among asthmatic women receiving an ICS or LABA; $PC_{0,}$ prevalence of confounder among asthmatic women not receiving an ICS or LABA; SGA, small for gestational age

*(fluticasone equivalent, µg/d)

The prevalence of smoking was retrieved from a chart review conducted in a previous study of our group[12] with smoking being less prevalent among ICS users compared to nonusers. The same smoking prevalences were used for LABAs due to absence of data specific to that medication class. From a literature review of the associations between smoking and LBW,[16-20] PB,[16-22] and SGA,[16-23] we selected the strongest, most statistically significant associations (LBW: 2.9 [1.2–6.9]; PB: 1.4 [1.1–1.9]; SGA: 2.63 [1.55, 4.49]). Most of the associations between smoking and PB were not statistically significant.

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