

Risk of perinatal mortality associated with inhaled corticosteroid use for the treatment of asthma during pregnancy

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Background: Four studies investigating the association between inhaled corticosteroid (ICS) use during pregnancy and perinatal mortality reported no significantly increased risk. These studies must be interpreted with caution because they have insufficient statistical power and a lack of adjustment for potential confounders.

Objectives: We sought to evaluate whether asthmatic women exposed to ICSs during pregnancy are more at risk of perinatal mortality than asthmatic women not exposed. We also sought to estimate the risk of perinatal mortality as a function of the daily ICS dose taken during pregnancy.

Methods: From the linkage of 3 administrative databases from Quebec, a cohort including 13,004 single pregnancies from asthmatic women was constructed. We used a 2-stage sampling cohort design to obtain information on cigarette smoking from the medical charts of 487 mothers. The final estimates of the odds ratios (ORs) of perinatal mortality were estimated with a logistic regression model.

Results: The cohort was formed of 4,140 women who used greater than 0 to 250 µg/d ICS, 1,140 women who used greater than 250 µg/d ICS, and 7,724 nonusers of ICSs during pregnancy. Women exposed to ICSs (any dose) had a nonsignificant increased risk of perinatal mortality (OR, 1.07; 95% CI, 0.70-1.61). The use of greater than 250 µg/d ICS was associated with a nonsignificant 52% increased risk of perinatal mortality (OR, 1.52; 95% CI, 0.62-3.76).

Conclusion: The risk of perinatal mortality was not found to be significantly associated with ICS use during pregnancy. The result associated with higher doses of ICSs is limited due to a lack of statistical power and a possibility of residual confounding by asthma severity and control. (*J Allergy Clin Immunol* 2010;126:772-7.)

Key words: Asthma, pregnancy, perinatal mortality, inhaled corticosteroids

Abbreviations used

ED:	Emergency department
GEE:	Generalized estimating equation
ICS:	Inhaled corticosteroid
ISQ:	Institut de la statistique du Québec
MED-ECHO:	Maintenance et Exploitation des données pour l'étude de la clientèle hospitalière
OR:	Odds ratio
RAMQ:	Régie de l'assurance-maladie du Québec
RR:	Relative risk

Asthma is considered the most common potentially serious medical problem to complicate pregnancy, with 4% to 7% of pregnant women taking asthma medications.¹⁻³ The most recent National Asthma Education and Prevention Program guidelines⁴ recommend the use of inhaled corticosteroids (ICSs) for all levels of severity for pregnant women with persistent asthma. Data in the literature are not sufficient to confirm the safety of ICSs during pregnancy, especially regarding relatively uncommon outcomes, such as perinatal mortality. Consequently, physicians might be reluctant to prescribe ICSs to pregnant women, and some women might also be reluctant to take ICSs because of fears of adverse effects on the fetus.^{5,6}

Although perinatal mortality (stillbirth and neonatal mortality) is one of the most dramatic complications during pregnancy for families, only 4 studies have investigated the association between ICS use during pregnancy and this perinatal outcome. In 2 recent studies no increased risk of perinatal mortality was reported for ICS use during pregnancy.^{7,8} However, the conclusion of these studies was based on crude estimates. Moreover, in 2 other studies^{9,10} the authors found that the rate of stillbirth among pregnant women exposed to beclomethasone dipropionate was lower than expected in the general population in one study and higher than expected in another study, but no statistical analyses were performed. The results of these studies must be interpreted with caution because they have important methodological limitations, such as insufficient statistical power to be able to exclude a clinically significant risk among ICS users and the absence of adjustment for potential confounding variables. The aim of our study was to evaluate whether asthmatic women exposed to ICSs during pregnancy are more at risk of perinatal mortality than asthmatic women not exposed to ICSs and to estimate the risk of perinatal mortality as a function of the daily ICS dose taken by the mother during pregnancy.

METHODS

Study design

The design of this study was a 2-stage sampling cohort. For the first stage of sampling, a cohort of 13,004 singleton pregnancies from asthmatic women

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was formed from the linkage of 3 health administrative databases from Quebec, Canada. Asthmatic women were aged between 13 and 50 years at the beginning of their pregnancy, had deliveries (live birth or stillbirth) between 1990 and 2002, and were covered by Quebec's Public Prescription Drug Insurance Plan for at least 1 year before and during their pregnancy. For each of these asthmatic women, we considered a maximum of 3 deliveries. The administrative database of the Régie de l'assurance-maladie du Québec (RAMQ) provides information related to the medical services dispensed to all residents of Quebec, as well as information related to medication prescriptions filled at community pharmacies for those residents who are covered by Quebec's Public Prescription Drug Insurance Plan, which represents approximately 43% of the population.¹¹ The Maintenance et Exploitation des données pour l'étude de la clientèle hospitalière (MED-ECHO) database contains information on all hospital admissions in Quebec. Administered by the Institut de la statistique du Québec (ISQ), the birth and death registry provides information on all births and perinatal deaths.

A woman was considered to have asthma if she filled at least 1 prescription for an asthma medication and had at least 1 diagnosis of asthma in accordance with International Classification of Diseases, Ninth Revision, codes 493.0, 493.1, and 493.9 either 2 years before or during her pregnancy. Once a woman was identified as having asthma, her status was kept unchanged for all subsequent pregnancies. A formal evaluation of the medical diagnoses for asthma recorded in the RAMQ Medical Services database has been performed, and the asthma diagnoses were found to be valid.¹²

At the second stage of sampling, we used the medical charts of a sample of women selected from the cohort to gather information on important potential confounding variables, such as cigarette smoking and history of stillbirth, which are not recorded in the administrative databases but are routinely recorded in the medical chart during prenatal visits or at delivery. We first measured the main exposure (ICS use vs no use) and the outcome (perinatal deaths) for all 13,004 pregnancies included in the cohort and displayed the frequencies in a 2×2 table (first stage of sampling). At the second stage of sampling, we sampled mothers from this 2×2 table, with sampling fractions inversely proportional to cell frequencies to oversample small cells (see Fig 1 for details). Indeed, perinatal deaths were all selected, and for each of them, 3 noncases matched for the administrative region of residence of the mother, the average daily ICS dose taken during pregnancy (0 $\mu\text{g}/\text{d}$, >0 to ≤ 500 $\mu\text{g}/\text{d}$, and >500 $\mu\text{g}/\text{d}$), and the year of birth of the baby were randomly selected. For these selected pregnancies, the RAMQ provided us the name of the hospital in which the mother gave birth and provided to the Medical Records Department of the hospital the insurance number of the selected mothers and the date of birth of the babies. The data collection in the mothers' medical charts was performed by a medical archivist, a research nurse, or Marie-Claude Breton, and the data were recorded on a paper data collection form. A double entry of the information collected in the medical chart was entered into 2 Microsoft Access databases. The 2 databases were compared to identify and correct data entry errors.

An authorization was obtained from the Commission d'Accès à l'information du Québec before retrieving information from the medical charts and for linking the information from the RAMQ or MED-ÉCHO databases, the ISQ, and medical charts. Moreover, this research project was first approved by the ethics committee and the Direction of Professional Services of the Hôpital du Sacré-Cœur de Montréal and then by all other hospital centers involved.

Exposure to ICSs

ICS exposure (beclomethasone, budesonide, flunisolide, fluticasone, and triamcinolone) was first divided into 2 categories: asthmatic women who did and did not use ICSs during pregnancy. We also investigated the effect of the average daily ICS dose taken by the mother during her pregnancy. Because more than 80% of the women in our cohort had mild asthma and used either no ICSs or low doses of ICSs, the mean daily dose was categorized as greater than 0 to 250 $\mu\text{g}/\text{d}$ or greater than 250 $\mu\text{g}/\text{day}$ in beclomethasone-chlorofluorocarbon equivalent. An algorithm was developed to estimate the mean daily ICS dose taken during pregnancy, with filled prescriptions recorded in the RAMQ database. This algorithm takes into account the potency of different ICSs, the form of the medication, the quantity dispensed,

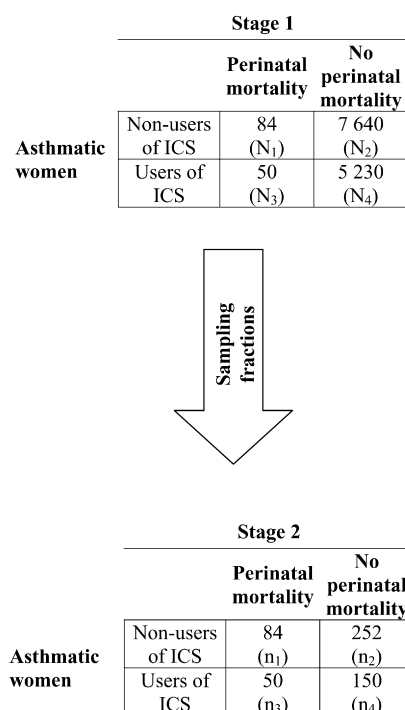


FIG 1. The 2-stage sampling design.

the date the medication is dispensed, and the prescription renewal rate. By using the equivalency table published in the Canadian asthma consensus report,¹³ the mean daily ICS dose was converted to a beclomethasone-chlorofluorocarbon equivalent. Measuring ICS use based on filled prescriptions takes into account both the physician's prescription and the patient's adherence. The details of the algorithm are available in Table E1 in this article's Online Repository at www.jacionline.org.

Perinatal mortality

Perinatal mortality includes stillbirths and neonatal mortality. Stillbirth was defined as fetal loss beyond 20 weeks of gestation or when the birth weight was 500 g or more. Stillbirths were identified from the ISQ or with International Classification of Diseases, Ninth Revision, codes 656.4, V27.1, V27.3, V27.4, V27.6, V27.7, V32, V35, and V36 recorded in the RAMQ database, the MED-ECHO database, or both. Neonatal mortality was defined as the death of a live-born neonate within the first 29 days of life. Deaths occurring within the first 29 days of life were identified from the ISQ or RAMQ databases.

Potential confounding variables

Retrieved from the administrative databases (first stage of sampling). The variables considered potential confounders were the risk factors of perinatal mortality identified in the literature. Four categories of variables retrieved from the administrative databases were considered potential confounders and measured for all pregnancies in the cohort. Maternal characteristics included the following: age at conception (<18 years old, 18-34 years old, and ≥ 35 years old); receipt of social assistance during pregnancy (yes/no); and level of education at delivery (≤ 11 years, ≥ 12 years, and missing values). The pregnancy-related variables included the following: pregnancy-induced hypertension (yes/no); diabetes mellitus (yes/no); gestational diabetes (yes/no); placental abruption (yes/no); and infections of the amniotic cavity (yes/no). The newborn characteristics included the following: cord around the neck (yes/no) based on a diagnosis recorded in the RAMQ or MED-ECHO databases; birth weight ($\leq 2,500$ g/ $>2,500$ g); gestational age at birth (<37 weeks/ ≥ 37 weeks); and small for gestational age (yes/no). However, only cord around the neck was considered a potential

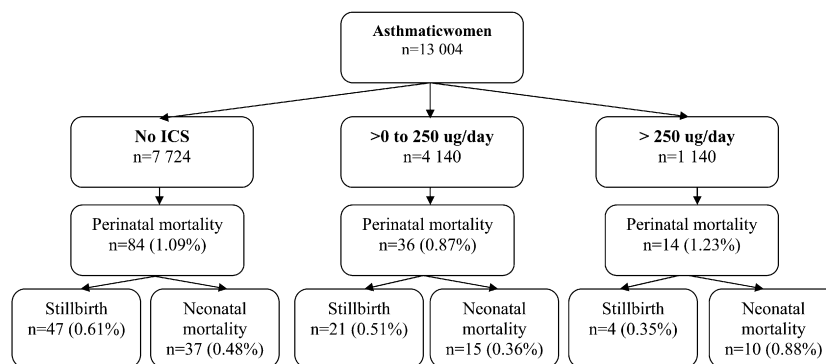


FIG 2. Rates of perinatal mortality, stillbirth, and neonatal mortality for asthmatic women who did not use ICSs, used greater than 0 to 250 µg/d ICS, and used greater than 250 µg/d ICS during pregnancy.

confounding variable. Birth weight, gestational age at birth, and small for gestational age were used only to describe the characteristics of the pregnancies for those women included in the cohort. Algorithms to measure birth weight and gestational age at birth from the data available in the MED-ECHO and ISQ databases were developed and found to be highly valid when compared with the data recorded in the mother's medical chart.¹⁴ Using specific algorithms that we developed for each condition, pregnancy-induced hypertension, gestational diabetes, and diabetes mellitus were identified based on either a diagnosis or a filled prescription for a related medication, as recorded in the RAMQ or MED-ECHO databases 1 year before or during the pregnancy. These variables were used in previous studies,^{15,16} and the algorithms are available on request. The other variables in this category were identified by using a diagnostic code recorded in the RAMQ or MED-ECHO databases. The asthma-related variables included the following: intranasal corticosteroids (yes/no); oral corticosteroids (yes/no); short-acting inhaled β_2 -agonists (<3 or ≥ 3 doses per week); theophylline (yes/no); other asthma therapy (long-acting β_2 -agonist or leukotriene receptor antagonists, yes/no); and emergency department (ED) visit or hospitalization for asthma (yes/no) during pregnancy.

Retrieved from the mother's medical chart (second stage of sampling). We collected information on cigarette smoking during pregnancy (including women who stopped smoking during pregnancy; yes, no, or missing values) and the history of stillbirths in preceding pregnancies (yes, no, or missing values).

Statistical analysis

Generalized estimating equation (GEE) models with a logistic link were used to evaluate the association between ICS use during pregnancy and the risk of perinatal mortality. These models were used to take into account the correlation between pregnancies from the same women and to provide valid variance estimates.¹⁷ Women contributed from 1 to 3 pregnancies to the analysis.

Two first-stage models were performed to compare asthmatic women who did and did not use ICSs during pregnancy, one providing a crude first-stage odds ratio (OR) and a second providing an adjusted first-stage OR for the ICS/perinatal mortality association. The adjusted OR was based on a reduced model, including the covariables listed in the section on potential confounding variables retrieved from the administrative databases that were found to act as confounders or risk factors for perinatal mortality. We also tried to fit a GEE model with the subsample of pregnancies selected at the second stage of sampling, but the model did not converge because the proportion of women with 2 or 3 pregnancies was too small. The 2 final analyses (combining first- and second-stage data) were thus performed with only 1 pregnancy per woman (more recent pregnancy in the cohort) by using logistic regression models, one providing a crude final OR and a second providing an adjusted final OR of the ICS/perinatal mortality association. The adjusted OR was based on a reduced model including the covariables listed in the section on potential confounding

variables retrieved from the administrative databases and the medical chart that were found to act as confounders or risk factors for perinatal mortality.

Confounding variables and risk factors were identified by using a backward selection procedure, starting with a model that included all potential confounders listed above.¹⁸ The reduced model was obtained when no confounding variable can be removed from the model without modifying the OR of ICSs by 5% or more. The final OR estimates used were obtained by correcting the second-stage OR estimate for the second-stage sampling fractions and the first-stage OR estimate according to the method described by Collet et al.¹⁹

Similarly, the GEE models were used to estimate the crude and adjusted first-stage OR of perinatal mortality associated with the mean daily ICS dose taken by the mother during pregnancy (0, >0 to 250, and >250 µg/d). Logistic regression models and the method described by Collet et al.¹⁹ were then used to estimate the crude and adjusted final ORs. Analyses were performed with SAS version 9.1.3 software (SAS Institute, Inc, Cary, NC).

RESULTS

At the first stage of sampling, the cohort was formed of 13,004 pregnancies from asthmatic women: 4,140 (31.8%) who used greater than 0 to 250 µg/d ICS; 1,140 (8.8%) who used greater than 250 µg/d ICS; and 7,724 (59.4%) who did not use ICSs during pregnancy. The rate of perinatal mortality was 0.87% ($n = 36$) among asthmatic women who used greater than 0 to 250 µg/d ICS, 1.23% ($n = 14$) among asthmatic women who used greater than 250 µg/d ICS, and 1.09% ($n = 84$) among asthmatic women who did not use ICSs during pregnancy (Table I). The corresponding rates for stillbirth and neonatal mortality are shown in Fig 2.

In Table I we present the characteristics of all asthmatic pregnant women included in the cohort (first stage of sampling). More asthmatic women using greater than 250 µg/d ICS used high doses of short-acting β_2 -agonists, oral corticosteroids, intranasal corticosteroids, theophylline, or other asthma therapy and had an ED visit or hospitalization for asthma during pregnancy compared with the other asthmatic women.

Table II presents the distribution of the variables retrieved from the medical chart for the women selected at the second stage of sampling. We were not able to retrieve the information on potential confounders from the mothers' medical charts for 49 women. Women using greater than 250 µg/d ICS were less likely to smoke cigarettes during pregnancy but were more likely to have had a preceding pregnancy with a stillbirth.

The final crude OR and the first-stage crude OR comparing pregnancies from asthmatic women who used ICSs with those

TABLE I. Characteristics of pregnancies of women with asthma included in the cohort at the first stage of sampling (n = 13,004)

	No ICS (n = 7724), no. (%)	>0-250 µg/d ICS (n = 4140), no. (%)	>250 µg/d ICS (n = 1140), no. (%)
Maternal characteristics			
Age (y)			
<18	492 (6.4)	289 (7.0)	75 (6.7)
18-34	6799 (88.0)	3595 (86.8)	946 (83.0)
≥35	433 (5.6)	256 (6.2)	119 (10.4)
Social assistance	6141 (79.5)	3272 (79.0)	911 (79.9)
Level of education (y)			
≤11	4616 (59.8)	2483 (60.0)	617 (54.1)
≥12	2525 (32.7)	1366 (33.0)	434 (38.1)
Missing	583 (7.6)	291 (7.0)	89 (7.8)
Pregnancy-related variables			
Pregnancy-induced hypertension	460 (6.0)	298 (7.2)	85 (7.5)
Diabetes mellitus	164 (2.1)	102 (2.5)	41 (3.6)
Gestational diabetes	528 (6.8)	360 (8.7)	115 (10.1)
Placental abruption	297 (3.9)	155 (3.7)	33 (2.9)
Infection of amniotic cavity	380 (4.9)	171 (4.1)	53 (4.7)
Newborn characteristics			
Birth weight			
≤2,500 g	735 (9.5)	328 (7.9)	135 (11.8)
Gestational age at birth			
<37 wk	850 (11.0)	369 (8.9)	133 (11.7)
Small for gestational age	1039 (13.5)	606 (14.7)	221 (19.5)
Cord around neck	1299 (16.8)	683 (16.5)	199 (17.5)
Asthma-related variables during pregnancy			
≥3 Doses of short-acting β ₂ -agonist per wk	1080 (14.0)	1740 (42.0)	1007 (88.3)
Oral corticosteroid use	189 (2.5)	511 (12.3)	316 (27.7)
Intranasal corticosteroid use	309 (4.0)	384 (9.3)	222 (19.5)
Theophylline use	101 (1.3)	110 (2.7)	99 (8.7)
Other asthma therapy (long-acting β ₂ -agonist or leukotriene receptor antagonist use)	12 (0.2)	95 (2.3)	143 (12.5)
One ED visit or hospitalization for asthma	488 (6.3)	834 (20.1)	339 (29.7)

from asthmatic women who did not use ICSs during pregnancy were identical (final crude OR, 0.87; 95% CI, 0.61-1.24). Both the adjusted first-stage (adjusted OR, 0.80; 95% CI, 0.53-1.22) and final (adjusted OR, 1.07; 95% CI, 0.70-1.61) OR estimates did not show a significant association between ICS use and perinatal mortality. The details of these analyses are available in [Table E2](#) in this article's Online Repository at www.jacionline.org.

In [Table III](#) we present the analysis that focused on the ICS dose. We observed a nonsignificant protective effect of perinatal mortality with smaller doses (>0-250 µg/d) of ICSs (first-stage and final estimates), but larger doses (>250 µg/d) of ICSs were associated with a nonsignificant 52% increased risk of perinatal mortality (adjusted final OR, 1.52; 95% CI, 0.62-3.76).

DISCUSSION

In this study the final estimate showed no significantly increased risk of perinatal mortality among asthmatic women who used ICSs during pregnancy compared with asthmatic women who did not use ICSs during pregnancy (OR, 1.07; 95% CI, 0.70-1.61). Moreover, a nonsignificant protective effect was observed among women exposed to greater than 0 to 250 µg/d ICS compared with asthmatic women not exposed during pregnancy (OR, 0.89; 95% CI, 0.55-1.44). However, the use of more than 250 µg/d ICS during pregnancy was associated with a 52% increased risk of perinatal mortality, but the association was not statistically significant.

TABLE II. Characteristics of the asthmatic women selected at the second stage of sampling (n = 487)

	No ICS (n = 312)	>0-250 µg/d ICS (n = 130)	>250 µg/d ICS (n = 45)
Cigarette smoking during pregnancy			
Yes	181 (58.0)	74 (56.9)	21 (46.7)
No	111 (35.6)	46 (35.4)	22 (48.9)
Missing	20 (6.4)	10 (7.7)	2 (4.4)
Preceding pregnancy with stillbirth			
Yes	10 (3.2)	8 (6.2)	4 (8.9)
No	282 (90.4)	111 (85.4)	38 (84.4)
Missing	20 (6.4)	11 (8.5)	3 (6.7)

None of the 4 studies published in the literature⁷⁻¹⁰ on this topic reported a statistically significantly increased risk of perinatal mortality (stillbirth and neonatal mortality) among women who used ICSs during pregnancy, but none of these studies adjusted for potential confounders or risk factors, and none considered the ICS dose. Norjavaara and de Verdier⁷ performed the largest study to date and reported no increased risk of stillbirth among 2,968 women who used inhaled budesonide during pregnancy compared with 293,948 women not using any asthma medication (boys: relative risk [RR], 0.3; girls: RR, 1.0; *P* > .05). In a

TABLE III. Crude and adjusted ORs of perinatal mortality for asthmatic women who used greater than 0 to 250 $\mu\text{g/d}$ and greater than 250 $\mu\text{g/d}$ ICS during pregnancy compared with asthmatic women who did not use ICSs during pregnancy

	First stage of sampling (n = 13,004)		Final estimates*	
	Crude OR (95% CI)	Adjusted OR (95% CI)†	Crude OR (95% CI)	Adjusted OR (95% CI)‡
ICS use during pregnancy ($\mu\text{g/d}$)				
0	Reference	Reference	Reference	Reference
>0-250	0.80 (0.54-1.19)	0.78 (0.50-1.20)	0.80 (0.54-1.16)	0.89 (0.55-1.44)
>250	1.14 (0.65-2.01)	1.01 (0.48-2.11)	1.13 (0.64-2.00)	1.52 (0.62-3.76)

*Final estimates were obtained by correcting the second-stage OR estimates (n = 487) for the second-stage sampling fractions and the first-stage OR estimates (n = 13,004).

†Adjusted OR for level of education, placental abruption, infection of amniotic cavity, cord around neck, short-acting β_2 -agonist use during pregnancy, intranasal corticosteroid use during pregnancy, and other asthma therapy (long-acting β_2 -agonists or leukotriene receptor antagonists).

‡Adjusted OR for level of education, diabetes mellitus, placental abruption, infection of amniotic cavity, cord around neck, intranasal corticosteroid use during pregnancy, other asthma therapy, ED visit or hospitalization for asthma, cigarette smoking during pregnancy, and preceding pregnancy with stillbirth.

randomized clinical trial performed by Dombrowski et al,⁸ no increased risk of perinatal mortality was observed among 194 women exposed to beclomethasone dipropionate compared with 190 women exposed to theophylline during pregnancy (beclomethasone dipropionate: 1.5% vs theophylline: 2.1%; RR, 0.7; 95% CI, 0.2-3.2). Greenberger and Patterson⁹ compared ICS use in 43 pregnancies, but no statistical inference was performed. In this study the risk of stillbirth and neonatal mortality was found to be lower for women receiving beclomethasone dipropionate than it was among the general population of the United States (stillbirth: 0% vs 0.9% to 1.0%; neonatal mortality: 0% vs 1.6%). In another study performed by Greenberger and Patterson,¹⁰ in which no statistical inference was performed, the risk of stillbirth was found to be 1.2% among 81 pregnant women exposed to beclomethasone dipropionate and 0.84% in the general population of the United States. Corresponding risks of neonatal mortality were 0% and 0.73%.

The results of our study suggest that ICSs have no effect on the risk of perinatal mortality when the dose was not considered. For doses ranging from 1 to 250 $\mu\text{g/d}$, we found no significantly increased risk, whereas we found a nonsignificantly increased risk of 52% among women who used higher doses (>250 $\mu\text{g/d}$). Based on this nonsignificant result, we cannot exclude the possibility of an increased risk associated with higher doses of ICSs because our study had only a 24% power to detect the observed OR of 1.52.

This study has several strengths. The use of a 2-stage sampling design allowed us to obtain exposure and outcome data for a large cohort of asthmatic women and data on a large number of potential confounders through the combination of data recorded in the administrative databases and the medical charts of the mothers. Using the RAMQ database to measure drug exposure provides several benefits over other means of data collection, such as interviews or self-administered questionnaires. It is usually difficult for patients to report the medications they are taking when details such as the exact name, dose, and quantity are required.²⁰⁻²³ The use of the RAMQ databases allows us to capture drug history over a long period of time and provide full details on the name, dose, and amount of drugs dispensed, information that is almost impossible to retrospectively obtain by means of questionnaire. A recall bias is thus avoided because drug exposure is prospectively collected. Collecting the data from the medical charts to measure confounders also avoided recall bias because these data were recorded before the outcome of pregnancy was known. In addition, the physician-based diagnoses of asthma recorded in the RAMQ databases have been shown to be valid.¹² Moreover, 99% of the cases of perinatal mortality identified in the cohort based on information recorded in the

administrative databases were confirmed by the information recorded in the mother's medical chart. Finally, pregnancy-related variables recorded in administrative databases were found to be highly valid compared with the information recorded in the mothers' medical charts.¹⁴

This study also has a few limitations that should be accounted for when interpreting the results.

First, data are not available on women who did not consult medical services during pregnancy or who did not give birth in a medical center. Second, drug use was estimated from filled medication prescriptions and might not reflect exactly the intake of the medications. However, a recent study has demonstrated that only 6% of drugs dispensed to pregnant women were not used.²⁴ Third, the RAMQ databases only provide information for women who are covered by the public drug insurance plan, which means that patients with a high socioeconomic status were underrepresented. Therefore generalization of our results might be limited to women with a lower socioeconomic status. Finally, the increased risk of perinatal mortality associated with higher doses of ICSs could be explained by residual confounding by asthma severity and control.

Indeed, in our cohort women who used higher doses of ICSs were more likely to use 3 or more doses of short-acting β_2 -agonist per week (88.3%) or oral corticosteroids (27.7%) and have an ED visit or hospitalization for asthma (29.7%) than users of smaller doses. Moreover, poor asthma control during pregnancy has been associated with an increased risk of low-birth-weight babies,²⁵ babies who are small for gestational age,²⁶ and fetal growth restriction,²⁷ outcomes that are associated with an increased risk of perinatal mortality.²⁸⁻³⁰ In addition, severe asthma has been associated with an increased risk of perinatal mortality.^{31,32} The ORs of perinatal mortality presented in our study were adjusted for markers of asthma control and severity, but residual confounding might be present because these markers do not measure asthma severity and control perfectly. We had no data for other markers of asthma severity and control, such as pulmonary function (FEV₁ and peak flow) and the frequency of daytime and nighttime symptoms.

Current asthma guidelines recommend ICSs for the management of all levels of persistent asthma during pregnancy and recommend that pregnant women be treated as aggressively as nonpregnant women to achieve and maintain control of asthma.⁴ The results of our study are reassuring because lower doses of ICSs (>0-250 $\mu\text{g/d}$) were not found to be associated with an increased risk of perinatal mortality. However, the information that we can extract from our study is limited for higher doses (>250 $\mu\text{g/d}$) because of a lack of statistical power and a possibility

of residual confounding. Consequently, we recommend that asthmatic women be managed with the minimum effective ICS dose to obtain optimal control of their asthma during pregnancy. More scientific evidence is needed before we can conclude that higher doses of ICSs are safe during pregnancy, but the available data suggest that if higher doses of ICSs (>250 µg/d) are needed to control asthma, their benefits outweigh their apparent risks. Although greater than 250 µg/d ICS was not found to be significantly associated with perinatal mortality, it does not eliminate the possibility that this dose might have other effects on the fetus.

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Clinical implications: Asthmatic pregnant women should be managed with the minimum effective ICS dose, but if higher doses of ICSs are needed to control asthma, their benefits outweigh their risks.

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TABLE E1. Algorithm to calculate the average daily dose of ICSs during pregnancy

1. All prescriptions of ICSs during pregnancy were identified.
2. The duration of the prescription during the pregnancy was determined. The duration of a prescription is equal to the number of days between 2 successive renewals. If the prescription was the last that the patient filled, the duration of this last prescription was equal to the mean duration of the previous prescriptions. If the patient had only 1 prescription, the duration was equal to the number of days recorded in the RAMQ database.
3. If the prescription started before the pregnancy or the last day of the prescription was beyond the end of the pregnancy, the duration of the prescription was adjusted accordingly.
4. The number of micrograms dispensed per prescription (as recorded in the RAMQ database) was calculated. If the prescription started before the pregnancy or the last day of the prescription was beyond the end of the pregnancy, the number of micrograms dispensed was adjusted accordingly.
5. The equivalences between the different ICS products according to the Canadian Asthma Consensus Guidelines were applied.
6. The total number of micrograms dispensed during pregnancy was calculated by summing the number of micrograms for all prescriptions falling during the pregnancy.
7. The average number of micrograms per day was calculated by dividing the total number of micrograms by the length of the pregnancy expressed in days.

TABLE E2. Crude and adjusted ORs of perinatal mortality for asthmatic women who used ICSs during pregnancy compared with asthmatic women who did not use ICSs during pregnancy

	First stage of sampling		Final estimates	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
ICS use during pregnancy ($\mu\text{g/d}$; yes/no)	0.87 (0.61-1.25)	0.80 (0.53-1.22)	0.87 (0.61-1.24)	1.07 (0.70-1.61)
Age (y)				
<18	0.81 (0.38-1.74)	NR	0.66 (0.27-1.64)	NR
18-34	Reference		Reference	
≥ 35	1.18 (0.61-2.28)	NR	0.80 (0.32-2.02)	NR
Social assistance (yes/no)	1.23 (0.79-1.93)	NR	1.27 (0.73-2.21)	NR
Level of education (y)				
≤ 11	1.09 (0.71-1.66)	1.07 (0.70-1.63)	1.02 (0.62-1.68)	1.04 (0.62-1.76)
≥ 12	Reference	Reference	Reference	
Missing	4.65 (2.86-7.56)	4.35 (2.63-7.20)	4.17 (2.18-7.98)	4.69 (2.35-9.34)
Pregnancy-induced hypertension (yes/no)	1.53 (0.84-2.78)	NR	2.22 (1.07-4.61)	NR
Diabetes mellitus (yes/no)	1.55 (0.61-3.9)	NR	1.47 (0.50-4.33)	NR
Gestational diabetes (yes/no)	1.04 (0.55-1.94)	NR	0.98 (0.43-2.23)	NR
Placental abruption (yes/no)	6.87 (4.37-10.80)	6.01 (3.71-9.74)	4.18 (2.29-7.62)	4.40 (2.23-8.69)
Infection of amniotic cavity (yes/no)	3.25 (1.95-5.42)	3.03 (1.74-5.27)	2.61 (1.29-5.28)	2.92 (1.31-6.48)
Cord around neck (yes/no)	0.54 (0.30-0.96)	0.55 (0.31-0.98)	0.51 (0.26- 1.01)	NR
Short-acting β_2 -agonist use during pregnancy (<3, ≥ 3 doses per wk)	1.21 (0.8-1.74)	1.36 (0.91-2.04)	0.91 (0.58-1.44)	NR
Oral corticosteroid use during pregnancy (yes/no)	1.26 (0.71-2.26)	NR	1.11 (0.52-2.36)	NR
Intranasal corticosteroid use during pregnancy (yes/no)	0.58 (0.24-1.41)	NR	0.83 (0.33-2.08)	NR
Theophylline use during pregnancy	1.22 (0.43-3.49)	NR	0.87 (0.24-3.17)	NR
Other asthma therapy (yes/no; long-acting β_2 -agonists or leukotriene receptor antagonists)	1.46 (0.51-4.20)	NR	0.96 (0.26-3.54)	NR
One ED visit or hospitalization for asthma (yes/no)	0.76 (0.43-1.33)	NR	0.40 (0.18-0.91)	0.27 (0.10-0.71)
Cigarette smoking during pregnancy				
Yes	NA	NA	1.51 (0.95-2.38)	NR
No			Reference	
Missing			1.94 (0.84-4.47)	NR
Preceding pregnancy with stillbirth				
Yes	NA	NA	1.90 (0.91-3.99)	NR
No			Reference	
Missing			1.99 (0.81-4.89)	NR

NA, Not available in the administrative databases for the first stage of sampling; NR, not retained in the reduced model.