

High doses of inhaled corticosteroids during the first trimester of pregnancy and congenital malformations

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Background: Although reassuring data exist on the use of low-to-moderate doses of inhaled corticosteroids (ICSs) during pregnancy, there are inadequate data for women receiving high doses.

Objective: To investigate the association between doses of ICS during the first trimester of pregnancy and the risk of congenital malformations among women with asthma.

Methods: We conducted a cohort study of 13,280 pregnancies of women with asthma (1990-2002) by linking 3 administrative databases from Quebec (Canada). By using generalized estimation equation models, we compared women taking >0 to 1000 µg/d ICS (beclomethasone dipropionate-chlorofluorocarbonyl equivalent) with women taking >1000 µg/d and those not taking ICSs. The main outcome measures were all and major congenital malformations.

Results: We identified 1257 infants with a congenital malformation (9.5%) and 782 infants with a major malformation (5.9%). We found that women who used >1000 µg/d ICS (n = 154) were significantly more likely (63%) to have a baby with a malformation than the 4392 women who used >0 to 1000 µg/d (adjusted risk ratio, 1.63; 95% CI, 1.02-2.60). On the other hand, women who used >0 to 1000 µg/d were not found to be more at risk than women who did not use ICSs during the first trimester (n = 8734). Nonsignificant trends of similar magnitude were found for major malformations.

Conclusions: Our study adds evidence on the safety of low-to-moderate doses of ICS taken during the first trimester but raises concerns about high doses. However, we cannot rule out the possibility of residual confounding by severity in this association. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, pregnancy, inhaled corticosteroids, congenital malformations, cohort study

Asthma is a frequent chronic disease encountered during pregnancy, affecting between 3% and 12% of all pregnant women.^{1,2} Although the goals of asthma therapy in pregnant women are similar to the ones for nonpregnant women, they particularly target preventing exacerbations, which would cause a decrease in oxygen supply to the fetus.¹ Inhaled corticosteroids (ICSs) are recognized as the first-line controller therapy, and the same doses are recommended during pregnancy and under other circumstances.¹

In a recent literature review,³ we identified 15 studies that investigated the risk of congenital malformations in association with the use of ICSs during pregnancy.⁴⁻¹⁸ In 6 of these studies,^{4-6,15-17} ICS users were compared with women with asthma who did not use any ICS during pregnancy, whereas in the other studies, ICS users were compared with the general population, women without asthma, or users of theophylline. None of these 6 studies reported a significant increased risk of congenital malformations associated with the use of ICS, but only 1 of these considered the average daily dose of ICSs used during the first trimester of pregnancy⁶ and found that high daily doses of ICSs (>1000 µg/d equivalent beclomethasone dipropionate) was associated with a nonsignificant trend toward an increased risk of major malformations (odds ratio [OR], 1.7).

To investigate further the association between the use of different doses of ICSs, and more specifically high doses, during the first trimester of pregnancy and the risk of congenital malformation, we performed a large population-based cohort study including 13,280 pregnancies of women with asthma.

METHODS

Source of data

Data for this study were retrieved from 3 administrative databases from the Canadian province of Quebec. The database of the Régie de l'assurance-maladie du Québec (RAMQ) provides information on medical services dispensed to all residents of Quebec and prescribed medications filled in community pharmacies for residents insured by the RAMQ Drug Insurance Plan, about 42% of the residents of the province.¹⁹ These include the elderly, and the recipients of social welfare since 1980, and since January 1997, 1.7 million other adherents, mainly workers and their families who are not covered under a private drug insurance plan at their workplace. Maintenance et Exploitation des données pour l'étude de la clientèle hospitalière (MED-ECHO) contains information on all hospitalizations occurring in the province, and the Fichier des événements démographiques, administered by the Institut de la statistique du Québec (ISQ), provides information on all births and stillbirths. These databases have often been used in the past for epidemiologic

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Abbreviations used

ED:	Emergency department
ICD-9:	International Classification of Diseases, Ninth Revision
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:	Risk ratio

research in the field of asthma.^{6,20-23} Data recorded in the RAMQ Medication Prescriptions database and the medical diagnosis for asthma recorded in the RAMQ Medical Services database have been formally evaluated and found to be valid.^{24,25} Moreover, pregnancy-related variables such as birth weight, gestational age, date of conception, and date of delivery directly recorded in or derived from the RAMQ, MED-ECHO, and ISQ databases based on our own algorithms have been formally evaluated and deemed to be highly valid.²⁶

Study design

A cohort of pregnancies from women with asthma and their children was formed from the linkage of the RAMQ, MED-ECHO, and ISQ databases. The cohort inclusion criteria were (1) having at least 1 pregnancy from a woman with asthma ending in a delivery (live birth or still birth) between 1990 and 2002, (2) being 13 to 50 years old at conception, (3) having at least 1 diagnosis of asthma (International Classification of Diseases, Ninth Revision [ICD-9] code: 493) and at least 1 prescription for an asthma medication at any time in the previous 2 years or during pregnancy, and (4) being covered by the RAMQ Drug Insurance Plan for at least 1 year before and throughout the duration of the pregnancy. This cohort is an update of our previous cohort of 4561 pregnancies of women with asthma.⁶ The cohort was formed of a maximum of 4 pregnancies per woman, keeping the most recent pregnancies. Using gestational age at birth and date of birth of the offspring, 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, during, and 1 year after pregnancy; date of filling, name, dose, dosage form, quantity, and duration of the prescription; and encrypted identification and specialty of the prescribing physician for at least 1 year before and during the pregnancy. 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. These data were also obtained for the baby during the first year of life. The RAMQ also provided the date of birth of the mothers and children, whether the mother was receiving social assistance, and the area of residence of the mother during her pregnancy. MED-ECHO provided data on all maternal acute care hospitalizations occurring in the year preceding, during, and after the pregnancy, including principal diagnosis, as many as 15 secondary diagnoses, date of admission, and length of hospitalization, in addition to the length of gestation and birth weight from the delivery hospitalization. With respect to the children, we received hospitalization data for the first year of life. The Fichier des événements démographiques provided data relevant to the level of education of the mother and the parity of the ongoing pregnancy.

Ethics approval

An authorization was obtained from the Commission d'accès à l'information du Québec before requesting and linking the information from the RAMQ, MED-ECHO, and ISQ databases. This research project was approved by the Ethics Committee of the Hôpital du Sacré-Coeur de Montréal.

Congenital malformations

All cases of a congenital malformation were identified within the cohort using ICD-9 diagnosis codes specific to congenital malformations (ICD-9: 152, 155, 186, 188, 190-192, 197-198, 204-205, 237, 740-759, 778) recorded in the RAMQ and MED-ECHO databases. Our list of congenital malformations was compared with the list provided by the Collaborative Perinatal Group²⁷ and verified by a geneticist from Montreal's Hôpital Ste-Justine for exactness and completeness. An infant was identified as a case if the infant had at least 1 diagnosis of a congenital malformation at birth or during the first year of life recorded in the databases.

The geneticist also classified the malformations as either minor or major. A congenital malformation was classified as major if it could be life-threatening or caused major cosmetic defects and if there was at least 1 hospitalization related to the malformation during the first year of life. All and major congenital malformations were the outcomes under study.

Maternal exposure to ICSs

The use of ICSs (beclomethasone dipropionate, budesonide, fluticasone propionate, flunisolide, and triamcinolone acetonide) during the first trimester of pregnancy was expressed in beclomethasone dipropionate–chlorofluorocarbonyl equivalent. The daily dose of ICSs was estimated with an algorithm that we developed and used in previous studies and that is based on the name of the medications and equivalences between the different ICS products as recognized by the Canadian Asthma Consensus Guidelines,²⁸ the dose prescribed, the date and duration of the prescription, and the rate of renewals of the prescription.^{6,22} A detailed description of the algorithm can be found in this article's Table E1 in the Online Repository at www.jacionline.org.

The average daily dose of ICSs used during the first trimester was categorized as 0, >0 to 1000, and >1000 µg/d beclomethasone dipropionate–chlorofluorocarbonyl equivalent (1000 µg beclomethasone dipropionate–chlorofluorocarbonyl is equivalent to 500 µg fluticasone propionate–hydrofluoro-alcane), with >1000 µg/d recognized as a high daily dose by the Canadian Asthma Consensus Guidelines.²⁸

Potential confounding variables

Four categories of variables were considered potential confounding variables. Maternal sociodemographic characteristics included age at conception (13-18, 19-34, 35-45 years), receipt of social assistance during or in the year before pregnancy (yes/no), education (≤11, 12-15, ≥16 years, missing), and area of residence at delivery (rural/urban). Pregnancy-related variables included parity (first/second pregnancy or more) and multiple pregnancies (twins or more/singleton). Maternal chronic conditions included chronic hypertension (yes/no), diabetes mellitus (yes/no), epilepsy (yes/no), and use of recognized teratogenic medications during the first trimester of pregnancy (yes/no).²⁹ Chronic hypertension, diabetes mellitus, and epilepsy were identified from diagnoses or filled prescriptions of related medications 1 year before or during pregnancy by using specific algorithms that we developed for each condition and used in other studies,^{6,22} details of which are available on request. Asthma-related variables included the use of inhaled or oral short-acting β₂-agonists (0, >0-3, >3 doses per week), use of long-acting inhaled β₂-agonists (yes/no), use of theophylline (yes/no), use of intranasal corticosteroids (yes/no), and asthma exacerbation (yes/no) in the first trimester of pregnancy. An asthma exacerbation was defined as a filled prescription of oral corticosteroids, an ED visit for asthma, or a hospitalization for asthma. Two or more markers of exacerbation occurring within 15 days were counted as only 1 exacerbation. The severity of asthma before pregnancy was also considered a potential confounding variable and measured with a validated index (mild, moderate, or severe asthma) on the basis of the use of asthma medications and acute care for asthma.³⁰

Statistical analysis

We first calculated descriptive statistics for the characteristics of the pregnancies as a function of the daily dose of ICSs during the first trimester. We also estimated the overall prevalence of all and major congenital malformations, and the distribution of specific malformations. In addition to

that, we estimated the prevalence and the crude risk ratio (RR) of all and major congenital malformations as a function of the daily dose of ICSs during the first trimester of pregnancy.

The association between the daily dose of ICSs taken during the first trimester and the risk of congenital malformations was investigated with 2 generalized estimation equation models, one for the outcome all malformations and the other for the outcome major malformations.³¹ On the basis of preliminary calculations, the independence correlation structure was chosen. In both models, the >1000 µg/d ICS category was compared with the >0 to 1000 µg/d ICS category to minimize bias by indication (in this case, bias by asthma severity) because nonusers of ICSs tend to have less severe asthma than users of ICS. The reduced models were found by using first a backward selection strategy that starts with a model including ICS doses and all potential confounding variables and that keeps in the model only ICS doses and variables that were found to act as confounders (a change of at least 10% in at least 1 RR associated with ICSs after the variable was removed from the model) or those that were significantly associated with the outcome (*P* value <.05), except for maternal age and asthma severity, which were forced in the model.³² To make sure that none of the variables eliminated during the backward selection procedure would act as a confounder, we reintroduced 1 by 1 the eliminated variables into the model and kept only those found to act as confounders for the ICS-malformation association.

We also performed an analysis stratified for the presence or not of a marker of uncontrolled or severe asthma (>3 doses of short-acting inhaled β₂-agonist per week, a filled prescription of oral corticosteroids, an ED visit for asthma, or a hospitalization for asthma) during the first trimester with 2 separate generalized estimation equation models.

RESULTS

The cohort was formed of 13,280 pregnancies from 10,099 women with asthma: 2570 women (25.5%) contributed 2 pregnancies or more to the analysis. Only 154 women used more than 1000 µg/d ICS (1.1%), whereas 4392 (33.1%) used a daily dose varying between >0 and 1000 µg/d, and 8734 (65.8%) did not use any ICSs during the first trimester. Among patients using more than 1000 µg/d, 33% filled prescriptions of beclomethasone dipropionate only, 38% filled prescriptions of fluticasone propionate only, 13% filled prescriptions of budesonide only, and 16% filled prescriptions of at least 2 of these medications. The different ICS products could have been used sequentially or at the same time.

The characteristics of the pregnancies included in the cohort as a function of the daily dose of ICS are presented in Table I. A majority of women were between 19 and 34 years old at conception, received social assistance, had 11 years or less of education, were living in an urban area, and were at their second pregnancy or more. Overall, less than 4% of the women had a chronic disease other than asthma or used a recognized teratogenic medication during the first trimester. Women taking high doses of ICSs during the first trimester were found to be older and more likely to have a multiple pregnancy, have a chronic disease other than asthma, and use teratogenic and asthma medications during the first trimester. They were also more likely to be hospitalized or to visit an ED for asthma during the first trimester and have severe asthma in the year before conception.

We identified 1633 congenital malformations in 1257 infants (prevalence, 9.5%; 95% CI, 9.0-10.0) and 1125 major malformations in 782 infants (prevalence, 5.9%; 95% CI, 5.5-6.3). The most frequent malformations were musculoskeletal and cardiac (see this article's Table E2 in the Online Repository at www.jacionline.org). The crude prevalence of all and major malformations were 9.6% and 5.9% for nonusers of ICSs, 9.0% and 5.7% for >0 to 1000 µg/d (186 µg on average), and 14.3% and 9.7%

for >1000 µg/d (1470 µg on average; see this article's Table E3 in the Online Repository at www.jacionline.org). Crude RRs of all and major congenital malformations in association with ICS doses and potential confounders can be found in this article's Table E4 in the Online Repository at www.jacionline.org.

In Table II we observe that the 154 women who used more than 1000 µg/d ICS were significantly (63%) more likely to have a baby with a malformation than the 4392 women who used >0 to 1000 µg/d (RR, 1.63; 95% CI, 1.02-2.60; crude RR can be found in Table E3). On the other hand, the 4392 women who used >0 to 1000 µg/d were not found to be more at risk than the 8734 women who did not use ICSs. Similar non significant trends were found for major malformations. The choice of the structure of the correlation matrix had no influence on the RR estimates and their related CIs. Multiple pregnancy, diabetes mellitus, and receipt of social assistance were found to be risk factors for the outcomes, whereas the use of intranasal corticosteroids during the first trimester was found to be a confounder. All other covariables were found to be neither confounders nor risk factors.

The explanatory stratified analysis presented in Table III revealed that the stratum-specific RRs associated with high doses of ICSs did not differ much in magnitude from the overall RRs.

DISCUSSION

In this study, we observed that women who took high doses of ICSs during the first trimester of pregnancy were 63% more likely to have a baby with a congenital malformation than women taking low to moderate doses of ICSs. This study also showed no increased risk of congenital malformation with low to moderate doses of ICSs compared with nonusers of ICSs. Nonsignificant associations of similar magnitude were observed for major malformations.

This study is the first to observe a statistically significant association between high doses of ICSs and congenital malformations. All previous published studies have failed to show an association between ICS use during pregnancy and congenital malformations.^{4-6,15-17} However, only 1 of these studies conducted by our group considered the dose of ICS and had observed a nonsignificant increased risk of major malformations of 1.7 within a cohort of 4561 pregnancies of women with asthma.⁶ With the cohort under study, we more than doubled the number of women exposed to high doses of ICSs and still found results of the same magnitude. However, in both studies, we have observed no associations between the use of low to moderate doses of ICSs and congenital malformations.⁶ In the current study, we had more than an 80% power to show a relative risk of congenital malformations of 1.2 for low to moderate doses of ICSs.

The first question that comes to mind when interpreting our study results is the following: is the increased risk of congenital malformations associated with high doses of ICSs caused by a teratogenic effect of the medication or the effect of severe uncontrolled asthma? An argument in favor of a teratogenic effect of ICSs is that at such high doses (1470 µg on average), ICSs have been recognized to have systemic effects,³³ and oral corticosteroids have been found to be associated with an increased risk of congenital malformations.³⁴⁻³⁶ Other arguments in favor of a teratogenic effect of ICSs are that we considered several well recognized markers of uncontrolled or severe asthma as potential confounders^{8,37,38} and that the stratified analysis showed RRs that were of the same magnitude as the overall RR estimates.

TABLE I. Characteristics of pregnancies according to the daily dose of ICSs during the first trimester

	All pregnancies	Daily dose of ICSs* during 1st trimester (μg)		
		0	>0-1,000	>1,000
No. of pregnancies	No. of pregnancies (%)			
	13,280	8,734 (65.8)	4,392 (33.1)	154 (1.1)
Maternal sociodemographic variables				
Age at the beginning of pregnancy (y)				
13-18	882 (6.6)	554 (6.3)	318 (7.2)	10 (6.5)
19-34	11,569 (87.1)	7,677 (87.9)	3,768 (85.8)	124 (80.5)
35-45	829 (6.3)	503 (5.8)	306 (7.0)	20 (13.0)
Receipt of social assistance during or the year before pregnancy	10,562 (79.5)	6,946 (79.5)	3,484 (79.3)	132 (85.7)
Level of education at delivery (y)				
≤11	7,898 (59.5)	5,200 (59.5)	2,608 (59.4)	90 (58.4)
12-15	3,729 (28.1)	2,401 (27.5)	1,284 (29.2)	44 (28.6)
≥16	672 (5.1)	467 (5.4)	197 (4.5)	8 (5.2)
Missing	981 (7.4)	666 (7.6)	303 (6.9)	12 (7.8)
Urban area of residence at delivery	10,731 (80.8)	7,098 (84.3)	3,514 (80.0)	119 (77.3)
Pregnancy-related variables				
1st pregnancy	4,229 (31.8)	2,615 (30.1)	1,557 (35.6)	57 (37.8)
Multiple pregnancy	194 (1.5)	122 (1.4)	68 (1.6)	4 (2.6)
Maternal chronic conditions				
Chronic hypertension	317 (2.4)	184 (2.1)	124 (2.8)	9 (5.8)
Diabetes mellitus	314 (2.4)	186 (2.1)	119 (2.7)	9 (5.8)
1st trimester use of teratogenic medications or epilepsy	250 (1.9)	149 (1.7)	95(2.2)	6 (3.9)
Asthma-related variables during the 1st trimester				
Use of SABA (doses/wk)				
0-3	9,443 (71.1)	7,386 (84.6)	2,045 (46.6)	12 (7.8)
>3	3,837 (28.9)	1,348 (15.4)	2,647 (53.4)	142 (92.2)
Use of LABA	169 (1.3)	8 (0.1)	132 (3.0)	29 (18.8)
Use of theophylline	285 (2.2)	97 (1.1)	164 (3.7)	24 (15.6)
Use of oral corticosteroids	487 (3.7)	99 (1.3)	360 (8.2)	28 (18.2)
Use of intranasal corticosteroids	529 (4.0)	218 (2.5)	288 (6.6)	23 (14.9)
Hospitalizations or ED visits for asthma	670 (5.1)	197 (2.3)	441 (10.0)	32 (20.8)
Exacerbation for asthma†	833 (6.3)	244 (2.8)	552 (12.6)	37 (24.0)
Asthma severity in the year before pregnancy				
Mild	10,899 (82.0)	8,070 (92.4)	2,802 (63.8)	17 (11.1)
Moderate	1,634 (12.3)	567 (6.5)	1,032 (23.5)	35 (22.7)
Severe	757 (5.7)	97 (1.1)	558 (12.7)	102 (66.2)

LABA, Long-acting inhaled β_2 -agonist; SABA, short-acting inhaled β_2 -agonist.

*ICSs in beclomethasone dipropionate-chlorofluorocarbonyl equivalent.

†A filled prescription for oral corticosteroids, an ED visit for asthma, or a hospitalization for asthma.

On the other hand, we observed that women who took high doses of ICSs had undoubtedly more severe or uncontrolled asthma during the first trimester as shown in Table I, and women experiencing moderate to severe exacerbations have been found to be at increased risk of congenital malformations.³⁹ Moreover, the number of women using high doses was relatively small, casting doubt on the capacity of the models to adjust fully for markers of asthma control and severity and potentially producing relative risk estimates that overestimate the effect of ICSs on congenital malformations. In addition, our models did not adjust for clinical measures of asthma severity and control such as the pulmonary function (FEV₁, peak flow) and the frequency of day and night symptoms. Another argument in favor of uncontrolled asthma is that women who did not use ICSs but had uncontrolled asthma during the first trimester we found to be more at risk of having a baby with a congenital malformation than women who used low to moderate doses of ICSs. A last argument in favor of an effect of uncontrolled or severe asthma is that uncontrolled asthma and exacerbations might provoke maternal and fetal

hypoxia combined with respiratory alkalosis, which in turn can decrease the placental blood flow,^{1,40-42} and these phenomena have been associated with congenital malformations in mice and rats.⁴³

The results of this study should be interpreted in light of the following weaknesses. First, the use of medications is based on medication claims, and this might not exactly reflect actual use. Second, medications dispensed in hospitals including the ED are not recorded in the RAMQ database. In certain cases, women who were hospitalized for asthma might have taken oral corticosteroids during their stay and not continued after discharge or might have been dispensed oral corticosteroids at discharge for the remaining days of the therapy, in which case their use of oral corticosteroids would not have been taken into account in our model. If present, this phenomenon could have led to an overestimation of the effect of ICSs on congenital malformations. Third, cases of congenital malformations were identified by using diagnoses recorded in the administrative databases and have not been formally validated, but there is no reason to believe that the outcome misclassification would be

TABLE II. Adjusted RRs of all and major congenital malformations in association with categories of ICS daily dose taken during the first trimester of pregnancy

	All malformations Adjusted OR* (95% CI)	Major malformations Adjusted OR* (95% CI)
Daily dose of ICSs (μg), 1st trimester†		
0	1.08 (0.94-1.24)	1.06 (0.89-1.26)
>0-1000	Reference	Reference
>1000	1.66 (1.02-2.68)	1.67 (0.91-3.06)
Maternal age at the beginning of pregnancy (y)		
≤18	0.80 (0.62-1.04)	0.81 (0.58-1.12)
19-34	Reference	Reference
≥35	1.19 (0.95-1.49)	1.18 (0.89-1.56)
Level of asthma severity before pregnancy		
Mild	Reference	Reference
Moderate	0.95 (0.72-1.25)	1.03 (0.73-1.45)
Severe	0.96 (0.80-1.17)	0.95 (0.75-1.21)
Multiple pregnancy (yes/no)	3.02 (2.16-4.23)	2.85 (1.92-4.25)
Maternal diabetes mellitus (yes/no)	1.49 (1.08-2.05)	1.50 (1.02-2.21)

*ORs are adjusted for all variables listed in the table unless otherwise specified.

†A total of 8,734 pregnancies in the 0 category, 4392 pregnancies in the >0 to 1000 category, and 154 pregnancies in the >1000 category.

TABLE III. Adjusted RRs of all and major congenital malformations in association with categories of ICS daily dose taken during the first trimester of pregnancy stratified for the presence or not of markers of uncontrolled or severe asthma during the first trimester

	No. of patients	All malformations No. of babies with a malformation	Adjusted RR (95% CI)	Major malformations No. of babies with a malformation	Adjusted RR (95% CI)
No markers* of uncontrolled or severe asthma during the first trimester					
Daily dose of ICSs* (μg) in the 1st trimester					
0	7229	679 (9.4)	1.00 (0.83-1.20)	429 (5.9)	1.03 (0.83-1.28)
>0-1000	1884	175 (9.3)	Reference	108 (5.7)	Reference
>1000	12	2 (16.7)	1.89† (0.44-8.15)	1 (8.3)	1.42† (0.83-9.62)
≥1 marker* of uncontrolled or severe asthma during the first trimester					
Daily dose of ICSs* (μg) in the 1st trimester					
0	1505	162 (10.8)	1.31 (1.06-1.63)	90 (6.0)	1.12 (0.85-1.48)
>0-1000	2508	219 (8.7)	Reference	140 (5.6)	Reference
>1000	142	20 (14.1)	1.56 (0.95-2.58)	14 (9.9)	1.68 (0.93-3.05)

*Markers of uncontrolled or severe asthma are a filled prescription of oral corticosteroids, an ED visit for asthma, a hospitalization for asthma, or >3 doses of short-acting inhaled β₂-agonist per week on average during the first trimester of pregnancy.†RR adjusted for the severity of asthma before conception, the use of long-acting inhaled β₂-agonist during the first trimester, maternal diabetes mellitus, and multiple pregnancy.||RR adjusted for the use of long-acting inhaled β₂-agonist during the first trimester and multiple pregnancy.

different in terms of the use of ICSs during pregnancy. Fourth, the cohort is underrepresented by women with average or high socioeconomic status, and this might limit the generalizability of the study results if the socioeconomic status is an effect modifier. However, we think that this is unlikely because the association between ICS use and congenital malformations is believed to be physiologic in nature. On the other hand, having a more homogenous study population would increase the internal validity of the study if the socioeconomic status is a confounder. Fifth, because of the relatively small number of women exposed to high doses of ICSs during pregnancy, we did not have the statistical power to study specific malformations such as cardiac malformations and cleft lip/palate that have been found to be associated with asthma.¹⁷ Our study also has several strengths, such as its large sample size allowing the assessment of the dose of ICSs used during the first trimester, data on prescribed

medications that have been collected prospectively and independently of the outcome, the absence of bias as a result of patients' recall, and the use of recognized and objective markers of asthma exacerbations.^{8,37,38}

In conclusion, our study adds evidence on the safety of low to moderate doses of ICSs taken during the first trimester, but raises concerns about high doses by comparison with low to moderate doses. On the basis of our results, it is not possible to attribute the observed increased risk of congenital malformation entirely to a teratogenic effect of ICSs because we cannot rule out the possibility of residual confounding by severity. Despite the uncertainty about the direct cause of the observed increased risk, women planning a pregnancy and using high doses of ICSs should be followed closely to identify the minimal dose needed to maintain asthma under control.

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Clinical implications: Prescribers should identify the lowest dose of ICSs needed to maintain asthma under control during pregnancy to avoid a possible increased risk of congenital malformations.

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TABLE E1. Algorithm to calculate the average daily dose of ICSs within a prespecified period

1. We first identify all prescriptions of ICSs that cross the period under study (the first trimester of pregnancy in the current study).
2. We determine the duration of the prescription within the period under study. The duration of a prescription is equal to the number of days between 2 successive renewals. If the prescription is the last that the patient filled, the duration will be equal to the mean duration of the previous prescriptions. If the patient had only 1 prescription, the duration will be equal to the number of days recorded in the RAMQ database.
3. If the prescription starts before the period under study or the last day of the prescription is beyond the end of the period under study, the duration of the prescription is adjusted accordingly.
4. We calculate the number of micrograms per prescription by taking care of the number of days of the prescription that fall within the period under study. The RAMQ database records the number of micrograms prescribed.
5. We apply the equivalences between the different ICS products according to the Canadian Asthma Consensus Guidelines.
6. We calculate the total number of micrograms for the period under study by summing the number of micrograms for all prescriptions falling within the period under study.
7. We calculate the average number of micrograms per day by dividing the total number of micrograms by the length of the period under study expressed in days.

TABLE E2. Distribution of congenital malformations

	All malformations		Major malformations	
	No.	Percent	No.	Percent
Musculoskeletal	354	21.7	139	12.4
Cardiac	268	16.4	266	23.6
Digestive system	139	8.5	128	11.4
Eye, ear, face, and neck	108	6.6	73	6.5
Genital organs	108	6.6	37	3.3
Circulatory system	105	6.4	90	8.0
Nervous system	95	5.8	95	8.4
Urinary system	64	3.9	63	5.6
Respiratory system	57	3.5	40	3.6
Limbs	53	3.3	30	2.7
Integument	42	2.6	26	2.3
Cleft palate and cleft lip	32	2.0	32	2.8
Chromosomal	21	1.3	21	1.9
Spina bifida	12	0.7	11	1.0
Other	175	10.7	74	6.6
Total*	1633	100.0	1125	100.0

*The total exceeds the number of cases (1257 for all malformations and 782 for major malformations) because an infant might have had more than 1 malformation.

TABLE E3. Crude prevalence of congenital malformations as a function of the daily dose of ICSs during the first trimester of pregnancy

Daily dose of ICSs* (μg) in in the 1st trimester	No. of patients (%)	Mean daily dose ± SD (μg)	All malformations	Major malformations
			No. (%)	No. (%)
0	8734 (65.8)	0	841 (9.6)	519 (5.9)
>0-1000	4392 (33.1)	185.5 ± 192.7	394 (9.0)	248 (5.7)
>1000	154 (1.1)	1469.4 ± 434.0	22 (14.3)	15 (9.7)

*ICSs in beclomethasone dipropionate-chlorofluorocarbonyl equivalent.

TABLE E4. Crude RRs for all and major congenital malformations

	All malformations	Major malformations
	Crude RR (95% CI)	
Maternal sociodemographic variables		
Age at conception (y)		
≤ 18	0.79 (0.61-1.02)	0.80 (0.57-1.10)
19-34	Reference	Reference
≥35	1.23 (0.98-1.54)	1.22 (0.92-1.60)
Receipt of social assistance during or the year before pregnancy	1.08 (0.93-1.25)	1.22 (1.01-1.48)
Level of education at delivery (y)		
≤11	Reference	Reference
12-15	1.00 (0.88-1.15)	0.98 (0.83-1.16)
≥16	1.04 (0.80-1.36)	0.92 (0.66-1.30)
Missing	0.90 (0.70-1.14)	0.89 (0.67-1.20)
Urban versus rural area of residence at delivery	0.87 (0.74-1.01)	0.87 (0.72-1.06)
Pregnancy-related variables		
1st pregnancy vs 2nd or more	0.94 (0.84-1.07)	1.04 (0.89-1.21)
Multiple pregnancy vs singleton	3.06 (2.19-4.28)	2.90 (1.95-4.32)
Maternal chronic conditions		
Chronic hypertension (yes/no)	1.18 (0.82-1.71)	1.31 (0.84-2.03)
Diabetes mellitus (yes/no)	1.53 (1.11-2.11)	1.54 (1.04-2.28)
Epilepsy (yes/no)	1.60 (0.99-2.58)	2.09 (1.23-3.54)
1st trimester use of teratogenic medications (yes/no)	1.33 (0.83-2.11)	1.76 (1.06-2.94)
Asthma-related variables during the 1st trimester		
Daily dose of ICSs* (µg)		
0	1.08 (0.95-1.23)	1.06 (0.90-1.24)
>0-1000	Reference	Reference
>1000	1.68 (1.06-2.67)	1.78 (1.01-3.13)
Use of SABA (doses/wk)		
0	Reference	Reference
>0-3	1.08 (0.94-1.24)	1.02 (0.85-1.22)
>3	1.00 (0.87-1.15)	0.94 (0.79-1.12)
Use of LABA (yes/no)	1.42 (0.91-2.23)	1.44 (0.83-2.50)
Use of theophyllines (yes/no)	1.00 (0.68-1.48)	1.04 (0.63-1.70)
Use of oral corticosteroids (yes/no)	1.13 (0.84-1.53)	1.16 (0.80-1.68)
Use of intranasal corticosteroids (yes/no)	1.09 (0.81-1.46)	1.36 (0.97-1.91)
Hospitalizations or ED visits for asthma (yes/no)	1.20 (0.93-1.54)	1.27 (0.93-1.72)
Asthma severity in the year before pregnancy		
Mild	Reference	Reference
Moderate	0.96 (0.80-1.15)	0.95 (0.76-1.20)
Severe	1.00 (0.78-1.29)	1.11 (0.82-1.50)

*ICSs in beclomethasone dipropionate-chlorofluorocarbene equivalent.