

Relationship Between Changes in Inhaled Corticosteroid Use and Markers of Uncontrolled Asthma During Pregnancy

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Study Objective. To describe changes in inhaled corticosteroid use during pregnancy and markers of uncontrolled asthma, and to evaluate the association between them.

Design. Population-based, cross-sectional study.

Data Source. Three administrative claims databases in Québec, Canada.

Patients. A cohort of 4434 asthmatic women (4920 pregnancies) who delivered their infants between 1990 and 2002 and who used inhaled corticosteroids before their pregnancy.

Measurements and Main Results. The average daily doses of inhaled corticosteroids during pregnancy and during the 9 months before conception were compared; the change in use was categorized as discontinuation (reduction of $\geq 75\%$), reduction (26–75% reduction), no change ($\pm 25\%$ change), or increase (increase of $\geq 25\%$). The markers of uncontrolled asthma included at least one asthma exacerbation and the use of three or more doses/week of a short-acting β_2 -agonist during pregnancy. Generalized estimating equation models were used for statistical analyses. In nearly 50% of the pregnancies (2388 [48.5%] of 4920), the women either stopped or reduced their doses of corticosteroid during pregnancy, and these doses were already quite low before pregnancy. The proportion of women who had an asthma exacerbation during pregnancy was 8.2% among women who discontinued corticosteroids and greater than 20% in all of the other groups. All of the groups used frequent doses of short-acting β_2 -agonists. Discontinuing inhaled corticosteroid use during pregnancy was associated with a lower risk of exacerbations (odds ratio [OR] 0.42, 95% confidence interval [CI] 0.33–0.54), whereas increasing inhaled corticosteroid use was associated with a higher risk (OR 1.42, 95% CI 1.17–1.72), compared with no change in use.

Conclusion. Because of residual confounding by asthma severity, our study was not able to show that women who stopped inhaled corticosteroids during pregnancy were at increased risk of having an asthma exacerbation. However, women who stopped corticosteroids tended to have a milder form of asthma, which is reassuring and suggests that women can recognize, to a certain extent, the need to continue taking their controller agents if necessary.

Key Words: asthma, pregnancy, inhaled corticosteroids, patterns of use, exacerbations, rescue agents.

(Pharmacotherapy 2012;32(3):202–209)

Asthma has become the most common chronic disease encountered during pregnancy, affecting approximately 8% of expectant women.^{1, 2} Because of the potential adverse effect of asthma exacerbations on both mother and fetus, current guidelines state that pregnant women with asthma must be treated during pregnancy as aggressively as at other times to maintain optimal asthma control for their health, as well as for the normal maturation of their fetus.³ In particular, the guidelines recommend continuous use of inhaled corticosteroids³ because of their effectiveness and their safety for both the mother and the infant compared with the risks of uncontrolled asthma.⁴⁻⁹

Many women, however, are concerned about the harm that asthma drugs could cause their unborn child and remain apprehensive about using them during pregnancy. A recent survey reported that 82% of women of childbearing age who used inhaled corticosteroids were concerned about potential adverse effects such as congenital malformations and fetal death,² and 39% of the women reported discontinuing or reducing their drug therapy during pregnancy, quite often without first seeking advice from their physician.² Another study found that 65% of pregnant women with asthma were undertreated for asthma for three or more months of pregnancy.¹⁰ Furthermore, a recent cohort study also showed that the use of different classes of asthma drugs dropped in the first trimester of pregnancy, with the largest declines occurring for inhaled and oral corticosteroids.¹¹ However, none of these studies focused on the daily dose of inhaled corticosteroids and simultaneously

reported the changes in use of inhaled corticosteroids and the risk of asthma exacerbations during pregnancy.

Based on a large cohort of pregnancies from asthmatic women, which has been used to study the impact of asthma and asthma drugs on the health of the mother and the newborn,¹²⁻¹⁸ we conducted a cross-sectional analysis to describe the changes in the doses of inhaled corticosteroids during pregnancy and markers of uncontrolled asthma, namely, asthma exacerbations and frequent use of rescue drugs.

Methods

Data Source

Data for this study were retrieved from three administrative databases from the Canadian province of Québec linked by a unique identifier. The Régie de l'Assurance-Maladie du Québec (RAMQ) database provides information on medical services dispensed to all residents of Québec and prescribed drugs filled in community pharmacies for residents insured by the RAMQ Drug Insurance Plan (~42% of the residents of Québec).¹⁹ These include the elderly and recipients of social welfare since 1980, and, since January 1997, 1.7 million other residents, mainly workers and their families who are not covered under a private drug insurance plan at their workplace. The Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (MED-ECHO) database contains information on all acute care 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 for epidemiologic research in the field of asthma.^{8, 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 previously evaluated and deemed to be valid.^{24, 25} Moreover, pregnancy-related variables such as birth weight, gestational age, beginning date of pregnancy, and date of delivery directly recorded in or derived from the RAMQ, MED-ECHO, and ISQ databases based on our own algorithms have also been formally evaluated and found to be highly valid.²⁶

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Funded by the Canadian Institutes of Health Research.

Presented as a poster at the 50th annual meeting of the Teratology Society, Louisville, Kentucky, June 26-30, 2010.

Manuscript received May 3, 2011. Accepted pending revisions June 23, 2011. Accepted for publication in final form September 13, 2011.

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An authorization was granted by the Commission d'Accès à l'Information du Québec before requesting and linking the information from the three databases. This research project was approved by the Ethics Committee of the Hôpital du Sacré-Coeur de Montréal.

Study Design

This cross-sectional analysis was conducted in a cohort of pregnancies from asthmatic women that was formed from the linkage of the RAMQ, MED-ECHO, and ISQ databases. This cohort has been used to answer other research questions and has previously been described.^{12–18} For the present study, the inclusion criteria were as follows: having at least one singleton pregnancy ending in a delivery with known gestational age and birth weight (live birth or stillbirth) between 1990 and 2002; being 13–50 years of age at the beginning of pregnancy; having at least one diagnosis of asthma (*International Classification of Diseases, Ninth Revision* [ICD-9] code 493) and at least one prescription for any asthma drug at any point in time in the previous 2 years or during the pregnancy; being covered by the RAMQ Drug Insurance Plan for at least 1 year before and throughout the duration of the pregnancy; having no other pregnancy during the 9 months before the current pregnancy; and having filled at least one prescription for inhaled corticosteroids during the 9 months before the current pregnancy.

For each pregnancy included in the cohort, we obtained data from the RAMQ medication prescriptions file on all prescriptions filled by the mother—date of filling, name of the drug, dose, dosage form, quantity and duration of the prescription, and specialty of the prescribing physician—for at least 1 year before and during the pregnancy. We also obtained data from the RAMQ medical services 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, hospital), diagnosis code, and specialty of the treating physician—in the year preceding and during the pregnancy. The RAMQ also provided the date of birth of the mothers and children, the social aid status, as well as the area of residence of the mother during her pregnancy. The MED-ECHO database provided data on all maternal acute care hospitalizations, such as date of admission, length of stay, and primary and secondary diagnoses, occurring in the year

preceding and during the pregnancy. The ISQ database provided data relevant to the level of education of the mother and the parity of the ongoing pregnancy. Using the gestational age at birth and the 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.

Changes in Inhaled Corticosteroid Use

The daily dose of inhaled corticosteroid—beclomethasone, budesonide, fluticasone, flunisolide, or triamcinolone—used during pregnancy and in the 9 months before pregnancy was estimated with an algorithm that we developed and used in previous studies.^{13, 18} The algorithm is based on the name of the drug and equivalences between the different inhaled corticosteroid products as recognized by the Canadian Asthma Consensus Guidelines,^{27, 28} the dose prescribed, the date and duration of the prescription, and the rate of renewals of the prescription.^{8, 23} The daily dose of inhaled corticosteroid was expressed in micrograms of beclomethasone-chlorofluorocarbon equivalent. The average daily dose of inhaled corticosteroid during pregnancy was then compared with the average daily dose in the 9 months before conception, and the change was categorized as discontinuation (reduction of $\geq 75\%$), reduction (26–75% reduction), no change ($\pm 25\%$ change), and increase (increase of $>25\%$) in the use of inhaled corticosteroid during pregnancy.

Markers of Uncontrolled Asthma

At least one asthma exacerbation and the use of three or more doses/week of short-acting β_2 -agonists (SABAs) on average were considered as markers of uncontrolled asthma during pregnancy. Based on the criteria used in the Canadian Asthma Consensus Guidelines,^{27, 28} asthma exacerbations were defined as a filled short-course (≤ 14 d) prescription of an oral corticosteroid, an emergency department visit for asthma, or a hospitalization for asthma, which are recognized as objective markers of asthma exacerbations.^{27–30} If any combination of these events occurred during an interval of 15 days, it was considered a single exacerbation.

To obtain an estimate of SABA use during pregnancy, we used an algorithm that we developed in another study and that calculates the number of doses used per week. This algorithm

is based on equivalencies between the different SABAs filled (available from the authors on request), date of filling, quantity dispensed, and time span between prescription renewals.³¹ We assumed that one dose was equivalent to two inhalations of salbutamol 100 µg (albuterol 90 µg).^{27, 28}

Maternal Characteristics

Maternal sociodemographic characteristics included age at conception (<18, 18–34, >34 yr), receipt of social assistance during or in the year before pregnancy (yes/no), level of education at delivery (≤ 11 , 12–15, ≥ 16 yr), and area of residence at delivery (rural/urban).

Pregnancy-related variables included parity (first/second pregnancy or more), high-risk pregnancy as identified by the physician providing prenatal care (yes/no), pregnancy-induced hypertension (yes/no), gestational diabetes mellitus (yes/no), gynecologist or obstetrician visit during pregnancy (yes/no), and number of prenatal visits (≤ 5 , 6–14, >14).

Maternal chronic conditions included chronic hypertension (yes/no) and diabetes mellitus (yes/no). Pregnancy-induced hypertension, chronic hypertension, gestational diabetes, and diabetes mellitus were identified from diagnoses or filled prescriptions of related drugs 1 year before or during the pregnancy using specific algorithms that we developed for each condition and used in other studies,^{8, 13, 14, 32, 33} details of which are available on request.

Asthma-related variables included the use of long-acting inhaled β_2 -agonists (yes/no), use of theophylline (yes/no), use of leukotriene-receptor antagonists (yes/no), and a visit to a respiratory physician (yes/no) during pregnancy, as well as markers of uncontrolled asthma in the year before pregnancy, as defined above. The severity of asthma before pregnancy was also considered and measured with a validated index (mild, moderate, or severe asthma) based on the use of asthma drugs and urgent care for asthma over the 12-month period before pregnancy.

Statistical Analysis

We first estimated the proportion of women who had discontinued, reduced, not changed, or increased their inhaled corticosteroid usage during pregnancy. Descriptive statistics were then used to describe the characteristics of the

women according to the categories of change in inhaled corticosteroid use during pregnancy. Proportions of women who had an asthma exacerbation and those who used three or more doses/week of a SABA during pregnancy were estimated within each of the inhaled corticosteroid use categories.

The comparison of the risk of an exacerbation and high use of SABAs across inhaled corticosteroid categories was made by using generalized estimating equation (GEE) models providing odds ratios and 95% confidence intervals. The GEE models can estimate the effect of independent variables on several types of outcomes, namely, dichotomous outcomes such as the occurrence of an exacerbation during pregnancy with a logit function and factor the fact that a woman could contribute to more than one pregnancy in the analysis by estimating the correlation between consecutive pregnancies.³⁴

In all models, all of the aforementioned characteristics were included as independent variables in addition to the variable describing the change in inhaled corticosteroid use for which the no change category was used as the reference.

Results

The cohort used in this study included 4434 asthmatic women who had a total of 4920 pregnancies ending with a live birth or a stillbirth between 1990 and 2002 and who fulfilled the inclusion criteria. In this cohort of 4920 pregnancies, 29.5% of the pregnancies were from women who discontinued, 19.0% from those who reduced, 28.8% from those who increased, and 22.7% from those who did not change their inhaled corticosteroid use during pregnancy (Table 1). Overall, there were no differences in sociodemographic characteristics, maternal chronic conditions, and most pregnancy-related variables among the groups. However, fewer women used long-acting inhaled β_2 -agonists, theophylline, or leukotriene-receptor antagonists and had a visit to a respiratory physician during pregnancy among those who discontinued corticosteroids than among the three other groups.

As shown in Table 2, the mean daily doses of inhaled corticosteroid during the 9 months before conception and during pregnancy itself were low for all groups. Women who discontinued had lower daily doses of inhaled corticosteroid than those who reduced or did not change

Table 1. Maternal Characteristics Stratified by Categories of Change in Inhaled Corticosteroid Use During Pregnancy Compared with the 9-Month Period Before Pregnancy in the 4434 Asthmatic Women with 4920 Pregnancies

Characteristic	Change in Inhaled Corticosteroid Use			
	Discontinuation (n=1454)	Reduction (n=934)	No Change (n=1115)	Increase (n=1417)
Proportion of all pregnancies	29.5%	19.0%	22.7%	28.8%
<i>Maternal sociodemographic variables</i>				
Age at conception (yrs)				
<18	115 (7.9)	83 (8.9)	78 (7.0)	95 (6.7)
18–34	1235 (85.0)	797 (85.3)	957 (85.8)	1209 (85.3)
>34	104 (7.1)	54 (5.8)	80 (7.2)	113 (8.0)
Received social assistance during or in year before pregnancy	1124 (77.3)	758 (81.6)	844 (75.7)	1135 (80.1)
Level of education at delivery (yrs)				
≤ 11	845 (58.1)	576 (61.7)	622 (55.8)	855 (60.3)
12–15	416 (28.6)	255 (27.3)	366 (32.8)	408 (28.8)
≥ 16	92 (6.3)	35 (3.8)	60 (5.4)	59 (4.2)
Data not available	101 (7.0)	68 (7.3)	67 (6.0)	95 (6.7)
Urban area of residence at delivery	1163 (80.0)	746 (79.9)	878 (78.7)	1138 (80.3)
<i>Pregnancy-related variables</i>				
First pregnancy	594 (40.9)	386 (41.5)	448 (40.3)	519 (36.8)
High-risk pregnancy	493 (33.9)	346 (37.0)	397 (35.6)	561 (39.6)
Pregnancy-induced hypertension	106 (7.3)	77 (8.2)	86 (7.7)	114 (8.1)
Gestational diabetes mellitus	110 (7.6)	76 (8.1)	94 (8.4)	130 (9.2)
Gynecologist or obstetrician visit during pregnancy	1085 (74.6)	672 (72.0)	799 (71.7)	1047 (73.9)
No. of prenatal visits				
≤ 5	191 (13.1)	149 (16.0)	163 (14.6)	199 (14.0)
6–14	1082 (74.4)	681 (72.9)	783 (70.2)	1030 (72.7)
>14	181 (12.5)	104 (11.1)	169 (15.2)	188 (13.3)
<i>Maternal chronic conditions</i>				
Hypertension	37 (2.5)	33 (3.5)	29 (2.6)	46 (3.3)
Diabetes mellitus	34 (2.3)	30 (3.2)	29 (2.6)	50 (3.5)
<i>Asthma-related variables</i>				
<i>During pregnancy</i>				
Use of long-acting β -agonists	12 (0.8)	51 (5.5)	50 (4.5)	77 (5.4)
Use of theophylline	24 (1.7)	46 (4.9)	56 (5.0)	70 (4.9)
Use of leukotriene-receptor antagonists	0 (0.0)	7 (0.8)	14 (1.3)	14 (1.0)
≥ 1 visit to a respiratory physician	35 (2.4)	61 (6.5)	93 (8.3)	181 (12.8)
<i>In year preceding pregnancy</i>				
Asthma severity				
Mild	1141 (78.5)	488 (52.2)	694 (62.2)	875 (61.7)
Moderate	230 (15.8)	263 (28.2)	243 (21.8)	344 (24.3)
Severe	83 (5.7)	183 (19.6)	178 (15.6)	198 (14.0)
Markers of uncontrolled asthma	835 (57.4)	687 (73.6)	672 (60.3)	906 (63.9)
≥ 1 asthma exacerbation	367 (25.2)	338 (36.2)	353 (31.7)	495 (34.9)
≥ 1 emergency department visit for asthma	262 (18.0)	249 (26.7)	244 (21.9)	357 (25.2)
≥ 1 hospitalization for asthma	22 (1.5)	40 (4.3)	28 (2.5)	32 (2.3)
Use of oral corticosteroids	239 (16.4)	246 (26.3)	255 (22.9)	352 (24.8)
≥ 3 doses/wk of short-acting β_2 -agonists	659 (45.3)	624 (66.8)	565 (50.7)	745 (52.6)

Data are no. (%) of pregnancies.

their inhaled corticosteroid dose during their pregnancy.

The overall proportion of women who had one or more asthma exacerbations during pregnancy was 19.5%. This proportion was the lowest (8.2%) among women who discontinued inhaled corticosteroid, and >20% in all other groups (Table 3). Moreover, the proportion of women with frequent SABA use was higher than 49% in all groups except among women who discontin-

ued (20%). Table 3 also shows that women who discontinued inhaled corticosteroid use during pregnancy were significantly less likely to have an asthma exacerbation and to use more than three doses/week of an SABA, whereas women who increased their dose of inhaled corticosteroid were more likely to have an exacerbation and to use more than three doses/week of an SABA compared with women who did not change their dose of inhaled corticosteroid.

Table 2. Daily Doses of Inhaled Corticosteroids Before and During Pregnancy Stratified by Categories of Change in Inhaled Corticosteroid Use During Pregnancy

Change Category	No (%) of Pregnancies	Daily Dose of Inhaled Corticosteroid (mean $\pm$ SD) ^a	
		9 Mo Before Conception	During Pregnancy
Discontinuation	1454 (29.5)	179.5 $\pm$ 187.5	8.0 $\pm$ 28.4
Reduction	934 (19.0)	325.6 $\pm$ 408.7	158.2 $\pm$ 219.3
No change	1115 (22.7)	228.7 $\pm$ 331.3	218.4 $\pm$ 320.9
Increase	1417 (28.8)	125.2 $\pm$ 181.7	290.0 $\pm$ 330.5

^aDaily dose expressed in μ g of beclomethasone-chlorofluorocarbon equivalent.

Table 3. Proportions of Women With Uncontrolled Asthma and the Association Between the Changes in Inhaled Corticosteroid Use During Pregnancy and Occurrence of These Markers

Variable	Change in Inhaled Corticosteroid Use			
	Discontinuation (n=1454)	Reduction (n=934)	No Change (n=1115)	Increase (n=1417)
Markers of uncontrolled asthma	No. (%) of Pregnancies			
≥ 1 asthma exacerbation during pregnancy	119 (8.2)	192 (20.6)	242 (21.7)	408 (28.8)
≥ 3 doses/wk of short-acting β_2 -agonists	291 (20.0)	486 (52.0)	550 (49.3)	898 (63.4)
	Adjusted OR (95% CI) ^a			
Association with change category				
≥ 1 asthma exacerbation during pregnancy	0.41 (0.32–0.53)	0.83 (0.67–1.04)	Reference	1.41 (1.16–1.71)
≥ 3 doses/wk of short-acting β_2 -agonists	0.24 (0.19–0.30)	0.71 (0.57–0.88)	Reference	2.24 (1.84–2.73)

OR = odds ratio; CI = confidence interval.

^aAdjusted for age at conception (<18, 18–34, >34 yr), receipt of social assistance during or in the year before pregnancy (yes/no), level of education at delivery ($\leq$ 11, 12–15, $\geq$ 16 yr, data not available), area of residence at delivery (rural/urban), parity (first/second pregnancy or more), high-risk pregnancy (yes/no), pregnancy-induced hypertension (yes/no), gestational diabetes (yes/no), gynecologist or obstetrician visit during pregnancy (yes/no), number of prenatal visits ($\leq$ 5, 6–14, >14), chronic hypertension (yes/no), diabetes mellitus (yes/no), use of long-acting inhaled β_2 -agonists (yes/no), use of theophylline (yes/no), use of leukotriene-receptor antagonists (yes/no), a visit to a respiratory physician (yes/no) during pregnancy, severity of asthma in the year before pregnancy (mild, moderate, or severe), and uncontrolled asthma (yes/no).

Discussion

Our study revealed that the women discontinued or reduced their use of inhaled corticosteroid during nearly 50% of the pregnancies and, overall, the mean daily doses of inhaled corticosteroid taken before and during pregnancy were very low. Moreover, the proportion of women who had an asthma exacerbation and the proportion of women who used a SABA frequently during pregnancy were very high in all groups, except for exacerbations among women who discontinued inhaled corticosteroid use. When asthma exacerbations were compared among groups, we found that women who discontinued inhaled corticosteroid use during pregnancy were significantly less likely to have an exacerbation than women who did not change their dose of inhaled corticosteroid, whereas those who increased their inhaled corticosteroid dose were more likely to have an asthma exacerbation.

Our observed proportions of women who discontinued or reduced their inhaled corticosteroid use during pregnancy are consistent with the findings contained in the literature.^{2, 10, 11} One cohort study showed that asthmatic women decreased and/or stopped their asthma drugs

during early pregnancy despite recommendations from the guidelines with, in particular, a 23% drop in inhaled corticosteroid use from week 5 to week 13 of pregnancy.¹¹ In another cohort study, results indicated that 65% of asthmatic women were not treated according to the National Asthma Education and Prevention Program guidelines; in effect, they were undertreated for three or more months of pregnancy.¹⁰ Finally, a survey study revealed that 39% of women reported discontinuing or reducing their asthma drug during pregnancy.²

The overall observed high prevalence (19.5%) of asthma exacerbation during pregnancy in our study also corroborates the data from the literature. A systematic review showed that during pregnancy, exacerbations of asthma requiring medical intervention occurred in about 20% of women.³⁵ Another group reported a prevalence of asthma exacerbation during pregnancy of 22.9%.³⁶

To the best of our knowledge, this is the first study to simultaneously report the change in inhaled corticosteroid use and markers of uncontrolled asthma. We found that women who discontinued their therapy were less likely to have an exacerbation and to frequently use a

SABA. One possible explanation is that the discontinuation of inhaled corticosteroid during pregnancy was the consequence of an improvement in the control of asthma during pregnancy and thus, less need for therapy. Indeed, women who discontinued inhaled corticosteroid therapy were less likely to use other asthma drugs and to have a medical visit with a respiratory physician during pregnancy. Moreover, it has been reported in the literature that asthma improves in one third of women during pregnancy.³⁷ However, for a better interpretation of our results, it is worth noting that women who discontinued their inhaled corticosteroid therapy took, on average, very low doses before pregnancy (179.5 $\mu\text{g}/\text{d}$)³ and that these prepregnancy inhaled corticosteroid doses were lower than the doses used by women who did not change their doses during pregnancy. These observations suggest that women who discontinued their inhaled corticosteroid therapy during pregnancy could have had a milder form of asthma before pregnancy.

However, our study showed that an increase of inhaled corticosteroid therapy (from 125 to 290 $\mu\text{g}/\text{d}$) was associated with an increased risk of exacerbations. We can hypothesize that the increase in inhaled corticosteroid use was the consequence of the deterioration of the control of asthma during pregnancy, and women and their treating physicians felt the necessity to increase the dose of the controller therapy. It has also been reported in the literature that asthma worsens in one third of women during pregnancy.³⁷

Limitations

Our study has several strengths, mainly, a large sample size; drug data collected prospectively and independent of the outcome, which eliminates the possibility of recall bias; and the use of recognized and objective markers of asthma exacerbations.^{29, 30} Nevertheless, our study has some limitations. The first is that the association between the change in inhaled corticosteroid use and markers of uncontrolled asthma cannot be interpreted from a causal point of view because of the cross-sectional nature of the study design. Indeed, inhaled corticosteroid change and markers of uncontrolled asthma were ascertained simultaneously, and the temporal sequence between the exposure and the outcomes is impossible to determine.

Second, as discussed previously, women who discontinued inhaled corticosteroid therapy appeared to have a milder form of asthma and this could have induced a confounding bias. Third, the measurement of drug exposure was based on filled prescriptions, which might not always represent the actual use of drug therapy, and drugs dispensed during hospital stays were not recorded in the RAMQ database. The latter could have contributed to underestimation of the number of asthma exacerbations in all study groups since prescription of oral corticosteroids was used as a marker of exacerbation.

Fourth, the reasons for which women changed their inhaled corticosteroid doses and whether they did it independent of or following their physician's advice could not be elucidated in this study. Finally, the external validity of the study might be reduced since our cohort tended to overrepresent women with a lower socioeconomic status; all of the women in the cohort were covered by the public drug insurance plan before and during their pregnancy.

Conclusion

Our study results show that a large proportion of women either stopped or reduced their doses of inhaled corticosteroid during pregnancy. Irrespective of the category of change in inhaled corticosteroid use during pregnancy, pregnant women tended to use very low doses of inhaled corticosteroid before and during pregnancy, which might explain why a high proportion of them had an asthma exacerbation or used high doses of rescue therapy. However, we observed that women who stopped inhaled corticosteroid use were less likely to have an exacerbation or to frequently use a SABA, which suggests that women can recognize, to a certain extent, the need to persist with their controller therapy if it is necessary. Consequently, the optimal dose of inhaled corticosteroid should be determined, as much as possible, before pregnancy and continued throughout pregnancy, with close monitoring to adjust it if asthma symptoms start to increase.

References

1. Kwon HL, Belanger K, Bracken MB. Asthma prevalence among pregnant and childbearing-aged women in the United States: estimates from national health surveys. *Ann Epidemiol* 2003;13:317–24.
2. Chambers K. Asthma education and outcomes for women of childbearing age. *Case Manager* 2003;14:58–61.

3. National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program Asthma and Pregnancy Working Group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment—2004 update. *J Allergy Clin Immunol* 2005;115:34–46.
4. SteniusAarniala BSM, Hedman J, Teramo KA. Acute asthma during pregnancy. *Thorax* 1996;51:411–4.
5. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D. The safety of asthma and allergy medications during pregnancy. *J Allergy Clin Immunol* 1997;100:301–6.
6. Schatz M, Leibman C. Inhaled corticosteroid use and outcomes in pregnancy. *Ann Allergy Asthma Immunol* 2005;95:234–8.
7. Namazy J, Schatz M, Long L, et al. Use of inhaled steroids by pregnant asthmatic women does not reduce intrauterine growth. *J Allergy Clin Immunol* 2004;113:427–32.
8. Blais L, Beaulieu MF, Rey E, Malo JL, Forget A. Use of inhaled corticosteroids during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. *Thorax* 2007;62:320–8.
9. Bakhireva LN, Jones KL, Schatz M, Johnson D, Chambers CD. Asthma medication use in pregnancy and fetal growth. *J Allergy Clin Immunol* 2005;116:503–9.
10. Belanger K, Triche EW, Leaderer BP, Hellenbrand K, Bracken MB. Asthma treatment during pregnancy: are national guidelines being met? Presented at the American Thoracic Society Meeting, Atlanta, GA, May 17–22, 2002.
11. Enriquez R, Wu PS, Griffin MR, et al. Cessation of asthma medication in early pregnancy. *Am J Obstet Gynecol* 2006;195:149–53.
12. Breton MC, Beaulieu MF, Lemiere C, Rey E, Forget A, Blais L. Risk of perinatal mortality associated with asthma during pregnancy: a 2-stage sampling cohort study. *Ann Allergy Asthma Immunol* 2010;105:211–7.
13. Breton MC, Beaulieu MF, Lemiere C, Rey E, Forget A, Blais L. Risk of perinatal mortality associated with inhaled corticosteroid use for the treatment of asthma during pregnancy. *J Allergy Clin Immunol* 2010;126:772–7.
14. Firoozi F, Lemiere C, Ducharme FM, et al. Effect of maternal moderate to severe asthma on perinatal outcomes. *Respir Med* 2010;104:1278–87.
15. Martel MJ, Rey E, Beaulieu MF, et al. Control and severity of asthma during pregnancy are associated with asthma incidence in offspring: two-stage case-control study. *Eur Respir J* 2009;34:579–87.
16. Martel MJ, Beaulieu MF, Malo JL, et al. Maternal asthma, its control and severity in pregnancy, and the incidence of atopic dermatitis and allergic rhinitis in the offspring. *J Pediatr* 2009;155:707–13.
17. Eltonsy S, Forget A, Blais L. Beta₂-agonists use during pregnancy and the risk of congenital malformations [published online ahead of print September 22, 2011]. *Birth Defects Res A Clin Mol Teratol*. 2011;91:937–947.
18. Blais L, Beaulieu MF, Lemiere C, Elftouh N. High doses of inhaled corticosteroids during the first trimester of pregnancy and congenital malformations. *J Allergy Clin Immunol* 2009;124:1229–34.
19. Régie de l'assurance maladie du Québec. Annual statistics, 2002. Available from http://www.ramq.gouv.qc.ca/fr/publications/documents/rapp0203/rappann0203_gestion.pdf. Accessed March 21, 2011.
20. Martel MJ, Rey E, Beaulieu MF, et al. Use of short-acting beta₂-agonists during pregnancy and the risk of pregnancy-induced hypertension. *J Allergy Clin Immunol* 2007;119:576–82.
21. Marceau C, Lemière C, Berbiche D, Perreault S, Blais L. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. *J Allergy Clin Immunol* 2006;118:574–81.
22. Blais L, Beaulieu MF. Use of inhaled corticosteroids following discharge from an emergency department for an acute exacerbation of asthma. *Thorax* 2004;59:943–7.
23. Martel MJ, Rey E, Beaulieu MF, et al. Use of inhaled corticosteroids during pregnancy and risk of pregnancy-induced hypertension: nested case-control study. *BMJ* 2005;330:230–3.
24. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Québec. *J Clin Epidemiol* 1995;48:999–1009.
25. Blais L, Lemière C, Menzies D, Berbiche D. Validity of asthma diagnoses recorded in the Medical Services database of Québec. *Pharmacoepidemiol Drug Saf* 2006;15:245–52.
26. Vilain A, Otis S, Forget A, Blais L. Agreement between administrative databases and medical charts for pregnancy-related variables among asthmatic women. *Pharmacoepidemiol Drug Saf* 2008;17:345–53.
27. Boulet LP, Becker A, Berube D, Beveridge R, Ernst P; for the Canadian Asthma Consensus Group. Canadian asthma consensus report, 1999. *CMAJ* 1999;161:S1–61.
28. Lemiere C, Bai T, Balter M, et al. Adult asthma consensus guidelines update 2003. *Can Respir J* 2004;11:A9–18.
29. Dombrowski MP, Schatz M, Wise R, et al. Randomized trial of inhaled beclomethasone dipropionate versus theophylline for moderate asthma during pregnancy. *Am J Obstet Gynecol* 2004;190:737–44.
30. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;368:744–53.
31. Blais L, Beaulieu MF, Lévesque S. Socioeconomic status and medication prescription patterns in pediatric asthma in Canada. *J Adolesc Health* 2006;38:607e9–16.
32. Breton MC, Beaulieu MF, Lemiere C, Rey E, Forget A, Blais L. Risk of perinatal mortality associated with asthma during pregnancy. *Thorax* 2009;64:101–6.
33. Blais L, Forget A. Asthma exacerbations during the first trimester of pregnancy and the risk of congenital malformations among asthmatic women. *J Allergy Clin Immunol* 2008;121:1379–84.
34. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics* 1988;44:1049–60.
35. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax* 2006;61:169–76.
36. Enriquez R, Griffin MR, Carroll KN, et al. Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J Allergy Clin Immunol* 2007;120:625–30.
37. Gluck LC. The change of asthma course during pregnancy. *Clin Rev Allergy Immunol* 2004;26:171–80.

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