

ASTHMA IN PREGNANCY

Associations of maternal asthma severity and control with pregnancy complicationsLucie Blais, PhD^{1,2}, Fatima-Zohra Kettani, MSc^{1,2}, and Amélie Forget, MSc¹¹Faculty of Pharmacy, Université de Montréal, Montréal, Québec, Canada and ²Hôpital du Sacré-Cœur de Montréal, Montréal, Québec, Canada**Abstract**

Objectives: To assess the associations of maternal asthma severity and control with pregnancy-induced hypertension (PIH), gestational diabetes and cesarean delivery. **Methods:** A cohort of 41 660 pregnancies from women with and without asthma who delivered between 1990 and 2002 was constructed by linking Québec's administrative databases. Maternal asthma was defined by at least one asthma diagnosis and one dispensed prescription for an asthma medication in the 2 years before or during pregnancy. Asthma severity and control were assessed using validated indexes during the entire pregnancy to study cesarean delivery and 1-year prior to week 20 of gestation to study PIH and gestational diabetes. Generalized Estimation Equation models were used to obtain odds ratios (OR) for PIH, gestational diabetes and cesarean in association with maternal asthma severity and control. **Results:** Almost one-third of the women had uncontrolled asthma and up to 5% had severe asthma. Severe asthma increased the risk of cesarean delivery (OR = 1.35; 95% CI: 1.11–1.63) compared with mild asthma, but no association was found between asthma severity and the other outcomes. The level of asthma control was not associated with any of the outcomes, except for a near-significant increased risk of PIH among uncontrolled women (OR = 1.18; 95% CI: 0.97–1.42). **Conclusions:** The risk of gestational diabetes was not associated with asthma severity or control, and the risk of PIH was not associated with asthma severity. However, further studies are needed to clarify the association between asthma control and PIH. The increased risk of cesarean among women with severe asthma may be explained by the physician's and patient's concerns over the safety of normal delivery.

Keywords

Administrative databases, asthma control, asthma severity, cesarean delivery, cohort study, gestational diabetes, pregnancy-induced hypertension

History

Received 20 September 2013

Revised 17 December 2013

Accepted 29 December 2013

Published online 30 January 2014

Introduction

Asthma is the most common respiratory condition that complicates pregnancy [1] and was found to be associated with an increased risk of adverse maternal outcomes, including pregnancy-induced hypertension (PIH) [2–10], gestational diabetes [3–5,7,9], and cesarean delivery [2–4,6,7,11,12].

Pregnancy-induced hypertension (including gestational hypertension, preeclampsia or eclampsia) and gestational diabetes are frequent complications of pregnancy that affect 5%–8% [13] and 7% of pregnancies [14], respectively. They can result in serious maternal and fetal complications including preterm birth [15], low birth weight [16], perinatal death [17] and maternal cardiovascular disease [18] among women with PIH; or result in macrosomic infants [19], PIH [19] and cesarean delivery [19] among women with gestational diabetes. In 2010–2011, the primary cesarean delivery rate was 18.1% in Canada [20]. Cesarean delivery

involves major abdominal surgery, and is associated with high rates of surgical complications, maternal rehospitalization and complications that require neonatal intensive care unit admission [21].

The associations of asthma severity and control with the occurrence of PIH, gestational diabetes and cesarean delivery are not well known, because relatively few studies have covered this topic, and they reported conflicting results [5,7,11,12,22–24]. Of the five studies that used appropriate comparison groups of women with mild or controlled asthma (to be able to estimate whether severe and uncontrolled asthma are associated with an increased risk of the maternal outcomes under study, above and beyond the risk associated with the disease *per se*), one study reported an increased risk of PIH among women who had markers for uncontrolled asthma in the year before pregnancy [22]. The four other studies found no impact of asthma severity or control during pregnancy on PIH, gestational diabetes or cesarean delivery [7,11,23,24]. However, these four studies were limited by their small sample size and lack of power or their measure of asthma control and severity during the entire pregnancy, and the possibility that the exposure was measured at any time during pregnancy, which may have been after the diagnosis of PIH or gestational diabetes.

Correspondence: Lucie Blais, Faculté de Pharmacie, Université de Montréal, C.P. 6128, Succursale Centre-Ville, Montréal, Québec, Canada H3C 3J7. Tel: +514 343 6111 extn 3786. Fax: +514 343 6120. E-mail: lucie.blais@umontreal.ca

Using a large cohort of pregnancies in asthmatic and non-asthmatic women, we estimated the associations of maternal asthma severity and control with the risk of PIH, gestational diabetes and cesarean delivery. Our secondary objective was to estimate the impact of asthma *per se* on the risk of these maternal outcomes, which enabled comparisons with previous studies.

Methods

Data sources

This study was based on data retrieved from three databases of Québec, Canada: the *Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* (MED-ECHO), the *Régie de l'assurance maladie du Québec* (RAMQ), and the Québec Births and Deaths Registry. The MED-ECHO database covers all residents of Québec and records data on acute care hospitalizations (e.g. admission, primary discharge, up to 15 secondary discharge diagnoses, date of entry and duration of hospital stay). The RAMQ gathers information on medical services (e.g. date of service; location of the clinic, emergency department or hospital; diagnoses coded with the International Classification of Disease [ICD-9] and the physician's specialty) dispensed to all residents of Québec as well as prescribed medications (e.g. date of filling, name, dose, quantity, dosage formulation, duration of the prescription, renewals and physician's specialty) that are filled at community pharmacies for residents covered by the RAMQ's Public Prescription Drug Insurance Plan. This database covers 43% of residents in Québec, including elderly individuals, recipients of social welfare, and, since January 1997, individuals (mainly workers and their families) who are not covered by a private drug insurance plan. The Births and Deaths Registry records data for all births and stillbirths in Québec, as well as other relevant information, including the mother's parity.

An authorization was obtained from the *Commission d'accès à l'information du Québec* to request and link the information from the three databases. The Research and Ethics Committee of the Hôpital du Sacré-Coeur de Montréal approved the study.

Study design

We constructed a cohort of women and their births by linking the three databases. All pregnant women with asthma and a 33% random sample of non-asthmatic women who had at least one delivery (live born or stillborn) between 1 January 1990 and 31 December 2002 were included in the cohort. Only women aged 13–50 years at conception who were covered by the RAMQ's Public Prescription Drug Insurance Plan for >1 year before the pregnancy and throughout its entire duration were eligible for this study. For this study, asthma was defined as a diagnosis of asthma recorded in the RAMQ or MED-ECHO databases (ICD-9 code 493, except 493.2) with at least one filled prescription for an asthma medication (inhaled corticosteroids (ICSs), inhaled corticosteroids in combination with long-acting beta-agonists, leukotriene receptor antagonists, long-acting beta-agonists, short-acting beta-agonists (SABA), theophylline, ipratropium

and mast cell stabilizers) recorded in the RAMQ database in the 2 years before or during the pregnancy. The asthma diagnostic codes recorded in the RAMQ medical database were shown to be a valid method of identifying patients with asthma [25], and data on medications recorded in the RAMQ prescription database were found to be comprehensive and valid [26]. This cohort has already been used to study the impact of asthma and asthma medications on the health of the mother and the newborn [27–30].

To study PIH, we excluded women diagnosed with chronic hypertension before pregnancy. To study gestational diabetes, we excluded women diagnosed with diabetes mellitus before pregnancy. We applied no exclusions for analyses of cesarean delivery.

The cohort was formed of a maximum of four pregnancies per woman (maximum possible for the statistical models to converge). For the few women who had five pregnancies or more between 1990 and 2002, we included the four most recent pregnancies.

Maternal outcomes

Pregnancy-induced hypertension was defined as: (1) a diagnosis of gestational hypertension (ICD-9 codes 642.3, 642.7 or 642.9), pre-eclampsia (ICD-9 codes 642.4 or 642.5) or eclampsia (ICD-9 code 642.6) recorded in the RAMQ or MED-ECHO databases after week 20 of gestation or (2) a prescription for an antihypertensive medication recommended during pregnancy (amlodipine, hydralazine, labetalol, methyldopa, metoprolol, nifedipine, oxprenolol or pindolol) filled after week 20 of gestation, without a similar prescription filled before or during week 20 of gestation. This algorithm was used to detect PIH in earlier studies [22,31].

Gestational diabetes was defined as one diagnosis of diabetes mellitus or gestational diabetes recorded in the RAMQ or MED-ECHO databases after week 24 of gestation (ICD-9 codes 250.0–250.9, 648.0, 648.8 or 271.3) or at least one filled prescription for an antidiabetic agent recommended during pregnancy (glyburide, metformin or insulin) after week 24 of gestation. All diagnostic codes for diabetes were considered, regardless of whether it was a code for diabetes mellitus or gestational diabetes, because the time at which the code was recorded is used to distinguish these two types of diabetes. This algorithm was used to measure gestational diabetes in prior studies [27,32].

Cesarean delivery was identified through the delivery hospitalization recorded in the MED-ECHO or RAMQ databases (ICD-9 codes 669.7 or 763.4).

Exposures

The main exposures were asthma severity and asthma control for up to 1 year before week 20 of gestation for PIH and gestational diabetes, or during the entire pregnancy for cesarean delivery, and were assessed using indexes that were validated for use in database studies [33]. Asthma severity and control were measured over 1 year before week 20 of gestation or during gestation because the indices were developed to reflect the definitions provided by the Canadian Asthma Consensus Guidelines [33–35], which include the use of asthma medications and acute care for asthma over 1 year.

Three levels of asthma severity (mild [reference group], moderate and severe) and two levels of asthma control (controlled [reference group] and uncontrolled) were considered. More specifically, mild asthma corresponds to ≤ 500 μg per day of ICS monotherapy (in beclomethasone chlorofluorocarbon equivalents) or ≤ 250 μg per day of ICS plus an additional controller therapy. Moreover, in order to be classified in the mild category, a patient must have used less than three doses of SABA per week on an average over 12 months (one dose of SABA equals two puffs of 100 μg of salbutamol) or have used 4–10 doses of SABA per week on an average and not have had a moderate to severe asthma exacerbation (defined as an emergency visit or hospitalization for asthma, or a filled prescription for a short-course of oral corticosteroids). According to the Canadian Asthma Consensus Guidelines, patients do not have acceptable asthma control if they use more than three doses of SABA per week as rescue medication, excluding one additional dose per day for exercise. We thus added the 3 recommended doses per week to 7 doses for exercise to come to a maximum of 10 doses per week of SABA. Severe asthma is characterized by >1000 μg per day of ICS with >3 doses of SABA per week on an average or with a ≥ 1 moderate to severe asthma exacerbation over 12 months OR lower doses of ICS with >10 doses of SABA per week on an average and with ≥ 1 moderate to severe asthma exacerbation over 12 months. Patients are characterized as having moderate asthma if they do not fit in the mild or severe category. Patients were considered as uncontrolled if they had ≥ 1 moderate to severe asthma exacerbation and >3 doses of SABA per week for mild asthma and >10 doses of SABA per week for moderate and severe asthma. The indexes for asthma severity and control are summarized in Supplementary e-Table 1. These indexes have been developed to be used in large database studies, and as such are not based on pulmonary function tests which are usually not recorded in administrative databases. However, in 2007, we performed a validation study [33] and we found that these indexes showed good correlations with lung function tests, including the forced expiratory volume in 1 s (FEV_1) and the ratio of the FEV_1 to the forced vital capacity (FVC) (i.e. FEV_1/FVC), which have been used to characterize asthma severity and control in national and international asthma guidelines [34,36]. The mean predicted FEV_1 ranged from 89.8% for mild asthma to 61.5% for severe asthma ($p < 0.001$), and from 89.5% for controlled asthma to 67.3% for uncontrolled asthma ($p < 0.001$) [33]. The FEV_1/FVC ratio ranged from 75.8% for mild asthma to 61.8% for severe asthma ($p = 0.030$), and from 75.3% for controlled asthma to 65.7% for uncontrolled asthma ($p < 0.001$) [33].

The secondary exposure was maternal asthma, as defined earlier in this article, where the reference group was non-asthmatic women.

Potential confounders

For the analysis of cesarean delivery, three categories of variables were considered as potential confounders: (1) maternal sociodemographic factors, which included age at conception ($<18/18\text{--}34/>34$ years) and receipt of social

assistance within 1 year before or during pregnancy (yes/no); (2) pregnancy-related factors, which included parity (first/second or later pregnancy), multiple pregnancy (singleton/twins or more), PIH (yes/no), gestational diabetes (yes/no), visit to a gynecologist or obstetrician during pregnancy (yes/no) and number of prenatal visits and (3) maternal chronic conditions, which included chronic hypertension (yes/no) and diabetes mellitus (yes/no). PIH and gestational diabetes were identified as described earlier. Chronic hypertension and diabetes mellitus were identified from diagnoses or filled prescriptions for related medications that were recorded in the RAMQ or MED-ECHO databases up to 1 year before pregnancy using the specific algorithms that we developed in earlier studies [28,37].

For the analyses of PIH and gestational diabetes, we used the same confounding factors as for cesarean delivery, except that we excluded prenatal visits and visits to a gynecologist or obstetrician during pregnancy because asthma severity and control were only measured during the first half of the pregnancy. We excluded chronic hypertension and PIH in analyses with PIH as the outcome, while diabetes mellitus and gestational diabetes were excluded in analyses with gestational diabetes as the outcome.

Statistical analyses

Descriptive statistics were used to compare the characteristics of pregnancies as a function of asthma severity and control. The prevalence rates of PIH, gestational diabetes and cesarean delivery were also estimated as a function of asthma severity and control, and among pregnancies in women with and without asthma.

Generalized estimation equation models were used to calculate unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CIs) for PIH, gestational diabetes and cesarean delivery in association with asthma severity and control among asthmatic women only, and with maternal asthma in the entire cohort, adjusting for the potential confounders described earlier. These models take into account the fact that a woman could contribute more than one pregnancy to the analysis, by estimating the correlation between consecutive pregnancies [38]. All analyses were performed using the SAS software version 9.2 (SAS Institute, Cary, NC).

Results

The total cohort consisted of 13 289 pregnancies in asthmatic women and 28 371 pregnancies in non-asthmatic women. For analyses of PIH, we excluded 318 pregnancies in asthmatic women and 372 pregnancies in non-asthmatic women who were diagnosed with chronic hypertension before conception. Similarly, in analyses of gestational diabetes, we excluded 314 pregnancies in asthmatic women and 382 pregnancies in non-asthmatic women who were diagnosed with diabetes mellitus before conception. The characteristics of the asthmatic pregnancies as a function of asthma severity and control (crude results) are presented in Tables 1–3 for cesarean delivery, PIH and gestational diabetes, respectively. Globally, almost one-third of the women had uncontrolled asthma and up to 5% had severe asthma. For all three conditions,

Table 1. Characteristics of the pregnancies used to study the associations of asthma severity and control with cesarean delivery.

	Asthma severity during pregnancy			<i>p</i> Value	Asthma control during pregnancy		
	Number (%)				Number (%)		
	Mild	Moderate	Severe		Uncontrolled	Controlled	<i>p</i> Value
Number of pregnancies	10 964	1652	673		4771	8518	
Age at conception (years)							
<18	753 (6.9)	90 (5.4)	39 (5.8)	<0.0001	302 (6.3)	580 (6.8)	0.007
18–34	9576 (87.3)	1432 (86.7)	570 (84.7)		4131 (86.6)	7447 (87.4)	
>34	635 (5.8)	130 (7.9)	64 (9.5)		338 (7.1)	491 (5.8)	
Receipt of social assistance up to 1 year before or during pregnancy (yes)	8670 (79.1)	1342 (81.2)	559 (83.1)	0.009	3892 (81.6)	6679 (78.4)	<0.0001
Parity							
Nulliparous	3416 (31.2)	551 (33.4)	262 (38.9)	<0.0001	1596 (33.5)	2633 (30.9)	0.006
Multiparous	7488 (68.3)	1094 (66.2)	403 (59.9)		3144 (65.9)	5841 (68.6)	
Missing	60 (0.5)	7 (0.4)	8 (1.2)		31 (0.6)	44 (0.5)	
Multiple pregnancy (yes)	151 (1.4)	26 (1.6)	15 (2.2)	0.178	72 (1.5)	120 (1.4)	0.642
Pregnancy-induced hypertension (yes)	693 (6.3)	115 (7.0)	57 (8.5)	0.066	347 (7.3)	518 (6.1)	0.008
Gestational diabetes (yes)	827 (7.5)	136 (8.2)	67 (10.0)	0.056	419 (8.8)	611 (7.2)	0.001
Gynecologist or obstetrician visit during pregnancy	8233 (75.1)	1222 (74.0)	514 (76.4)	0.436	3541 (74.2)	6428 (75.5)	0.112
Number of prenatal visits (mean ± SD)	9.8 ± 4.5	9.9 ± 4.5	10.3 ± 4.6	0.0435	9.9 ± 4.6	9.8 ± 4.5	0.1939
Maternal chronic conditions (yes)							
Chronic hypertension	250 (2.3)	43 (2.6)	25 (3.7)	0.051	119 (2.5)	199 (2.3)	0.568
Diabetes mellitus	245 (2.2)	54 (3.3)	15 (2.2)	0.0349	121 (2.5)	193 (2.3)	0.3249

SD, standard deviation.

Table 2. Characteristics of the pregnancies^a used to study the associations of asthma severity and control with pregnancy-induced hypertension.

	Asthma severity within 1 year before week 20 of gestation				Asthma control within 1 year before week 20 of gestation		
	Number (%)				Number (%)		
	Mild	Moderate	Severe	<i>p</i> Value	Uncontrolled	Controlled	<i>p</i> Value
Number of pregnancies	10 965	1586	420		4300	8671	
Age at conception (years)							
<18	760 (6.9)	91 (5.7)	26 (6.2)	0.070	294 (6.8)	583 (6.7)	0.166
18–34	9565 (87.2)	1379 (86.9)	365 (86.9)		3722 (86.6)	7587 (87.5)	
>34	640 (5.8)	116 (7.3)	29 (6.9)		284 (6.6)	501 (5.8)	
Receipt of social assistance up to 1 year before or during pregnancy (yes)	8696 (79.3)	1267 (79.9)	349 (83.1)	0.155	3466 (80.6)	6846 (79.0)	0.028
Parity							
Nulliparous	3403 (31.0)	560 (35.3)	172 (41.0)	<0.0001	1531 (35.6)	2604 (30.0)	<0.0001
Multiparous	7506 (68.5)	1016 (64.1)	245 (58.3)		2743 (63.8)	6024 (69.5)	
Missing	56 (0.5)	10 (0.6)	3 (0.7)		26 (0.6)	43 (0.5)	
Multiple pregnancy (yes)	146 (1.3)	28 (1.8)	10 (2.4)	0.093	68 (1.6)	116 (1.3)	0.269
Gestational diabetes (yes)	822 (7.5)	121 (7.6)	34 (8.1)	0.890	342 (8.0)	635 (7.3)	0.200
Maternal chronic conditions (yes)							
Chronic hypertension ^a	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Diabetes mellitus	226 (2.1)	35 (2.2)	11 (2.6)	0.6978	94 (2.2)	178 (2.1)	0.618

^aExcluding pregnancies in women with chronic hypertension.

women with severe or uncontrolled asthma were more likely to be nulliparous than women with mild or controlled asthma ($p < 0.01$). As shown in Table 1, women with severe or uncontrolled asthma were more likely to be >34 years old and to receive social assistance, and that women with uncontrolled asthma were more likely to suffer from PIH or gestational diabetes compared with women with mild or controlled asthma ($p < 0.01$). Table 2 shows that women with uncontrolled asthma were more likely to receive social assistance than women with mild or controlled asthma ($p = 0.028$). Table 3 shows that women with severe asthma were more likely to suffer from chronic hypertension ($p = 0.025$), while those with uncontrolled asthma were

more likely to have PIH ($p = 0.002$) than women with mild or controlled asthma. The characteristics of the pregnancies in asthmatic and non-asthmatic women are presented in Supplementary e-Table 2.

The crude rates presented in Table 4 indicate that women with severe or uncontrolled asthma were more likely to have PIH, gestational diabetes or cesarean delivery than women with mild or controlled asthma. However, in the adjusted analysis presented in Table 5, asthma severity was independently associated with cesarean delivery (OR 1.35; 95% CI 1.11–1.63) but not with PIH or gestational diabetes. Maternal age, nulliparity, multiple pregnancy, PIH, gestational diabetes and diabetes mellitus were also independent risk factors

Table 3. Characteristics of the pregnancies^a used to study the associations of asthma severity and control with gestational diabetes.

	Asthma severity within 1 year before week 20 of gestation			<i>p</i> Value	Asthma control within 1 year before week 20 of gestation			<i>p</i> Value
	Number (%)				Number (%)			
	Mild	Moderate	Severe		Uncontrolled	Controlled		
Number of pregnancies	10 959	1591	425		4311	8664		
Age at conception (years)								
<18	755 (6.9)	93 (5.8)	26 (6.1)	0.046	294 (6.8)	580 (6.7)		0.113
18–34	9568 (87.3)	1380 (86.7)	368 (86.6)		3730 (86.5)	7586 (87.6)		
>34	636 (5.8)	118 (7.4)	31 (7.3)		287 (6.7)	498 (5.7)		
Receipt of social assistance up to 1 year before or during pregnancy (yes)	8692 (79.3)	1275 (80.1)	352 (82.8)	0.173	3477 (80.7)	6842 (79.0)		0.025
Parity								
Nulliparous	3407 (31.1)	557 (35.0)	173 (40.7)	<0.0001	1540 (35.7)	2597 (30.0)		<0.0001
Multiparous	7492 (68.4)	1023 (64.3)	248 (58.4)		2742 (63.6)	6021 (69.5)		
Missing	60 (0.5)	11 (0.7)	4 (0.9)		29 (0.7)	46 (0.5)		
Multiple pregnancy (yes)	148 (1.4)	29 (1.8)	10 (2.4)	0.093	69 (1.6)	118 (1.4)		0.283
Pregnancy-induced hypertension (yes)	671 (6.1)	117 (7.4)	29 (6.8)	0.151	311 (7.2)	506 (5.8)		0.002
Maternal chronic conditions (yes)								
Chronic hypertension	220 (2.0)	40 (2.5)	16 (3.8)	0.025	105 (2.4)	171 (2.0)		0.086
Diabetes mellitus ^a	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		

^aExcluding pregnancies in women with diabetes mellitus.

Table 4. Crude rates of women with pregnancy-induced hypertension, gestational diabetes or cesarean delivery according to asthma severity and control, or the presence of asthma itself.

	Number or number (%)		
	Pregnancy-induced hypertension ^a	Gestational diabetes ^a	Cesarean delivery ^b
Asthmatic cohort			
Number of pregnancies	12 971	12 975	13 289
Asthma severity			
Mild	620 (5.7)	862 (7.9)	2058 (18.8)
Moderate	107 (6.7)	129 (8.1)	344 (20.8)
Severe	28 (6.7)	39 (9.2)	167 (24.8)
Asthma control			
Controlled	470 (5.4)	668 (7.7)	1614 (18.9)
Uncontrolled	285 (6.6)	362 (8.4)	955 (20.0)
Entire cohort			
Number of pregnancies	40 960	40 974	41 660
Asthmatic women	755 (5.8)	1030 (7.9)	2569 (19.3)
Non-asthmatic women	1359 (4.9)	1936 (6.9)	4987 (17.6)

^aAsthma severity/control measured within 1 year before week 20 of gestation.^bAsthma severity/control measured during pregnancy.

for cesarean delivery. Although non-significant, the risk of PIH was increased among women with uncontrolled asthma (OR 1.18; 95% CI 0.98–1.42).

The second adjusted analysis presented in Table 6 shows that asthmatic women were at increased risk of PIH (OR 1.27; 95% CI 1.15–1.41), gestational diabetes (OR 1.17; 95% CI 1.08–1.28) and cesarean delivery (OR 1.10; 95% CI 1.04–1.17) compared with non-asthmatic women.

Discussion

Using definitions of asthma control and severity that are based on the Canadian Asthma Consensus Guidelines, we observed that almost one-third of women had uncontrolled asthma and up to 5% had severe asthma. If we had used the

National Asthma Education and Prevention Program (NAEPP) criteria which states that uncontrolled asthma corresponds to the use of more than two doses of SABA per week [39], we would have even observed a higher proportion of women with uncontrolled asthma. The results of our study suggest that asthma severity during pregnancy is not associated with the risk of PIH and gestational diabetes, but women with severe asthma were more likely to undergo cesarean delivery compared with women with mild asthma. Asthma control was not significantly associated with any of the outcomes, although the risk of PIH was increased by 18%, albeit not significantly, among women with uncontrolled asthma. Nevertheless, the risks of PIH, gestational diabetes and cesarean delivery were higher among asthmatic women than in non-asthmatic women, confirming the findings of several previous studies [2–7,9–12].

Only two prior studies have determined associations between markers of uncontrolled asthma and PIH (including gestational hypertension, preeclampsia or eclampsia) using an appropriate reference category [22,23]. The definitions of uncontrolled asthma used by Murphy et al. [23] differed slightly from those used in the current study. In particular, Murphy et al. defined uncontrolled asthma as a hospital admission, emergency visit or unscheduled visit to a physician for asthma, or a course of oral corticosteroids (primary exposure). They found that the risk of PIH was no higher in women with uncontrolled asthma than in women with controlled asthma (crude rate ratio 0.8; $p > 0.5$). However, that study had some limitations, including the small sample size (146 asthmatic women), no adjustment for confounding factors and inclusion of markers for uncontrolled asthma that were measured at any time during pregnancy, which may have been after the diagnosis of PIH. The second study was conducted by our group using a smaller cohort of women [22]. As secondary outcomes, we found that asthmatic women were more likely to have PIH if they visited an emergency department or were admitted for asthma before pregnancy (59%), used oral corticosteroids during pregnancy

Table 5. Associations of asthma severity and control with pregnancy-induced hypertension, gestational diabetes and cesarean delivery.

	Adjusted odds ratio (95% confidence interval)		
	Pregnancy-induced hypertension ^a	Gestational diabetes ^a	Cesarean delivery ^b
Asthma severity			
Mild	Reference	Reference	Reference
Moderate	1.00 (0.78–1.29)	0.91 (0.72–1.15)	1.06 (0.92–1.22)
Severe	0.93 (0.61–1.41)	1.07 (0.75–1.53)	1.35 (1.11–1.63)
Asthma control (yes versus no)	1.18 (0.98–1.42)	1.06 (0.89–1.25)	0.95 (0.86–1.05)
Age			
<18	0.65 (0.48–0.89)	0.44 (0.31–0.64)	0.68 (0.56–0.82)
18–34	Reference	Reference	Reference
>34	1.35 (1.00–1.80)	2.59 (2.12–3.18)	1.76 (1.50–2.06)
Social assistance (yes versus no)	0.93 (0.78–1.11)	1.10 (0.93–1.31)	0.90 (0.81–1.00)
Parity (yes or no)			
Nulliparous	Reference	Reference	Reference
Multiparous	0.42 (0.36–0.48)	1.04 (0.90–1.21)	0.80 (0.73–0.87)
Missing	0.99 (0.44–2.26)	0.80 (0.32–1.99)	0.49 (0.29–0.84)
Multiple pregnancy (yes versus no)	1.52 (0.89–2.60)	1.48 (0.96–2.28)	5.72 (4.24–7.71)
Pregnancy-induced hypertension (yes versus no)	NA	2.03 (1.64–2.52)	1.49 (1.27–1.74)
Gestational diabetes (yes versus no)	2.08 (1.65–2.62)	NA	1.39 (1.21–1.60)
Chronic hypertension (yes versus no)	NA	1.93 (1.39–2.67)	1.46 (1.16–1.83)
Diabetes mellitus (yes versus no)	2.58 (1.77–3.76)	NA	1.81 (1.43–2.29)
Number of prenatal visits	NA	NA	1.00 (0.99–1.01)
Gynecologist or obstetrician during pregnancy (yes versus no)	NA	NA	0.49 (0.44–0.55)

NA, not applicable.

^aAsthma severity and control measured within 1 year before week 20 of gestation.^bAsthma severity and control measured during pregnancy.

Table 6. Associations of asthma with pregnancy-induced hypertension, gestational diabetes and cesarean delivery.

	Adjusted odds ratio (95% confidence interval)		
	Pregnancy-induced hypertension	Gestational diabetes	Cesarean delivery
Asthma (yes versus no)	1.27 (1.15–1.41)	1.17 (1.08–1.28)	1.10 (1.04–1.17)
Age			
<18	0.71 (0.57–0.88)	0.39 (0.30–0.52)	0.67 (0.59–0.77)
18–34	Reference	Reference	Reference
>34	1.39 (1.19–1.62)	2.57 (2.31–2.86)	1.59 (1.46–1.72)
Social assistance (yes versus no)	0.92 (0.84–1.02)	1.21 (1.11–1.32)	0.97 (0.92–1.03)
Parity (yes versus no)			
Nulliparous	Reference	Reference	Reference
Multiparous	0.40 (0.37–0.44)	1.08 (0.99–1.17)	0.74 (0.70–0.78)
Missing	0.62 (0.39–1.00)	1.00 (0.66–1.51)	0.73 (0.56–0.95)
Multiple pregnancy (yes versus no)	1.95 (1.44–2.64)	1.50 (1.14–1.96)	6.02 (5.03–7.19)
Pregnancy-induced hypertension (yes versus no)	NA	2.10 (1.84–2.39)	0.64 (0.58–0.70)
Gestational diabetes (yes versus no)	2.10 (1.83–2.42)	NA	0.70 (0.65–0.77)
Chronic hypertension (yes versus no)	NA	1.90 (1.53–2.36)	1.55 (1.32–1.82)
Diabetes mellitus (yes versus no)	2.83 (2.20–3.63)	NA	1.80 (1.52–2.13)
Number of prenatal visits	NA	NA	1.00 (1.00–1.01)
Gynecologist or obstetrician during pregnancy (yes versus no)	NA	NA	0.47 (0.44–0.50)

NA, not applicable.

(57%) and used more than three doses of short-acting β_2 -agonists per week before pregnancy (37%) [22]. In the present study, we found an increased, albeit not significant, risk of PIH among women with uncontrolled asthma. The difference between the two studies might be explained by the fact that asthma control was measured during 1 year before week 20 of gestation in the current study, whereas it was evaluated before or during pregnancy (according to the specific marker) in the previous study, and by the fact that the index of control used in the present study was also based on the use of short-acting β_2 -agonists during

pregnancy, which were reported to reduce the risk of PIH [31].

Regarding gestational diabetes, three studies [7,11,24] revealed that the prevalence of this outcome tended to be higher in asthmatic women with severe or uncontrolled asthma than in women with mild or controlled asthma, affecting 12.9% versus 4.0% of women in the study by Perlow et al. [7], 6.4% versus 4.2% of women in the study by Stenius-Aarniala et al. [24], and 6.6% versus 3.3% of women in the study by Dombrowski et al. [11]. However, these differences were not statistically significant. The prevalence rates of

cesarean delivery across the different levels of asthma severity in our study were similar to those reported by Dombrowski [11], although the association was not statistically assessed in that study. Perlow et al. [7] reported no increase in the risk of cesarean delivery in asthmatic women requiring long-term oral corticosteroid therapy compared with non-steroid-dependent asthmatic women, which was consistent with our results.

The higher risk of cesarean delivery in women with more severe asthma and the absence of an increased risk in those with uncontrolled asthma during pregnancy may be due to the physician's and patient's concerns over the safety of normal delivery in women with severe asthma rather than exacerbation of asthma itself. In fact, cesarean delivery is rarely necessary in women with acute exacerbation of asthma [11].

One question remains: Why did we observe non-significant associations between asthma severity and control and the risk of gestational diabetes and PIH, even though the risk of these outcomes was significantly higher in asthmatic women than in non-asthmatic women? We believe that the associations between asthma and PIH or gestational diabetes reflect the impact of the disease itself, possibly via hypoxic mechanisms, as well as the medications used to treat asthma. Indeed, hypoxemia, i.e. the decrease in the partial pressure of oxygen in the blood, is a feature of acute severe asthma or status asthmaticus and has been proposed as a mechanism among others to explain pre-eclampsia [40]. Moreover, a recent animal study demonstrated that chronic hypoxia during gestation induces preeclamptic symptoms in pregnant rats via heightened endothelin-1-mediated signaling (endothelin-1 is a peptide hormone with a potent vasoconstriction effect), providing a molecular mechanism linking gestational hypoxia and increased risk of preeclampsia [41]. Regarding asthma drugs, the potential for systemic adverse effects with high-dose ICS, including hyperglycemia, has been reported [42,43] and the increased risk of hyperglycemia and insulin resistance associated with the use of oral corticosteroids is well-recognized [44,45]. It has also been shown that β_2 -agonists stimulate the β_2 -adrenergic receptors in smooth muscle, thereby activating adenylate cyclase. It results in a cascade effect that increases hepatic glycogenolysis and maternal hyperglycemia [46]. In addition, the effect size for the association between asthma and PIH was of a similar magnitude to that between uncontrolled asthma and PIH. However, the sample size of the entire pregnancy cohort, which included asthmatic and non-asthmatic women, is larger than that of the asthmatic cohort, which allowed us to detect a significant increased risk in the former cohort.

The main strengths of our study are its large sample size, and that we measured asthma severity and control using validated indices during appropriate time-frames [33]. Moreover, we avoided recall bias in measuring outcomes and exposures because the variables were retrieved from administrative databases that recorded clinical data in a prospective manner. Finally, we could control for several potential confounders, particularly parity and multiple pregnancy [12]. However, some residual confounding may remain because some imbalances could exist between the groups for variables such as obesity that are not recorded in these

administrative databases, but are associated with asthma [47] and also with PIH or gestational diabetes [48,49]. Also, the fact of averaging the weekly use of SABA over a year could have missed patients with intermittent poor asthma control (i.e. during allergy seasons or infections). Yet, by using an index of asthma control that is assessed over a 1-year period, we identified the women that have uncontrolled asthma in a chronic way, therefore, we believe that if we did not find an association between asthma control and the outcomes under study with our index, it is unlikely that we find an increased risk of maternal outcomes associated with a short period of uncontrolled asthma. Additionally, we were unable to determine whether cesarean delivery was primary or repeated, or whether it was elective or emergent, because the procedural codes were not specific and because we did not have access to the complete medical history of each woman. Another weakness is that our cohort, which consists of women with public drug insurance, is less representative of women with a higher socioeconomic status. Nevertheless, a recent review noted that lower socioeconomic status is a predictor of poor asthma control [50].

Conclusion

In summary, our study confirmed previous reports suggesting that asthma is a risk factor for adverse maternal outcomes. We also provide evidence that the risk of gestational diabetes is not affected by asthma severity or control, and that the risk of PIH is not affected by asthma severity within 1 year before week 20 of gestation. However, further studies are needed to clarify the association between asthma control and PIH. It is worth pointing out the high frequency of women with uncontrolled asthma as reflected by the continued high use of SABA in our study. The increased risk of cesarean delivery in women with more severe asthma may reflect a tendency of physicians to take more precautions in such patients.

Acknowledgements

We thank *the Régie de l'assurance maladie du Québec* and *l'Institut de la Statistique du Québec* for assistance with the data. We are grateful to the Commission d'accès à l'information du Québec for authorizing the study.

Declaration of interest

This study was funded by the Canadian Institutes of Health Research and Genentech. Lucie Blais also received research grants from AstraZeneca, Pfizer, sanofi-aventis, Novartis and Merck for research projects and co-chairs the AstraZeneca Endowment Pharmaceutical Chair in Respiratory Health. Fatima-Zohra Kettani and Amélie Forget have no competing interests to declare.

References

1. Kwon HL, Triche EW, Belanger K, Bracken MB. The epidemiology of asthma during pregnancy: prevalence, diagnosis, and symptoms. *Immunol Allergy Clin North Am* 2006;26:29–62.
2. Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. *Am J Respir Crit Care Med* 1998;158:1091–1095.

3. Wen SW, Demissie K, Liu S. Adverse outcomes in pregnancies of asthmatic women: results from a Canadian population. *Ann Epidemiol* 2001;11:7–12.
4. Macmullen NJ, Shen JJ, Tymkow C. Adverse maternal outcomes in women with asthma versus women without asthma. *Appl Nurs Res* 2010;23:e9–e13.
5. Enriquez R, Griffin MR, Carroll KN, Wu PS, Cooper WO, Gebretsadik T, Dupont WD, et al. Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J Allergy Clin Immunol* 2007;120:625–630.
6. Liu S, Wen SW, Demissie K, Marcoux S, Kramer MS. Maternal asthma and pregnancy outcomes: a retrospective cohort study. *Am J Obstet Gynecol* 2001;184:90–96.
7. Perlow JH, Montgomery D, Morgan MA, Towers CV, Porto M. Severity of asthma and perinatal outcome. *Am J Obstet Gynecol* 1992;167(Pt 1):963–967.
8. Stenius-Aarniala B, Piirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. *Thorax* 1988;43:12–18.
9. Mendola P, Laughon SK, Mannisto TI, Leishear K, Reddy UM, Chen Z, Zhang J. Obstetric complications among US women with asthma. *Am J Obstet Gynecol* 2013;208:127–128.
10. Murphy V, Namazy J, Powell H, Schatz M, Chambers C, Attia J, Gibson PG. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG* 2011;118:1314–1323.
11. Dombrowski M, Schatz M, Wise R, Monane M, Landon M, Mabie W, Newman R, et al. Asthma during pregnancy. *Obstet Gynecol* 2004;103:5–12.
12. Tata L, Lewis S, McKeever T, Smith C, Doyle P, Smeeth L, West J, Hubbard RB. A Comprehensive analysis of adverse obstetric and pediatric complications in women with asthma. *Am J Respir Crit Care Med* 2007;175:991–997.
13. Magee LA, Helewa M, Moutquin JM, Dadelszen PD. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *J Obstet Gynaecol Can* 2008;30(Suppl):S1–S48.
14. American Diabetes Association. Gestational diabetes mellitus. *Diabetes Care* 2004;27:S88–S90.
15. Zeitlin JA, Ancel PY, Saurel-Cubizolles MJ, Papiernik E. Are risk factors the same for small for gestational age versus other preterm births? *Am J Obstet Gynecol* 2001;185:208–215.
16. Xiong X, Mayes D, Demianczuk N, Olson DM, Davidge ST, Newburn-Cook C, Saunders LD. Impact of pregnancy-induced hypertension on fetal growth. *Am J Obstet Gynecol* 1999;180:207–213.
17. Xiong X, Buekens P, Pridjian G, Fraser WD. Pregnancy-induced hypertension and perinatal mortality. *J Reprod Med* 2007;52:402–406.
18. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007;335:974.
19. Reece EA. The fetal and maternal consequences of gestational diabetes mellitus. *J Matern Fetal Neonatal Med* 2010;23:199–203.
20. Canadian Institute of Health Information. Highlights of 2010–2011 selected indicators describing the birthing process in Canada; 2012. Available from: https://secure.cihi.ca/free_products/Childbirth_Highlights_2010-11_EN.pdf.
21. Liston FA, Allen VM, O'Connell CM, Jangaard KA. Neonatal outcomes with caesarean delivery at term. *Arch Dis Child Fetal Neonatal Ed* 2008;93:F176–F182.
22. Martel MJ, Rey É, Beauchesne M-F, Perreault S, Lefebvre G, Forget A, Blais L. Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study. *BMJ* 2005;330:230–233.
23. Murphy VE, Gibson P, Talbot PL, Clifton VL. Severe asthma exacerbations during pregnancy. *Obstet Gynecol* 2005;106:1046–1054.
24. SteniusAarniala BSM, Hedman J, Teramo KA. Acute asthma during pregnancy. *Thorax* 1996;51:411–414.
25. Blais L, Lemiere C, Menzies D, Berbiche D. Validity of asthma diagnoses recorded in the Medical Services database of Quebec. *Pharmacoepidemiol Drug Saf* 2006;15:245–252.
26. 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 Quebec. *J Clin Epidemiol* 1995;48:999–1009.
27. Breton MC, Beauchesne 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;105:211–217.
28. Firoozi F, Lemiere C, Ducharme FM, Beauchesne MF, Perreault S, Berard A, Ferreira E, et al. Effect of maternal moderate to severe asthma on perinatal outcomes. *Respir Med* 2010;104:1278–1287.
29. Martel MJ, Rey E, Beauchesne MF, Malo JL, Perreault S, Forget A, Blais L. Control and severity of asthma during pregnancy are associated with asthma incidence in offspring: two-stage case-control study. *Eur Respir J* 2009;34:579–587.
30. Eltonsy S, Forget A, Blais L. Beta2-agonists use during pregnancy and the risk of congenital malformations. *Birth Defects Res A Clin Mol Teratol* 2011;91:937–947.
31. Martel MJ, Rey E, Beauchesne MF, Perreault S, Forget A, Maghni K, Lefebvre G, Blais L. Use of short-acting beta2-agonists during pregnancy and the risk of pregnancy-induced hypertension. *J Allergy Clin Immunol* 2007;119:576–582.
32. Breton MC, Beauchesne 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;126:772–777.
33. Firoozi F, Lemiere C, Beauchesne MF, Forget A, Blais L. Development and validation of database indexes of asthma severity and control. *Thorax* 2007;62:581–587.
34. Boulet LP, Becker A, Berube D, Beveridge R, Ernst P. Canadian Asthma Consensus Report, 1999. Canadian Asthma Consensus Group. *CMAJ* 1999;161:S1–S61.
35. Loughheed MD, Lemiere C, Dell SD, Ducharme FM, FitzGerald JM, Leigh R, Licksai C, et al. Canadian Thoracic Society Asthma Management Continuum – 2010 Consensus Summary for children six years of age and over, and adults. *Can Respir J* 2010;17:15–24.
36. Global Initiative for asthma. Global strategy for asthma management and prevention; 2002. Report No.: NIH Pub No.: 02-3659.
37. Blais L, Beauchesne 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;62:320–328.
38. Zeger SL, Liang KY, Albert PS. Models for longitudinal data – a generalized estimating equation approach. *Biometrics* 1988;44:1049–1060.
39. NAEPP Expert Panel Report. Managing asthma during pregnancy: recommendations for pharmacologic treatment – 2004 update. *J Allergy Clin Immunol* 2005;115:34–46.
40. Murphy VE, Gibson PG, Smith R, Clifton VL. Asthma during pregnancy: mechanisms and treatment implications. *Eur Respir J* 2005;25:731–750.
41. Zhou J, Xiao D, Hu Y, Wang Z, Paradis A, Mata-Greenwood E, Zhang L. Gestational hypoxia induces preeclampsia-like symptoms via heightened endothelin-1 signaling in pregnant rats. *Hypertension* 2013;62:599–607.
42. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med* 1999;159:941–955.
43. Ernst P, Suissa S. Systemic effects of inhaled corticosteroids. *Curr Opin Pulm Med* 2012;18:85–89.
44. Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. *Pharmacol Ther* 2002;96:23–43.
45. Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J. Glucocorticoids and the risk for initiation of hypoglycemic therapy. *Arch Intern Med* 1994;154:97–101.
46. Fisher JE, Smith RS, Lagrandeur R, Lorenz RP. Gestational diabetes mellitus in women receiving beta-adrenergics and corticosteroids for threatened preterm delivery. *Obstet Gynecol* 1997;90:880–883.
47. Boulet LP. Asthma and obesity. *Clin Exp Allergy* 2013;43:8–21.
48. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ* 2005;330:565.
49. Torloni MR, Betran AP, Horta BL, Nakamura MU, Atallah AN, Moron AF, Valente O. Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. *Obes Rev* 2009;10:194–203.
50. Schatz M. Predictors of asthma control: what can we modify? *Curr Opin Allergy Clin Immunol* 2012;12:263–268.

Supplementary Table 1. Indexes of Asthma Severity and Control

Asthma Severity and Control	Daily Dose of Inhaled Corticosteroids (μg) ^a	Other Controller Therapy ^b	Number of Doses of Short-Acting β 2-Agonists per Week ^c	Moderate-to-Severe Exacerbations ^d
Mild				
Controlled	0–500	No	0–3	No
	0–250	Yes	0–3	No
Uncontrolled	0–250	Yes	0–3	Yes
	0–500	No	0–3	Yes
	0–250	Yes	4–10	No
	0–500	No	4–10	No
Moderate				
Controlled	251–500	Yes	0–10	No
	501–1000	Yes/No	0–10	No
	>1000	Yes/No	0–3	No
Uncontrolled	0–250	Yes	4–10	Yes
	0–500	No	4–10	Yes
	0–250	Yes	>10	No
	0–500	No	>10	No
	251–500	Yes	>10	No
	251–500	Yes	0–10	Yes
	501–1000	Yes/No	>10	No

	501–1000	Yes/No	0–10	Yes
Severe				
Controlled	>1000	Yes/No	4–10	No
Uncontrolled	0–1000	Yes/No	>10	Yes
	>1000	Yes/No	0–10	Yes
	>1000	Yes/No	>10	Yes/No

^a Daily dose given in beclomethasone/chlorofluorocarbon equivalents over 12 months

(dose equivalencies for ICS drugs in adults below).^{4, 6}

Product	Dose (µg/d)		
	Low	Medium	High
Beclomethasone dipropionate pMDI -CFC	≤ 500	501-1000	> 1000
Beclomethasone dipropionate pMDI -HFA	≤ 250	251-500	> 500
Fluticasone (pMDI and DPI)	≤ 250	251-500	> 500
Budesonide DPI	≤ 400	401-800	> 800
Mometasone	200	≥ 400-800	> 800

CFC : chlorofluorocarbon; HFA : hydrofluoralkane; pMDI : pressurized metered-dose inhaler; DPI: dry-powder inhaler

^b Defined as ≥6 prescriptions of a long-acting β₂-agonist, theophylline, or leukotriene-receptor antagonist over 12 months.

^c Mean number of doses of inhaled short-acting β₂-agonists **per week** calculated over 12 months. One dose equals 2 puffs of 100 µg of salbutamol. According to the Canadian Asthma Consensus Guidelines ¹, patients do not have acceptable asthma control if they use more than 3 doses of SABA per week as rescue medication, excluding 1 additional dose per day for exercise. We thus added the 3 recommended doses per week to 7 doses

for exercise to come to a maximum of 10 doses per week of SABA. In addition, we considered the cases in which patients have severe asthma and might need more than 10 doses per week to reduce symptoms (>10 doses of a SABA per week and >1,000 µg beclomethasone-CFC per day). This explains our three categories of SABA use (0-3; 4-10 and > 10 doses/week).

^d Defined as an emergency department visit or hospitalization for asthma, or a filled prescription of an oral corticosteroid over 12 months.

Supplementary Table 2. Characteristics of the Pregnancies Included in the Analyses of the Associations of Asthma With Cesarean delivery, Pregnancy-induced hypertension, and Gestational Diabetes

i) Cesarean Delivery Cohort

	Asthmatic Women Number (%) ^a	Non-asthmatic Women	<i>P</i> -value
Number of pregnancies	13,289	28,371	
Age at conception (years)			
<18	882 (6.6)	998 (3.5)	<0.001
18–34	11,578 (87.1)	24,632 (86.8)	
>34	829 (6.2)	2,741 (9.7)	
Receipt of social assistance up to 1 year before or during pregnancy (yes)	10,571 (79.5)	16,269 (57.3)	<0.001
Parity			
Nulliparous	4,229 (31.8)	9,718 (34.3)	<0.001
Multiparous	8,985 (67.6)	18,380 (64.8)	
Missing	75 (0.6)	273 (1.0)	
Multiple pregnancy (yes)	192 (1.4)	344 (1.2)	0.05
Pregnancy-induced hypertension (yes)	865 (6.5)	1,480 (5.2)	<0.001
Gestational diabetes (yes)	1,030 (7.8)	1,936 (6.8)	0.001

Gynecologist or obstetrician visit during pregnancy (yes)	9,969 (75.0)	20,291 (71.5)	<0.001
Number of prenatal visits (mean $\pm$ SD)	9.9 $\pm$ 4.5	9.4 $\pm$ 4.4	<0.001
Maternal chronic conditions (yes)			
Chronic hypertension	318 (2.4)	382 (1.3)	<0.001
Diabetes mellitus	314 (2.4)	372 (1.3)	<0.001

ii) Pregnancy-Induced Hypertension Cohort

	Asthmatic	Non-asthmatic	<i>P</i> -value
	Women	Women	
	Number (%)		
Number of pregnancies	12,971	27,989	
Age at conception (years)			
<18	877 (6.8)	992 (3.5)	< 0.001
18–34	11,309 (87.2)	24,348 (87.2)	
>34	785 (6.1)	2649 (9.5)	
Receipt of social assistance up to 1 year before or during pregnancy (yes)	10,312 (79.5)	16,048 (57.3)	<0.001
Parity			
Nulliparous	4,135 (31.9)	9,617 (34.4)	<0.001
Multiparous	8,767 (67.6)	18,103 (64.7)	
Missing	69 (0.5)	269 (1.0)	
Multiple pregnancy (yes)	184 (1.4)	338 (1.2)	0.077
Gestational diabetes (yes)	977 (7.5)	1,872 (6.7)	0.002
Maternal chronic conditions			
Chronic hypertension ^b	0 (0.0)	0 (0.0)	NA
Diabetes mellitus	272	350	<0.001

iii) Gestational Diabetes Cohort

	Asthmatic	Non-asthmatic	<i>P</i> -value
	Women	Women	
	Number (%)		
Number of pregnancies	12,975	27,999	
Age at conception (years)			
<18	874 (6.7)	996 (3.6)	<0.001
18–34	11,316 (87.2)	24,341 (86.9)	
>34	785 (6.1)	2,662 (9.5)	
Receipt of social assistance up to 1 year before or during pregnancy (yes)	10,319 (79.5)	16,052 (57.3)	<0.001
Parity			
Nulliparous	4,137 (31.9)	9,615 (34.3)	<0.001
Multiparous	8,763 (67.5)	18,116 (64.7)	
Missing	75 (0.6)	268 (1.0)	
Multiple pregnancy (yes)	187 (1.4)	340 (1.2)	0.058
Pregnancy-induced hypertension (yes)	817 (6.3)	1,429 (5.1)	<0.001
Maternal chronic conditions (yes)			
Chronic hypertension	276 (2.1)	360 (1.3)	<0.001
Diabetes mellitus ^c	0 (0.0)	0 (0.0)	NA

^a Unless otherwise specified.

^b Excluding pregnancies in women with chronic hypertension.

^c Excluding pregnancies in women with diabetes mellitus.

SD, standard deviation; NA, not applicable.

Reference List

- (1) Boulet LP, Becker A, Berube D et al. Canadian Asthma Consensus Report, 1999. Canadian Asthma Consensus Group. CMAJ 1999; 161(11 Suppl):S1-61.