ERJ Express. Published on June 18, 2010 as doi: 10.1183/09031936.00029109

Impact of Maternal Asthma on Perinatal Outcomes

Faranak Firoozi
Université de Montréal, Québec, Canada
PhD candidate

Catherine Lemière
Université de Montréal, Québec, Canada
Centre de Recherche de l'Hôpital du Sacré-Cœur de Montréal, Québec, Canada
MD, Associate Professor

Marie-France Beauchesne
Université de Montréal, Québec, Canada
Centre de Recherche de l'Hôpital du Sacré-Cœur de Montréal, Québec, Canada
PharmD, Associate Professor

Sylvie Perreault
Université de Montréal, Québec, Canada
PhD, Associate Professor

Amélie Forget
Centre de Recherche de l'Hôpital du Sacré-Cœur de Montréal, Québec, Canada
MSc, Master in Computer Science

Lucie Blais
Université de Montréal, Québec, Canada
Centre de Recherche de l'Hôpital du Sacré-Cœur de Montréal, Québec, Canada
PhD, Associate Professor

Corresponding author: Lucie Blais
Université de Montréal
Faculté de pharmacie
C.P. 6128, succursale Centre-ville
Montréal (Québec)
Canada – H3C 3J7
Tel: (514) 343-6111, extension 1-3786
Fax: (514) 343-6120
Email: lucie.blais@umontreal.ca

Lucie Blais and Sylvie Perreault are the recipients of a career salary award from the *Fonds de la recherche en santé du Québec* (FRSQ). Catherine Lemière is the recipient of a of a career salary award from the FRSQ. Lucie Blais and Marie-France Beauchesne hold the AstraZeneca Chair in Respiratory Health. Faranak Firoozi is the recipient of a Doctoral Training Award from the FRSQ. This study was funded through a grant from the CIHR.

Running title: Asthma in Pregnancy
Word count: 3698

Abstract

Background/ Objectives

The are conflicting results concerning the impact of maternal asthma during pregnancy on perinatal outcomes. We investigated the associations between maternal asthma during pregnancy and the risk of a small-for-gestational-age (SGA) infant, a low-birth-weight (LBW) infant, and preterm birth using a large population-based cohort.

Methods

A population-based cohort of 40,788 pregnancies from asthmatic and non-asthmatic women was reconstructed through the linking of three Quebec (Canada) administrative databases between 1990 and 2002. A two-stage sampling cohort design was used to collect additional information by way of a mailed questionnaire. The generalized estimation equation models were used to obtain adjusted odds ratios of SGA, LBW and preterm birth comparing asthmatic and non-asthmatic women.

Results

The cohort included 13,007 pregnancies from asthmatic and 27,781 pregnancies from non-asthmatic women. Final estimates showed that the risk of SGA (OR: 1.27, 95% CI: 1.14-1.41), LBW (OR: 1.41, 95% CI:1.22-1.63) and preterm delivery (OR: 1.64, 95%CI:1.46-1.83) was significantly higher among asthmatic than non-asthmatic women.

Conclusions

Mothers with asthma during pregnancy have a higher risk of having SGA, LBW, or preterm birth infants than non-asthmatic women. However, external validity might be an issue since the cohort under represents women with high socio-economic status.

Keywords

Asthma, perinatal outcomes, pregnancy, LBW, SGA, preterm birth, administrative databases, two stage sampling cohort

Introduction

The prevalence of asthma among pregnant women is between 4 to 7% and is known as one of the most frequent chronic diseases encountered during pregnancy (1-5). Adverse perinatal outcomes, such as a preterm birth, a low-birth-weight (LBW) infant and a small-for-gestational-age (SGA) infant, have been reported to be higher in pregnant women with asthma when compared to women without asthma in some studies (6-13), but not in other studies (1, 14-21). In a recent meta-analysis, conducted by Murphy et al., asthmatic women with and without asthma exacerbations during pregnancy were compared to non-asthmatic women for the risk of LBW infant and preterm delivery (22). The authors found no significant increased risk of preterm delivery among asthmatic women, but observed a significant increased risk of LBW in women who had an exacerbation (RR: 2.54) and no significant increased risk in women who did not have an asthma exacerbation during pregnancy (RR: 1.12) (22).

Methodological differences between studies as well as the lack of power of some of them due to small sample sizes make it difficult to estimate, with any reasonable degree of certainty, the risk of adverse perinatal outcomes in pregnant women with asthma. Moreover, the meta-analysis of Murphy et al. evaluated the association between exacerbations of asthma during pregnancy rather than asthma per se on adverse perinatal outcomes (22). To estimate more precisely the risk of SGA infants, LBW infants, and preterm births associated with maternal asthma and exacerbations of the disease, we performed a two-stage sampling cohort study based on a cohort of 40,788 pregnancies from asthmatic and non-asthmatic women reconstructed by the linkage of three administrative databases from Quebec (Canada) between 1990 and 2002.

Materials and Methods

Source of Data

The data for our study came from three administrative databases of the province of Quebec; the *Régie de l'Assurance Maladie du Quebec* (RAMQ), MED-ECHO, and the *Fichier des événements démographiques du Québec* (birth and death registries) managed by the *Institut de la statistique du Québec* (ISQ). These data were supplemented by a mailed questionnaire completed by selected mothers. The RAMQ databases provide information on medical services for all residents of Quebec and on prescribed medications filled in community pharmacies by residents covered by the RAMQ Public Drug Insurance Plan. Between 1980 and 1997, only the elderly and social assistance beneficiaries were covered by the RAMQ Public Drug Insurance Plan. However, since the enactment of mandatory drug coverage in 1997, the RAMQ Public Drug Insurance Plan provides coverage for an additional 1.7 million adherents, mainly workers and their families who have no access to a private drug insurance plan from their workplace(2). Since 1997, approximately 43% of the population of Quebec is covered by the RAMQ Public Drug Insurance Plan. The RAMQ Prescription Medications database provides information on dispensed medications – i.e. date of filling, name, dose, quantity, dosage form and duration of the prescription – while the RAMQ Medical Services database provides information on medical services dispensed in a clinic, an emergency department (ED) or a hospital and includes information pertaining to date, diagnosis coded with ICD-9, where the service was dispensed, etc. Data recorded in the RAMQ Prescription Medications database and asthma diagnoses recorded in the RAMQ Medical Services database have been formally evaluated and found to be valid (3, 4). The MED-ECHO

database is a provincial database which records data on acute care hospitalizations and covers all residents of Quebec (25). The *Fichier des événements démographiques* provides information on all births and stillbirths in the province of Quebec. Some additional information regarding siblings and maternal life styles during pregnancy which are not included in the administrative databases were retrieved from a mailed questionnaire completed by a number of selected women.

Study Design and Population

A two-stage sampling cohort design (balanced selection) was used for this study (26-29). In our study, the first stage of sampling corresponds to a cohort formed of singleton pregnancies of asthmatic and non-asthmatic women ending in a delivery (live birth or stillbirth) between January 1st, 1990 and December 31st, 2002 in the province of Quebec (Canada). Pregnant women and newborns were identified in the RAMQ database using diagnostic and act codes related to prenatal care, pregnancy complications, and deliveries (30). Moreover, to be included in our cohort, a woman must have been between 13-50 years of age at the beginning of her pregnancy as well as being covered by the RAMQ Public Prescription Drug Insurance Plan for at least one year prior to and throughout the duration of her pregnancy. Women were considered as having asthma if they had a diagnosis of asthma (ICD-9 code 493, except 493.2 which corresponds to chronic obstructive asthma), and one or more prescriptions for an asthma medication dispensed in the two years prior or during pregnancy. We allowed a maximum of four pregnancies per woman to enter in the cohort and only the more recent ones were retained. For each pregnancy, the data from the RAMQ and MED-ECHO databases were obtained one year before and during pregnancy. The date of the last menstruation was calculated using the

gestational age and date of birth of the infant, obtained from the MED-ECHO and RAMQ databases. This mother-child cohort was then linked with the *Fichier des événements démographiques* database to obtain information on socio-demographic variables for the mothers and the newborns.

At the second stage of sampling, we selected, from the cohort, a sample of women to whom a questionnaire was sent by mail, using a balance sampling strategy (26, 28). This strategy oversamples women who had a SGA infant, a LBW infant, or a preterm delivery in order to increase the statistical power (26). A maximum of two pregnancies per woman were selected at this stage of sampling to avoid overloading women who had more than two live deliveries during our study period with questionnaires. Selected women had to be at least 18 years old at the beginning of their pregnancy to be eligible for the second stage of sampling due to ethical considerations. For all pregnancies selected at this stage, the RAMQ provided us with the current postal addresses of the mother as well as their spoken language.

The questionnaire was used to obtain information pertaining life styles (including maternal cigarette smoking, maternal alcohol consumption, and paternal cigarette smoking), maternal characteristics, and pregnancy related variables that are not recorded in the administrative databases. The questionnaire underwent prior testing by about 40 women for its clarity and also its facility to be understood and answered. By pretesting, we also assessed the capacity of women to remember the events which happened up to 15 years ago. First, we sent 5,384 questionnaires to selected women. A second questionnaire was sent a month and half later as a reminder. A 10$ compensation was given to women

who completed the questionnaire. The questionnaires' data were recorded in a computerized database, using a double entry method to improve data quality.

The linkage between data obtained from the RAMQ, MED-ECHO and ISQ databases, and the filled questionnaires as well as the request of the name and the mailing address of selected women at the second stage of sampling was approved by the *Commission d'accès à l'information du Quebec* (CAI). This research project was also approved by the ethics committee of the *Hôpital du Sacré-Cœur de Montréal* (Montreal, Quebec, Canada).

Exposure

In this study, the main exposure variable is maternal asthma during pregnancy as previously defined in the section "Study design and Population". Women with asthma during pregnancy were compared to non-asthmatic pregnant women.

Outcomes

The outcomes of interest included SGA infants, preterm births, and LBW infants. SGA was defined as a birth weight below the 10^{th} percentile for gestational age and gender, using new Canadian standards (31, 32). Preterm birth was defined as a birth before 37 weeks of gestation while LBW was defined as birth weight lower than 2,500g. Validated algorithms based on data recorded in the RAMQ, MED-ECHO or ISQ databases were used to measure these variables (33).

Confounding Variables

Four categories of variables were considered as potential confounding variables. **Maternal characteristics derived from administrative databases** include age at the beginning of the pregnancy (< 18, 18-34, > 34 years) (34), receiving social assistance benefits in the year before or during pregnancy (yes/no), urban residency at delivery (yes/no), and being primiparous (yes/no). **Maternal characteristics derived from the questionnaire** include maternal education (highest level reached: elementary school, high school, college & University), annual family income during pregnancy (<$18,000, $18,000-$46,000, >$46,000) (34) and birth weight (<2.5, 2.5-5, >5 kg)**. Pregnancy-related variables derived from administrative databases** include high risk pregnancies (ICD-9 codes V23 except V238, 6932, 6938, 6939, 6941, 9157 and 9167 recorded in the RAMQ or MED-ECHO databases) (yes/no), gestational diabetes (yes/no), pregnancy-induced hypertension (yes/no), a gynecologist or obstetrician visit during pregnancy (yes/no), and number of prenatal visits (≤5, 6-14, >14). **Pregnancy-related variables derived from the questionnaire** include maternal weight gain during pregnancy (<8, 8-16, >16 kg), maternal body mass index (BMI) (<18.5, 18.5-24.9, 25-29.9, >29.9) at beginning of pregnancy and another preterm or LBW infant prior to the current delivery (yes/no) (35). **Maternal co-morbidities derived from administrative databases** include diabetes mellitus (yes/no) and chronic hypertension (yes/no). **Life style habits derived from the questionnaire** include maternal and paternal cigarette smoking during pregnancy (yes/no) and maternal alcohol consumption during pregnancy (yes/no).

Data Analysis

Descriptive statistics were used to report the characteristics of the asthmatic and non-asthmatic women included in the cohort (first stage of sampling) and those selected at the

second stage of sampling. In addition, the asthmatic related characteristics were reported for the asthmatic women. The maternal asthma severity and control level during pregnancy were measured with an index that we had previously developed and validated (36). These indexes are based on dispensed prescriptions of asthma medications as well as acute care for asthma recorded in the RAMQ and MED-ECHO databases. We also calculated the distribution of the variables measured at the first stage of sampling for women who answered the questionnaire and women who did not in order to investigate whether or not there is any difference between these two groups. The unit of analysis was the pregnancy, due to the fact that a woman could contribute up to four pregnancies during the study period at the first stage of sampling and up to two pregnancies at the second stage of sampling.

We calculated the prevalence of the study outcomes for asthmatic and non-asthmatic women, separately for the first and second stage of sampling. Crude and adjusted odds ratios (OR) for SGA infants, LBW infants and preterm births comparing asthmatic to non-asthmatic women were then estimated for the first stage of sampling using Generalized Estimation Equation (GEE) models (37). The GEE models can estimate the effect of independent variables, including the main exposure and confounding variables, on several types of outcomes, namely dichotomous outcomes such as the presence or the absence of SGA, LBW or preterm delivery with a logit function as well as take into account the fact that a woman could contribute more than one pregnancy to the analysis by estimating the correlation between consecutive pregnancies. The best reduced models were found using a backward selection strategy, keeping in the model only covariates that

were found to act as a confounder or those that were significantly associated with the outcome (p-value < 0.05).

We also obtained adjusted OR estimates for each outcome based on pregnancies selected at the second stage of sampling and GEE models that adjusted for confounding variables collected at the first (administrative databases) and second (questionnaire) stages of sampling. Missing values for variables retrieved from the questionnaire were included in the reference category for modeling purposes since the proportion of missing values was low. The final adjusted OR estimates were then obtained by correcting the second stage adjusted OR with the second stage sampling fractions and the adjusted OR found at the first stage of sampling using the methodology proposed by Collet et al (26). This methodology is based on a statistical analysis that takes into account the fact that certain cells of the outcome/main exposure cross table have been over sampled and provide unbiased estimates of the association under study.

We also performed an analysis stratified by the presence or the absence of an asthma exacerbation during pregnancy in order to be able to compare with the results of the meta-analysis published by Murphy et al. (22). Asthma exacerbations were defined as either a filled prescription of an oral corticosteroids, an emergency visit for asthma or a hospitalization for asthma occurring during pregnancy.

Results

At the first stage of sampling, the cohort included 13,007 singleton pregnancies of asthmatic women and 27,781 singleton pregnancies of non-asthmatic women. At the second stage of sampling, we sent a total of 5,384 questionnaires to selected asthmatic (n=3,168) and non-asthmatic (n=2,216) women. We received 2,080 completed

questionnaires (response rate: 38.6%): 1,274 questionnaires from asthmatic women (response rate: 40.2%) and 806 questionnaires from non-asthmatic women (response rate: 36.4%).

In Table 1, we present the distribution of the variables retrieved from the administrative databases for all pregnancies of asthmatic and non-asthmatic women included in the cohort (first stage of sampling). We found that the prevalence of several characteristics was higher among the pregnancies of asthmatic than those of non-asthmatic women: recipients of social assistance (79.5% vs. 57.5%), high risk pregnancies (36.1% vs. 29.3%), gestational diabetes (7.7% vs. 6.8%), pregnancy induced hypertension (6.5% vs. 5.2%), maternal chronic diabetes (2.4% vs. 1.4%), and maternal chronic hypertension (2.3% vs. 1.3%). Table E2 in the electronic attachment presents the crude associations (OR and 95% CI) between selected maternal characteristics, the asthmatic status of the mother and the perinatal outcomes under study.

Table 2 shows the distribution of variables retrieved from the questionnaires among women selected at the second stage of sampling and who responded to the questionnaire. In this sample, asthmatic women had a lower education (15.2% vs. 28.0%, for college and university levels) and a lower annual family income (37.9% vs. 51.3%, for >$ 18,000) than non-asthmatic women. However, the prevalence of several other characteristics was higher among asthmatic than non-asthmatic women: maternal birth weight <2.5 kg (19.5% vs. 15.4%), maternal weight gain >16 kg (40.6% vs. 30.4%), maternal BMI pre-pregnancy >29.9 (12.2% vs. 7.6%), preterm birth prior to the current

delivery (16.5% vs. 13.8%), maternal cigarette smoking (63.2% vs. 49.0%), and paternal cigarette smoking (50.9% vs. 42.9%).

Furthermore, we found that among asthmatic and non-asthmatic women, respondents (1,274 vs. 1,894, respectively) and non respondents (806 vs. 1,410) were quite similar except that there was a lower proportion of women who received social assistance (54.6% vs. 64.8% for non-asthmatics and 77.2% vs. 84.0% for asthmatics), and lived in an urban area (71.6% vs. 80.1% for non-asthmatics and 77.2% vs. 83.7% for asthmatics) among respondents. The details of this analysis are available in the electronic attachment.

In Table 3, we present the distribution of asthma related variables among pregnancies of asthmatic women included in the first stage of sampling. We found that 82.6%, 12.4% and 5.0% of pregnancies of asthmatic women included at the first stage of sampling were from women with mild, moderate and severe asthma, respectively. Among these women, 3.6% used more than 500 μg of inhaled corticosteroids (ICS) per day, 29.5% used more than three doses of SABA per week during pregnancy and 34.0% filled no asthma medications during pregnancy.

Table 4 shows the prevalence of SGA infants, LBW infants and preterm deliveries among pregnancies of asthmatic and non-asthmatic women at the first stage of sampling. In addition, in this table we present the first stage and the final crude and adjusted estimates of the ORs and corresponding 95% CIs for the three perinatal outcomes, comparing asthmatic to non-asthmatic women. The prevalence of the three perinatal outcomes was

higher among pregnancies of asthmatic than those of non-asthmatic women (SGA: 14.5% vs. 10.6%, LBW: 9.2% vs. 5.7% and preterm births: 10.3% vs. 6.7%).

The first stage adjusted ORs showed that the risk of the three adverse perinatal outcomes was significantly higher among asthmatic than non-asthmatic women. In the final models, all potential confounding variables were initially included, but only some of them remained in the final reduced models. The covariables were kept in the GEE models only if they were found to act as a confounder for the association between asthma and perinatal outcomes or if they were significantly associated with the outcome under study. Adjusted final estimates showed that the risk of the three adverse perinatal outcomes was significantly higher among asthmatic than non-asthmatic women. The risk was OR:1.27 (95% CI: 1.14-1.41) for SGA, OR:1.41 (95% CI: 1.22-1.63) for LBW and OR:1.64 (95% CI: 1.46-1.83) for preterm births.

The stratified analysis presented in Table 5 shows that asthmatic women who had an asthma exacerbation during pregnancy were significantly more likely to have a SGA, LBW or a preterm baby than non-asthmatic women. Similar results, but with lower magnitude except for preterm birth, were observed when asthmatic women without an asthma exacerbation during pregnancy were compared with non-asthmatic women.

Discussion

We have found that asthmatic women with low socio-economic status, whether or not they had an asthma exacerbation during pregnancy, were significantly more at risk of giving birth to a SGA, LBW and preterm baby. One of the possible mechanism causing

these adverse outcomes, although not tested in this study, would be the lack of oxygen to the fetus which can lead to intrauterine growth retardation, preterm birth, or neonatal hypoxia (38, 39).

Our results support the findings of Demissie et al, Liu et al and Enriquez et al who reported a significant association between maternal asthma and the risk of SGA infants with relative risk estimates ranging between 1.16 and 1.20 (6, 7, 13). On the other hand, our results differ from those of Perlow et al, Bracken et al and Dombrowski et al who found no significant increased risk of SGA associated with asthma (20, 21, 40). Lack of adjustment for several potential confounders and lack of power due to small sample sizes probably explain the differences in results.

Murphy et al. investigated the effect of asthma exacerbation on LBW and preterm births through a meta-analysis using data from three and four studies, respectively (22). The authors found no significant increased risk of preterm delivery in women who had (RR: 1.46, 95%CI: 0.77-2.78) and in women who did not have an asthma exacerbation during pregnancy (RR: 0.93, 95% CI: 0.74-1.17). We found a similar significant OR for women who had an asthma exacerbation (OR= 1.47, 95% CI: 1.17-1.83), but we found a higher OR for women who did not have an asthma exacerbation 1.64 (1.44-1.86). For LBW, Murphy et al. observed a significant increased risk in women who had (RR: 2.54, 95% CI:1.52-4.25), but no increased risk in women who did not have an asthma exacerbation during pregnancy (RR: 1.12, 95% CI: 0.89-1.40) (22). We observed ORs that are in the same direction, but in our study both ORs were statistically significant. The differences between the two studies could be partly explained by important differences in the study

sample sizes. In their meta-analysis, Murphy et al compared 855 asthmatic women with 31,662 non-asthmatic women coming from three studies as to their risk of having a LBW infant. To investigate the impact of asthma on prematurity, Murphy et al. compared 1,312 pregnancies from asthmatic women to 31,899 pregnancies from non-asthmatic women. The corresponding samples in our study were 13,007 asthmatic women and 27,781 non-asthmatic women at the first stage of sampling.

The major strength of our study is that it was based on a large cohort of 13,007 pregnancies of asthmatic women and 27,781 pregnancies of non-asthmatic women selected over a 12-year period. All asthma diagnoses were made by a physician and asthma diagnoses recorded in the RAMQ database were formally evaluated and found to be valid (54). We also avoided recall bias in measuring outcomes and the main exposure since these variables were collected using administrative databases in which data are prospectively collected. Moreover, the validity of the outcomes; birth weight and length of gestation have been evaluated by comparing the database values to the woman's medical chart values for 728 pregnant women and found to be highly valid (33). Another strength of the study is the two-stage sample design in which database data were coupled with questionnaire data in order to obtain information on confounding variables that are not recorded in the databases. We were thus able to construct models that considered a large number of variables that may intervene in the development of the fetus.

This study has also some limitations that should be kept in mind while interpreting the results. Our cohort is less representative of women with higher socio-economic level and it would be a threat to external validity if, for example, maternal asthma would have a

stronger effect on perinatal outcomes among poorer women than among richer women. The possibility of an effect modification of the mother's socio-economic status cannot be ruled out completely, but is unlikely since the impact of asthma on perinatal outcomes is more likely to be physiologic than behavioural. Asking questions related to a pregnancy that occurred many years ago could result in recall bias. However, Yawn et al. have shown that "maternal reports of perinatal events in which they directly participated can be accurately and reliably reported 10 to 15 years after birth" (55). Finally, the response rate to the questionnaire was 40.2% for asthmatic women and 36.4% for non-asthmatic women, but it is reassuring to see that the distribution of the databases driven variables were quite similar between responders and non responders.

As opposed to the latest meta-analysis on the topic which reported that asthmatic pregnant women who had an asthma exacerbation were only at risk of having a LBW baby (22), our study showed that asthmatic women, whether or not they had an asthma exacerbation, were at increased risk of having a LBW, preterm and SGA baby. Considering the high prevalence of asthma among pregnant women and the fact that uncontrolled asthma has been associated with adverse perinatal outcomes (12, 20, 40), it is essential to develop preventive, therapeutic and health care strategies to insure an optimal treatment of asthma during pregnancy to minimize the adverse perinatal outcomes of asthma.

Acknowledgements

We thank Mrs Marie-Claude Giguère from the *Régie de l'assurance maladie du Québec*, Mrs Chantal Girard from the *Institut de la statistique du Québec* and Mrs Louise Légaré and collaborators from the *Ministère de la Santé et des Services sociaux du Québec* for

assistance with the data. We are grateful to the *Commission d'accès à l'information du Québec* for authorizing the study. We thank Mrs Karine Chouinard for helping with the logistics of the study. Finally, many thanks to all the women who kindly participated in this study by filling out the questionnaire.

Conflict of interest

The authors declare no competing interests for the submitted manuscript.

Copy right

Table 1. Characteristics of all pregnancies of asthmatic and non-asthmatic women include in the cohort: database driven variables at the first stage of sampling

	Pregnancies of asthmatic women (n=13007)	**Pregnancies of non-asthmatic women (n=27781)**
	Number (%)	
Maternal socio-demographic variables		
Age at beginning of pregnancy (years)		
< 18	875 (6.7)	987 (3.5)
18 - 34	11,333 (87.1)	24,136 (86.9)
> 34	799 (6.1)	2658 (9.6)
***Recipient of social assistance**	10,346 (79.5)	15,970 (57.5)
Urban residency at delivery	10,528 (80.9)	21,407 (77.1)
Pregnancy related variables		
Primiparous	4,191 (32.3)	9,611 (34.8)
High risk pregnancy	4,700 (36.1)	8,131 (29.3)
Gestational diabetes	1,000 (7.7)	1,886 (6.8)
Pregnancy induced hypertension	846 (6.5)	1,437 (5.2)
Gynecologist or obstetrician visit during pregnancy	10,713 (82.4)	22,453 (80.8)
Number of prenatal visits		
≤ 5	2,048 (15.8)	4,831 (17.4)
6-14	9,477 (72.9)	20,577 (74.1)
> 14	1,482 (11.4)	2,373 (8.5)
Maternal co-morbidities		
Chronic diabetes	314 (2.4)	381 (1.4)
Chronic hypertension	304 (2.3)	368 (1.3)

*Social assistance status in the year before pregnancy

Table 2. Characteristics of the pregnancies of asthmatic and non-asthmatic women selected at the second stage of sampling (n=2080): questionnaire driven variables

	Pregnancies of asthmatic women (n=1274)	**Pregnancies of non-asthmatic women (n=806)**
	Number (%)	
Maternal characteristics		
Highest level of education attained during pregnancy		
Elementary school	105 (8.2)	35 (4.3)
High school	948 (74.4)	527 (65.4)
College & University	194 (15.2)	226 (28.0)
Unknown	27 (2.1)	18 (2.2)
Annual family income during pregnancy		
< $18,000	762 (59.8)	377 (46.8)
$18,001 - $46,000	407 (31.9)	323 (40.1)
> $46,001	76 (6.0)	90 (11.2)
Unknown	29 (2.3)	16 (2.0)
Weight at birth		
< 2.5 kg	248 (19.5)	124 (15.4)
2.5 – 5.0 kg	879 (69.0)	548 (68.0)
> 5.0 kg	16 (1.3)	11 (1.4)
Unknown	131 (10.3)	123 (15.3)
Pregnancy related variables		
Weight gain during pregnancy		
< 8 kg	179 (14.1)	115 (14.3)
8 - 16 kg	531 (41.7)	423 (52.5)
> 16 kg	517 (40.6)	245 (30.4)
Unknown	47 (3.7)	23 (2.8)
BMI pre-pregnancy		
< 18.5	178 (14.0)	124 (15.4)
18.5 – 24.9	667 (52.4)	468 (58.1)
24.9 – 29.9	231 (18.1)	132 (16.4)
> 29.9	155 (12.2)	61 (7.6)
Unknown	42 (3.4)	21 (2.6)
Preterm birth prior to the current delivery		
Yes	210 (16.5)	111 (13.8)
No	1,055 (82.8)	692 (85.9)
Unknown	9 (0.7)	3 (0.4)
LBW infant prior to the current delivery		
Yes	192 (15.1)	119 (14.8)
No	1,073 (84.2)	684 (84.9)
Unknown	9 (0.7)	3 (0.4)
Life style habits during pregnancy		
Maternal cigarette smoking		
Yes	805 (63.2)	395 (49.0)
No	462 (36.3)	402 (49.9)
Unknown	7 (0.5)	9 (1.1)
Paternal cigarette smoking		
Yes	648 (50.9)	346 (42.9)

No	601 (47.2)	451 (56.0)
Unknown	25 (2.0)	9 (1.1)
Maternal alcohol consumption		
Yes	221 (17.4)	148 (18.4)
No	1,008 (79.1)	619 (76.8)
Unknown	45 (3.5)	39 (4.8)

Table 3. Asthma related characteristics of the pregnancies of asthmatic women (n=13007)

During pregnancy		**Number (%)**
Asthma severity level	Mild	10,737 (82.6)
	Moderate	1,618 (12.4)
	Severe	652 (5.0)
Asthma control level	Controlled	8,331 (64.1)
	Uncontrolled	4,676 (35.9)
* Average daily dose of ICS (µg)	0	7,729 (59.4)
	0-500	4,812 (37.0)
	500-1000	334 (2.6)
	>1000	132 (1.0)
**Average number of doses of SABA per week	0	4,973 (38.2)
	> 0-3	4,199 (32.3)
	> 3	3,835 (29.5)
Leukoteriene-receptor antagonists use		34 (0.3)
Long-acting beta2-agonists use		229 (1.8)
Theophyline use		311 (2.4)
Oral corticosteroids use		980 (7.5)
At least one asthma medication		8,580 (66.0)
≥ 1 respiratory physician visit		750 (5.8)
≥ 1 ED visit for asthma		1,611 (12.4)
≥ 1 hospitalization for asthma		196 (1.5)

***** ICS daily dose in beclomethasone-CFC equivalent

**SABA: short-acting inhaled $beta_2$-agonist

Table 4. Crude and adjusted odds ratio of adverse perinatal outcomes comparing pregnancies of asthmatic and non-asthmatic women

	Pregnancies of asthmatic women N=13,007	Pregnancies of non-asthmatic women N=27,781	OR (95% CI) Asthmatic versus non-asthmatic women (first stage estimates)		OR (95% CI) Asthmatic versus non-asthmatic women (final estimates)	
	Number (%)		Crude	Adjusted	Corrected Crude	Corrected Adjusted
SGA	1,886 (14.5)	2,948 (10.6)	1.43 (1.34-1.52)	1.29 (1.21-1.37)†	1.43 (1.34-1.52)	1.27 (1.14-1.41)*
LBW	1,197 (9.2)	1,575 (5.7)	1.69 (1.56-1.82)	1.52 (1.40-1.65)††	1.69 (1.56-1.82)	1.41 (1.22-1.63)**
Preterm	1,340 (10.3)	1,848 (6.7)	1.61 (1.50-1.73)	1.51 (1.40-1.64) †††	1.61 (1.50-1.73)	1.64 (1.46-1.83)***

†Adjusted for socio-economic status, urban residency at delivery, parity, high risk pregnancy, gestational diabetes, chronic diabetes, pregnancy induced hypertension, gynecologist or obstetrician visit during pregnancy, and prenatal visits.
††Adjusted for socio-economic status, urban residency at delivery, parity, high risk pregnancy, gestational diabetes, pregnancy induced hypertension, chronic hypertension, gynecologist or obstetrician visit during pregnancy, and prenatal visits.
†††Adjusted for socio-economic status, parity, high risk pregnancy, chronic diabetes, pregnancy induced hypertension, chronic hypertension, gynecologist or obstetrician visit during pregnancy, and prenatal visits
* Adjusted for socio-economic status, parity, pregnancy induced hypertension, prenatal visits, maternal weight at birth, maternal weight gain during pregnancy, maternal BMI pre-pregnancy, preterm birth prior to the current delivery, LBW infant prior to the current delivery and maternal cigarette smoking.
** Adjusted for socio-economic status, parity, high risk pregnancy, pregnancy induced hypertension, gynecologist or obstetrician visit during pregnancy, prenatal visits, chronic hypertension, maternal weight at birth, maternal weight gain during pregnancy, maternal BMI pre-pregnancy, LBW infant prior to the current delivery and maternal cigarette smoking.
*** Adjusted for socio-economic status, high risk pregnancy, gynecologist or obstetrician visit during pregnancy, prenatal visits, maternal weight gain during pregnancy, preterm birth prior to the current delivery.

Table 5. Adjusted odds ratio of adverse perinatal outcomes comparing pregnancies of women with and without an asthma exacerbation to pregnancies of non-asthmatic women

Outcomes	Asthmatic women with an exacerbation (n=1970) vs non- asthmatic women (n=27 781)	Asthmatic women without an exacerbation (11 037) vs non-asthmatic women (n=27 781)
	Adjusted final OR* (95%CI)	Adjusted final OR* (95%CI)
SGA	1.41 (1.18-1.68)	1.23 (1.10-1.37)
LBW	1.55 (1.20-2.01)	1.37 (1.18-1.60)
Preterm	1.47 (1.17-1.83)	1.641.44-1.86)

*OR adjusted for all potential confounders

References

(1) **Alexander S, Dodds L, Armson BA. Perinatal outcomes in women with asthma during pregnancy. Obstet Gynecol 1998 Sep;92(3):435-40.**

(2) **Kwon HL, Belanger K, Bracken MB. Asthma prevalence among pregnant and childbearing-aged women in the United States: Estimates from national health surveys. Annals of Epidemiology 2003 May;13(5):317-24.**

(3) **Olesen C, Steffensen FH, Nielsen GL, de Jong-van den Berg, Olsen J, Sorensen HT. Drug use in first pregnancy and lactation: a population-based survey among Danish women. The EUROMAP group. Eur J Clin Pharmacol 1999 Apr;55(2):139-44.**

(4) **Luskin AT. An overview of the recommendations of the Working Group on Asthma and Pregnancy. National Asthma Education and Prevention Program. J Allergy Clin Immunol 1999 Feb;103(2 Pt 2):S350-S353.**

(5) **Schatz M. Asthma treatment during pregnancy. What can be safely taken? Drug Saf 1997 May;16(5):342-50.**

(6) **Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. Am J Respir Crit Care Med 1998 Oct;158(4):1091-5.**

(7) **Liu S, Wen SW, Demissie K, Marcoux S, Kramer MS. Maternal asthma and pregnancy outcomes: a retrospective cohort study. Am J Obstet Gynecol 2001 Jan;184(2):90-6.**

(8) **Wen SW, Demissie K, Liu S. Adverse outcomes in pregnancies of asthmatic women: results from a Canadian population. Ann Epidemiol 2001 Jan;11(1):7-12.**

(9) **Bahna SL, Bjerkedal T. The course and outcome of pregnancy in women with bronchial asthma. Acta allergol 1972 Dec;27(5):397-406.**

(10) **Sorensen TK, Dempsey JC, Xiao R, Frederick IO, Luthy DA, Williams MA. Maternal asthma and risk of preterm delivery. Annals of Epidemiology 2003 Apr;13(4):267-72.**

(11) **Kallen B, Rydhstroem H, Aberg A. Asthma during pregnancy--a population based study. Eur J Epidemiol 2000 Feb;16(2):167-71.**

(12) **Kramer MS, Coates AL, Michoud MC, Dagenais S, Moshonas D, Davis GM, et al. Maternal asthma and idiopathic preterm labor. Am J Epidemiol 1995 Nov 15;142(10):1078-88.**

(13) Enriquez R, Griffin MR, Carroll KN, Wu PS, Cooper WO, Gebretsadik T, et al. Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. Journal of Allergy and Clinical Immunology 2007 Sep;120(3):625-30.

(14) Doucette JT, Bracken MB. Possible role of asthma in the risk of preterm labor and delivery. Epidemiology 1993 Mar;4(2):143-50.

(15) Schaefer G SF. Pregnancy complicated by asthma. Am J Obstet Gynecol 1961;82:182-91.

(16) Gordon M, Niswander KR, Berendes H, Kantor AG. Fetal morbidity following potentially anoxigenic obstetric conditions. VII. Bronchial asthma. Am J Obstet Gynecol 1970 Feb 1;106(3):421-9.

(17) Lao TT, Huengsburg M. Labour and delivery in mothers with asthma. Eur J Obstet Gynecol Reprod Biol 1990 May;35(2-3):183-90.

(18) Mabie WC BJWNSB. Clinical observations on asthma in pregnancy. J Matern Fetal Med 1992;1:45-50.

(19) Jana N, Vasishta K, Saha SC, Khunnu B. Effect of bronchial asthma on the course of pregnancy, labour and perinatal outcome. J Obstet Gynaecol 1995 Jun;21(3):227-32.

(20) Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms, severity, and drug therapy: A prospective study of effects on 2205 pregnancies. Obstetrics and Gynecology 2003 Oct;102(4):739-52.

(21) Dombrowski M, Schatz M, Wise R, Monane M, Landon M, Mabie W, et al. Asthma during pregnancy. Obstet Gynecol 2004;103:5-12.

(22) Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. Thorax 2006 Feb;61(2):169-76.

(23) Régie de l'assurance maladie du Québec. Statistiques annuelles. Québec; 1997 Oct 1.

(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(8):999-1009.

(25) Blais L, Lemière C, Menzies D, Berbiche D. Validity of asthma diagnoses recorded in the Medical Services database of Quebec. Pharmacoepidemiology and drug safety 2006;15 :245-52.

(26) Collet JP, Schaubel D, Hanley J, Sharpe C, Boivin JF. Controlling confounding when studying large pharmacoepidemiologic databases: a case study of the two-stage sampling design. Epidemiology 1998 May;9(3):309-15.

(27) Schaubel D, Hanley J, Collet JP, Bolvin JF, Sharpe C, Morrison HI, et al. Two-stage sampling for etiologic studies. Sample size and power. Am J Epidemiol 1997 Sep 1;146(5):450-8.

(28) Breslow NE, Cain KC. Logistic-Regression for 2-Stage Case-Control Data. Biometrika 1988 Mar;75(1):11-20.

(29) Hanley JA, Csizmadi I, Collet JP. Two-stage case-control studies: Precision of parameter estimates and considerations in selecting sample size. American Journal of Epidemiology 2005 Dec 15;162(12):1225-34.

(30) Martel MJ, Rey É, Beauchesne M-F, Perreault S, Lefebvre G, Forget A, et al. Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study. BMJ 2005;330:230-3.

(31) Lee PA, Chernausek SD, Hokken-Koelega ACS, Czernichow P. International small for gestational age advisory board consensus development conference statement: Management of short children born small for gestational age, April 24 October 1, 2001. Pediatrics 2003 Jun;111(6):1253-61.

(32) Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M, et al. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics 2001 Aug;108(2).

(33) Vilain A, Otis S, Forget A, Blais L. Agreement between administrative database and medical charts for pregnancy-related variables among asthmatic women. Pharmacoepidemiol Drug Saf 2008;Epub ahead of print.

(34) Tjepkema M. Measured Obesity. Adult obesity in Canada: measured height and weight. 2004.

(35) Cedergren M. Effects of gestational weight gain and body mass index on obstetric outcome in Sweden. International Journal of Gynecology & Obstetrics 2006 Jun;93(3):269-74.

(36) Firoozi F, Lemiere C, Beauchesne MF, Forget A, Blais L. Development and validation of database indexes of asthma severity and control. Thorax 2007 Jul;62(7):581-7.

(37) Zeger SL, Liang KY, Albert PS. Models for Longitudinal Data - A Generalized Estimating Equation Approach. Biometrics 1988 Dec;44(4):1049-60.

(38) Beckmann CA. The effects of asthma on pregnancy and perinatal outcomes. Journal of Asthma 2003;40(2):171-80.

(39) Schatz M, Zeiger RS, Hoffman CP. Intrauterine growth is related to gestational pulmonary function in pregnant asthmatic women. Kaiser-Permanente Asthma and Pregnancy Study Group. Chest 1990 Aug;98(2):389-92.

(40) Perlow JH, Montgomery D, Morgan MA, Towers CV, Porto M. Severity of asthma and perinatal outcome. Am J Obstet Gynecol 1992 Oct;167(4 Pt 1):963-7.

(41) Magee BD, Hattis D, Kivel NM. Role of smoking in low birth weight. Journal of Reproductive Medicine 2004 Jan;49(1):23-7.

(42) Horta BL, Victora CG, Menezes AM, Halpern R, Barros FC. Low birthweight, preterm births and intrauterine growth retardation in relation to maternal smoking. Paediatric and Perinatal Epidemiology 1997 Apr;11(2):140-51.

(43) Zeitlin JA, Ancel PY, Saurel-Cubizolles MJ, Papiernik E. Are risk factors the same for small for gestational age versus other preterm births? American Journal of Obstetrics and Gynecology 2001 Jul;185(1):208-15.

(44) Cnattingius S. The epidemiology of smoking during pregnancy: Smoking prevalence, maternal characteristics, and pregnancy outcomes. Nicotine & Tobacco Research 2004 Apr;6:S125-S140.

(45) Cnattingius S, Granath F, Petersson G, Harlow BL. The influence of gestational age and smoking habits on the risk of subsequent preterm deliveries. New England Journal of Medicine 1999 Sep 23;341(13):943-8.

(46) Windham GC, Hopkins B, Fenster L, Swan SH. Prenatal active or passive tobacco smoke exposure and the risk of preterm delivery or low birth weight. Epidemiology 2000 Jul;11(4):427-33.

(47) Wang X, Zuckerman B, Coffman GA, Corwin MJ. familial aggregation of low birth weight among whites and balcks in the united states. N Engl J Med 1995;333(26):1744-9.

(48) Surkan PJ, Stephansson O, Dickman PW, Cnattingius S. Previous preterm and small-for-gestational-age births and the subsequent risk of stillbirth. New England Journal of Medicine 2004 Feb 19;350(8):777-85.

(49) Ahluwalia IB, GrummerStrawn L, Scanlon KS. Exposure to environmental tobacco smoke and birth outcome: Increased effects on pregnant women aged 30 years or older. American Journal of Epidemiology 1997 Jul 1;146(1):42-7.

(50) Parazzini F, Chatenoud L, Surace M, Tozzi L, Salerio B, Bettoni G, et al. Moderate alcohol drinking and risk of preterm birth. European Journal of Clinical Nutrition 2003 Oct;57(10):1345-9.

(51) Kesmodel U, Olsen SF, Secher NJ. Does alcohol increase the risk of preterm delivery? Epidemiology 2000 Sep;11(5):512-8.

(52) Passaro KT, Little RE, Savitz DA, Noss J. The effect of maternal drinking before conception and in early pregnancy on infant birthweight. Epidemiology 1996 Jul;7(4):377-83.

(53) Mills JL, Graubard BI, Harley EE, Rhoads GG, Berendes HW. Maternal Alcohol-Consumption and Birth-Weight - How Much Drinking During Pregnancy Is Safe. Jama-Journal of the American Medical Association 1984;252(14):1875-9.

(54) Blais L, Lemiere C, Berbiche D. Validation of asthma diagnostic codes in the administrative health databases of Quebec, Canada. 13 ed. 2004. p. S32.

(55) Yawn BP, Suman VJ, Jacobsen SJ. Maternal recall of distant pregnancy events. J Clin Epidemiol 1998 May;51(5):399-405.