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Effect of maternal moderate to severe asthma on perinatal outcomes[☆]

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Received 14 July 2009; accepted 20 March 2010

KEYWORDS

Asthma;
Severity;
Databases;
Infant;
Pregnancy;
Two stage sampling

Summary

Background/objectives: It has been reported that adverse fetal outcomes are more prevalent in pregnant women with asthma than they are in women without asthma. In our study, we investigated the effect that the severity of asthma during pregnancy has on the risk of a small for gestational age (SGA) infant, low birth weight (LBW), and preterm birth.

Methods: A population-based cohort of 13,007 pregnancies from asthmatic women was reconstructed through the linking of three of Quebec's (Canada) administrative databases covering the period between 1990 and 2002. A two-stage sampling cohort design was used to collect additional information on the selected women's life-style habits via a mailed questionnaire. Asthma severity during pregnancy was measured with a validated database index. A logistic regression model was used to obtain the adjusted odds ratios of SGA, LBW and preterm birth as a function of the level of asthma severity.

Results: The proportions of women with mild, moderate and severe asthma were 82.5%, 12.5% and 5.0%, respectively. We sent 3,168 questionnaires to selected women, with a 40.2%

[☆] Lucie Blais and Sylvie Perreault are the recipients of a career salary award from the *Fonds de la recherche en santé du Québec* (FRSQ). Anick Bérard is the recipients of a career salary award from the *Canadian Institutes of Health Research* (CIHR). Francine M Ducharme is the recipient of two career salary awards, namely the National Scientist Award from the FRSQ and the William-Dawson award from McGill University. Catherine Lemièr is the recipient of a New Investigator Award for salary support from the Canadian Institutes for Health Research (CIHR). Lucie Blais and Marie-France Beauchesne hold the AstraZeneca Chair in Respiratory Health. Anick Bérard and Ema Ferreira hold the research Chair of the Famille Louis-Boivin on 'Medications, Pregnancy and Lactation' at the Faculty of Pharmacy of the University of Montreal. Faranak Firoozi is the recipient of a Doctoral Training Award from the FRSQ. This study was funded through a grant from the CIHR.

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doi:10.1016/j.rmed.2010.03.010

Please cite this article in press as: Firoozi F, et al., Effect of maternal moderate to severe asthma on perinatal outcomes, Respiratory Medicine (2010), doi:10.1016/j.rmed.2010.03.010

($n = 1274$) response rate. Final estimates showed that the risk of SGA was significantly higher among severe (OR:1.48, 95%CI: 1.15–1.91) and moderate asthmatic women (OR: 1.30, 95%CI:1.10–1.55) than mild asthmatic women. No significant associations were found between asthma severity, preterm birth and LBW.

Conclusions: Mothers with severe and moderate asthma during pregnancy have a higher risk of SGA babies than those with mild asthma.

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Introduction

Asthma is one of the most frequent chronic diseases encountered during pregnancy and its prevalence among pregnant women is estimated to be between 4 and 7%.^{1–5} Lack of oxygen to the fetus can lead to perinatal mortality, intrauterine growth retardation, preterm birth or neonatal hypoxia.^{6,7} Maternal severe or uncontrolled asthma is potentially dangerous to the fetus since it can induce hypoxia combined with respiratory alkalosis that decrease the placental blood flow.^{8,9} Decreased fetal blood oxygen could result in both an abnormal growth and abnormal fetal development.^{10–12} Indeed, adverse fetal outcomes such as preterm birth and low birth weight have been reported as being more prevalent in pregnant women with asthma than women without asthma.^{13–17} However, scientific evidence is scarce regarding the impact of asthma severity during pregnancy on these perinatal outcomes.

Jana et al. found that the mean birth weight of neonates born to mothers who were hospitalized for asthma during pregnancy was about 400 g ($p < 0.05$) lower than that of neonates born to asthmatic mothers who were not hospitalized.¹⁸ These results have also been confirmed in other studies.^{19,20} Moreover, Fitzsimmons reported a statistically significant increased incidence of small for gestational age (SGA) babies born to mothers who were hospitalized for asthma during pregnancy compared to asthmatic mothers who were not hospitalized.¹⁹

Although studies have reported associations between severe exacerbations requiring hospitalization during pregnancy and adverse perinatal outcomes, there is little evidence on the impact of the level of asthma severity on perinatal outcomes. Only a few small studies investigated the association between the level of asthma severity during pregnancy and perinatal outcomes and yielded inconsistent results. Bracken et al. found that intrauterine growth retardation (IUGR, defined as below the tenth percentile of birth weight for gestational age) was more common among infants of mothers with mild persistent to moderate persistent asthma as compared to those with no symptoms or medication use.²¹ However, in a more recent study, Dombrowski et al. found that the rate of pre-term birth (37 weeks or less) and SGA did not vary according to the level asthma severity.²² Moreover, Stenius-Aarniala et al. found no significant difference in birth weight between mothers with moderate to severe asthma and mothers with very mild to mild asthma.²³ But the large study from Enriquez R et al. reported lower birth weight among infants of women with exacerbated asthma during pregnancy.²⁴

Methodological differences between studies, such as the definition of asthma severity, the choice of the outcome,

and lack of adjustment for potential confounding variables, as well as the small sample size make it difficult to conclude with a reasonable degree of certainty that pregnant women with severe asthma are more likely to give birth to infants with adverse perinatal outcomes than women with mild asthma.

A population-based cohort of 13,007 pregnancies of asthmatic women was reconstructed from the Canadian province of Quebec to further investigate the effect of the severity of asthma during pregnancy on the risk of an SGA infant, low birth weight (LBW), and preterm birth.

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 Québec* (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)). The RAMQ databases provide information on the medical services dispensed to all residents of Quebec since the entire population is covered by the RAMQ medical insurance and on prescribed medications filled in community pharmacies by residents covered by the RAMQ's Public Drug Insurance Plan. Between 1980 and 1997, most notably the elderly and social assistance beneficiaries were covered with the Public Drug Insurance Plan. However, since the enactment of mandatory drug coverage in 1997, the RAMQ's 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.²⁵ 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.^{26,27} The MED-ECHO database is a provincial database which records data on acute care hospitalizations and covers all residents of Quebec.²⁷ The *Fichier des événements démographiques* provides

information on all births and stillbirths in the province of Quebec. The data obtained from three administrative databases were later supplemented by data retrieved from the mailed questionnaires filled by a number of selected mothers. The additional information which are not included in the administrative databases and that were gathered by the questionnaire are mostly about siblings and maternal life styles during pregnancy.

Study design and population

A two-stage sampling cohort design (balanced selection) was used for this study.^{28–31} In the “balanced design” at the second stage of sampling, individuals should be selected according to their exposure/disease characteristics to have an equal number of individuals in each cell of the second stage cross table.^{28,30} This strategy decreases the occurrence of small cells (responsible for large variance) by forcing an overrepresentation of individuals who belong to small groups in the exposure/disease cross-classification.²⁸ In our study, the first stage of sampling corresponds to the cohort formed of singleton pregnancies of asthmatic women ending in a delivery (live birth or stillbirth) between January 1, 1990 and December 31, 2002 in the province of Quebec (Canada). Pregnant women and newborns were identified in the RAMQ databases using diagnostic and act codes related to prenatal care, pregnancy complications, and deliveries.³² Moreover, to be included in our cohort, a women must have been between 13–50 years of age at the beginning of their pregnancy, have had a diagnosis of asthma (9th international classification of diseases (ICD-9) code 493, except 493.2), one or more prescriptions for an asthma medication dispensed in the two years prior or during pregnancy, and being covered by the RAMQ Drug Insurance Plan for at least one year prior to, and throughout the duration of pregnancy. We allowed a maximum of four pregnancies per woman to enter in the cohort and only the more recent ones were kept. For each pregnancy, the data from 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 a sample of women to whom a questionnaire was sent by mail, using a balance sampling strategy.^{28,30} This strategy oversamples women with moderate to severe asthma who had a SGA baby, a LBW baby, or a preterm delivery in order to increase the statistical power.²⁸ A maximum of two pregnancies per woman were selected at this stage of sampling. Selected women had to be at least 18 years old to be eligible for the second stage. For all pregnancies selected at this stage, the RAMQ provided us with the current postal addresses of the mother and their spoken language.

The questionnaire was used to obtain information on life styles, maternal characteristics, and pregnancy related variables that are not recorded in the administrative databases. The questionnaire was pre-tested for clarity and

assessed the ability of the women to remember the answers to the questions that related to a pregnancy that occurred several years ago. First, we sent 3168 questionnaires to selected women. A second questionnaire was sent a month and half later as a reminder to women who did not respond to the first mailing. 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.

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

Exposure

The main exposure variable is the level of severity of maternal asthma during pregnancy measured with an index that we had previously developed and validated.³³ This severity index is based upon the criteria detailed in the Canadian Asthma Consensus Guidelines for the assessment of the severity of asthmatic patients, who are already taking anti-asthmatic medications.³⁴ Three levels of asthma severity were defined over a 12-month period based upon the following: the average daily dose of inhaled corticosteroid (ICS) in beclomethasone-chlorofluorocarbon (CFC) equivalent, the use of additional controller therapies defined as at least 6 filled prescriptions of inhaled long-acting beta₂-agonists, theophylline, or leukotriene-receptor antagonists within a 12-month period, the average number of doses of SABA per week, and the presence of markers of moderate to severe asthma exacerbations – a filled prescription of oral corticosteroids, an emergency department (ED) visit for asthma, or a hospitalization for asthma.³⁵ Details of the severity index are provided in the electronic attachment.

Outcomes

The outcomes of interest included SGA newborns, preterm birth and LBW. SGA was defined as a birth weight below the 10th percentile for gestational age and gender, using new Canadian standards.^{36,37} Preterm birth was defined as a birth before 37 weeks of gestation while LBW was defined as birth weight lower than 2500 g. Validated algorithms based on data recorded in the RAMQ, MED-ECHO or ISQ databases were used to measure these variables.³⁸

Potential confounding variables

Four categories of variables were considered as potential confounding variables. *Maternal characteristics* which include age at beginning of pregnancy (<18, 18–34, >34 years),³⁹ receiving social assistance benefits in the year before or during pregnancy (yes/no), urban residency at delivery (yes/no), being primiparous (yes/no), maternal education (highest level reached) (elementary school, high

school, college & University), annual family income during pregnancy (<\$18000, \$18000–\$46000, >\$46000)³⁹ and birth weight (<2.5, 2.5–5, >5 kg). *Pregnancy-related variables* which include high risk pregnancies (yes/no), gestational diabetes (yes/no), pregnancy-induced hypertension (yes/no), gynecologist or obstetrician visit during pregnancy (yes/no), number of prenatal visits (≤ 5 , 6–14, >14), maternal weight gain during pregnancy (<8, 8–16, >16 kg), maternal body mass index (BMI) (<18.5, 18.5–24.9, 24.9–29.9, >29.9) at beginning of pregnancy and another preterm or LBW infant prior to the current delivery (yes/no).⁴⁰ *Maternal co-morbidities* which include diabetes mellitus (yes/no), and chronic hypertension (yes/no). *Life styles* which include maternal & 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 pregnancies included in the first stage of sampling (cohort) and those selected at the second stage of sampling as a function of asthma severity levels during pregnancy. We also calculated the prevalence of perinatal outcomes by maternal asthma severity level among all pregnancies included in the cohort.

Crude and adjusted odds ratios (OR) for SGA, LBW and preterm birth comparing pregnancies of mild asthmatic women with those with moderate and severe forms of the disease were first estimated for the first stage of sampling using separate Generalized Estimation Equation (GEE) models. 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.

We also obtained adjusted OR estimates 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. 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).

The final adjusted OR estimates were then obtained by correcting the second stage adjusted estimates with the second stage sampling fractions and estimates formed at the first stage of sampling using the methodology proposed by Collet et al.²⁸

Results

At the first stage of sampling, the cohort included 13,007 singleton pregnancies of 9925 asthmatic women. Among them, 7425 women contributed to the analysis with only one pregnancy, and 2500 with at least two pregnancies.

From this cohort, a total of 3347 pregnancies were selected for the second stage of sampling. The RAMQ provided us with the addresses of 3152 women which corresponded to 3168 pregnancies. We received 1274 completed questionnaires which represents a response rate of 40.2%.

Table 1 shows the distribution of the variables retrieved from the administrative databases by asthma severity level for women included in the first stage of sampling. In our cohort, 82.6%, 12.4% and 5.0% of pregnancies were from women with mild, moderate and severe asthma, respectively. A high risk pregnancy was more frequent among pregnancies of severe asthmatic than moderate and mild ones (40.5% vs. 36.2% and 35.9%, respectively).

In Table 2, we present the distribution of variables retrieved from the questionnaire by asthma severity level among pregnancies selected at the second stage of sampling. The prevalence of maternal cigarette smoking during pregnancy was higher among women with severe asthma (67.1%) compared to women with moderate and mild asthma (57.7% and 63.9%), respectively. Also, on average women with severe asthma had a lower annual family income and were less likely to have post high school education. Maternal weight gain during pregnancy was more important among women with severe asthma (58.5% >16 kg) than in women with moderate or mild asthma (40.7% and 39.1%, respectively). Also, these women had a higher pre-pregnancy BMI as compared to women in the two other groups.

We compared the characteristics of 1274 pregnancies of women who answered to the questionnaires with the characteristics of the 1894 pregnancies of women who did not answer. Overall, there was no difference between the responders and non responders except for social assistance (77.2% vs 84.1%), urban residency (77.2% vs 83.7%), being primiparous (59.2 vs. 66.9%), and the number of prenatal visits (14.3 vs. 20.6% for ≤ 5). The details of this analysis are available in the electronic attachment.

We identified 1886 SGA babies (14.5%) from the first stage of sampling (Table 3). The prevalence of SGA babies was higher among pregnancies of severe than moderate or mild asthmatic women: 19.5%, 17.4% and 13.8%, respectively. However, the same trend was not observed for the two other outcomes. The prevalence of LBW and preterm birth was about 10% for all three categories of asthma severity. The prevalence of SGA, LBW and preterm birth found among asthmatic women in our study was higher than provincial statistics (Québec, Canada) that showed a prevalence of 8.3%, 4.3% and 6.3% for these perinatal outcomes.⁴¹ The prevalence of adverse perinatal outcomes was much higher at the second stage of sampling since SGA, LBW and premature infants were oversampled.

We present the main findings of this study in Table 4 that are the first stage and final estimates of the ORs for the three perinatal outcomes comparing levels of asthma severity during pregnancy. Final estimates showed that the risk of SGA was significantly higher among severe (OR: 1.48, 95%CI: 1.15–1.91) and moderate asthmatic women (OR: 1.30, 95%CI: 1.10–1.55) than mild asthmatic women. On the other hand, final estimates showed a 25% non significant increased risk of LBW (OR = 1.25; 95% CI: 0.87–1.80) and no increased risk of preterm birth 0.93 (0.67–1.29) among severe as compared to mild asthmatic mothers. Similar

Table 1 Characteristics of all study women included in the cohort by asthma severity level during pregnancy (database driven variables, $n = 13,007$).

	Pregnancies of Severe asthmatic women <i>N</i> = 652 (5.0%)	Pregnancies of moderate asthmatic women <i>N</i> = 1618 (12.4)	Pregnancies of mild asthmatic women <i>N</i> = 10,737 (82.6)	<i>P</i> -value
	Numbers (%)			
<i>Maternal characteristics</i>				
Age at beginning of pregnancy				
<18 years old	39 (6.0)	89 (5.5)	747 (7.0)	
18–34 years old	552 (84.7)	1401 (86.6)	9380 (87.4)	
>34 years old	61 (9.4)	128 (7.9)	610 (5.7)	<0.0001
Recipient of social assistance ^a	541 (83.0)	1312 (81.1)	8493 (79.1)	0.0151
Urban residency at delivery	532 (81.6)	1287 (79.5)	8709 (81.1)	0.2591
Primiparous	391 (60.3)	1067 (66.2)	7319 (68.4)	<0.0001
<i>Pregnancy related variables</i>				
High risk pregnancy	264 (40.5)	585 (36.2)	3851 (35.9)	0.0580
Gestational diabetes	64 (9.8)	132 (8.2)	804 (7.5)	0.0718
Pregnancy induced hypertension	55 (8.4)	115 (7.1)	676 (6.3)	0.0569
Gynecologist or obstetrician visit during pregnancy	554 (85.0)	1349 (83.4)	8810 (82.1)	0.0863
Number of prenatal visits				
≤5	95 (14.6)	253 (15.6)	1700 (15.8)	
6–14	481 (73.8)	1173 (72.5)	7823 (72.9)	
>14	76 (11.7)	192 (11.9)	1214 (11.3)	0.8833
<i>Asthma related variables measured during pregnancy</i>				
ICS use (μg per day) ^b				
0	57 (8.7)	404 (25.0)	7268 (67.7)	
0–500	364 (55.8)	979 (60.5)	3469 (32.3)	
500–1000	106 (16.3)	228 (14.1)	0 (0.0)	
>1000	125 (19.2)	7 (0.4)	0 (0.0)	<0.0001
SABA use (number of doses per week) ^c				
0	0 (0.0)	12 (0.7)	4961 (46.2)	
>0–3	0 (0.0)	22 (1.4)	4177 (38.9)	
>3	652 (100.0)	1584 (97.9)	1599 (14.9)	<0.0001
Leukoteriene-receptor antagonists use	14 (2.2)	14 (0.9)	6 (0.1)	<0.0001
Oral corticosteroids use	384 (58.9)	260 (16.1)	336 (3.1)	<0.0001
≥1 respiratory physician visit	170 (26.1)	179 (11.1)	401 (3.7)	<0.0001
≥1 ED visit for asthma	457 (70.1)	444 (27.4)	710 (6.6)	<0.0001
≥1 hospitalization for asthma	90 (13.8)	49 (3.0)	57 (0.5)	<0.0001
<i>Maternal co-morbidities</i>				
Chronic diabetes	14 (2.2)	56 (3.5)	244 (2.3)	0.0133
Chronic hypertension	23 (3.5)	43 (2.7)	238 (2.2)	0.0652

^a Social assistance status in the year before pregnancy.^b ICS daily dose in beclomethasone-CFC equivalent over a 12-month period.^c SABA: short-acting inhaled beta₂-agonist.

results were found for LBW and preterm birth when women with moderate and mild asthma were compared.

Discussion

Our results show that severe and moderate asthma during pregnancy were significantly associated with a 48% and 30% increased risk of SGA babies, respectively, when compared to mild asthma. On the other hand, we found a non

significant increased risk of LBW babies and no increased risk of preterm delivery among severe and moderate asthmatic women. Post-hoc power calculations revealed that, if present, we had more than 80% power to detect an increased risk of LBW and preterm birth of 40% among severe asthmatic women and of 25% among moderate asthmatic women when compared to mild asthmatic women.

Some physiologic hypotheses can explain our results. The effects of chronic oxygen deprivation on the fetus are

Table 2 Characteristics of women selected at the second stage of sampling by asthma severity level during pregnancy (questionnaire driven variables, $n = 1274$).

	Pregnancies of Severe asthmatic women <i>N</i> = 82 (6.4%)	Pregnancies of moderate asthmatic women <i>N</i> = 189 (14.8%)	Pregnancies of mild asthmatic women <i>N</i> = 1003 (78.7%)	<i>p</i> -value	
	Numbers (%)				
Maternal characteristics					
Maternal education (highest level attained)					
Elementary school	12 (14.6)	7 (3.7)	86 (8.6)	0.0798	
High school	59 (72.0)	143 (75.7)	746 (74.4)		
College & University	10 (12.2)	35 (18.5)	149 (14.9)		
Unknown	1 (1.2)	4 (2.1)	22 (2.2)		
Annual family income during pregnancy					
<\$ 18,000	56 (68.3)	115 (60.9)	591 (58.9)	0.1471	
\$18,001–\$46,000	22 (26.8)	52 (27.5)	333 (33.2)		
>\$46,001	2 (2.4)	35 (9.5)	56 (5.6)		
Unknown	2 (2.4)	4 (2.1)	23 (2.3)		
Maternal weight at birth					
<2.5 kg	16 (19.5)	27 (14.3)	205 (20.4)	0.4100	
2.5–5.0 kg	58 (70.7)	141 (74.6)	680 (67.8)		
>5.0 kg	1 (1.2)	4 (2.1)	11 (1.1)		
Unknown	7 (8.5)	17 (9.0)	107 (10.7)		
Pregnancy related variables					
Maternal weight gain during pregnancy					
<8 kg	9 (11.0)	24 (12.7)	146 (14.6)	0.0012	
8–16 kg	19 (23.2)	77 (40.7)	435 (43.4)		
>16 kg	48 (58.5)	77 (40.7)	392 (39.1)		
Unknown	6 (7.3)	11 (5.8)	30 (3.0)		
Maternal BMI pre-pregnancy					
<18.5	12 (14.6)	17 (9.0)	149 (14.9)	0.3589	
18.5–24.9	41 (50.0)	99 (52.4)	527 (52.5)		
24.9–29.9	14 (17.1)	40 (21.2)	177 (17.7)		
>29.9	14 (17.1)	26 (13.8)	115 (11.5)		
Unknown	1 (1.2)	7 (3.7)	35 (3.5)	0.2370	
Preterm birth prior to the current delivery					
Unknown	0 (0.0)	2 (1.1)	7 (0.7)		
LBW infant prior to the current delivery					
Unknown	6 (7.3)	23 (12.2)	163 (16.3)	0.0673	
Life style habits					
Maternal cigarette smoking during pregnancy					
Yes	55 (67.1)	109 (57.7)	641 (63.9)	0.4521	
No	27 (32.9)	79 (41.8)	356 (35.5)		
Unknown	0 (0.0)	1 (0.5)	6 (0.6)		
Paternal cigarette smoking during pregnancy					
Yes	40 (48.8)	95 (50.3)	513 (51.2)	0.4689	
No	39 (47.6)	93 (49.2)	469 (46.7)		
Unknown	3 (3.7)	1 (0.5)	21 (2.1)		
Maternal alcohol consumption during pregnancy					
Yes	17 (20.7)	34 (18.0)	170 (17.0)	0.7015	
No	64 (78.1)	149 (78.8)	795 (79.2)		
Unknown	1 (1.2)	6 (3.2)	38 (3.8)		

Table 3 Prevalence of adverse perinatal outcomes by asthma severity level: first and second stages of sampling.

		Pregnancies of Severe asthmatic women	Pregnancies of moderate asthmatic women	Pregnancies of mild asthmatic women
		Number (%)		
1st stage (<i>N</i> = 13,007)	Number of patients	652	1618	10737
	SGA	127 (19.5)	281 (17.4)	1478 (13.8)
	LBW	65 (10.0)	160 (9.9)	972 (9.1)
	Preterm	65 (10.0)	146 (9.0)	1129 (10.5)
2nd stage (<i>N</i> = 1274) ^a	Number of patients	82	189	1003
	SGA	26 (31.7)	48 (25.4)	416 (41.5)
	LBW	13 (15.9)	18 (9.5)	231 (23.0)
	Preterm	12 (14.6)	15 (7.9)	268 (26.7)

^a The prevalence of outcomes obtained at the second stage of sampling is not representative of the real prevalence because of the sampling method which oversamples pregnancies with an adverse perinatal outcome that we used to select women at this stage of sampling.

described by several clinicians and were also confirmed by observation of pregnancies at high altitude and in females with congenital heart diseases.¹² Maternal asthma can induce hypoxia combined with respiratory alkalosis that decreases the placental blood flow.^{8,9} Lack of oxygen to the fetus and the long-term effect of hypoxemia could affect fetal growth.^{10–12} Our results support the findings of Schatz et al. who reported a significant association between lower maternal mean FEV₁ during pregnancy and the risk of a birth weight in the lower quartile of the infant population ($p = 0.002$) and ponderal indices < 2.2 (suggestive of asymmetric intrauterine growth retardation) ($p < 0.05$), but

no increased risk of preterm birth and LBW infants.⁷ These results suggest that severe maternal asthma is more likely to affect the growth of the baby than the timing of the delivery which is more precisely captured by the SGA measure than the weight at birth alone.

The literature reports conflicting results on the association between the severity of maternal asthma and perinatal outcomes. The results found in this study are consistent with those of Fitzsimmons et al. and Mabie et al.^{19,42} who reported a significant increased risk of SGA babies associated with severe asthma ($p = 0.02$ and $p < 0.05$, respectively). However, their definition of severe asthma

Table 4 Crude and adjusted odds ratios for perinatal outcomes comparing severe and moderate asthmatic to mild asthmatic women.

OR (95% CI)		Severe vs. Mild	Moderate vs. Mild
SGA			
1st stage	Crude	1.52 (1.24–1.85)	1.32 (1.14–1.51)
	Adjusted	1.44 (1.18–1.76) ^b	1.30 (1.13–1.49) ^b
Final estimates ^a	Adjusted	1.48 (1.15–1.91) ^c	1.30 (1.10–1.55) ^c
LBW			
1st stage	Crude	1.11 (0.85–1.45)	1.10 (0.92–1.31)
	Adjusted	1.04 (0.80–1.37) ^d	1.08 (0.90–1.29) ^d
Final estimates ^a	Adjusted	1.25 (0.87–1.80) ^e	1.04 (0.81–1.34) ^e
Preterm birth			
1st stage	Crude	0.94 (0.72–1.23)	0.84 (0.70–1.01)
	Adjusted	0.90 (0.69–1.18) ^f	0.82 (0.68–0.99) ^f
Final estimates ^a	Adjusted	0.93 (0.67–1.29) ^g	0.83 (0.65–1.05) ^g

^a Final estimates obtained by adjusting the second stage estimates with the second stage sampling fractions.

^b Adjusted for recipient of social assistance in the year before pregnancy, primiparous and high risk pregnancy.

^c Adjusted for primiparous, chronic diabetes, maternal cigarette smoking during pregnancy, maternal weight at birth, maternal weight gain during pregnancy, preterm birth prior to the current delivery, and LBW infant prior to the current delivery.

^d Adjusted for recipient of social assistance in the year before pregnancy, urban residency at delivery, primiparous, high risk pregnancy, gynaecologist or obstetrician visit during pregnancy, number of prenatal visits and chronic hypertension.

^e Adjusted for recipient of social assistance in the year before pregnancy, primiparous, high risk pregnancy, number of prenatal visits, chronic hypertension, maternal weight at birth, maternal weight gain during pregnancy, and LBW infant prior to the current delivery.

^f Adjusted for recipient of social assistance in the year before pregnancy, high risk pregnancy, gynaecologist or obstetrician visit during pregnancy, number of prenatal visits, and chronic diabetes and hypertension.

^g Adjusted for high risk pregnancy, gynaecologist or obstetrician visit during pregnancy, number of prenatal visits, maternal weight gain during pregnancy and preterm birth prior to the current delivery.

was quite restrictive including only patients who were hospitalized for status asthmaticus, had mechanical ventilation or required chronic maintenance therapy with oral prednisone. Another factor that differentiates these studies from our study is the lack of any adjustment for confounding variables.^{19,42} On the other hand, our results differ from those of Perlow et al., Greenberg et al. and Dombrowski et al. who found no significant increased risk of SGA associated with severe asthma.^{22,43,44}

Bracken et al. used a definition of asthma severity that is closer to ours (based on asthma symptoms and medication use), but reported inconsistent results. Indeed, they reported adjusted significant increased risks of IUGR (defined as below the tenth percentile of birth weight for gestational age) that ranged from 1.74 to 1.98 among women with moderate to mild persistent asthma and no significant increased risk among women with severe persistent asthma (OR = 1.39; 95% CI: 0.69–2.77) as compared to asthmatic women with no symptoms or medication use.²¹

There are several studies that have evaluated the association between severe asthma and the risk of preterm delivery.^{7,18,19,21,23,42–44} Perlow et al. found a significant increased risk of preterm delivery among infants of corticosteroid dependent mothers as compared to non-corticosteroid dependant mothers. However, it is difficult to know if this increased risk is the result of severe asthma or the corticosteroid therapy itself.⁴⁴ Jana et al. and Bracken et al. have found a non significant increased risk of preterm birth when they compared severe asthmatic mothers to mild ones (1.61 and 1.67 respectively), but the small sample size of these studies and the lack of adjustment for confounding variables in the Jana et al. study make it difficult to come to any conclusion.^{18,21} Several other studies also evaluated the effect of maternal asthma severity on preterm birth and reported no association.^{7,19,23,42,43}

A significant increase in LBW (OR:5.1, 95%CI: 1.6–17.0) was found by Perlow et al. among infants of corticosteroid dependent mothers as compared to non-corticosteroids dependent mothers.⁴⁴ Also, Jana et al. found a significantly higher incidence of LBW among infants of 15 mothers requiring as compared to 167 mothers not requiring emergency admission (53.3% vs. 20.5%; $p < 0.01$).¹⁸ Greenberg et al. and Fitzsimmons et al. have found a significant decrease in mean birth weight (ranging from 300 to 500 g) among women who were hospitalized for asthma during pregnancy.^{19,43} However, the lack of adjustment for any confounding variables including maternal smoking and also the use of a much stricter definition of severe asthma could explain the discrepancies between these studies and our study. In concordance with our results, Stenius-Aarniala et al. found no difference between the birth weight of infants of mothers with moderate to severe and very mild to mild asthma (3418 vs. 3479 g).²³

The high prevalence of cigarette smoking during pregnancy among women with severe asthma could be explained by their low socio-economic status and also the fact that we oversampled the women with moderate to severe asthma who had a SGA baby, a LBW baby, or a preterm delivery.

Our study has some limitations that should be taken into account when interpreting the results. Firstly, asking

questions related to a pregnancy that occurred many years ago could result in recall bias. However, a recent study has demonstrated that “maternal reports of perinatal events in which they directly participated can be accurately and reliably reported 10 to 15 years after birth.”⁴⁵ Secondly, the response rate of the mailed questionnaire was about 40%, and the risk of participation bias could have been present, if women who answered the questionnaire were different from women who did not answer. In our study, however, it is reassuring to observe that responders were quite similar to non-responders for all first-stage potential confounding variables (data available upon request). Thirdly, we cannot fully differentiate the effect of asthma medication use from asthma severity itself and it is possible that some of the observed adverse perinatal outcomes were due to the use of asthma medications. Finally, our cohort is less representative of women in the higher socio-economic level. This could explain, at least in part, the high prevalence of cigarette smoking among women with severe asthma. High prevalence of cigarette smoking can also be explained by the oversampling of women with moderate to severe asthma who had a SGA baby, a LBW baby, or a preterm delivery at the second-stage of sampling. The non representativeness of our cohort in this study would be a threat to external validity only if socio-economic status is an effect modifier for the associations under study i.e. severity of asthma and perinatal outcomes. But there is no evidence in the literature suggesting that the impact of severity of asthma on newborns differs according to the socio-economic status of the mother. However, this possibility cannot be ruled out completely.

Our study has also several strengths. Firstly, we had a very large sample size, which provided adequate power to detect small but clinically important differences. Secondly, the measurement of the severity of asthma during pregnancy was based on a validated database index, which assesses asthma severity among patients already under treatment.³⁴ Thirdly, the gestational age at birth and birth weight were validated by comparing the database values to medical chart values and were found to be highly valid.³⁸ Fourthly, we used an SGA definition which is based on new Canadian standards and considers the Canadian growth pattern in its definition.^{36,37} Finally, the two-stage sampling design allowed us to obtain confounding variables that are not recorded in the administrative databases; for example, cigarette smoking and environmental exposure during pregnancy. Having the possibility to adjust the association under study for a large number of potential confounding variables led to a better model, more representative of “real life,” one that takes into consideration the wide variety of variables that may intervene in the development of the fetus.

In conclusion, the results of this study provide evidence that moderate and severe asthma could result in a higher risk of SGA babies than mild asthma with no detectable impact on LBW and prematurity.

Conflict of interest statement

The authors declare no competing interests for the submitted manuscript.

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.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:[10.1016/j.rmed.2010.03.010](https://doi.org/10.1016/j.rmed.2010.03.010).

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Electronic attachment

Comparison of the characteristics of the women who responded and those who did not respond to the mailed questionnaires

	Pregnancies of responding women	Pregnancies of non- responding women
	Numbers (%)	
Numbers	1274 (40.2)	1894 (59.8)
Age		
< 18 years old	117 (9.2)	167 (8.8)
18 - 34 years old	1096 (86.0)	1627 (85.9)
> 34 years old	61 (4.8)	100 (5.3)
Recipient of social assistance	983 (77.2)	1592 (84.1)
Urban residency at delivery	984 (77.2)	1586 (83.7)
Primiparous	750 (59.2)	1265 (66.9)
High risk pregnancy	493 (38.7)	755 (39.9)
Gestational diabetes	107 (8.4)	128 (6.8)
Chronic diabetes	27 (2.1)	54 (2.9)
Pregnancy induced hypertension	98 (7.7)	105 (5.5)
Chronic hypertension	31 (2.4)	46 (2.4)
Gynecologist or obstetrician visit during pregnancy	1037 (81.4)	1614 (85.2)
Number of prenatal visits		
≤ 5	182 (14.3)	390 (20.6)
6-14	950 (74.6)	1331 (70.3)
> 14	142 (11.2)	173 (9.1)
SGA delivery	490 (38.5)	714 (37.7)
LBW delivery	262 (20.6)	432 (22.8)
Premature delivery	295 (23.2)	516 (27.2)
Control of asthma		
Controlled	740 (58.1)	1110 (58.6)
Uncontrolled	534 (41.9)	784 (41.4)
Severity of asthma		
Mild	1003 (78.7)	1509 (79.7)
Moderate	189 (14.8)	280 (14.8)
Severe	82 (6.4)	105 (5.5)

Electronic attachment

Definition of the Database Indexes of Asthma Severity Developed According to the Canadian Asthma Consensus Guidelines

Asthma severity and control	*ICS daily dose (µg)	**Other controller therapy	+SABA doses per week	++ Marker of moderate to severe exacerbations
Mild				
	0-500	No	0-3	No
	0-250	Yes	0-3	No
	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				
	251-500	Yes	0-10	No
	501-1000	Yes/No	0-10	No
	>1000	Yes/No	0-3	No
	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				
	>1000	Yes/No	4-10	No
	0-1000	Yes/No	>10	Yes
	>1000	Yes/No	0-10	Yes
	>1000	Yes/No	>10	Yes/No

*ICS daily dose in beclomethasone-CFC equivalent over a 12-month period

** Other controller therapy: at least 6 prescriptions of long-acting beta₂-agonist (LABA), theophylline or leukotriene-receptor antagonists dispensed over a 12-month period

+SABA: Average number of inhaled short-acting beta₂-agonist doses per week calculated over a 12-month period

++ An emergency department visit for asthma, a hospitalization for asthma or a filled prescription of an oral corticosteroid over a 12-month period.