Université de Montréal

# Asthma During Pregnancy

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Asthma during Pregnancy

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# Résumé

L'asthme est connu comme l'une des maladies chroniques les plus fréquentes chez la femme enceinte avec une prévalence de 4 à 8%. La prévalence élevée de l'asthme fait en sorte qu'on se préoccupe de l'impact de la grossesse sur l'asthme et de l'impact de l'asthme sur les issus de la grossesse. La littérature présente des résultats conflictuels concernant l'impact de l'asthme maternel sur les issus périnatales comme les naissances prématurées, les bébés de petit poids et les bébés de petit poids pour l'âge gestationnel (PPGA). De plus, les données scientifiques sont rares concernant l'impact de la sévérité et de la maîtrise de l'asthme durant la grossesse sur les issus périnatales. Donc, nous avons mené cinq études pour réaliser les objectifs suivants: 1. Le développement et la validation de deux indexes pour mesurer la sévérité et la maîtrise de l'asthme. 2. L'évaluation de l'impact du sexe du fœtus sur le risque d'exacerbation de l'asthme maternel et l'utilisation de médicaments antiasthmatiques durant la grossesse; 3. L'évaluation de l'impact de l'asthme maternel sur les issus périnatales; 4. L'évaluation de l'impact de la sévérité de l'asthme maternel durant la grossesse sur les issus périnatales; 5. L'évaluation de l'impact de la maîtrise de l'asthme maternel durant la grossesse sur les issus périnatales. Pour réaliser ces projets de recherche, nous avons travaillé avec une large cohorte de grossesse reconstruite à partir du croisement de trois banques de données administratives du Québec recouvrant la période entre 1990 et 2002. Pour les trois dernières études, nous avons utilisé un devis de cohorte à deux phases d'échantillonnage pour obtenir, à l'aide d'un questionnaire postal, des informations complémentaires qui ne se trouvaient pas dans les banques de données, comme la consommation de cigarettes et d'alcool pendant la grossesse.

Nous n'avons trouvé aucune différence significative entre les mères de fétus féminins et de fétus masculins pour les exacerbations de l'asthme pendant la grossesse (aRR=1.02; IC 95%: 0.92 to 1.14). Par contre, nous avons trouvé que le risque de bébé PPGA (OR: 1.27, IC 95%: 1.14-1.41), de bébé de petit poids (OR: 1.41, IC 95%:1.22-1.63) et de naissance prématurée (OR: 1.64, IC 95%:1.46-1.83) était significativement

plus élevés chez les femmes asthmatiques que chez les femmes non asthmatiques. De plus, nous avons démontré que le risque d'un bébé PPAG était significativement plus élevé chez les femmes avec un asthme sévère (OR:1.48, IC 95%: 1.15-1.91) et modéré (OR: 1.30, IC 95%:1.10-1.55) que chez les femmes qui avaient un asthme léger. Nous avons aussi observé que les femmes qui avaient un asthme bien maîtrisé durant la grossesse étaient significativement plus à risque d'avoir un bébé PPAG (OR:1.28, IC 95%: 1.15-1.43), un bébé de petit poids (OR: 1.42, IC 95%:1.22-1.66), et un bébé prématuré (OR: 1.63, IC 95%:1.46-1.83) que les femmes non asthmatiques. D'après nos résultats, toutes les femmes asthmatiques même celles qui ont un asthme bien maîtrisé doivent être suivies de près durant la grossesse car elles courent un risque plus élevé d'avoir des issus de grossesses défavorables pour leur nouveau-né.

**Mots-clés** : Asthme, grossesse, bébé de petit poids pour son âge gestationnel, bébé de petit poids, bébé prématuré, fétal gender, Exacerbation de l'asthme

# Abstract

Asthma is known as one of the most frequent chronic diseases encountered during pregnancy with prevalence estimated between 4 and 8%. The high prevalence of asthma during pregnancy results in some concerns about the impact of pregnancy on maternal asthma and also the impact of maternal asthma on perinatal outcomes. The literature presents conflicting results concerning the impact of maternal asthma during pregnancy on perinatal outcomes, such as preterm birth, low-birth-weight (LBW) infant and small-for-gestational-age (SGA) infant. Also, scientific evidence is scarce regarding the impact of asthma severity and control during pregnancy on these perinatal outcomes. We thus conducted a research project composed of five studies to achieve the following objectives: 1. to develop and validate two database indexes, one to measure the control of asthma and the other to measure asthma severity; 2. to evaluate the effect of fetal gender on maternal asthma exacerbations and the use of asthma medications during pregnancy; 3. to evaluate the impact of maternal asthma on adverse perinatal outcomes; 4. to evaluate the impact of the severity of asthma during pregnancy on adverse perinatal outcomes; 5. to evaluate the impact of adequately controlled maternal asthma during pregnancy on adverse perinatal outcomes. A large population-based cohort 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 women's life-style habits by way of a mailed questionnaire for the three last studies.

We have observed no significant differences between mothers of a female and male fetus as to the occurrence of asthma exacerbations (aRR=1.02; 95% CI: 0.92 to 1.14). We have found 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. Moreover, our results 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. Also, mothers with adequately controlled asthma during pregnancy were found to be at higher risk of adverse perinatal outcomes than non-asthmatic women (SGA (OR:1.28, 95%CI: 1.15-1.43), LBW (OR: 1.42, 95%CI:1.22-1.66), and preterm deliveries (OR: 1.63, 95%CI:1.46-1.83)). According to our results, all asthmatic women even those with adequately controlled asthma should be closely monitored during pregnancy because they are at increased risk of adverse perinatal outcomes.

**Keywords** : Asthma, Pregnancy, Small for gestational age, Low birth weight, Preterm birth, Fetal gender, Asthma exacerbation

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*To my loved ones: Madjid and Melody*

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# Abbreviations

**RR:** Relative risk

**aRR:** Adjusted Relative risk

**OR:** Odds Ratio

**CI:** Confidence Interval

**aRR:** Adjusted relative risk

**LBW**: Low birth weight

**SGA**: Small for gestational age

**RAMQ**: Régie de l'Assurance Maladie du Quebec

**SABA**: Short-acting beta$_2$-agonists

**ICS**: Inhaled corticosteroids

**IgE**: Immunoglobulin E

**ASA**: Acetylsalicylic acid

**NSAIDs**: Nonsteroidal anti-inflammatory drugs

**FEV$_1$**: Forced expiratory volume in the first second

**PEF**: Peak expiratory flow

**LTRAs**: Leukotriene receptor antagonists

**US**: United States

**IUGR**: Intrauterine growth retardation

**NAEP**: National Asthma Education Program

**ED**: Emergency department

**CIHI**: Canadian Institute for Health information

**aOR**: Adjusted odds ratio

**USA**: United States of America

**GINA**: Global initiative for asthma

**OCS**: Oral corticosteroid

**ICD**: International classification of disease

**ISQ**: Institut Statistique de Quebec

**NAM**: Numéro d'assurance maladie

**GEE**: Generalized estimation equation

**GLM**: Generalized linear models

**CAI**: Commission d'accès à l'information du Québec

**COPD** : Chronic obstructive disease

**FVC** : Forced expiratory vital capacity

**AMD** : Adjusted mean difference

**LABA** : Long-acting $beta_2$ agonist

# 1. Introduction

Asthma is one of the most prevalent chronic diseases affecting Canadians. According to 2000-2001 Statistics Canada survey, 8.4% of the adult population (aged 12 and more) had physician-diagnosed asthma (over 2.5 million Canadians) (1). Despite several advances in the treatment of asthma, there has been an increase in the prevalence of asthma among adults in the past 20 years in Canada and in many other industrialized countries (2). This increase over the past decades has made asthma the most common chronic disease during pregnancy affecting approximately 8% of women (3-7). The high prevalence of asthma during pregnancy results in some concerns about the impact of pregnancy on maternal asthma and also the impact of maternal asthma on perinatal outcomes.

It has been reported that fetus gender could influence the course of maternal asthma. A few studies have suggested that a pregnant woman's asthma may worsen when carrying a female fetus (8-11). It has also been reported that asthma during pregnancy could increase the risk of pregnancy induced hypertension, caesarean delivery, prematurity, low birth weight (LBW) infant and perinatal/neonatal mortality (12-16). In addition, it is reported that women with poorly controlled asthma during pregnancy are more likely to deliver LBW, small for gestational age (SGA) and preterm infants than non asthmatic pregnant women (14, 17-19). Also, it has been concluded by a few authors that there was no difference between women with adequately controlled asthma and non-asthmatic women for the risk of adverse perinatal outcomes (20-22).

Although there are several studies in the literature examining the impact of fetal gender on the course of asthma and the impact of maternal asthma on perinatal outcomes,

conflicting results, methodological differences between studies, questionable clinical significance of some of the results as well as lack of statistical power in several studies, make it difficult to conclude with a reasonable degree of certainty on these associations. To overcome these methodological issues and in order to further investigate the association between fetal gender and maternal asthma, we conducted a large population-based cohort study. To study the association between maternal asthma and perinatal outcomes including low birth weight (LBW), preterm birth and small for gestational age (SGA) baby, we added a second stage of sampling to the cohort in order to obtain additional essential confounding variables.

This thesis is presented by articles including one methodological article and four articles presenting the results of the epidemiologic studies in which we investigated the associations described in the previous paragraph. The methodological paper presents the results of a study related to the development and validation of database indexes of asthma severity and control. These indexes measure the control and the severity of asthma in currently treated asthmatic patients using the information obtained from the administrative healthcare databases of the Canadian province of Quebec; *Régie de l'Assurance Maladie du Quebec* (RAMQ) and MED-ECHO over a period of 12 months. These two indexes were used to measure asthma severity and control in two of the four epidemiologic studies.

This thesis includes six other chapters. The objectives of our studies are presented in the second chapter. The third chapter is devoted to the literature review, wherein, a summary of existing knowledge in the field of asthma during pregnancy and its consequences on the health of the mother and the newborn is presented. The pathophysiology of asthma and asthma treatment which were not covered in the articles were also discussed in details to give a better understanding of the disease. In the fourth

chapter, the methodology employed to conduct the studies is explained. In this section, more details regarding the two-stage sampling design and the data collection via questionnaires which were not presented in the articles will be presented. Chapter five includes five articles which form the result section of my thesis. The last two chapters are devoted to the general discussion and conclusion, respectively.

# 2. Objectives

This thesis includes five scientific articles which describe the five studies that were undertaken. The research objectives pursued within each of the five studies are described in this chapter.

**Study 1. Development and Validation of Database Indexes of Asthma Severity and Control**

To develop and validate two database indexes, one to measure the control of asthma and the other to measure the severity of asthma in currently treated asthma patients using information related to dispensed asthma medications and medical services.

**Study 2. Effect of Fetal Gender on Maternal Asthma Exacerbations in Pregnant Asthmatic Women**

To evaluate the effect of fetal gender on the risk of uncontrolled maternal asthma through the study of exacerbations, use of inhaled short-acting beta$_2$-agonists (SABA) and inhaled corticosteroids (ICS) during pregnancy.

**Study 3. Impact of maternal asthma on perinatal outcomes**

To evaluate the potential effect of asthma during pregnancy on adverse perinatal outcomes including SGA infant, LBW infant, and preterm birth.

**Study 4. Effect of maternal moderate to severe asthma on perinatal outcomes**

To evaluate the effect of the severity of asthma during pregnancy on the risk of having a SGA infant, a LBW infant, and a preterm birth.

**Study 5. Are controlled asthmatic pregnant women more at risk of perinatal outcomes than non-asthmatic women?**

To investigate whether or not asthmatic women with controlled asthma are at increased risk of having a SGA infant, a LBW infant, or a preterm birth over non asthmatic women.

# 3. Literature review

## 3.1. Asthma

The Greek physician Hippocrates used the word asthma for the first time to describe an illness. In Greek it means 'labour breathing' (23). Asthma is a chronic inflammatory disease which affects the respiratory tract and is characterized by intermittent or persistent episodes of reversible bronchoconstriction due to increased responsiveness of airways to various stimuli (2, 23-26). Both genetic and environmental factors are believed to contribute to the initiation and progression of the disease (27). Clinically, asthma is manifested by wheezing, dyspnea, chest tightness, and cough (25-27). Although the first manifestation of the disease can occur at any age, half of the patients have asthma onset prior to age 10 years, occurring twice often in boys than in girls, and by the age 30, the prevalence of asthma has become equal between sexes (28, 29). In addition, half of the children suffering from asthma have a substantial or complete remission of symptoms during adolescence, but in many cases, the patients may suffer from recurrence of asthma symptoms in adult life (27, 28, 30).

### 3.1.1. Prevalence of asthma

Asthma is one of the most prevalent chronic diseases affecting Canadians. According to the 2000-2001 Statistics Canada survey, about 2.2 million Canadians have been diagnosed with asthma by a physician (8.4 % of the population aged 12 years or more) (31). In Canada, an estimated 12% of children and 6% of adults have active asthma (taking medications for asthma or experiencing some symptoms in the past twelve months) (32, 33). There has been an increase in the prevalence of asthma in the past 15 years and mostly in the westernized countries (2, 34). Prevalence rates tend to be higher in economically developed countries with temperate climate in comparison to rural and economically developing countries (27).

Although there is no clear explanation for the observed increasing incidence of asthma, it has been proposed that it may be the result of some alterations in the everyday life-styles (35). The early exposure to various allergens during pregnancy and childhood may influence the development of the immune system (2). In genetically predisposed individuals, the altered immune system may result in an increased allergic response to foreign substances and in this way predispose the child to asthma (2). Possible factors include changes in nowadays housing conditions with greater exposure to indoor aeroallergens, such as cats, house dust mites, cockroaches, and moulds, changes in diet, environmental changes such as outdoor pollution and indoor poor air quality as a result of more insulated home constructions (2, 35). The known risk factors related to developing asthma (incidence) are (23, 30, 36-40):

- A family history of asthma or allergic reaction (eczema, allergic rhinitis),
- Exposure to high levels of aeroallergens during infancy,
- Exposure to environmental tobacco smoke both prenatally and postnatally
- Exposure to chemical irritants in the workplace
- Extensive vaccination programmes
- Changes in diet
    - Food preservation
    - Adding antibiotic to the food
- Inappropriate use of broad-spectrum antibiotics
- Changes in life style;
    - Better insulated and more energy efficient homes which result in a warm and humid environment with low ventilation rate
    - More indoor living pets

### 3.1.2. Pathology of asthma

The pathology of asthma is characterized by various changes in the respiratory tract (27). In a normal airway, the lumen is free of mucus, there are few eosinophils in the bronchial wall and a layer of ciliated epithelial cells protects the bronchial wall (23, 28). However, on postmortem examination of patients with asthma, several changes have been

identified including hypertrophy of smooth muscles, thickening of the basement membrane due to collagen deposition, filling up of the airways by mucus and inflammatory cells, and engorgement of the vessels and microvascular leakage (23, 27, 30). The swelling and the mucus plugging inside the airways lead to chronic airways narrowing which makes it hard for the air to pass through resulting in distressed breathing (23, 30).

### 3.1.3. Pathophysiology of asthma

The aetiology of asthma is not completely known, but it is suggested that bronchial inflammation or its consequences plays an important role in the pathogenesis and persistence of asthma (25). Generally, asthma is classified into two major categories based on the presence or absence of an underlying immune reaction (23, 25, 28, 30).

The *Extrinsic asthma (allergic)* occurs in atopic individuals who show allergic reaction to foreign bodies such as house dust mites, grass pollen, and cat and dog dander (history of allergic disease) (23, 28). The term 'extrinsic' implies that an inhaled allergen is the cause of the initiation of the broncho-spasm. Allergic or atopic asthma is the most common type of asthma and type I hypersensitivity reaction explains the cause of the bronchial inflammation in this group of patients (25). The type I hypersensitivity or immunoglobulin E (IgE) mediated hypersensitivity is caused by inappropriate production of IgE to specific allergens (23, 30, 41). In allergic asthma, IgE binds tightly on the surface of the mast cells, which result in mast cell degranulation and rapid releasing of histamine and other inflammatory mediators (Figure 1) (28, 30). The inflammatory mediators induce bronchial smooth muscle contraction, mucus hyper secretion and increased vascular permeability (2, 23, 27, 28).

The *Intrinsic asthma* often exhibits in middle-age individuals and the cause of bronchial inflammation is much less clear in this type of asthma (23, 25, 28). Generally, the non-immunological mechanisms contribute to initiate bronchospasm responsible for other symptoms (23, 25, 27, 28). The common non-allergic triggers are occupational exposures to chemical irritants, respiratory tract viral infection, cold weather, air pollution, tobacco smoke, strong odours, drugs such as Acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs), antiadrenergic and cholinergic drugs (e.g. beta blockers and bethanechol), physical exercise, and psychological stress (23, 25, 28, 30). In clinical practice, making a clear distinction between extrinsic and intrinsic asthma is often difficult.

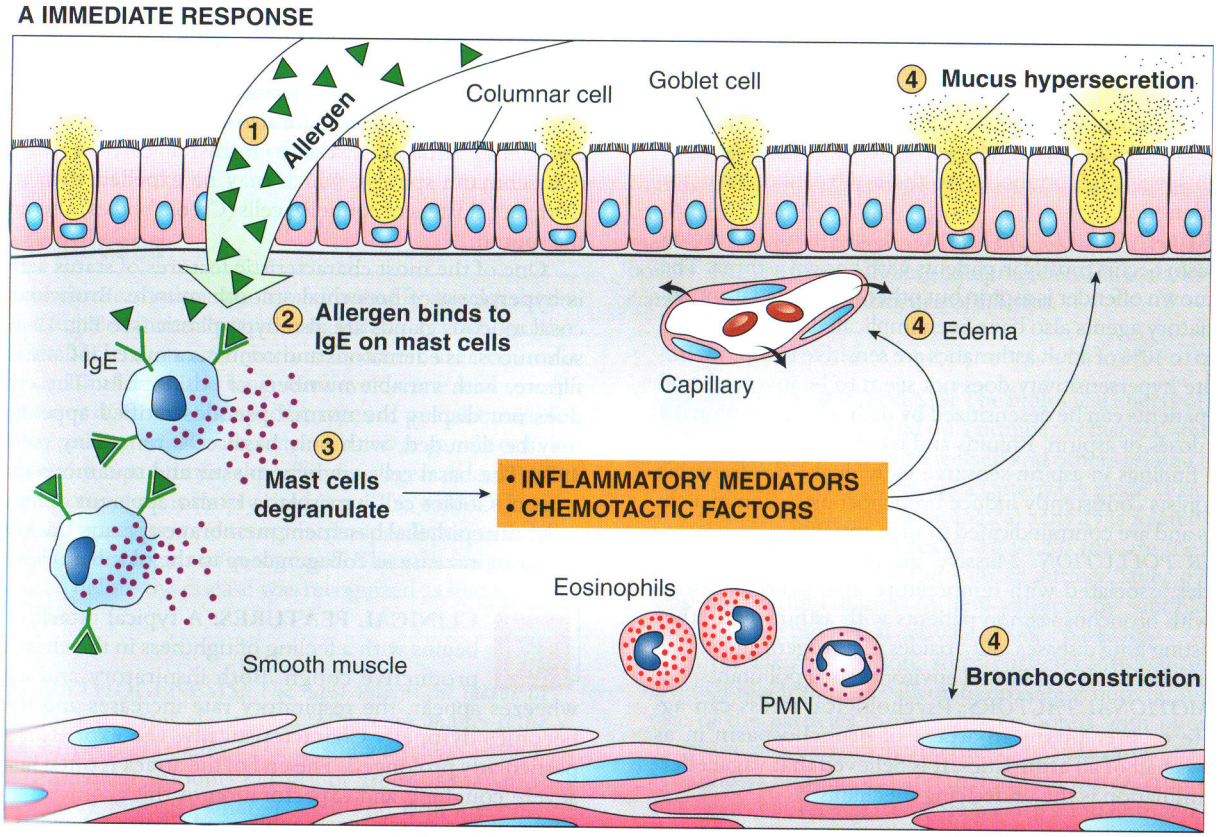



**Figure 1.** Pathogenesis of asthma. A. Immunologically mediated asthma. Allergens interact with IgE on mast cells, either on the surface of the epithelium or, when there is abnormal permeability of the epithelium, in the submucosa. Mediators are released and may react locally or by reflexes mediated through the vagus (From Rubin R., Strayer D.

*Rubin's Pathology.* Wolters Kluwer, Lippincott Williams & Wilkins; 2008, with permission from the editors (28).

**Airway remodeling**

When asthma is poorly controlled, the persistent inflammation can result in the airway remodeling. Damage to the protective endothelial layer allows infiltration of inflammatory mediators into the mucosa and can yield permanent airway abnormalities due to subbasement membrane collagen deposition and fibrosis (23, 27, 30). These changes provide the grounds for proposing prompt and continuous use of corticosteroid in the treatment of asthma (23, 27).

## 3.1.4. Diagnosis of asthma

The clinical diagnosis of asthma is based on a complete medical history, physical examination and lung function tests (35). A family history of asthma or atopic disease, the presence of typical asthma symptoms that improve with asthma medication, objective evidences of variability in lung function over time and evidences of hyper-responsiveness of the airways using a provocation challenge test can help to make an accurate asthma diagnosis (2, 27, 39). Generally, an increase of 15% or more in $FEV_1$ (an absolute improvement of at least 200 ml) after inhaling a bronchodilator (short-acting beta-2 agonist) is considered as a significant response and is a confirmation of the diagnosis of asthma (23, 41, 42).

**Asthma symptoms**

The principal asthma symptoms are wheezing, dyspnea, chest tightness, cough, tachypnea (usually during an acute asthma exacerbation) and difficulty in sleeping (23, 24, 30, 39, 43). The duration and frequency of these symptoms vary from patient to

patient and can change over time (41). Symptoms are frequently nocturnal or occur in early morning and from one acute asthma exacerbation to another one, patients may be asymptomatic (30). Significant sputum production is present in about 30% to 50% of patients with asthma (41). The microscopic examination of the sputum manifests large amount of eosinophils (41).

**Objective measurements**

Lung function measurements reflect the degree of airway obstruction and may be normal between exacerbations. Performing these measurements are required to confirm the diagnosis of asthma and the severity of the disease (30, 44). A spirometer is used to objectively measure the volume of air inhaled and exhaled, and to determine how effectively and how quickly the lungs can be emptied and filled again (23, 30). In clinical practice, the following tests are usually carried out to measure the lung function, the forced expiratory volume in the first second ($FEV_1$), the peak expiratory flow (PEF) and the provocation test (24, 30).

FEV1 is the maximum volume of air expired in the first second of maximal expiration after a full inspiration and is a useful measure of how quickly full lungs can be emptied (23). PEF is the maximal flow rate achieved during expiration and this occurs very early in the forced expiratory manoeuvre (23). The PEF and $FEV_1$ are both decreased in asthma and during an acute asthma exacerbation as result of increased airway resistance (23, 24, 30). The PEF variation greater than 20% during the day suggests airway hyperresponsivenesss and poorly controlled asthma (30). PEF and $FEV_1$ with less than 50% of predicted value (or personal best value) are signs of respiratory distress and severe asthma exacerbation (24, 30).

Broncho-provocation challenge testing with methacoline or histamine is conducted in patients whose pulmonary function tests are normal, but the diagnosis of asthma is not completely ruled out (30, 44). Changes in patient's lung function (usually $FEV_1$) are measured after inhalation of incremental doses of stimulant (methacoline or histamine) (23). The concentration of stimulant that causes a 20% decrease in the patient's $FEV_1$ is known as the Pc20 and a Pc20 of less than 4 mg/ml methacoline is highly suggestive of diagnosis of asthma (23).

### 3.1.5. Management of asthma

According to Canadian guidelines, treatment should be determined on the basis of frequency and severity of symptoms, occurrence of acute exacerbations, activity limitation, degree of airway obstruction and response to medication (2, 26, 39). The main objectives in the treatment of chronic asthma are to prevent irreversible airway damage and to control asthma (23). The control of asthma is usually defined as reducing airway inflammation to achieve minimal symptoms during the day and night, to achieve normal lung function (PEF or $FEV_1$ greater than 80% of the predicted value or personal best value), and normal daily activity including sports (23, 39, 43). ICSs are very effective at suppressing inflammation in asthma; however, symptoms and airway obstruction usually recur when the drugs are discontinued (27).

**Lifestyle management**

Medication is not the only way to control asthma. Non-pharmacological options such as environmental control approaches are also important to avoid or eliminate known exacerbating allergens like pollens that induce or trigger asthma (24, 41). In addition, management of asthma involves prophylactic measures such as smoking cessation, avoiding ASA and other NSAIDs, and patient education about a self-management plan and using the peak flow meter to adjust their therapy (2, 24, 41).

**Pharmacological management of asthma**

According to the Canadian Asthma Consensus Conference Guidelines for asthma management, there are two types of medication to treat persistent asthma; controllers and relievers (39). The controller medications or preventers (anti-inflammatory and some bronchodilators) should be used on a regular basis to control the underlying inflammation and prevent bronchospasm symptoms and attacks. The relievers (short-acting bronchodilators) are used to relieve airway constriction and its accompanying acute symptoms, only on demand and at the minimum required dose and frequency. (2).

The choice of medication is based on the severity of the disease and may vary over the time as symptoms change (2, 41). Since persistent asthma is a chronic condition, patients have to take long-term anti-inflammatory medication daily to control the underlying inflammation and to prevent symptoms and attacks (23, 41). Most asthma guidelines propose a stepwise approach, which ranges from administrating short-acting inhaled beta agonists for very mild intermittent asthma to oral corticosteroids for severe asthma (23, 24, 27, 41). Therapy is preferably given by inhalation to deliver the drugs to the desired site of action with a much smaller dose and lower systemic drug concentrations which reduces systemic adverse effects (24, 27, 39, 41).

**Pharmacologic agents (39, 45)**

**1. Relievers**

**a. Bronchodilators**

- **Inhaled short-acting beta$_2$ agonists** medications are the best choices for treatment of acute exacerbations and prophylaxis of exercise-induced asthma, they can produce almost immediate bronchodilating effect (24, 30, 44). Salbutamol, terbutaline, fenoterol and orciprenaline are available in Canada (24).

- **Anticholinergic agents** such as Ipratropium bromide are recommended for patients who present tremor or tachycardia with SABA, or are unresponsive to these agents or suffer from bronchospasm induced by a beta-blocker (24, 44). Ipratropium bromide is administrated by inhalation and has a delayed onset of action comparing to inhaled $beta_2$ agonists, but its bronchodilator effect lasts longer (23, 30).

**2. Controllers**

**a. Anti-inflammatory agents**

- **Corticosteroids** decrease the airway hyper responsiveness via their anti-inflammatory properties (24, 44). They should be used regularly to achieve maximum effect (30).

    - **Inhaled** corticosteroids have less systemic and side effects than oral steroids (24, 44). Inhaled budesonide, beclomethasone dipropionate, fluticasone propionate and ciclesonide block the late phase of asthma and are recommended for chronic asthma prophylaxis (24).

    - **Oral** corticosteroids are helpful in managing acute exacerbations and their regular use may be necessary in severe asthma (30, 39). Improvement in pulmonary function may begin within 1-3 hours after their administration; however, the maximum effect could achieve about 6-9 hours later (23, 44). To avoid their significant side effects, the treatment should be administered on short periods (one to two weeks) (23).

- **Inhaled Nonsteroidal agents** such as **Cromolyn sodium** and **Nedocromil sodium** prevent both the early and late phase of asthma exacerbation (24, 44). They could be used for prophylaxis of exercise-induced asthma or be used regularly in conjunction with other asthma therapy or as an alternative to ICS in less severe asthma cases (30, 44). However, ICSs are more effective and used more commonly than these medications.

- **Leukotriene receptor antagonists** (LTRAs) have anit-inflammatory and bronchodilator properties and are equivalent to low dose of ICS (30, 46). Zafirlukast and montelukast, currently available in Canada are usually used as an add-on therapy in patients who are inadequately controlled by ICSs (23, 44, 46).

**b. Bronchodilators**

- **Inhaled long-acting beta$_2$ agonists** are used regularly twice a day and considered as an add-on therapy for patients who already taking ICSs without achieving the desired control of asthma (24, 44). Salmeterol and formoterol are available in Canada (24, 44).

- **Theophylline compounds** such as theophylline, aminophylline and oxtriphylline are the third-line therapy (24, 30, 44). Due to their systemic toxicity and their mild clinical effect, these medications are only recommended if patients cannot tolerate or are unresponsive to other bronchodilators (30).

## 3.2. Asthma in pregnancy

The prevalence of asthma among pregnant women is estimated between 4 to 7% and it is known as one of the most frequent chronic diseases encountered during pregnancy (3-5, 7, 47). In a recent study, Known et al investigated the trends in asthma prevalence during pregnancy in the United States (US) over the past decades and they concluded that the prevalence of self-reported asthma in the US was between 8.4% and 8.8% (48). In the same study the authors assessed international reports of asthma in pregnancy using standardized definitions of asthma within a shared time frame. They found significant differences in asthma prevalence during pregnancy worldwide, and an overall increasing prevalence of asthma during pregnancy over time (48). In addition, these percentages are probably underestimated because, in many cases, either the women do not report their previously diagnosed asthma or they are simply undiagnosed beforehand (49). The increasing prevalence of asthma during pregnancy necessitates a better understanding of the pathophysiology of asthma during pregnancy, and the reciprocal effect of asthma and pregnancy.

### 3.2.1. Pathophysiology of asthma during pregnancy

Several physiological respiratory alterations occur normally in pregnant women (50). Estrogen changes in pregnancy affect the upper respiratory tract and the airway mucosa resulting in mucosal edema, hypersecretion and capillary congestion (23, 50). Also, the increasing abdominal growth during pregnancy induces an elevation of the diaphragm which is associated with pulmonary function changes (23, 50). As a result, the expiratory reserve volume is reduced, however, the total lung capacity and $FEV_1$ remains unchanged (50, 51). Increased circulating levels of progesterone and its stimulatory impact on the respiratory center induce an increase in minute ventilation (the total amount of gas expelled from the lungs per minute) and, consequently, a relative hyperventilation (23, 50-52). As a result, respiratory alkalosis occurs which induces secondary

compensation through renal loss of bicarbonate (50, 52). Thus, during pregnancy, normal blood gases reveal a higher pO2 (100 to 106 mmHg) and a lower pCO2 (28 to 30 mmHg) than in the non-pregnant state and pCO2 > 35 mmHg or pO2<70 mmHg associated with bronchial obstruction represent more severe respiratory failure during pregnancy compared to the same blood gas measurements in the nongravid state (50-52).

Normal fetal oxygen pressure of placental blood flow is 30 to 37 mmHg (51, 52). To compensate this low level of pO2 in the fetus comparing to the adult (about one third), the fetus shows some adaptations: high fetal cardiac output, high affinity of fetal haemoglobin for oxygen, high fetal haemoglobin concentration (about 15 to 20 g per L) and a system of vascular shunts which directs available blood oxygen to high priority organs (liver, heart and brain) (50-52).

Asthma during pregnancy can induce hypoxia combined with acute or compensated respiratory acidosis, as well as potentially an acute respiratory alkalosis that decreases the placental blood flow , increases systemic and pulmonary vascular resistance and decreases cardiac output (52-54). Asthmatic pregnant women who suffer from acute asthma exacerbations during their pregnancy can experience hypoxia and hypercapnia (28). Consequently, to obtain a reduction in oxygen consumption, the fetus may reduce breathing and body movements to redistribute oxygen to high priority organs (50, 51). In fetus suffering from lack of oxygen, the rate of oxygen extraction by fetal tissues may increase and can lead to perinatal long term effects of hypoxia including intrauterine growth retardation (IUGR), preterm birth, neonatal hypoxia or perinatal morbidity and mortality (50, 51, 55, 56).

### 3.2.2. Management of asthma during pregnancy

The goal of asthma therapy in pregnancy is to provide adequate oxygenation to the mother and baby. Concerns about teratogenicity of asthma medications during pregnancy might lead women to stop or reduce their use, but this fear must be balanced against the risk of asthma exacerbations and their potential adverse effects on the mother and the developing fetus.

The National Asthma Education Program (NAEP) in the US has issued guidelines for the treatment of asthma during pregnancy which recommend to treat asthma as aggressively in pregnant women as in non pregnant women (57). ICS are recommended as the first line maintenance therapy in women with persistent asthma during pregnancy and different studies have shown that ICS can be used with relative safety with minimal systemic absorption and few side effects (39, 57, 58). Inhalation has advantages as means of giving drugs during pregnancy because the therapeutic action can be achieved with minimum pharmacological effect to the fetus (24). The relatively low molecular weight and high lipidosolubility of budesonide predicts its substantial placental transfer. (59). However, the actual amount of active budesonide reaching the fetus may be small because of the low systemic bioavailability after inhalation and extensive placental metabolism to inactive compounds (59). In addition, it has been reported that ICS taken at recommended doses during pregnancy were associated with a reduction in the risk of congenital malformations (60). Systemic treatment should not be withheld if indicated, because the risk of asthma exacerbations and their potential adverse effects on the mother and the developing fetus is important and they should be treated rapidly. Prednisolone is an appropriate corticosteroid for oral use since very little of the drug reaches the fetus (24).

Indeed, none of the drugs usually used to treat asthma has been shown to cause congenital malformations (61-67). However, using the systemic corticosteroids should be kept only for severe cases of asthma exacerbation during pregnancy because it has been reported that the risk of cleft lip and palate may increase up to 3 folds by these medications (62, 65). A significant higher incidence of congenital abnormalities in the children of asthmatic women comparing to non-asthmatic ones has been reported by a few studies (aOR ranging from 1.10 to 1.37) (14, 68, 69) however, the results of some preceding studies were not the same (21, 22, 70). Therefore, it is important that concerns about teratogenicity of asthma medications be balanced against the risk of asthma exacerbations and their potential adverse effects on the developing fetus.

Leukotriene modifiers should be avoided during pregnancy because limited safety information is available for this situation (27, 65, 71). The pharmacologic and toxicologic profiles of inhaled long-acting beta2 agonist are similar to the short-acting $beta_2$ agonists, with the exception of their prolonged retention in the lungs (71). However, they should be used only if there is no other alternative because limited data are available on their use during pregnancy (71-73). ICSs are the cornerstone of therapy in asthma during pregnancy and in fact, different studies have shown that ICS can be used with relative safety and minimal side effects during pregnancy (39, 57, 58).

Under-treatment of asthma during pregnancy remains one of the main problems in the management of pregnant asthmatic women and the most important reasons leading to uncontrolled asthma during pregnancy, which may contribute to the increased risk of adverse maternal and perinatal outcomes (57, 74). In a study, done by Belanger et al., they reported under treatment with ICS in 65% of asthmatic women (N=761) for at least 3 months during their pregnancy (75). Also, a published survey conducted in 2003 with 501 asthmatic women 18 to 44 years old reported that 39% of women who had been pregnant before the survey discontinued or reduced their asthma medications during

pregnancy (76). Of this subset, a third did so without first discussing it with their prescribing physician or obstetrician.

## 3.3. Impact of pregnancy on asthma

Pregnancy could influence the course of asthma. A few studies have shown that asthma worsened during pregnancy in about 33% of women, improved in about 33% and stay unchanged in about 33% (77, 78). Both the variable nature of the disease as well as the asthma variability due to pregnancy could explain in part the change in the course of asthma during pregnancy (79). However, the mechanisms of these changes have not been well clarified and in general the course of asthma during pregnancy is not predictable (79). It was shown that the first trimester and the last month of pregnancy are relatively free of exacerbation and the second and third trimester have more potential for increased symptoms and the need for medications (77, 78, 80, 81). The course of asthma during pregnancy is influenced by the severity of the pre-existing asthma and severe asthma is more likely to worsen during pregnancy than mild asthma (77, 78, 82). The majority of women who experience increased severity of asthma during one pregnancy will have increased severity during subsequent pregnancies (83).

### 3.3.1. Impact of fetal gender on maternal asthma exacerbation

A few studies have suggested that fetal gender could influence the course of asthma during pregnancy (8-10). These studies have concluded that asthmatic mothers pregnant with female fetus reported more symptoms and had slightly lower lung function than mothers pregnant with male fetus (8-11).

In a review of case series three mothers who had been followed in successive pregnancies reported more asthma attacks when pregnant with a female fetus than when they were carrying a male fetus (11).

In a blind-controlled prospective study (n=34), Beecroft et al. have found that asthmatic women pregnant with a female fetus reported significantly more shortness of breath (72% vs. 31%), nocturnal awakening (55% vs. 37%), and general asthma symptoms (50% vs. 31%) than women pregnant with a male fetus (8).

Dodds et al. have evaluated steroids use during pregnancy among a sample of 817 pregnant asthmatic women without having specific data on asthma severity or symptoms and found an increased usage of steroids during pregnancy among mothers of a female fetus as compared to mothers of a male fetus (20% vs. 14%) (9). This outcome is difficult to interpret since it is unclear whether or not it includes only oral corticosteroids or both inhaled and oral formulations, which in the later case would not necessarily reflect uncontrolled asthma. Moreover, no conclusion on the statistical significance of this difference can be made since no statistical inference was reported in the article.

In a recent study, Kwon et al. used a prospective cohort design to assess the association between fetal gender and maternal airway lability among pregnant asthmatic women (10). Among 702 pregnant women with asthma, they measured an objective outcome i.e. peak expiratory flow (PEF). The PEF was assessed at enrolment and at 21, 29, and 37 weeks of gestation. The 10% reported difference in log diurnal variation of the PEF between pregnancies of male and female fetuses reached statistical significance, but the clinical significance of the observed difference is questionable (10).

Conversely, Baibergenova et al. did not find any significant association between fetal gender and visits to an emergency department (ED) for asthma during pregnancy between pregnancies of male and female fetuses (84). This study was based on a large cohort of 109,173 live singleton deliveries reconstructed from a hospital and an ambulatory care administrative database provided by the Canadian Institute for Health

Information (CIHI). From this cohort, Baibergenova et al. first identified all patients who visited an ED during pregnancy and then found that 0.49% and 0.48% of those ED visits were for asthma among women pregnant with a female and a male fetus, respectively (p-value > 0.05).

Among the hypotheses put forward to explain the mechanisms behind the association between fetal gender and maternal asthma control during pregnancy, the one related to the regulation of placental glucocorticoid and immune response in asthmatic pregnancies seems the most plausible (8, 10, 84). Indeed, Clifton and Murphy and their research teams have reported that female fetus alters maternal asthma during pregnancy by upregulating maternal inflammatory pathways (85-88) and thus if asthma-associated inflammatory pathways are not treated with inhaled steroids during pregnancy, the mother could suffer asthma exacerbation.

## 3.4. Impact of asthma on pregnancy

Asthma could affect pregnancy outcomes. Asthma in pregnancy has been associated with maternal and fetal morbidity (16, 21, 89). It has been reported that pregnant asthmatic women have an increased risk of vaginal bleeding (16), pregnancy-induced hypertension (16, 89), cesarean section (90, 91) and complicated labor (90) comparing to non-asthmatic women . However, it seems that the magnitude of these adverse outcomes is related to the degree of control and severity of maternal asthma (49). The association between maternal asthma and adverse perinatal outcomes has been evaluated by several studies; however, the literature reports inconsistent results.

## 3.5. Impact of asthma on adverse perinatal outcomes

Studies comparing adverse perinatal outcomes such as preterm birth, LBW infant or SGA infant between pregnancies of asthmatic women and non-asthmatic women are summarized in Table1. Different study designs were used in 36 studies presented in Table 1. There are 14 prospective studies, 5 case series, 14 retrospective studies, 2 case-control studies, and one cross-sectional survey. The results of one other systematic review (meta-analysis) are also presented in this table. The sample size of asthmatic group ranged from 32 (92) to 36,985 (93) pregnancies and the sample size of non-asthmatic group ranged from 77 (94) to 1,320,000 (93) pregnancies. Among these studies, 27 adjusted for diverse potential confounding variables, but only 14 studies adjusted for smoking.

In Table 1, for each study, general information regarding the study design, the period of data collection, the sample size of the asthmatic and non-asthmatic groups and the list of confounding variables are presented. The magnitude of the risk for the adverse perinatal outcomes and its statistical significance are also presented in this table.

### 3.5.1. Small for gestational age

Most of the older studies evaluated the impact of maternal asthma on adverse perinatal outcomes did not assess the risk of delivering SGA infant in asthmatic women compared to non-asthmatic women. Among 13 studies that evaluated the risk of this adverse perinatal outcome among asthmatic women, 5 large studies reported a significant association between maternal asthma and the risk of SGA infants (adjusted relative risk (aRR) ranged from 1.16 to1.50) (14, 17, 95-97). However, 8 other studies found no significant increased risk of SGA associated with asthma (21, 63, 91, 94, 98-101). Lack of adjustment for several potential confounders and lack of power due to small sample sizes probably explain the differences in results.

### 3.5.2. Preterm birth

Preterm birth, occurring prior to 37 weeks of gestation was evaluated in 29 studies and 10 of them have reported a significant increase of risk in asthmatic women that ranged from 1.15 to 4.00. Risk of preterm birth has been reported to be significantly increased in asthmatic women as compared to non-asthmatic women in 5 large studies (asthmatic population size > 2000) that adjusted for several potential confounders (aOR: 1.11-1.78) (14, 17, 19, 93, 97). In addition, 4 other smaller studies (asthmatic population size < 500) reported a significant increased risk of preterm birth with ORs ranging from 1.48 to 4.00 (16, 91, 102, 103). The fourfold significant increased risk of preterm delivery has been reported by Perlow et al. in asthmatic women receiving regular non-steroid medication (91). However, 18 studies have not found a significant increased risk of preterm birth in asthmatic women versus non-asthmatic women (7, 15, 20, 21, 61, 90, 92, 94, 96, 98, 100, 104-110). Four other studies reported no significant difference in mean gestational age between asthmatic and non-asthmatic pregnant women (22, 95, 111, 112). Moreover, in a recent meta-analysis, conducted by Murphy and al, the asthmatic women

with and without asthma exacerbation during pregnancy were compared to non asthmatic women (113). The authors found no significant increased risk of preterm delivery in women who had (RR: 1.46, 95%CI: 0.77-2.78) and those who did not have an asthma exacerbation during pregnancy (RR: 0.93, 95% CI: 0.74-1.17).

### 3.5.3. Low birth weight

Among 22 studies which evaluated the impact of maternal asthma on the risk of LBW infant (weight<2500 g at birth), 7 reported a statistical significant 1.15 to 9.36 increase in the incidence of LBW. Bahna et al were the first authors who reported a significant increased risk of LBW (OR: 1.92) in asthmatic women (16). This increased risk was later confirmed in 3 large studies (asthmatic population size > 2000) conducted retrospectively and adjusted for some potential confounders including smoking (OR: 1.15 to 1.32) (14, 93, 97). Two other smaller studies also reported a significant increased risk of LBW ranging from 2.95 to 9.36 (90, 114). No significant differences in the risk of LBW was observed among asthmatic women as compared to non-asthmatic women in 15 other studies (7, 15, 20, 21, 61, 63, 91, 92, 94, 95, 105, 106, 109, 115, 116). In addition, Murphy et al investigated the effect of asthma and asthma exacerbation on LBW through a meta-analysis using data from three studies (113). They observed a significantly increased risk in women who had (RR: 2.54, 95% CI:1.52-4.25) but no increased risk in those who did not have an asthma exacerbation during pregnancy (RR: 1.12, 95% CI: 0.89-1.40) (113).

**Table 1. Description of studies that assessed the impact of maternal Asthma on SGA, preterm birth and LBW**

| Author, year of publication (Ref number) | Study design (period of data collection) | Source of data | Sample size (pregnancy) | | OR / RR (95% Confidence Interval) or incidence % | | | Adjustment for any confounders |
|---|---|---|---|---|---|---|---|---|
| | | | Asthmatic | Non-asthmatic | SGA | Preterm <37 wk | LBW | |
| **Schaefer et al. 1961 (115)** | Case series (1953-1959) | New-York Lying-in hospital | 293 | 30,000 | NE | NE | 1.10 NS | No adjustment |
| **Gordon et al. 1970 (15)** | Retrospective Cohort (unknown) | Collaborative Study of neurological diseases (USA) | 277 | 30,861 | NE | 0.80 NS | 1.33 NS | No adjustment |
| **Bahna et al. 1972 (16)** | Retrospective Cohort (1967-1968) | Medical birth registry of Norway | 365 | 108,622 | NE | **1.48 (p<0.01)** | **1.92 (p<0.001)** | No adjustment |
| **Schatz et al. 1975 (107)** | Case series (1975) | 3 Medical Centers (USA) | 70 | General population | NE | 1.50 NS | NE | No adjustment |
| **Fitzsimmons et al. 1986 (61)** | Case series (1981-1984) | North-western University Allergy Service | 56 | General population | NE | 1.30 NS | 2.53NS | No adjustment |
| **Dombrowski et al. 1986 (111)** | Prospective (1982-1985) | Medical records in Hutzel Hospital (USA) | 153 | 116 | NE | NS difference in mean gestational age (39weeks vs. 39weeks) | NS difference in mean birth weight (3000g vs. 3050g) | Matched for parity |
| **Stenius et al. 1988 (22)** | Prospective (1978-1982) | Helsinki University Central Hospital | 198 | 198 | NE | NS difference in mean gestational age (278days vs. 276days) | NS difference in mean birth weight (3479g vs. 3483g) | Matched for age, parity and time of delivery |
| **Greenberg et al. 1988 (106)** | Case series (1981-1987) | North-western University Allergy Service | 80 | General population | NE | 1.03 NS | 2.17 NS | No adjustment |
| **Schatz et al. 1988 (105)** | Prospective (1978-1984) | San Diego Kaiser-Permanente Medical Care | 259 | 295 | NE | 2.22 NS | 1.93 NS | Matched for age and smoking |

| Author, year of publication (Ref number) | Study design (period of data collection) | Source of data | Sample size (pregnancy) | | OR / RR (95% Confidence Interval) or incidence % | | | Adjustment for any confounders |
|---|---|---|---|---|---|---|---|---|
| | | | Asthmatic | Non-asthmatic | SGA | Preterm <37 wk | LBW | |
| **Lao et al. 1990 (90)** | Retrospective (1984-1987) | Hospital, Hong Kong | 87 | 87 | NE | 3.09 NS | **9.36 (p<0.01)** | Matched for age and parity |
| **Mabie et al. 1992 (98)** | Case series (1986-1989) | Hospital, Tennessee | 200 | 22,651 | 0.87 NS | 0.90 NS | NE | No adjustment |
| **Perlow et al. 1992 (91)** | Retrospective (1985-1990) | Long Beach Memorial Medical Center Hospital | [1]50 | 130 | 5.6 (0.8-40.2) | **4.0 (1.1-15.5)** | 3.4 (0.9-12.1) | No adjustment |
| **Doucette et al. 1993 (92)** | Prospective (1980-1982) | Yale-New Haven Hospital | 32 | 3,850 | NE | 1.78 (0.53-6.02) | 0.73 (0.1-5.29) | Adjusted for education, race, vaginal bleeding, smoking in 2nd month |
| **Schatz et al. 1995 (21)** | Prospective Cohort (1978-1990) | San Diego Kaiser-Permanente Medical Care | 486 | 486 | 1.33 (p=0.33) | 1.65 (p=0.14) | 1.64 (p=0.16) | Matched for age, smoking, parity, year of delivery |
| **Stenius et al. 1995 (108)** | Prospective (1982-1990) | Helsinki University Central Hospital and Helsinki Maternity Hospital | 504 | 237 | NE | 1.15 NS | NE | Matched for age and parity |
| **Jana et al. 1995 (20)** | Prospective (1983-1992) | Nehru hospital, India | 182 | 364 | NE | p>0.05 | p>0.05 | Matched for age and parity |
| **Corchia et al. 1995 (114)** | Cross-Sectional Survey (1987) | 3 areas of Lazio Region, Italy | 55 | 2,871 | NE | NE | Smoking **6.62 (1.75-25.07)** No smoking 1.17 (0.28-4.99) | Adjusted for infant gender, and maternal education within each level of smoking |

| Author, year of publication (Ref number) | Study design (period of data collection) | Source of data | Sample size (pregnancy) | | OR / RR (95% Confidence Interval) or incidence % | | | Adjustment for any confounders |
|---|---|---|---|---|---|---|---|---|
| | | | Asthmatic | Non-asthmatic | SGA | Preterm <37 wk | LBW | |
| **Kramer et al. 1995 (102)** | Case-Control (1990-1992) | 3 McGill University-affiliated hospitals | among cases [2]44 [3]41 | among cases 200 | NE | [2] **2.32 (1.38-3.89)** [3] **2.42 (1.44-4.08)** | NE | Matched for race, and smoking prior and during pregnancy |
| **Stenious et al. 1996 (104)** | Prospective Cohort (1982-1992) | Helsinki University Central Hospital | [4]457 | 237 | NE | 1.0 NS | NE | Matched for age and parity |
| **Alexander et 1998 al. (7)** | Retrospective Cohort (1991-1993) | Nova Scotia Perinatal Database | [5]N: 375 [6]B: 303 [7]S: 139 | 13,709 | NE | [5]N: 1.0 (0.5-1.7) [6]B: 1.0 (0.5-1.8) [7]S: 1.4 (0.6-3.0) | [5]N: 0.9 (0.5-1.5) [6]B: 1.4 (0.8-2.2) [7]S: 1.0 (0.4-2.5) | Adjusted for age, previous delivery of LBW, parity, pre-delivery weight, and smoking |
| **Demissie et 1998 al. (14)** | Retrospective Cohort (1989-1992) | Administrative databases of New Jersey Hospitals | 2,289 | 9,156 | Crude **1.33 (1.17-1.51)** Adjusted **1.26 (1.10-1.45)** | Crude **1.59 (1.40-1.80)** Adjusted **1.36 (1.18-1.55)** | Crude **1.57 (1.34-1.86)** Adjusted **1.32 (1.10-1.58)** | Adjusted for age, education, marital status, parity, race, chronic &gestational diabetes, chronic HTA, smoking, alcohol and drug use |
| **Kallen et al. 2000 (93)** | Retrospective Cohort (1984-1995) | The Sweden Medical Birth Registry | All 36,985 Severe 1,396 | [8]1,320,000 | NE | All **1.15 (1.09-1.21)** Severe **1.56 (1.27-1.90)** | All **1.21 (1.14-1.29)** Severe **1.98 (1.52-2.59)** | Adjusted for year of delivery, age, and smoking |
| **Wen et al. 2001 (19)** | Retrospective Cohort (1990-1996) | Hospital discharge data from Canadian Institute for Health Information | 8,672 | 34, 688 | NE | Crude **1.83 (1.57-2.11)** Adjusted **1.78 (1.53-2.07)** | NE | Adjusted for age, chronic and gestational diabetes, chronic and gestational HTA, and caesarean delivery |

| Author, year of publication (Ref number) | Study design (period of data collection) | Source of data | Sample size (pregnancy) | | OR / RR (95% Confidence Interval) or incidence % | | | Adjustment for any confounders |
|---|---|---|---|---|---|---|---|---|
| | | | Asthmatic | Non-asthmatic | SGA | Preterm <37 wk | LBW | |
| **Minerbi-Codish et al. 1998 (94)** | Prospective Cohort (1993-1994) | Medical Center (Israel) | 101 | 77 | No statistically significant difference | No statistically significant difference | No statistically significant difference | Matched for age and ethnic origin |
| **Liu et al. 2001 (17)** | Retrospective Cohort (1991-1996) | Med-Echo database (Quebec) | 2,193 | 8,772 | Crude **1.19 (1.02-1.37)** Adjusted **1.16 (1.00-1.35)** | Crude **1.59 (1.35-1.87)** Adjusted **1.40 (1.18-1.66)** | NE | Adjusted for age, chronic and gestational diabetes, chronic HTA, and caesarean delivery |
| **Olesen et al. 2001 (63)** | Retrospective Cohort (1991-1996) | Hospital Discharge Registry and North Jutland Prescription Database (Denmark) | [9]303 | [10]8,717 | higher among exposed one | NE | higher among exposed one | Adjusted for age, co-habitation status, smoking and child gender |
| **Sobande et al. 2002 (112)** | Prospective Cohort (1997-2000) | Maternity Hospital (Saudi Arabia) | 88 | 106 | NE | 39.41 vs. 39.43 (p>0.05) | **2,855g vs. 3,051g (p=0.006)** | No adjustment |
| **Sorensen et al. 2003 (103)** | Nested case-control (1994-1995) | Healthcare network of Swedish Medical center, (Seattle, USA) | among cases 20 | among cases 292 | NE | Crude **2.03 (1.01-4.09)** Adjusted **2.37 (1.15-4.88)** | NE | Adjusted for age, race, parity, Medicaid status and smoking |
| **Bracken et al. 2003 (99)** | Prospective Cohort (1996-2001) | 56 obstetric practices and 15 clinics (Connecticut, Massachusetts) | 873 | 1,333 | Crude 1.22 (0.89-1.68) Adjusted 1.15 (0.79-1.67) | Crude **1.49 (1.07-2.08)** Adjusted 1.36 (0.92-2.00) | NE | Adjusted for age, marital status, race, education, pre-pregnancy weight, height, smoking, daily caffeine, parity |

| Author, year of publication (Ref number) | Study design (period of data collection) | Source of data | Sample size (pregnancy) | | OR / RR (95% Confidence Interval) or incidence % | | | Adjustment for any confounders |
|---|---|---|---|---|---|---|---|---|
| | | | Asthmatic | Non-asthmatic | SGA | Preterm <37 wk | LBW | |
| **Mihrshahi et al. 2003 (109)** | Prospective data collection (2003) | Questionnaires to women identified in antenatal clinics of 6 Sydney hospitals | 340 | 271 | NE | 2.13 NS | 1.47 NS | Adjusted for age, parity, nulliparous, socioeconomic factors, exposure to smoking |
| **Dombrowski et al. 2004 (100)** | Prospective Cohort (1994-1999) | 16 centers of Maternal-Fetal Medicine Unit Network (USA) | Mild: 873<br>Moderate-Severe:866<br>Severe: 52 | 881 | Mi:1.2 (0.8-1.7)<br>MS:1.2 (0.8-1.8)<br>Sev: 1.6 (0.6-4.4) | Mi: 1.0 (0.6-1.8)<br>MS: 0.9 (0.5-1.6)<br>**Sev: 2.2 (1.2-4.2)** | NE | Adjusted only for analyses of severe patients for previous preterm, smoking, race, BMI |
| **ACS et al. 2005 (116)** | Retrospective (1980-1996) | Hungarian Congenital Abnormality Registry | 757 | 37,394 | NE | 1.56 statistical significance not reported | 1.61 Statistical significance not reported | Adjusted for age, birth order, employment status. Anti-asthmatic drugs |
| **Sheiner et al. 2005 (95)** | Retrospective Cohort (1988-2002) | Soroka University Medical center (Israel) | 1,963 | 137,205 | **1.5 (1.1-1.9)** | No difference in mean | 1.10 NS | Adjusted for failure to progress in labour, mal-presentation |

| Author, year of publication (Ref number) | Study design (period of data collection) | Source of data | Sample size (pregnancy) | | OR / RR (95% Confidence Interval) or incidence % | | | Adjustment for any confounders |
|---|---|---|---|---|---|---|---|---|
| | | | Asthmatic | Non-asthmatic | SGA | Preterm <37 wk | LBW | |
| **Murphy 2006 (113)** | Meta analyse, (2006) | 3 studies for evaluating LBW and 4 studies for evaluating preterm birth | No-exacerbation 855<br>Exacerbation 79<br>---<br>No-exacerbation 1,312<br>Exacerbation 126 | For No-exacerbation 31,662<br>For Exacerbation 31,285<br>---<br>For No-exacerbation 31,662<br>For Exacerbation 31,899 | NE | No-exacerbation vs. non-asthmatic 0.93 (0.74-1.17)<br>Exacerbation vs. non-asthmatic 1.46 (0.77-2.78) | No-exacerbation vs. non-asthmatic 1.12 (0.89-1.40)<br>Exacerbation vs. non-asthmatic **2.54 (1.52-4.25)** | LBW: (15), (20), (21)<br>---<br>Preterm birth: (15), (20), (21), (104) |
| **Enriquez et al. 2007 (96)** | Retrospective cohort (1995-2003) | Tennessee Medical Program | Asthmatic 9,154<br>Exacerbation 2,105<br>No-Exacerbation 7,049 | 131,145 | Asthmatic vs. Non-asthmatic 1.19 NS<br>very SGA **1.20 (p< .0001)** | Asthmatic: Ns<br>Exacerbation: NS<br>No-exacerbation: NS | Asthmatic: Mean **3,131g vs. 3,173g (p< .0001)**<br>Exacerbation **1.22 (< .0002)**<br>No-exacerbation **1.16 (< .0002)** | Adjusted for race, age, smoking, education, comorbidity and adequacy of prenatal care |
| **Clark et al. 2007 (101)** | Prospective; Clinic (2001-2003) | Antenatal clinics of Manchester Children's University Hospitals | 370 No med.<br>170 ICS& $\beta_2$<br>178 $\beta_2$ only | 718 | ICS& $\beta_2$<br>Boys: **1.56 (p=.011)**<br>Girls: 0.95 (p=.56)<br>NS (other group) | NE | ICS& $\beta_2$<br>↓ in mean birth weigh **-112 (-193, -30.7)**<br>NS for other groups | Adjusted for smoking, race, parity, gestational age |

| Author, year of publication (Ref number) | Study design (period of data collection) | Source of data | Sample size (pregnancy) | | OR / RR (95% Confidence Interval) or incidence % | | | Adjustment for any confounders |
|---|---|---|---|---|---|---|---|---|
| | | | Asthmatic | Non-asthmatic | SGA | Preterm <37 wk | LBW | |
| **Kallen et al. 2007 (97)** | Retrospective cohort (1995-2004) | Swedish Medical Birth Registry | 23,988 All birth registered | 846,635 | **1.16 (1.07-1.26)** | **1.11 (1.05-1.18)** | **1.15 (1.07-1.23)** | No adjustment mentioned |

NS: statistically non significant
NE: not evaluated
HTA: hypertension
[1]Receiving chronic medication but non-steroid dependent
[2]history of Asthma
[3]Physician diagnosed asthma
[4]No acute attack of asthma during the study period
[5]N: No asthma medication use
[6]B: beta agonist use only
[7]S: Steroid use
[8]All birth during study period
[9]Receiving at least one prescription for asthma during pregnancy
[10]Buying no drug prescription during pregnancy

The differences between these results could be partly explained by important differences between studies in:

- The study sample sizes,
- Study designs,
- Asthmatic definition,
- Non-asthmatic definition,
- Data collections,
- Control for confounders,
- Asthma severity during pregnancy,
- Adequacy of control of asthma during pregnancy.

## 3.6. Asthma severity and asthma control

Control and severity of asthma are two different but complementary concepts (117). In fact, one can have severe asthma but adequately controlled and another one can have mild asthma but poorly controlled. The severity of asthma could influence the control over time. Canadian experts have recommended that the dose of ICS necessary to obtain good control of asthma should be included when evaluating severity (39). The accurate classification of asthma severity and control is a definite challenge both in clinical practice and in research since they are conceptually related and some of the criteria used in their assessment overlap.

### 3.6.1. Asthma control

Current series of criteria in the assessment of the control of asthma were established by the Global Initiative for Asthma (GINA) and the Canadian Asthma Consensus Guidelines (39, 43). They include daytime and nocturnal symptoms, physical activity limitations, the occurrence of asthma exacerbations, the need for inhaled SABA, school or work absenteeism, and forced expiratory volume in the first one second ($FEV_1$) or peak respiratory flow (PEF) values. The optimal control of asthma based on Canadian Asthma Consensus Guidelines has been defined by the presence of minimal respiratory symptoms, no physical activity limitation, normal respiratory function, and absence of the need for rescue bronchodilator more than recommended (see table 2) (39).

**Table 2. Indications of asthma control**
From *Canadian asthma consensus report, 1999* (39)

| **Parameter** | **Frequency or value** |
|---|---|
| Daytime symptoms | < 4 days/week |
| Night-time symptoms | <1 night/week |
| Physical activity | Normal |
| Exacerbations | Mild, infrequent |
| Absence from work or school | None |
| Need for short-acting $\beta_2$-agonist | <4 doses/week * |
| $FEV_1$or PEF | > 85% of personal best, ideally 90% |
| PEF diurnal variation† | < 15% of diurnal variation |

$FEV_1$= forced expiratory volume in 1 second; PEF = peak expiratory flow obtained with a portable peak flow meter.

*May use 1 dose/day for prevention of exercise-induced symptoms.

† Diurnal variation is calculated by subtracting the lowest PEF from the highest and dividing by the highest PEF multiplied by 100.

### 3.6.2. Asthma severity

Different methods are advocated by various guidelines for the assessment of asthma severity (39, 43, 118). The GINA guidelines as well as the US National Asthma Education and Prevention Program Consensus guidelines relative to the assessment of severity rely upon the evaluation of the disease's clinical features (asthma symptoms, occurrence of asthma exacerbation and respiratory function) prior to the initiation of any anti-asthmatic treatment (43, 118). However, the Canadian Asthma Consensus Guidelines assess asthma severity once the treatment has been instigated and rely upon a combination of factors, many of which overlap with measures of asthma control. These include pulmonary function tests, the treatment required to obtain asthma control, the history of hospital admissions, and life-threatening asthma attacks (see table 3) (39).

**Table 3: Levels of asthma severity based on treatment needed to obtain control**
From *Canadian asthma consensus report, 1999* (39)

| **Asthma severity** | **Symptoms** | **Treatment required** |
|---|---|---|
| Very mild | Mild-infrequent | None, or inhaled SABA rarely |
| Mild | Well-controlled | SABA (occasionally) and low-dose ICS |
| Moderate | Well-controlled | SABA and low to moderate doses of ICS with or without additional therapy |
| Severe | Well-controlled | SABA and high doses of ICS and additional therapy |
| Very Severe | May be controlled or not well-controlled | SABA and high doses of ICS and additional therapy and OCS |

## 3.7. Impact of adequately controlled asthma during pregnancy on adverse perinatal outcomes

Poorly controlled asthma is potentially dangerous to the fetus since hypoxia combined with respiratory alkalosis decrease placental blood flow and potentially impaired fetal oxygenation (50, 52, 57, 119). Decreased fetal blood oxygen could result in abnormal growth and development of the fetus (120). Jana et al. found that maternal uncontrolled severe asthma (ED visit and systemic corticosteroids use during pregnancy) leads to fetal growth retardation (mean birth weight: 2469g vs 2842g; $p<0.05$) and low birth weight (53.3% vs 20.5%; $p<0.01$) more often than women with adequately controlled asthma during pregnancy (20). These results have also been confirmed in other studies (56, 61, 106).

The question is whether better controlled asthma lead to improve fetal growth. To our knowledge, only one study evaluated directly whether or not women with adequately controlled asthma are at higher risk of perinatal outcomes than non-asthmatic women. In a prospective controlled study comparing women with actively managed asthma during pregnancy and non-asthmatic women, Schatz et al observed relative risks as large as 1.65 for perinatal outcomes, but concluded that there was no difference between the groups since the relative risks were not statistically significant (21). In two other studies, Stenius-Aarniala et al and Jana et al. came to the same conclusion, although the association between the control of asthma and perinatal outcomes was only indirectly evaluated (20, 22).

In a prospective study conducted between 1978-1990, Schatz et al assessed perinatal outcomes in 486 actively managed pregnant asthmatic women as compared with 486 non asthmatic pregnant women matched for age, smoking, parity and year of delivery (21). All asthmatic women had a history of asthma or asthma symptoms with a

reconfirmation of their diagnostic of asthma at the entry to the study and they were managed in the allergy clinic to prevent acute asthmatic episodes and asthma symptoms that interfere with sleep or normal activity. Moreover, all women received routine obstetric care. The authors reported a RR of 1.33 for SGA (p value =0.33), a RR of 1.64 for LBW (p=0.16), and a RR of 1.65 (p=0.14) for preterm births. However, they concluded that there was no difference between the groups since these RRs were not found to be statistically significant (21).

Jana et al. compared the perinatal outcomes in 182 pregnancies from asthmatic women with those of 364 non-asthmatic women matched for age and parity between 1983-1992 (20). The asthmatic women were followed in an Obstetric-Medical Disorder Clinic and there were close cooperation between the obstetrician and chest physician in the patient's management. The asthmatic women were advised to continue anti-asthmatic medication throughout pregnancy and they were provided with instructions in the case of acute exacerbation of asthma.

In this study, the authors investigated the risk of adverse perinatal outcomes in women who required emergency hospitalization and was managed with high flow of oxygen, high doses of inhaled $\beta_2$-agonists, intravenous corticosteroids and aminophylline infusion during the study period (severe asthmatic patients) as compared with non-asthmatic controls (20). Moreover, they compared women who had used oral and/or parental $\beta_2$-agonists, theophylline, aminophylline, corticosteroids, and inhaled salbutamol and beclomethasone during the study period (mild asthmatics) to non-asthmatic ones for adverse perinatal outcomes. In summary, the authors investigated the effect of asthma severity level on adverse perinatal outcomes and they concluded indirectly regarding well controlled asthma without any clear distinction between asthma severity and control.

In another study, Stenius-Aarniala et al. prospectively followed 198 pregnancies of asthmatic women and 198 pregnancies of non-asthmatic women matched for age, parity and time of delivery from 1978 to 1982 (22). In this study, asthmatic women were divided into four severity groups based on the treatment necessary to control asthma during pregnancy and the occurrence of acute asthma exacerbation. The authors examined the risk of adverse perinatal outcomes in each severity group as compared to the non-asthmatic women and they concluded that there is no difference in adverse perinatal outcomes between well controlled asthmatic women and healthy women (22).

## 3.8. Impact of maternal asthma severity on adverse perinatal outcomes

Although studies have reported associations between severe exacerbations requiring hospitalization during pregnancy and adverse perinatal outcomes (20, 61, 106), 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. Studies comparing adverse perinatal outcomes such as preterm birth, LBW infant or SGA infant between pregnancies of women with moderate to severe asthma and women with mild asthma are summarized in Table4.

### 3.8.1. Small for gestational age

Fitzsimmons et al. and Mabie et al. reported a significant increased risk of SGA infants associated with severe asthma as compared with mild asthma ($p$=0.02 and $p$<0.05 and respectively) (61, 98). However, their definition of severe asthma was quite restrictive including only patients who were hospitalized for status asthmaticus, had mechanical ventilation or required chronic maintenance therapy with oral prednisone (61, 98). In another study, Schatz et al. reported a significant increase in the ponderal indices < 2.2 (suggestive of asymmetric intrauterine growth retardation) ($p$=0.04) in women who had lower mean percent predicted $FEV_1$ during pregnancy (56). However, in this study the authors did not evaluate directly SGA infants but they examined the ponderal index<2.2 which is considered to be indicative of IUGR (56). Among these three studies, only Schatz et al. adjusted their results for some potential confounding variables including smoking (56).

A few other studies found a non-significant increased risk of SGA among women with severe asthma compared to women with mild asthma (99, 106, 121). Bracken et al found that IUGR (defined as below the tenth percentile of birth weight for gestational age) was more common among infants of mothers with mild to moderate persistent asthma as compared to those with no symptoms or medication use (OR ranged from 1.74 to 1.98) (99). However, they reported no significant increased risk among women with severe persistent asthma (aOR=1.57; 95% CI: 0.72-3.45) as compared to asthmatic women with no symptoms or medication use (99). Perlow et al. and Dombrowski et al. also found no increased risk of SGA associated with severe asthma (91, 100).

### 3.8.2. Preterm birth

There are several studies that have evaluated the association between markers of severe asthma and the risk of preterm delivery (Table 4.). Three studies found a significant increased risk of preterm delivery associated with severe asthma which ranged from 1.38 to 7.5 (91, 121, 122). Perlow et al. defined severe asthma as the mother being corticosteroid dependent during pregnancy (91). This definition is quite restrictive, identifies the most severe asthmatic and corresponds to only a small proportion of women with severe asthma. However, in two other studies, severe asthma was defined as women who had mean $FEV_1$<80% during study period (121) or women who had asthma symptoms during the prior 2 weeks before each interview that interfere with sleep or activity occasionally, frequently or constantly (122).

Some other studies have found non-significant increase in the risk of preterm birth associated with asthma severity (20, 61, 99, 106, 108, 123). However, all of them had a small sample size and except one (99) all suffered from the lack of adjustment for important confounding variables, including cigarette smoking during pregnancy. Five

other studies have not found any association between asthma severity and preterm birth (22, 90, 98, 100, 104).

### 3.8.3. Low birth weight

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 (91). 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 during pregnancy (53.3% vs. 20.5%; $p<0.01$) (20). Moreover, Schatz et al. reported a 36% significant increased risk of LBW among pregnant women having a mean $FEV_1<80\%$ during pregnancy as compared with women with higher mean $FEV_1$ during pregnancy (121).

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 (61, 106). However, these authors found no significant increased risk of LBW among women who were hospitalized for asthma during pregnancy. On the other hand, Stenius-Aarniala et al found no difference in birth weight between mothers with moderate-to-severe asthma and mothers with very mild-to-mild asthma (3418 vs. 3479 g) (22). Moreover, Lao et al. found no association between level of asthma severity and the risk of LBW (90).

**Table 4. Description of studies that assessed the impact of asthma severity during pregnancy on adverse perinatal outcomes**

| Author, year of publication (Ref number) | Study design (period of data collection) | Source of data | Severity definition | | Sample size (pregnancy) | | OR / RR (95% Confidence Interval) or incidence % | | | Adjustment for any confounders |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Severe asthmatic | Mild asthmatic | Severe asthmatic | Mild asthmatic | SGA | Preterm <37 wk | LBW | |
| **Fitzsimmons et al., 1986 (61)** | Case series (1981-1984) | North-western University Allergy Service | Emergency therapy | No emergency therapy | 17 | 41 | OR, *NR (p=0.08) | 1.87 (p=0.55) | 2.42 (p=0.12) | No adjustment |
| **Fitzsimmons et al. 1986 (61)** | Case series (1981-1984) | North-western University Allergy Service | Status-asthmaticus | No emergency therapy | 8 | 41 | OR, NR **(p=0.02)** | †NE | **2,764g vs. 3,284g (p=0.03)** | No adjustment |
| **Stenius et al. 1988 (22)** | Prospective (1978-1982) | Helsinki University Central Hospital | Exacerbation and hospital admission | No exacerbation or hospital admission | 91 | 109 | NE | ‡NS difference in mean gestational age (272d vs. 278d) | NS difference in mean birth weight (3,418g vs. 3,479g) | Matched for age, parity and time of delivery |
| **Greenberg et al. 1988 (106)** | Prospective Cohort (1981-1987) | North-western University Allergy Service | Emergency therapy | No emergency therapy | 25 | 55 | OR, NR (p=0.16) | 2.11(p=0.23) | 2.97(p=0.06) | No adjustment |
| **Greenberg et al. 1988 (106)** | Prospective Cohort (1981-1987) | North-western University Allergy Service | Status-asthmaticus | No emergency therapy | 16 | 55 | **5.75 (p=0.05)** | NE | **-434g (p=0.02)** | No adjustment |
| **Schatz el al. 1990 (56)** | Prospective; (1978-1984) | Kaiser-Permanente Medical Care | Individual mean % predicted $FEV_1$<83% | Individual mean % predicted $FEV_1$>99% | 89 | 91 | SGA, NE **[1]IUGR (p=0.04)** | NS | NS for LBW **mean birth weight (p=0.002)** | Adjusted for age, parity, smoking |

| Author, year of publication (Ref number) | Study design (period of data collection) | Source of data | Severity definition | | Sample size (pregnancy) | | OR / RR (95% Confidence Interval) or incidence % | | | Adjustment for any confounders |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Severe asthmatic | Mild asthmatic | Severe asthmatic | Mild asthmatic | SGA | Preterm <37 wk | LBW | |
| **Lao et al. 1990 (90)** | retrospective (1984-1987) | Hospital, Hong Kong | with treatment | without treatment | 54 | 33 | NE | 0.31 NS | 0.31NS | Matched for age and parity |
| **Mabie et al. 1992 (98)** | Case series (1986-1989) | Hospital, Tennessee | At least one hospitalization or OCS therapy or mechanical ventilation | No OCS therapy or hospital admission | 31 | 169 | **4.54 (p<0.05)** | 1.01 NS | NE | No adjustment |
| **Perlow et al. 1992 (91)** | retrospective (1985-1990) | Long Beach Memorial Medical Center Hospital | Steoid-dependent | Non-steroid-dependent | 31 | 50 | 0.8 (0.1-5.5) | **7.5 (2.3-25.2)** | **5.1 (1.6-17.0)** | No adjustment |
| **Stenius et al. 1995 (108)** | Prospective (1982-1990) | Helsinki University Central Hospital and Helsinki Maternity Hospital | theophylline users | Non-theophylline users | 212 | 292 | NE | 1.39 NS | NE | Matched for age and parity |
| **Jana et al. 1995 (20)** | Prospective (1983-1992) | Nehru hospital, India | hospitalization | No ER visits | 15 | 167 | NE | 1.61 NS | **2.60 (p<0.01)** | Matched for age and parity |
| **Stenious et al. 1996 (104)** | Prospective Cohort (1982-1992) | Helsinki University Central Hospital | Exacerbation | No exacerbation | 47 | 457 | NE | 1.1 NS | NE | Match for age and parity |

| Author, year of publication (Ref number) | Study design (period of data collection) | Source of data | Severity definition | | Sample size (pregnancy) | | OR / RR (95% Confidence Interval) or incidence % | | | Adjustment for any confounders |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Severe asthmatic | Mild asthmatic | Severe asthmatic | Mild asthmatic | SGA | Preterm <37 wk | LBW | |
| **Bracken et al. 2003 (99)** | Prospective Cohort (1996-2001) | 56 obstetric practices and 15 clinics (Connecticut Massachusetts) | | | 80 | 94 | Crude 1.39 (0.69-2.77)<br>Adjusted 1.57 (0.72-3.45) | Crude 1.67 (0.74-3.81)<br>Adjusted 1.88 (0.73-4.82) | NE | Adjusted for age, marital status, race, education, pre-pregnancy weight, height, smoking, daily caffeine, parity, and vitamin use |
| **Dombrowski et al. 2004 (100)** | Prospective Cohort (1994-1999) | 16 centers of Maternal-Fetal Medicine Unit Network (USA) | Moderate and severe | | 866 | 873 | 7.1% vs. 6.9% Statistical sig NE | 15.8% vs. 16.1% Statistical sig NE | NE | _____ |
| **Murphy et al. 2005 (123)** | Prospective Cohort (1997-2003) | John Hunter Hospital antenatal clinic | Severe exacerbation | No severe exacerbation | 52 | 92 | NE | 2.66 (p>0.05) | 7.06 (p>0.05) | No adjustment |
| **Schatz et al. 2006 (121)** | Prospective Cohort (1994-2000) | 16 centers of MFMU network of National Institute of Child health and human development | Mean $FEV_1$<80% | Mean $FEV_1$≥80% | 354 | 1,769 | 1.06 NS | **1.38 (P<0.01)** | **1.36 P<0.05** | Adjusted for age, parity, smoking, race, pre-pregnancy weight, ER or hospital visit, OCS |

| Author, year of publication (Ref number) | Study design (period of data collection) | Source of data | Severity definition | | Sample size (pregnancy) | | OR / RR (95% Confidence Interval) or incidence % | | | Adjustment for any confounders |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Severe asthmatic | Mild asthmatic | Severe asthmatic | Mild asthmatic | SGA | Preterm <37 wk | LBW | |
| **Bakhireva et al. 2008 (122)** | Prospective Cohort (1998-2003) | Multicenter prospective study of asthma medication use in pregnancy | [2]Poor to fair asthma symptom control ≤ 20 gestational weeks | Adequate asthma symptom control ≤ 20 gestational weeks | 308 | 396 | NE | **1.83 (1.04-3.25)** | NE | Adjusted for age, BMI, gravidity, parity, socioeconomic status, smoking, ethnicity, use of OCS |

*NR: not reported
†NE: not reported
‡NS: statistically non significant
[1]IUGR: ponderal index<2.2
[2]Poor to fair asthma symptom control ≤ 20 gestational weeks: the presence of asthma symptoms during the prior 2 weeks that interfere with sleep or activity occasionally, frequently or constantly

## 3.9. Risk factors for SGA, LBW infants or preterm birth

### 3.9.1. SGA Babies

Preeclampsia, a history of stillbirth, spontaneous abortion in preceding pregnancies, vaginal bleeding, and multiple gestations are reported in the literature to be risk factors of SGA babies (124-131). Marital status, maternal age, maternal height and body mass index, pregnancy weight gain, maternal birth weight and parity are also known to be risk factors for SGA (125, 128, 129, 132-137). The other factors which are known in the literature to be strongly associated with intrauterine growth restriction are maternal smoking, alcohol intake or being exposed to environmental tobacco smoke during pregnancy (131, 138-148). Whereas, maternal diabetes (OR, 0.7; 95% CI, 0.6-0.9), and being overweight or obese offered protection against SGA (128, 129, 135). Socio-demographic risk factors like low income level, unemployment, low maternal education and black race are also known to increase SGA new borns (126, 128, 129, 137, 149).

### 3.9.2. Preterm Birth

Alcohol intake before and during the three trimesters of pregnancy has been significantly associated with an increased risk of preterm birth (OR=2 for the first trimester) (146, 147, 150, 151). Cigarette smoking and illicit drug use during pregnancy has also been significantly associated with an increased risk of preterm birth (126, 131, 144-148, 150-154). Hypertension during pregnancy is strongly associated with preterm birth (adjusted OR=17.5 among SGA babies and adjusted OR=3.11 among non-SGA babies) (125). After adjustment for marital status, education level and adequacy of prenatal care, it is shown that younger mothers (13 to 17 years of age) in comparison to mothers who were 20 to 24 years old had a significantly higher risk of preterm delivery (RR: 1.9, 95%CI: 1.7-2.1) (132). Previous preterm delivery is also strongly associated with an increased risk of preterm delivery in a subsequent pregnancy (155, 156).

Maternal anemia, bacteriuria, bacterial vaginosis or systemic infection, vaginal bleeding, prior abortions, and multiple gestation are known to be risk factors for preterm birth (124-126, 131, 155-158). Advanced maternal age, low or high maternal body mass index, and poor maternal weight gain have also an increased risk effect on preterm births (126, 132, 135, 136, 158).

### 3.9.3. Low Birth Weight

Smoking during pregnancy has been strongly associated with low birth weight, as well as an overall 150-250 g reduction in mean birth weight (125, 142, 155, 159-161). The relation between exposure to environmental tobacco smoke in pregnant women and low birth weight have also been shown in several studies (138-143). Less than 6 to 9 months or more than 120 months between pregnancies are risk factors for low birth weight (162, 163). In addition, maternal birth weight and that of the siblings are independent predictors of the low birth weight of a newborn (134).

The summary table of other risk factors for SGA, LBW infants or preterm birth is shown in table 5.

**Table 5: Summary of Risk factors for SGA, LBW infants and preterm birth**

| Risk factors | SGA | LBW | Preterm birth |
|---|---|---|---|
| **Socio-demographic risk factors** | | | |
| Maternal age | ✓ (125, 129, 132) | ✓(164, 165) | ✓ (126, 132, 158) |
| Race/ethnicity | ✓ (148) | ✓(166, 167) | |
| Low socio-economic level | ✓ (128, 168) | ✓ (169) | |
| Low educational level | ✓ (128, 129) | ✓ (170) | |
| Unemployment | ✓ (137) | | |
| Marital status | ✓ (128, 129, 137) | ✓ (171) | |
| **Medical and obstetrical complications** | | | |
| Preeclampsia | ✓(125, 127, 128, 137) | ✓ (172) | ✓ (125) |
| Gestational diabetes | ✓ (128) | | |
| Vaginal bleeding | ✓ (124, 126, 131) | ✓ (173) | ✓ (124, 126, 131) |
| Prior abortions | ✓ (130) | | ✓ (126) |
| Prior history of preterm delivery | | | ✓ (155-157) |
| History of stillbirths | ✓ (126) | | ✓ (156, 158) |
| Multiple pregnancies | ✓ (131) | ✓ (174) | ✓ (131) |
| Anemia | | ✓ (175) | ✓ (176) |
| Infections | | ✓ (177, 178) | ✓ (179, 180) |
| Birth intervals | ✓ (128) | ✓ (162, 163) | |
| Placental anomalies | | ✓ (181) | |
| **Maternal risk characteristics** | | | |
| Pregnancy weight gain | ✓ (128, 129) | | ✓ (136) |
| Body mass index | ✓ (125, 128, 137) | ✓ (182) | ✓ (135) |
| Height | ✓ (129) | | |
| Maternal birth weight | ✓ (135) | ✓ (133, 134) | |
| Parity | ✓ (128, 129) | | ✓ (126) |
| **Environmental and behavior risks** | | | |
| Maternal tobacco smoking | ✓(128, 137, 142, 145) | ✓(125, 142, 155, 159-161) | ✓(126, 144, 145, 148) |
| Environmental tobacco smoke exposure | ✓(138-141, 143) | ✓(138-141, 143) | |
| Alcohol consumption | ✓ (146, 148) | | ✓(146, 147, 150, 151) |
| Illicit drug consumption | | | ✓ (152-154) |

# 4. Method

## 4.1. Study Design

As it is shown in Table 6., to achieve the proposed objectives we used a cohort design for the two first studies (183). Moreover, the two-stage sampling cohort design (balanced selection) was used for the three last studies (184, 185). This design is recommended for observational studies when data on the main exposure and outcomes are available for a large number of subjects but the data on confounding variables can be retrieved only for a subset of the study subjects (when data collection is time and cost-consuming) (184).

**Table 6. Summary of five studies included in the present thesis**

| | Objective | Study Design | Exposure | Outcomes | Sample Size | Statistical analyses |
|---|---|---|---|---|---|---|
| **Study 1** | Development and validation of a database index of asthma control and a database index of asthma severity | Cohort (asthma clinic) | Levels of asthma severity and control | **A.** Differences in mean $FEV_1$<br>**B.** Differences in mean $FEV_1$/FVC | **71 asthmatic patients**<br>**35**: mild<br>**21**: moderate<br>**15**: severe<br>---<br>**38**: adequately controlled<br>**33**: poorly controlled | Student's *t*- test for independent samples |
| **Study 2** | Impact of fetal gender on maternal asthma | Cohort (administrative databases) | Fetal gender | **A.** Maternal asthma exacerbation during pregnancy<br>**B.** SABA use during pregnancy<br>**C.** ICS use during pregnancy | **11,257 pregnancies**<br>**5,529**: female fetus<br>**5,728**: male fetus | Logistic regression |
| **Study 3** | Impact of maternal asthma on adverse perinatal outcomes | 2-stage sampling Cohort: balanced selection (administrative databases and a mailed questionnaire) | Asthma during pregnancy | **A.** SGA infant,<br>**B.** LBW infant,<br>**C.** Preterm birth | 40,788 pregnancies<br>13,007: asthmatic<br>27,781: non-asthmatic | GEE (logistic link) |
| **Study 4** | Impact of severity of asthma during pregnancy on adverse perinatal outcomes | 2 stage sampling Cohort: balanced selection (administrative databases and a mailed questionnaire) | Level of asthma severity during pregnancy | **A.** SGA infant,<br>**B.** LBW infant,<br>**C.** Preterm birth | **13,007 pregnancies**<br>**10,737**: mild asthmatic<br>**1,618**: moderate asthmatic<br>**652**: severe asthmatic | GEE (logistic link) |

| | Objective | Study Design | Exposure | Outcomes | Sample Size | Statistical analyses |
|---|---|---|---|---|---|---|
| **Study 5** | Impact of adequately controlled maternal asthma on adverse perinatal outcomes | 2 stage sampling Cohort: balanced selection (administrative databases and a mailed questionnaire) | Adequately controlled asthma during pregnancy vs. non-asthmatic women | **A.** SGA infant,<br>**B.** LBW infant,<br>**C.** Preterm birth | **<u>36,115 pregnancies</u>**<br>**8,334:** controlled asthmatic<br>**27,781:** non-asthmatic | GEE (logistic link) |

## 4.2. Sources of data

The historical data from the administrative databases of the province of Quebec as well as data obtained from a postal questionnaire that was sent to a sample of the study subjects were our sources of data.

### 4.2.1. Administrative databases

To construct our cohort, we worked with three administrative databases from the province of Quebec, i.e. the *Régie de l'Assurance Maladie du Quebec* (RAMQ) database, the MED-ECHO database 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 medical services dispensed to all residents of Quebec and on prescribed medications filled in community pharmacies by residents covered by the RAMQ's Public Drug Insurance Plan. Approximately 43% of the population of Quebec is covered by the RAMQ's Public Drug Insurance Plan, most notably the elderly and social assistance beneficiaries since 1980. Furthermore, since the enactment of mandatory drug coverage in 1997, the RAMQ's Public Drug Insurance Plan now provides coverage for an additional 1.7 million adherents, mainly workers and their families who have no access to a group drug insurance plan at work (186).

The **RAMQ Prescribed Medications** database provides information on dispensed medications – i.e. date of filling, name, dose, quantity, dosage form and duration of the prescription and on the prescribing physician. The **RAMQ Medical Services** database provides information on medical services dispensed in a physician office, a clinic, an emergency department (ED), or a hospital; including information pertaining to date, diagnosis coded with 9$^{th}$ international classification of diseases (ICD-

9), where the service was dispensed and who was the physician in charge. Also RAMQ database provides information on socio-demographic data such as age, gender, social assistance status, area of residence, and, where relevant, date of death. Data recorded in the RAMQ Public Prescribed Medications database and asthma diagnoses recorded in the RAMQ Medical Services database have been formally evaluated and found to be valid (187, 188). Data from the RAMQ was obtained for 2 years preceding conception and during pregnancy, for each pregnancy included in the cohort.

The **MED-ECHO** database is a provincial database which records data on acute care hospitalizations and covers all residents of Quebec (187). MED-ECHO provides information on all acute care hospitalizations- i.e. deliveries, medical and obstetrical complications, neonatal complications, asthma-related hospitalizations, etc. For all hospitalizations, MED-ECHO provides data on primary and up to 15 secondary discharge diagnoses, date of entry, duration of hospital stay, and treatments received during the stay. For delivery-related hospitalizations, data on the gestational age and birth weight of the newborn are also available. Data from the MED-ECHO was obtained for each woman and baby included in the cohort.

The **Fichier des événements démographiques** database provides information on all births and stillbirths in the province of Quebec. From this database we obtained demographic variables on the mother (date of birth, age, marital status, mother tongue, place of birth, area of residence, education level, number of live births, number of deliveries), on the father (date of birth, age, mother tongue, place of birth), and on the baby (sex, type of delivery, birth weight, gestational age, date of birth).

### 4.2.2. Questionnaire

Some additional information regarding siblings and maternal life styles during pregnancy which are not recorded in the administrative databases were retrieved from a mailed questionnaire completed by a number of selected women in a strategic way in order to capture the most information at the least cost. A 10$ compensation was given to women who completed the questionnaire.

The questionnaire underwent prior testing by a sample of asthmatic and non-asthmatic women for its clarity and also its facility to be understood and answered. Among the 40 women who pre-tested the questionnaire, some women were questioned about a pregnancy that occurred up to 25 years ago and they had no problem to remember their life style habits such as cigarette smoking during the pregnancy.

The questionnaire provided us with data pertaining to 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 (for the list of the questions, see appendix A). Data collected through the questionnaire was linked anonymously to the cohort.

## 4.3. Study Population

### 4.3.1. Cohort of pregnant women and newborns, first stage of sampling

The cohort used for our studies was reconstructed from the linkage of RAMQ, MED-ECHO and ISQ databases and formed of singleton deliveries (live births or still births) of asthmatic and non-asthmatic women. Pregnant women and newborns were

identified in the RAMQ and MED-ECHO databases using diagnostic and act codes related to prenatal care, pregnancy complications, and deliveries (189). All pregnancies corresponded to an abortion was eliminated.

**Inclusion criteria**

To be included in the cohort a woman should fulfill the following criteria:

1. having at least one pregnancy ending in a delivery (live births and still births) between January 1st, 1990 and December 31st, 2002 in the province of Quebec (Canada);
2. being 13-50 years old at the beginning of the pregnancy;
3. being covered by the RAMQ Drug Insurance Plan for at least one year prior to and throughout the duration of the pregnancy.

To be included in the cohort of asthmatic pregnancies, a woman should fulfill also the following criterion

4. being asthmatic i.e. having at least one diagnosis of asthma (ICD-9 code 493, except 493.2 which corresponds to chronic obstructive asthma) and at least one dispensed prescription for an asthma medication (see appendix B for the list of asthma medications) recorded in any type of RAMQ database or MED-ECHO either two years before or during the first pregnancy that occurred after January 1, 1990.

**Exclusion criteria**

A woman was excluded from the cohort if at least one of the following conditions was present:

1. multiple pregnancy
2. unavailable data regarding:
    a. newborn's weight

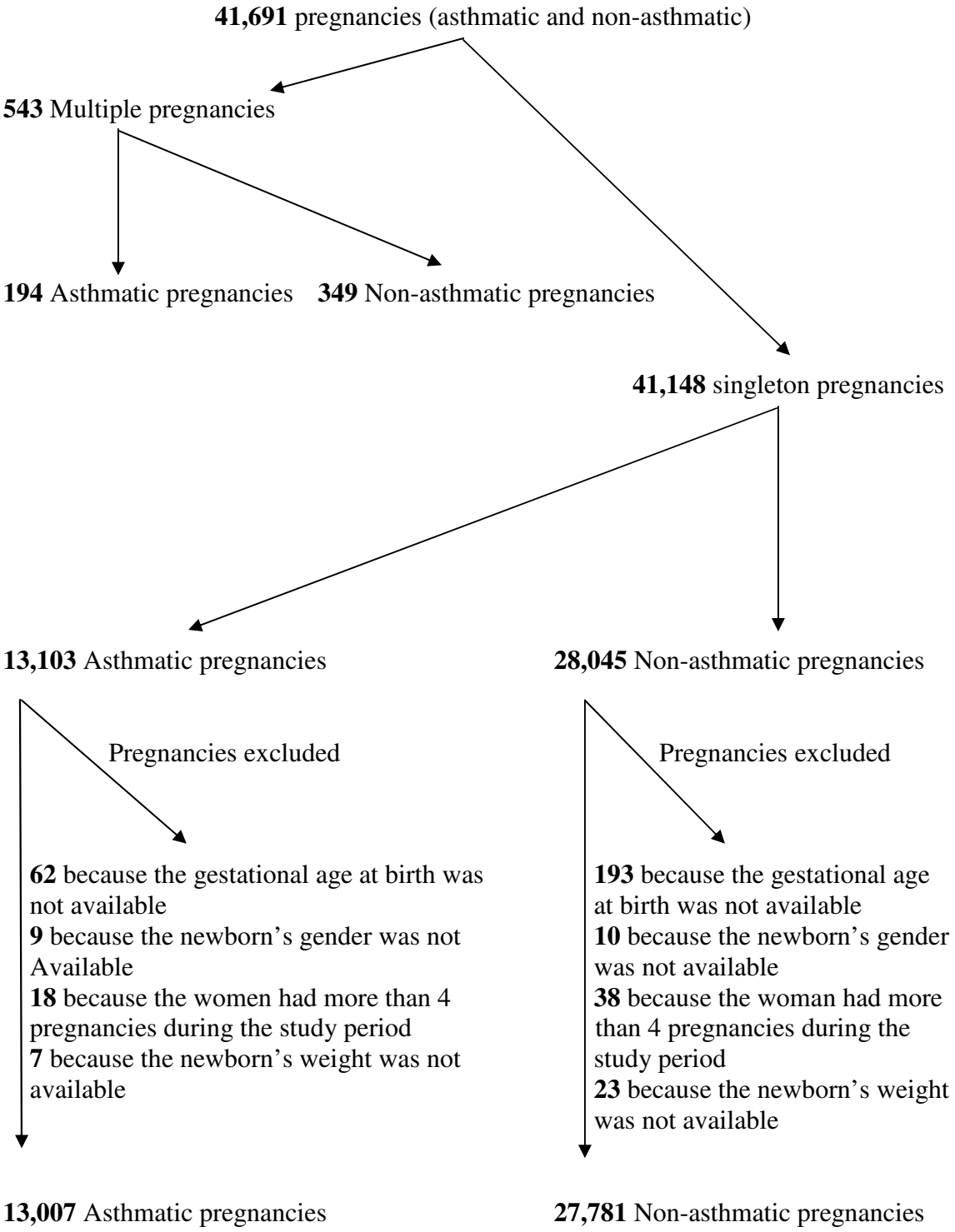
b. newborn's gender
c. gestational age at birth

Within the RAMQ database women and their children are paired to allow the link between them. A woman can have more than one pregnancy during the study period. 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 gestational age and date of birth of the infant were obtained from the MED-ECHO, RAMQ and ISQ 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.

**Final cohort details**

The original cohort composed of 41,691 pregnancies including 13,297 asthmatic and 28,394 non-asthmatic pregnancies. The final cohort includes 13,007 asthmatic and 27,781 non-asthmatic pregnancies after the exclusion criteria were applied (see Figure 2. for more details).

**Figure 2.** Summary of final cohorts of asthmatic and non-asthmatic pregnancies



## 4.4. Two-Stage Sampling

A two-stage sampling cohort design was used for the three last studies (see table 5.). This design was appropriate for these studies because some of the important risk factors of adverse perinatal outcomes such as maternal cigarette smoking and maternal weight gain during pregnancy were not available through administrative databases. However, we did not use this design for the second study because we could obtain the necessary data on confounding variables through administrative databases.

### 4.4.1. Sub-cohort of selected pregnant women, second stage of sampling

At the second stage of sampling, we used the balance sampling strategy to improve the statistical power (184, 185). A maximum of two pregnancies per woman were selected at this stage of sampling to avoid overloading women with more than two questionnaires. Selected women should be aged 18 years old or more at the beginning of their pregnancy to be eligible for the second stage of sampling due to ethical considerations (we were not allowed to contact women aged under 18 years).

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 (184, 190). This strategy decrease 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 (184).

First, we constructed the cross table of exposure-outcome based on pregnancies included in the first stage of sampling (see Table 7. for more details).

**Table 7. Distribution of adverse perinatal outcomes per maternal asthma status at the first stage of sampling (N), the number of pregnancies selected per each exposure-outcome category (*n*) and the number of pregnancies of women who answered to the questionnaire (n)**

| Level of asthma severity and control | SGA | | | | Non SGA | | | |
|---|---|---|---|---|---|---|---|---|
| | Preterm birth | | Non- Preterm birth | | Preterm birth | | Non- Preterm birth | |
| | LBW | Non-LBW | LBW | Non-LBW | LBW | Non-LBW | LBW | Non-LBW |
| **Adequately controlled mild asthmatic** | [1]N=77<br>[2]***n=77***<br>[3]n=28 | ------- | N=190<br>***n=190***<br>n=80 | N=638<br>***n=638***<br>n=239 | N=265<br>***n=265***<br>n=89 | N=305<br>***n=305***<br>n=112 | N=10<br>***n=10***<br>n=4 | N=5269<br>*n=419*<br>n=172 |
| **Poorly controlled mild asthmatic** | N=9<br>***n=9***<br>n=1 | ------- | N=44<br>***n=44***<br>n=10 | N=147<br>***n=147***<br>n=58 | N=58<br>***n=58***<br>n=18 | N=64<br>***n=64***<br>n=20 | N=1<br>***n=1***<br>n=1 | N=1043<br>*n=419*<br>n=171 |
| **Non-asthmatic** | N=144<br>***n=144***<br>n=45 | ------- | N=515<br>***n=515***<br>n=153 | N=2030<br>*n=419*<br>n=132 | N=643<br>*n=419*<br>n=162 | N=825<br>*n=419*<br>n=139 | N=25<br>***n=25***<br>n=8 | N=2195<br>*n=419*<br>n=167 |
| **Adequately controlled moderate to severe asthmatic** | ------ | ------- | N=3<br>***n=3***<br>------- | N=6<br>***n=6***<br>n=1 | N=3<br>***n=3***<br>------- | N=1<br>***n=1***<br>------- | N=1<br>***n=1***<br>------- | N=30<br>***n=30***<br>n=15 |
| **Poorly controlled moderate to severe asthmatic** | N=10<br>***n=10***<br>n=6 | ------- | N=38<br>***n=38***<br>n=13 | N=113<br>***n=113***<br>n=54 | N=35<br>***n=35***<br>n=12 | N=41<br>***n=41***<br>n=9 | N=1<br>***n=1***<br>------- | N=719<br>*n=419*<br>n=161 |

[1]N=Distribution of pregnancies of the first stage of sampling
[2]*n*=Distribution of pregnancies selected for the second stage of sampling
[3]n= Distribution of pregnancies of women who answered to the questionnaire

To select women at the second stage of sampling, we exhaustively sampled all pregnancies with the exposure (i.e. women with moderate to severe or poorly controlled asthma) and outcomes under study (i.e. SGA infant, preterm delivery or LBW infant). The total number of pregnancies selected in this way was 2,774 ($n_{total}$***=2,774***) (see Table 7. for more details). Then, we sampled an equal number of pregnancies per each exposure-outcome category from the remaining cells. In total, we selected 2,933 pregnancies, to achieve the total number of 5,707 pregnancies that we were allowed to send the questionnaires. Thus, we selected an equal number of 419 pregnancies per cell from 7 remaining cells ($n_{total}$*=2,933*) (see Table 7. for more details).

### 4.4.2. Sample constructed based on RAMQ data

As described in the previous section, we first selected 5,324 women (5,707 pregnancies) from the cohort of pregnant women and newborns (first stage of sampling). Then, we sent their encrypted NAM to the RAMQ in order to obtain women's current address. RAMQ provided us with the current postal addresses and spoken language of only 5,021 women (303 addresses were unknown to the RAMQ). The final sample included 5,384 pregnancies which corresponded to 3,168 asthmatic and 2,216 non-asthmatic pregnancies (see Table 8. for more details).

**Table 8. Details regarding the sample of selected women at the second stage of sampling and final sample constructed after receiving RAMQ data**

| | Date | N of women | N of pregnancy | N of asthmatic pregnancies | N of women with 1 child | N of women with 2 children |
|---|---|---|---|---|---|---|
| **Sending Encrypted NAM of selected women to the RAMQ** | 14 December 2006 | 5,324 | 5,707 | 3,347 | 4,941 | 383 |
| **Receiving women's addresses from RAMQ (final cohort)** | 16 January 2007 | 5,021* | 5,384 | 3,168 | 4,658 | 363 |

*303 addresses were unknown to the RAMQ

### 4.4.3. Mailing procedure

During the first phase of mailing, we sent 4,658 questionnaires (see appendix A) to women with one live delivery during the study period. 4,143 questionnaires were in French and 515 were in English. The remaining questionnaires were sent to 363 women who had two live births during the study period. Among them 327 spoke French and 36 spoke English. About two months later, during the second phase of mailing, a total of 3,555 questionnaires were sent as a reminder to women who did not answer to the first questionnaire (see Table 9. for more details).

Of the 5,384 sent questionnaires, we received 2,119 completed questionnaires and the notice of move for 314 women. The Ascii & Élite Services Informatiques seized 2,117 questionnaires (2 questionnaires were removed because they were not lisible). The questionnaires' data were recorded in a computerized database, using a double-checking entry method to improve the data quality. After reviewing the recorded data, 37 questionnaires were removed mostly because of the errors found in them. The data of 2080 questionnaires were kept and used for our second stage analyses. These questionnaires corresponded to 806 and 1,274 pregnancies from non-asthmatic and asthmatic women (see Table 9. for more details).

**Table 9. Summary of two phases of mailing; Questionnaires sent and received**

| | **First phase of mailing** | **Second phase of mailing** |
|---|---|---|
| **Date** | 2 March 2007 | 16 May 2007 |
| **N of women** | 5,021 | 3,328 |
| **N of pregnancy (questionnaires sent)** | 5,384 | 3,555 |
| **N of women with 1 child** | 4,658 | 3,098 |
| **N of women with 2 children** | 363 | 230 |
| **N of questionnaire received** | 1,571[1] | 571[2] |
| **N of questionnaires seized by Elite Services** | 1,570 | 547 |
| **Questionnaires retained for our cohort of 2nd stage** | 1543[3] | 537[4] |

[1]One questionnaire was deleted and not seized by firm because of non consistency of the answers
[2] 19 were the double, 1 was torn and 3 was received after the end of the study
[3]27 questionnaires were deleted after reviewing the data
[4]10 questionnaires were deleted after reviewing the data

## 4.5. Outcomes definition

### 4.5.1. Small for gestational age

To construct a Canadian valid fetal growth reference, Kramer et al. have developed a gender-specific reference of birth weight for gestational age based on all births contained in the linked files of live birth and infant death occurring in the provinces and territories of the Canada (with the exception of Ontario) born between 1994-1996 (191). The results of their study was a tabular presentation of means, standard deviations, and the 3rd, 5th, 10th, 50th (median), 90th, 95th, and 97th percentiles of birth weight (g) for gestational age, for males and female singleton (191).

In our studies, SGA was defined as a birth weight below the 10th percentile for gestational age and gender, (the conventional SGA cutoff) (191). This definition is based on new Canadian standards and considers the Canadian growth pattern in its definition. Algorithms based on data obtained from the MED-ECHO database or from the Birth and death registry (ISQ) were used to measure the birth weight and gestational age at birth. Vilain et al. evaluated the validity of gestational age at birth and birth weight recorded in administrative databases of Quebec using patient medical charts as the gold standard among 726 asthmatic pregnant women who delivered in 1990-2000 (192). They found that these variables are highly valid with Pearson correlation coefficients of 0.972 for gestational age at birth and 0.979 for birth weight (192).

### 4.5.2. Preterm birth

Preterm birth was defined as a birth before completing 37 weeks of gestation. In the MED-ECHO and ISQ databases, the gestational age at birth was reported as the completed gestational weeks. According to the algorithm that was constructed to measure the gestational age, we compared the gestational age recorded at the databases and we

kept the value that was the more frequent. In case of missing values or inconsistencies, the following algorithm was used to determine the gestational age: 1) If the gestational age was recorded in the MED-ECHO-Mother (mother data) database then this value was retained; 2) If the gestational age was missing at the MED-ECHO-Mother and recorded at ISQ-Infant (infant's data) then the ISQ value was retained; and 3) If the gestational age was missing at the MED- ECHO-Mother and ISQ-Infant, the value recorded at MED-ECHO-Infant (infant's data) was retained. If the gestational age was not recorded in any of the three databases, the pregnancy was excluded.

### 4.5.3. Low birth weight

LBW was defined as birth weight lower than 2,500g. For each infant, we had data relating to his birth weight in three databases; ISQ, MED-ECHO-Infant and MED-ECHO-Mother. In case of inconsistency between values in three databases, the following priority algorithm was used to determine the birth weight: 1) ISQ; 2) MED-ECHO-Infant and 3) MED- ECHO-Mother. If the birth weight was not recorded in any of the three databases, the pregnancy was excluded.

### 4.5.4. Moderate to severe maternal asthma exacerbations

Based upon the criteria used in the Canadian Asthma Consensus Guidelines, asthma exacerbations were defined as a short ($\leq$ 14 days) course of oral corticosteroids dispensed by a pharmacy, an emergency department (ED) visit for asthma, or a hospitalization for asthma (39). To avoid the overestimation of the number of exacerbations, all the aforementioned events occurring within a 15-day period accounted for one exacerbation. Asthma diagnosis recorded in the RAMQ databases have been formally evaluated and found to be valid (193).

### 4.5.5. ICS or SABA use during pregnancy

The mean daily dose of ICS and the mean weekly dose of SABA during pregnancy, calculated using data from the RAMQ's database using validated algorithms based upon the name, dose, formulation and quantity of the dispensed medication, duration of the prescription and time intervals between renewals (189, 194). The equivalencies of the mean daily dose of ICS into beclomethasone-CFC were calculated using the equivalency table published in the Canadian Asthma Consensus Guidelines (39). The equivalencies for SABA were established by the pharmacist collaborating with this research project; for example, one dose of SABA was equivalent to two inhalations of salbutamol from a metered-dose inhaler (100μg/inhalation) (194).

## 4.6. Exposures definition

### 4.6.1. Fetal Gender

The gender of the baby was extracted from the RAMQ database and was checked for consistency with that recorded in the ISQ and MED-ECHO databases. In case of missing values or inconsistencies, the following algorithm was used to determine the gender: 1) If the gender of the baby was recorded in the RAMQ database then this value was retained; 2) If the gender of the baby was missing at the RAMQ and recorded at ISQ then the ISQ value was retained; and 3) If the gender of the baby was missing at the RAMQ and ISQ, the value recorded at MED-ECHO was retained. If the gender of the baby was not recorded in any of the three databases, the pregnancy was excluded. Fetal gender has been formally evaluated and found to be highly valid as compared to the information recorded in the medical chart of the mother with specificity and sensitivity higher than 0.97 (195).

### 4.6.2. Asthma during pregnancy

Asthma during pregnancy is defined as having at least one diagnosis of asthma (ICD-9 code 493, except 493.2 which corresponds to chronic obstructive asthma) and at least one dispensed prescription for an asthma medication (see appendix B for the list of asthma medications) recorded in the RAMQ or MED-ECHO databases either two years before or during the pregnancy.

### 4.6.3. Asthma severity during pregnancy

The level of severity of maternal asthma during pregnancy measured with an index that we had developed and validated in study 1 (196). This index is based on dispensed prescriptions of asthma medications (controller therapies, short-acting $beta_2$-agonists, oral corticosteroids) as well as acute care for asthma (ED visits and hospitalizations) recorded in the RAMQ and MED-ECHO databases. This severity index covers three categories, mild, moderate, and severe, and is based upon the definitions provided in the Canadian Asthma Consensus Guidelines (26). Details of the severity index are provided in the first article included in the present thesis.

### 4.6.4. Asthma control during pregnancy

Asthma control during pregnancy was measured with an index that we had developed and validated in study 1 (196). This control index is based upon the definition provided in the Canadian Asthma Consensus Guidelines (26). Two levels of asthma control during pregnancy were defined based on the average number of doses of short-acting $beta_2$-agonists (SABA) per week and the presence of markers of moderate-to-severe asthma exacerbations – a filled prescription of oral corticosteroids (less than 14 days), an ED visit for asthma, or a hospitalization for asthma (197). Patients were considered adequately controlled if they had no marker of moderate-to-severe asthma exacerbation and no more than three doses of SABA per week for mild asthma and ten

doses of SABA per week for moderate and severe asthma (196). Details of the index of control are provided in the first article included in the present thesis.

## 4.7. Confounding variables

The large number of confounding variables that we adjusted for are known risk factors for outcomes under study. For the complete list of risk factors, see the literature review section.

### 4.7.1. Risk factors for maternal asthma exacerbation during pregnancy

**Variables retrieved from the administrative databases**

*Asthma-related variables*

- Respiratory specialist visit during pregnancy (yes/no),
- ICS use during pregnancy (yes/no),
- Pre-conception asthma severity (mild, moderate, severe) (details of the index of severity are provided in the first article included in the present thesis),
- Pre-conception asthma control (adequately controlled, poorly controlled) (details of the index of control are provided in the first article included in the present thesis).

### 4.7.2. Risk factors for adverse perinatal outcomes

**Variables retrieved from the administrative databases**

*Maternal characteristics*

- Age at the beginning of the pregnancy (recorded in the RAMQ database) (< 18, 18-34, > 34 years),
- Receiving social assistance benefits in the year before or during pregnancy (recorded in the RAMQ database) (yes/no),
- Urban residency at delivery (recorded in the RAMQ or ISQ databases) (yes/no),
- Being primiparous (recorded in the RAMQ database) (yes/no).

*Pregnancy-related variables*

- 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 (algorithm developed by Amélie Forget, Marie-Josée Martel and Dr. Lucie Blais based on data recorded in the RAMQ databases) (yes/no) (for details of algorithm, see appendix C),
- Pregnancy-induced hypertension (algorithm developed by Amélie Forget, Marie-Josée Martel and Dr. Lucie Blais based on data recorded in the RAMQ databases) (yes/no) (for details of algorithm, see appendix D),
- A gynecologist or obstetrician visit during pregnancy (recorded in the RAMQ or MED-ECHO databases) (yes/no),
- Number of prenatal visits (recorded in the RAMQ database) (≤5, 6-14, >14).

*Maternal co-morbidities*

- Diabetes mellitus (recorded in the RAMQ database) (yes/no) and
- Chronic hypertension (recorded in the RAMQ database) (yes/no).

**Variables retrieved from the questionnaire**

*Maternal characteristics*

- Maternal education (highest level reached: elementary school, high school, college & University),
- Annual family income during pregnancy (<$18,000, $18,000-$46,000, >$46,000)
- Birth weight (<2.5, 2.5-5, >5 kg)

*Pregnancy-related variables*

- 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
- Another preterm or LBW infant prior to the current delivery (yes/no)

*Life style habits*

- Maternal and paternal cigarette smoking during pregnancy (yes/no) and
- Maternal alcohol consumption during pregnancy (yes/no).

## 4.8. Statistical analysis

Details regarding statistical analysis used in the five studies were described in the five articles included in the present thesis. A summary of these analyses was also reported in Table 5. in the beginning of the Method section. In all studies, the unit of analysis was the pregnancy and not the woman, since a non negligible proportion of women contributed to two or more pregnancies in the analysis.

In study 1, using the Student's *t*- test for independent samples, two-tailed pair wise comparisons were performed to compare the differences in mean $FEV_1$ (percent predicted value) between the levels of asthma severity and control within the sample of patients recruited at the asthma clinics (for more details, see first article included in the present thesis).

In study 2, logistic regression models were used to obtain crude and adjusted odds ratios of maternal asthma exacerbation during the whole pregnancy and for each trimester separately comparing pregnancies of female with male fetus (for more details, see second article included in the present thesis).

In the three last studies, descriptive statistics were used to report the characteristics of the exposed and non-exposed women included in the cohort (first stage of sampling) and for those selected at the second stage of sampling. Also, descriptive statistics were used to calculate the distribution of the variables retrieved from administrative databases for women who answered the questionnaire and women who did not. 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. In these studies, we calculated the prevalence of the study outcomes (i.e. SGA infant, preterm births and LBW infant) for exposed and non-exposed women, separately for the first and second stage of sampling. Crude and adjusted odds ratios (OR) for the study outcomes comparing exposed to non- exposed women were then estimated for the first stage of sampling using Generalized Estimation Equation (GEE) models (198).

### 4.8.1. GEE for Logistic Regression

The method of GEE, introduced by Liang and Zeger in 1986, is a generalization of generalized linear models (GLM) to analyze correlated data (198, 199). The data sets for the GEE models can come from longitudinal studies with repeated measurements or multilevel studies (clustering). The GEE analysis is implemented with a repeated statement in which the clustering information regarding the correlation of successive measurements is specified (200).

The GEE using a logit link estimates the same model as the standard logistic regression (dichotomous dependent variable), however, unlike in logistic regression, GEE logit allows for dependence within clusters, such as in longitudinal data (201). The GEE logit can estimate the effect of independent variables, including the main exposure and confounding variables, on dichotomous outcomes such as the presence or the absence of SGA, 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.

In the three last studies, the GEE models were used to take into account the fact that some women had two pregnancies or more during the study period (i.e. correlation between the different pregnancies of a woman) and all potential confounders. The models were first constructed using the subjects drawn from the second stage of sampling for which we have information on all variables, including confounding variables collected with the questionnaire. The estimates was then adjusted to reflect the sampling fractions and the first stage of sampling (202, 203). 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 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).

### 4.8.2. Two stage sampling analyses

To study the association between exposure and outcomes in the three last studies, we used the methodology proposed by Collet et al (184). 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 (184).

In the three last studies, the stage 2 confounding variables (obtained from questionnaires) was combined with that already available for stage 1 (obtained from administrative databases) to obtain confounder-adjusted estimates and its confidence interval (184). First, we obtained adjusted OR estimates for each outcome based on

pregnancies selected at the second stage of sampling by the GEE models that adjusted for confounding variables collected at the first (administrative databases) and second (questionnaire) stages of sampling. 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 (see Figure 3. For more details) (184).

**Figure 3.** Summary of statistical methods of Collet et al. to correct the logistic regression estimate and its variance for two-stage sampling design (184)

**Stage 1**

| Outcome / Exposure | Yes | No |
|---|---|---|
| **Yes** | $N_1$ | $N_2$ |
| **No** | $N_3$ | $N_4$ |

**Stage 2**

| Outcome / Exposure | Yes | No |
|---|---|---|
| **Yes** | $n_1$ | $n_2$ |
| **No** | $n_3$ | $n_4$ |

**Sampling fraction of stage 2**

$\mathbf{S_1} = n_1/N_1$

$\mathbf{S_2} = n_2/N_2$

$\mathbf{S_3} = n_3/N_3$

$\mathbf{S_4} = n_4/N_4$

Where N represents the number of observations at the first stage of sampling and n represents the number of observations at the second stage of sampling.

**Correction of logistic regression estimate and its variance (184)**

$$\beta_{corrected} = \beta_{adjusted} + \ln (N_1 N_4 n_2 n_3 / N_2 N_3 n_1 n_4)$$

OR

$\beta_{corrected} = \beta_{adjusted} + \ln S_2 + \ln S_3 - \ln S_1 - \ln S_4$

$\text{Var } \beta_{corrected} = \text{Var } \beta_{adjusted} - [\ (\text{Sum } 1/n) - (\text{Sum } 1/N)\ ]$

## 4.9. Ethic consideration

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* prior to proceeding with the studies.

# 5. Results

The five papers presenting the results of five studies included in this thesis are the contents of the chapter 5:

1. **Development and Validation of Database Indexes of Asthma Severity and Control**
   Faranak Firoozi, Catherine Lemière, Marie-France Beauchesne, Amélie Forget, Lucie Blais
   **Published** in *Thorax* 2007; 62:581-7.

2. **Effect of Fetal Gender on Maternal Asthma Exacerbations in Pregnant Asthmatic Women**
   Faranak Firoozi, Francine M Ducharme, Catherine Lemière, Marie-France Beauchesne, Sylvie Perreault, Amélie Forget, Lucie Blais
   **Published** in *Respiratory Medicine*, 2009; Volume 103, Issue 1, Pages 144-151.

3. **Impact of maternal asthma on perinatal outcomes**
   Faranak Firoozi, Catherine Lemière, Marie-France Beauchesne, Sylvie Perreault, Amélie Forget, Lucie Blais,
   **Submitted** to *ERJ*

4. **Effect of maternal moderate to severe asthma on perinatal outcomes**
   Faranak Firoozi, Catherine Lemière, Francine M Ducharme, Marie-France Beauchesne, Sylvie Perreault, Anick Bérard, Ema Ferreira, Amélie Forget, Lucie Blais,
   **Submitted** to *Respiratory Medicine*

5. **Does Good Asthma Control in Pregnant Women Annihilate the Risk of Perinatal Outcomes?**
   Faranak Firoozi, Catherine Lemière, Marie-France Beauchesne, Francine M Ducharme, Sylvie Perreault, Amélie Forget, Lucie Blais,
   **Submitted** to *Annals of Allergy, Asthma & Immunology*

## 5.1. First article

**Titre:** Development and Validation of Database Indexes of Asthma Severity and Control

**Published** in Thorax 2007; 62:581-7.

Included in the present thesis by the permission of the co-authors and editors.

**The role of each author**

Faranak Firoozi, Catherine Lemière, Marie-France Beauchesne, and Lucie Blais participated in the design of the study. The same authors and Amélie Forget conducted the study. The statistical analyses were done by Faranak Firoozi, and Amélie Forget. The article was written by Faranak Firoozi and all the authors revised this article.

# Development and validation of database indexes of asthma severity and control

Faranak Firoozi, Catherine Lemière, Marie-France Beauchesne, Amélie Forget and Lucie Blais

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**Development and Validation of Database Indexes of Asthma Severity and Control**

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**Abstract**

**Background**

The use of administrative databases to perform epidemiologic studies in the field of asthma has expanded in recent years. The unavailability of clinical parameters to measure the level of asthma severity and control is considered as one of the major limitations of database studies. The aim of our study was to develop and validate two database indexes, one to measure the control of asthma and the other to measure asthma severity.

**Methods**

The database index of asthma severity (3 categories) and the database index of asthma control (2 categories) were derived from the definitions found in the Canadian Asthma Consensus Guidelines and were based upon dispensed prescriptions (controller therapies, short-acting $beta_2$-agonists, oral corticosteroids) as well as the medical services for asthma (ED visits and hospitalizations), which were recorded in two large administrative databases from the Canadian province of Quebec; *Régie de l'Assurance Maladie du Quebec* (RAMQ) and MED-ECHO over 12 months. For validation purposes, 71 asthmatic patients were randomly selected from two asthma clinics and their spirometric lung function measures were retrieved from their medical chart. For these patients, we also obtained data on prescriptions and medical services from the aforementioned databases. The database indexes of asthma severity and control were validated against the pulmonary function test results using t-tests. Our database indexes of asthma severity and control were also applied in the Quebec cohort which was comprised of 139 283 person-years of follow-up of asthmatic patients who were selected from RAMQ and MED-ECHO databases between January 1st 1997 and December 31st 2004.

**Results**

According to the database indexes, 49.3%, 29.6% and 21.1% of patients recruited at the asthma clinics were found to respectively have mild, moderate and severe asthma while 53.5% were found to have controlled asthma. The mean predicted value of forced expiratory volume in one second ($FEV_1$) ranged from 89.8% for mild asthma to 61.5% for severe asthma (p-value<0.001) whereas the range from controlled to uncontrolled asthma was 89.5% to 67.3% (p-value<0.0001). The ratio of the $FEV_1$ to the forced vital capacity

($FEV_1$/FVC ratio) was measured for 56 patients and ranged from 75.8% for mild asthma to 61.8% for severe asthma (p-value of pairwise comparison=0.030) whereas the range from controlled to uncontrolled asthma was 75.3% to 65.7% (p-value =0.0009).

**Conclusions**

In the absence of clinical data, our database indexes could be used in epidemiologic studies using administrative databases that record data on dispensed prescriptions and medical services for asthma to reasonably assess the severity and control of asthma.

**Keywords:** Asthma severity, asthma control, administrative databases, validity

## Introduction

The accurate classification of asthma severity and control is a definite challenge since they are conceptually related and some of the criteria used in their assessment overlap. The optimal control of asthma has been defined by the presence of minimal respiratory symptoms, no activity limitation, normal respiratory function, and absence of the need for rescue bronchodilator (39, 43, 118). Current series of criteria in the assessment of the control of asthma were established by the Global Initiative for Asthma (GINA) and the Canadian Asthma Consensus Guidelines (39, 43) and they include daytime and nocturnal symptoms, the occurrence of asthma exacerbations, the need for inhaled short-acting beta$_2$-agonists (SABA), physical activity, absenteeism, and forced expiratory volume in one second ($FEV_1$) or peak expiratory flow (PEF) values.

Different methods are advocated by various guidelines in the assessment of asthma severity (39, 43, 118). The GINA guidelines as well as the US National Asthma Education and Prevention Program Consensus guidelines relative to the assessment of severity rely upon the evaluation of the disease's inherent symptoms in the patient and his or hers lung function before instigating any treatment relative to the assessment of its severity (43, 118). However, the Canadian Asthma Consensus Guidelines assess asthma severity once the treatment has been instigated and rely upon a combination of factors, many of which overlap with measures of symptom control. These include pulmonary function tests, the treatment required to obtain asthma control, the history of hospital admissions, and life-threatening asthma attacks (39).

The use of administrative health databases to perform epidemiologic studies in the field of asthma has widely expanded in recent years (204-206). The unavailability of clinical parameters to measure the level of asthma severity and control has always been considered as one of the limitations of using administrative databases in this field of research. Therefore, the development of an index of asthma severity and an index of asthma control based on electronically-available data seems necessary. Indeed, it is important to be able to measure asthma severity and control separately since, for example, in some studies it might be required to evaluate the control of asthma following

a new treatment strategy, while in other studies it might be required to measure the level of severity of asthma before starting a new treatment.

Several validated multidimensional indexes of asthma control and severity have been developed for use in epidemiologic and clinical studies (207-212). These indexes are usually based on one or several factors that are considered clinically important in the assessment of asthma severity and control; for example, frequency, duration & intensity of symptoms, and pulmonary function tests. However and to the best of our knowledge, none of these indexes rely solely on data that are usually recorded in administrative health databases.

Therefore, the aim of this study was to develop and validate two database indexes, one to measure the control of asthma and the other to measure the severity of asthma in currently treated asthmatics using information related to dispensed asthma medications and medical services, which were obtained from the administrative healthcare databases of the Canadian province of Quebec.

## Method

### Source of Data

Our database indexes of asthma severity and control are based upon variables that were recorded in two administrative databases of the Province of Quebec, Canada; *Régie de l'Assurance-Maladie du Québec* (RAMQ) and MED-ECHO. The RAMQ database provides information on medical services dispensed to all residents of Quebec and on prescribed medications provided to residents covered by the RAMQ's Prescription Drug Insurance Plan. Approximately 43% of the population of Quebec are covered by the RAMQ's Prescription Drug Insurance Plan and mainly include the elderly, social aid recipients since 1980, and about 1.7 million new adherents since 1997, mostly workers and their families who in socio-economic terms, represent the average population (186). The RAMQ's Prescription Drug Insurance Plan database provides information on dispensed medications (date of filling, name, dose, quantity, dosage form and duration of the prescription) while the RAMQ's Medical Services database provides information on

medical services dispensed in a clinic, an emergency department (ED), or a hospital (date, and diagnosis coded with ICD-9). The RAMQ's databases also provide socio-demographic data such as age, gender, social aid status and where relevant, date of death. Data recorded in the RAMQ's Prescription Drug Insurance database and asthma diagnoses recorded in the RAMQ's Medical Services database have been formally evaluated and deemed valid (188, 213).

The MED-ECHO database is a provincial database, which records data on acute care hospitalizations and covers all residents of Quebec. For each hospitalization, we obtained data on primary & up to 15 secondary discharge diagnoses, date of admission, duration of hospital stay as well as the treatments received during the hospitalization (213).

**Description of the Database Indexes of Asthma Severity and Control**

The database indexes of asthma severity and control that we developed are based upon the criteria detailed in the Canadian Asthma Consensus Guidelines for the assessment of the severity and control of asthmatic patients, who are already taking anti-asthmatic medications (39). Three levels of asthma severity and two levels of asthma control were defined over a 12-month period based upon the following: the average daily dose of inhaled corticosteroid (ICS) in beclomethasone-chloroflurocarbon (CFC) equivalent, the use of additional controller therapies defined as at least 6 filled prescriptions of inhaled long-acting beta$_2$-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 (197). The details of the two database indexes are presented in Table 1. Briefly, the mild asthma category corresponds to doses of ICS ranging from 0 to 500 µg per day for patients who do not have an additional controller therapy, and doses of ICS ranging from 0 to 250 µg per day for patients who have an additional controller therapy. Moreover, in order to be classified in this mild category, a patient must not have had a marker of a moderate to severe asthma exacerbation and nor have used more than an average of 3 doses of SABA per week during the 12-month period under study. The

moderate asthma category corresponds to ICS doses larger than 500 μg per day for patients who do not have an additional controller therapy, and doses larger than 250 μg per day for patients who have an additional controller therapy, except for patients with high use of SABA and moderate to severe asthma exacerbations. Severe asthma is mainly characterized by doses of ICS that are greater than 1000 μg per day, except for patients with both markers of uncontrolled asthma; for example, patients who are taking more than 10 doses of SABA per week and a marker for a moderate to severe asthma exacerbation.

Patients were considered as controlled if they had no marker for moderate to severe asthma exacerbation and were taking no more than 3 doses of SABA per week for mild asthma and 10 doses of SABA per week for moderate and severe asthma.

Using data from the RAMQ's databases, an algorithm was developed to calculate the mean daily dose of ICS and the mean weekly dose of SABA on the basis of prescription renewals, quantity of medication dispensed, duration of the prescription, and time intervals between renewals (189, 214). In order to calculate the equivalence of the mean daily dose of ICS into beclomethasone-CFC, we used the equivalency table published in the Canadian Asthma Consensus Guidelines (39). The pharmacist established the equivalencies for SABA; for example, one dose of SABA was equivalent to two inhalations of salbutamol from a metered-dose inhaler (100μg/inhalation) (215).

**Validation of the Database Indexes of Asthma Severity and Control**

In order to validate the database indexes of asthma severity and control, we applied the indexes of severity and control that we had created to the administrative database information available for a sample of asthmatic patients recruited in two different asthma clinics. We then compared the actual mean pulmonary function test values for these patients across the classification categories to determine if pulmonary function corresponded with our indexes of severity and control. All the patients had a confirmed diagnosis of asthma with no diagnosis of a chronic obstructive pulmonary disease (COPD). From the Montreal Chest Institute, we recruited 56 asthmatic patients between

May 2001 and February 2002. The most recent measures of $FEV_1$ (predicted value) and $FEV_1$/FVC were retrieved from their medical charts. From the asthma clinic of the Hôpital du Sacré-Coeur de Montréal (HSCM), we recruited 15 asthmatic patients between January 2003 and March 2003. The patients' most recent value of $FEV_1$ was obtained from their medical chart. However and for this set of patients, the $FEV_1$/FVC values were unavailable.

The information concerning the use of prescribed medications, the history of hospitalizations, and ED visits for asthma was obtained from the RAMQ and MED-ECHO databases for all patients. The data obtained from the RAMQ and MED-ECHO provided us with the necessary information to classify the severity and control of each patient using our database indexes.

**Application of the Database Indexes of Asthma Severity and Control**

Our database indexes of asthma severity and control were applied in a cohort of asthmatic patients from Quebec in order to obtain the distribution of asthma severity and control as classified by our indexes at a population level. The Quebec cohort was comprised of 139 283 person-years of follow-up of asthmatic patients aged from 14 to 44 years old, who were selected from RAMQ and MED-ECHO databases between January 1$^{st}$ 1997 and December 31$^{st}$ 2004. In order to be included in the cohort, patients had to have been diagnosed with asthma at least once between January 1$^{st}$ 1997 and December 31$^{st}$ 2004. Furthermore, their medications must have been covered by the RAMQ Prescription Drug Insurance Plan for at least one year prior and one year after the index date; which was defined as, the coming January 1$^{st}$ after having been diagnosed with asthma. Based upon the aforementioned conditions, we found all the non-overlapping one-year periods that fulfilled our criteria. Therefore, a patient could contribute more than one episode of one year of follow-up into the cohort. The level of asthma severity and control was evaluated for each one-year period included in the cohort using our database indexes. The RAMQ provided us with the data on dispensed medications, medical services, and socio-demographic data while MED-ECHO provided us with data related to hospitalizations for all patients included in the cohort.

**Comparison of the Distribution of Asthma Severity Levels across Different Study Populations and Severity Indexes**

For validation purposes, the distribution of the severity levels found in the Quebec cohort using our database index of severity was compared to the distribution of the severity levels found in different populations worldwide using other severity indexes. The first severity index with which we compared ours was based on the GINA classification of symptoms and $FEV_1$ that was then applied in a sample of 4,333 asthmatic patients (51% female) aged from 16-45 years old, who had been examined by clinical specialists in private practice throughout France (216). The second severity index with which we compared ours was also based on the measure of asthma severity reported in the GINA guidelines – frequency of symptoms – and was applied to a sample of 2509 asthmatic patients identified in the Asthma Insights and Reality (AIR) survey conducted in the United States (217). The third severity index with which we compared ours was based on patient's reported daily medication usage and was applied to a sample of 1279 asthmatic patients, who had completed a telephone questionnaire and had filled inhaler prescriptions in community pharmacies in Ontario, Canada (207).

**Statistical Analysis**

The differences in mean $FEV_1$ (percent predicted value) were compared between the levels of asthma severity and control within the sample of patients recruited at the asthma clinics. The comparison of the $FEV_1$/FVC ratio between levels of asthma severity and control was only completed for patients recruited at the Montreal Chest Institute. We also performed the same analysis stratified by age: $\leq$ 45 and > 45 years old. Using the Student's *t*- test for independent samples, two-tailed pair wise comparisons were performed and p-values smaller than 0.05 were considered significant. No adjustment for multiple testing was done. The distribution of the levels of asthma severity and control using our database indexes was estimated among the Quebec cohort of asthmatic patients. All statistical analyses were performed using SAS version 8.02.

**Ethical consideration**

The link between the data obtained from the RAMQ database, the MED-ECHO database and the medical chart was approved by the *Commission d'accès à l'information* du

Québec. This research project was approved by the ethic board of the Hôpital du Sacré-Cœur de Montréal and the Montreal Chest Institute.

## Results

*Study Population Characteristics*

In Table 2, we present the characteristics of the populations under study; i.e. patients from the asthma clinics and the Quebec cohort. Mean age of 139 283 person-years of asthmatic patients of the Quebec cohort was lower (30.3 yrs) than those from the asthma clinics (49.0 yrs). Patients from the asthma clinics used more ICS than those from the Quebec cohort (71.8% vs. 63.0%). The use of more than 10 doses of SABA per week was higher among patients from the asthma clinics than patients in the Quebec cohort (26.8% vs. 24.0%). In the sample of patients from the asthma clinics, 11.3% had at least one ED visit and 4.2% had at least one hospitalization for asthma over a 12-month period, while these figures were 18.1% and 6.2% for patients in the cohort.

*Application of our Database Index of Asthma Severity and Control*

In Table 3, we present the distribution of the levels of asthma severity and control based on our database indexes for the sample of 71 patients from the asthma clinics and the Quebec cohort. In patients from the asthma clinics, we found that 35 (49.3%), 21 (29.6 %), and 15 (21.1%) of them respectively had mild, moderate and severe asthma. Overall, in the asthma clinic sample, we classified 46.5% of patients as having poorly controlled asthma, and we found that of those we classified as mild, moderate or severe, 20.0 %, 57.1 % and 93.3 % respectively had poorly controlled asthma by our criteria. When this sample was stratified by age, we observed that younger patients were more likely to have mild asthma and controlled asthma than older patients. In the Quebec cohort, we found that 63.4%, 22.6%, and 14.0% respectively had mild, moderate and severe asthma and that 54.5 % had uncontrolled asthma.

*Validation of the Database Indexes of Asthma Severity and Control*

In Table 4, we present the results of the analyses performed to validate our database indexes against pulmonary function measures. With respect to the index of severity, among the 71 patients from the asthma clinics, the mean predicted value of $FEV_1$ was

found to be 89.8% for mild, 74.1 % for moderate, and 61.5 % for severe asthma. All pair wise comparisons of $FEV_1$ between the three levels of asthma severity were found to be statistically significant (P-value=0.0066 for moderate vs. mild, < 0.0001 for severe vs. mild and 0.0333 for severe vs. moderate respectively). In the sample of 56 patients from the Montreal Chest Institute, the $FEV_1$/FVC ratio ranged from 75.8 % for mild to 61.8 % for severe asthma. Pair wise comparisons of the ratio were found to be statistically significant when mild patients were compared to moderate (P-value=0.0056) and severe patients (P-value=0.0302), but the observed difference between moderate and severe patients was not found to be statistically significant (P-value=0.2049).

With respect to the index of control, we found that patients we classified as well controlled had a mean $FEV_1$ of 89.5 % and a $FEV_1$/FVC ratio of 75.3% while corresponding figures were 67.3 % and 65.7 % for those we classified as poorly controlled, using different subsets of clinic patients for the $FEV_1$ and $FEV_1$/FVC comparisons as described in methods. Differences between controlled and uncontrolled patients were found to be statistically significant (P-value=< 0.0001 for differences in $FEV_1$ and P-value=0.0009 for differences in $FEV_1$/FVC ratio).

In Table 5, we present the results of the analysis comparing $FEV_1$ across the different levels of asthma severity and control stratified by age (≤ 45 and > 45 years old). Statistically significant differences were observed for all pair wise comparisons between severity levels except for the moderate to severe comparison in younger patients and the mild to moderate comparison in the older patients. Differences in $FEV_1$ between controlled and uncontrolled patients were found to be statistically significant in both subgroups.

*Comparison of the Distribution of Asthma Severity among Different Populations*

The comparison of the distribution of asthma severity in the Quebec cohort assessed against our database index and the distribution of asthma severity in other populations worldwide assessed against other severity indexes is presented in Table 6. In the Quebec cohort, the distribution of severity levels was 63%, 23%, and 14% for mild, moderate and severe respectively. This distribution was similar to those of two of the three study

populations: between 59% and 66% for mild, around 22% for moderate, and between 13% and 19% for severe. However, the Ontarian population had quite a different distribution of severity with 28% of mild, 49% of moderate, and 23% of severe patients.

**Discussion**

We have demonstrated that our database indexes of asthma severity and control correlate well with lung function measures, such as the $FEV_1$ and the $FEV_1$/FVC ratio, which are reliable indices reflecting asthma severity and control (39, 118). Moreover, the application of our database severity index to a population-based cohort of asthmatic patients led to a distribution of asthma severity similar to that found with other severity indexes applied in two of the three comparison samples.

The need to adjust for the level of asthma severity and control to minimize confounding is encountered in most of the epidemiologic studies carried out in the field of asthma. However, these disease characteristics are not always easy to measure because of the lack of clinical data, especially in the case of studies performed with administrative databases. To the best of our knowledge, our indexes of asthma severity and control are the first of this kind to be entirely based on data available from health administrative databases, and it will be possible to use them in future epidemiologic studies in the field of asthma.

Differences in the distribution of asthma severity and control found in the populations that we studied are worthy of comments. Patients followed in asthma clinics of tertiary healthcare centers are more likely to have moderate or severe asthma and are more properly controlled due to the fact that they benefit from follow up from respiratory specialists. Our results do reflect this since the percentage of controlled patients in each level of severity was greater among the patients from the asthma clinics than those from the Quebec cohort. Moreover, we found that patients treated in the asthma clinics more commonly suffer from severe asthma, according to our criteria, than patients in the Quebec cohort.

Our results also demonstrated that the distribution of the level of asthma severity obtained by applying our database index to the Quebec cohort was close to the

distribution found within two of the three asthma severity indexes based upon the symptoms and pulmonary function that have been applied in other populations, France and the United States (216, 217). The distribution of severity found in the study conducted in Ontario was different from the one found in the Quebec cohort and this might be due to differences in how we define severity. According to the Ontarian index, patients were classified as having mild asthma if they had only bronchodilators to treat asthma, and they were classified as having moderate or severe asthma when they were prescribed ICS, while in our index of severity, patients with a low dose of ICS could be classified as having mild asthma. Indeed, the other two indexes resemble more than the Ontarian one to our indexes.

This study has some limitations that should be kept in mind when interpreting the results. First, with our database indexes it could, in some cases, be difficult to precisely distinguish the difference between asthma severity and control since the markers of exacerbations and use of rescue medications were used in both definitions. The overlap in the definitions of asthma severity and control could also result in an asthma that is more uncontrolled among severe patients than mild ones. This overlap could also have played a role in the validation against $FEV_1$ and $FEV_1$/FVC measures for the asthma clinic sample since these pulmonary function values may reflect both severity and control. However, the difficulty in making a clear distinction between asthma severity and control is not specific to our indexes and is also encountered in clinical practice (218). Second, our database index of severity was developed to measure disease severity among patients already treated for asthma and is at least in part based on the level of medication needed to attain control (39). Moreover, our indexes were validated among patients likely to be compliant to their treatment, because they were under the care of respiratory specialists. However and with respect to general clinical practice, a proportion of patients will not attain control and this might reduce the capacity of our severity index to accurately classify patients. Third, our database index of control cannot detect short-term changes since it is based on medications and health care services dispensed over a one-year period. Fourth, another limit of our study concerns the use of a single measure of lung function to validate the indexes. Only one measure of lung function might not be optimal to assess a parameter that can fluctuate over time. Fifth, patients included in the Quebec

cohort are not fully representative of the population since they do not include patients with private drug insurance plans and tend to over represent patients with a low to moderate socio-economic status.

This study has also several strengths. The database indexes can assess asthma severity and control among patients already treated for asthma and are at least in part based on the use of acute care for asthma, which are well-recognized markers of asthma severity and lack of control (39). Moreover, the data obtained from the Prescription Drug Insurance database regarding the mean dose of ICS and SABA are considered to be good reflection of usual dosage (219-223). Our indexes were validated against pulmonary function measures that are well established measures of asthma severity and control. Moreover, the age-stratified analysis allowed us to assess the validity of our database index across different age groups. Finally, the distribution of asthma severity found with our database index when applied to the Quebec cohort was found to be comparable to the distribution of severity assessed with other indexes applied to two of the three different population samples we used for comparison.

In conclusion, we have demonstrated that the database indexes that we developed based on dispensed asthma medications and medical services are valid to the extent we could test this and could adequately classify currently treated asthmatic patients into categories of severity and control. In the absence of clinical data, our database indexes could be used in epidemiologic studies using administrative databases to reasonably assess the severity and control of asthma among adult patients and thus, improve the quality of database studies in the field of asthma. Further research will be needed to confirm these findings, and to adapt and validate these database indexes for use in special populations including pregnant women, the elderly or pediatric patients.

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## COMPETING INTERESTS

The authors declare no competing interests for the submitted manuscript.

**Table 1. Definition of the Database Indexes of Asthma Severity and Control 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** | | | | |
| **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 |

*ICS daily dose in beclomethasone-CFC equivalent over a 12-month period
** Other controller therapy: at least 6 prescriptions of long-acting beta$_2$-agonist (LABA), theophylline or leukotriene-receptor antagonists dispensed over a 12-month period
**+**SABA**:** Average number of inhaled short-acting beta$_2$-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.

**Table 2. Characteristics of the Study Population over a 12-Month Period**

| | **Patients selected from the asthma clinics (n=71)** | ***Quebec cohort of asthmatic patients (n=139 283 person-years)** |
|---|---|---|
| **Mean age ± s.d, years** | 49.0 ± 17.8 | 30.3 ± 8.7 |
| **Female, %** | 62.9 | 62.2 |
| ****ICS use, µg per day, %** | | |
| **0** | 28.2 | 37.0 |
| **1-250** | 15.5 | 34.3 |
| **251-500** | 18.3 | 11.9 |
| **501-1000** | 18.3 | 10.9 |
| **> 1000** | 19.7 | 5.9 |
| **+SABA, number of doses per week, %** | | |
| **0-3** | 57.7 | 53.6 |
| **4-10** | 15.5 | 22.4 |
| **> 10** | 26.8 | 24.0 |
| **++LABA use, %** | 54.9 | 23.4 |
| **Theophyline use, %** | 9.9 | 2.3 |
| **Anti-leukoterienes use, %** | 21.1 | 7.7 |
| **Oral corticosteroids use, %** | 31.0 | 16.5 |
| **Respiratory physician visit, %** | 98.6 | 12.3 |
| **ED care for asthma, %** | 11.3 | 18.1 |
| **Hospital care for asthma, %** | 4.2 | 6.2 |

* On average, patients contributed 2.1 episodes of one year into the cohort. The cohort correspond the asthmatics selected from January 1st 1997 to December 31st 2004

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

**+**SABA**:** Average number of inhaled short-acting $beta_2$-agonist doses per week calculated over a 12-month period

**++**LABA: inhaled long-acting $beta_2$-agonist

**Table 3. Distribution of the Levels of Asthma Severity and Control**

| | All patients from asthma clinics (n=71) | Patients aged 45 ys old or less (n=34) | Patients aged more than 45 ys old (n=37) | Quebec cohort of asthmatic patients (n=139 283 person-years) |
|---|---|---|---|---|
| | Numbers (Percent) | | | |
| **Mild** | 35 (49.3) | 20 (58.8) | 15 (40.5) | 88 250 (63.4) |
| **Controlled** | 28 (80.0) | 17 (85.0) | 11 (73.3) | 57 529 (65.2) |
| **Uncontrolled** | 7 (20.0) | 3 (15.0) | 4 (26.7) | 30 721 (34.8) |
| **Moderate** | 21 (29.6) | 9 (26.5) | 12 (32.4) | 31 552 (22.6) |
| **Controlled** | 9 (42.9) | 4 (44.4) | 5 (41.7) | 5 488 (17.4) |
| **Uncontrolled** | 12 (57.1) | 5 (55.6) | 7 (58.3) | 26 064 (82.6) |
| **Severe** | 15 (21.1) | 5 (14.7) | 10 (27.0) | 19 481 (14.0) |
| **Controlled** | 1 (6.7) | 0 (0.0) | 1 (10.0) | 377 (1.9) |
| **Uncontrolled** | 14 (93.3) | 5 (100.0) | 9 (90.0) | 19 104 (98.1) |
| **Controlled** | 38 (53.5) | 21 (61.8) | 17 (45.9) | 63394 (45.5) |
| **Uncontrolled** | 33 (46.5) | 13 (38.2) | 20 (54.1) | 75889 (54.5) |

**Table 4. Comparison of the Database Indexes of Asthma Severity and Control against Lung Function Measures**

| **Asthma severity N=71** | **Variable** | **N** | **Mean** | **P-value** |
|---|---|---|---|---|
| **Mild** | $FEV_1$ predicted % | 35 | 89.8 | |
| **Moderate** | $FEV_1$ predicted % | 21 | 74.1 | *0.0066 |
| **Severe** | $FEV_1$ predicted % | 15 | 61.5 | **< 0.0001 |
| | | | | ***0.0333 |
| **N=56** | | | | |
| **Mild** | $FEV_1$ /FVC | 30 | 75.8 | |
| **Moderate** | $FEV_1$ /FVC | 18 | 68.1 | *0.0056 |
| **Severe** | $FEV_1$ /FVC | 8 | 61.8 | **0.0302 |
| | | | | ***0.2049 |

| **Asthma control N=71** | | | | |
|---|---|---|---|---|
| **Controlled** | $FEV_1$ predicted % | 38 | 89.5 | |
| **Uncontrolled** | $FEV_1$ predicted % | 33 | 67.3 | < 0.0001 |
| **N=56** | | | | |
| **Controlled** | $FEV_1$ /FVC | 33 | 75.3 | |
| **Uncontrolled** | $FEV_1$ /FVC | 23 | 65.7 | 0.0009 |

***** Moderate vs. Mild

**Severe vs. Mild

*** Severe vs. Moderate

**Table 5. Age Stratified Comparison of the Database Indexes of Asthma Severity and Control and $FEV_1$ Measures**

| Asthma severity | Variable | N | Mean | P-value |
|---|---|---|---|---|
| **≤ 45 ys old N=34** | | | | |
| **Mild** | $FEV_1$ predicted % | 20 | 95.2 | |
| **Moderate** | $FEV_1$ predicted % | 9 | 68.7 | *0.0016 |
| **Severe** | $FEV_1$ predicted % | 5 | 61.1 | **0.0018 |
| | | | | ***0.5193 |
| **>45 ys old N=37** | | | | |
| **Mild** | $FEV_1$ predicted % | 15 | 82.6 | |
| **Moderate** | $FEV_1$ predicted % | 12 | 78.1 | *0.5523 |
| **Severe** | $FEV_1$ predicted % | 10 | 61.6 | **0.0261 |
| | | | | ***0.0146 |

| Asthma control | | | | |
|---|---|---|---|---|
| **≤ 45 ys old N=34** | | | | |
| **Controlled** | $FEV_1$ predicted % | 21 | 92.0 | |
| **Uncontrolled** | $FEV_1$ predicted % | 13 | 68.9 | 0.0044 |
| **>45 ys old N=37** | | | | |
| **Controlled** | $FEV_1$ predicted % | 17 | 86.4 | |
| **Uncontrolled** | $FEV_1$ predicted % | 20 | 66.2 | 0.0041 |

***** Moderate vs. Mild
**Severe vs. Mild
*** Severe vs. Moderate

**Table 6. Comparison of the Distribution of Asthma Severity Based on Different Indexes Applied to Different Populations**

| | ***Cohort of asthmatic patients, Quebec, Canada (n=139 283 person-years)** | ****Cohort of asthmatic patients, France (20) (n= 4333)** | *****AIR America survey, United States (21) (n=2509)** | ******Cohort of asthmatic patients, Ontario, Canada (7) (n=1279)** |
|---|---|---|---|---|
| | **Percent** | | | |
| **Mild asthma** | 63 | 66 | 59 | 28 |
| **Moderate asthma** | 23 | 21 | 22 | 49 |
| **Severe asthma** | 14 | 13 | 19 | 23 |

*****The index is based on dispensed medications and medical services for asthma
******The index is based on symptoms and $FEV_1$.
*******The index is based on symptoms and the current state of asthma management.
********The index is based on reported daily medication use.

## 5.2. Second article

**Titre:** Effect of Fetal Gender on Maternal Asthma Exacerbations in Pregnant Asthmatic Women

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**The role of each author**

Faranak Firoozi, Francine M Ducharme, Catherine Lemière, Marie-France Beauchesne, Sylvie Perreault and Lucie Blais participated in the design of the study. Faranak Firoozi, Lucie Blais and Amélie Forget conducted the study. The statistical analyses were done by Faranak Firoozi, and Amélie Forget. The article was written by Faranak Firoozi and all the authors revised this article.

# EFFECT OF FETAL GENDER ON MATERNAL ASTHMA EXACERBATIONS IN PREGNANT ASTHMATIC WOMEN

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**Summary**

Recent studies have found that asthmatic women pregnant with a female fetus reported more symptoms and had slightly lower lung function than women pregnant with a male fetus. In order to further investigate this association, we studied the effect of fetal sex on maternal asthma exacerbations and the use of asthma medications during pregnancy. A large cohort of pregnant asthmatic women and their babies was reconstructed between 1990 and 2002 from the linkage of three administrative databases of the Canadian province of Quebec. Asthma exacerbations were defined as a filled prescription of oral corticosteroids, an emergency department visit, or a hospitalization for asthma. Women pregnant with a female fetus were compared to women with a male fetus with respect to their rate of asthma exacerbation, their weekly doses of inhaled short-acting $beta_2$-agonists (SABA), and their daily dose of inhaled corticosteroids (ICS) during pregnancy. Logistic and linear regression models were used to obtain effect measures adjusted for several potential confounders such as, asthma severity and control prior to pregnancy. The cohort included 5529 pregnancies with a single female fetus and 5728 pregnancies with a single male fetus. No significant differences were found between mothers of a female and male fetus as to the occurrence of asthma exacerbations (adjusted rate ratio=1.02; 95% CI: 0.92 to 1.14), the daily dose of ICS (adjusted mean difference (AMD): 2.46 μg; 95% CI: -4.01 to 8.93), and the weekly dose of SABA (AMD: 0.004 dose; 95% CI: -0.23 to 0.24). Based on the results, we conclude that fetal gender is unlikely to affect maternal asthma during pregnancy to the point where acute care and medications are more often required among women pregnant with a female fetus.

**Introduction:**

The prevalence of asthma among pregnant women varies between 4 and 7% and it is known as one of the most frequent chronic diseases encountered during pregnancy (3-5, 7, 47). The course of asthma may remain unchanged, improve or worsen during pregnancy and usually returns to the pre-pregnancy state within three months after delivery (77, 78). The control of asthma during pregnancy can be influenced by several factors, namely physiologic hormonal changes that are triggered during pregnancy (78).

A few studies have suggested that a pregnant woman's asthma may worsen when carrying a female fetus (8-11). In a review of case series, (11) three mothers who had been followed in successive pregnancies reported more asthma attacks when pregnant with a female fetus than when they were carrying a male fetus. Moreover and in comparison with mothers carrying a male fetus, Beecroft et al. observed that pregnant asthmatic mothers with a female fetus had reported an increase in asthma symptoms (8) while Dodds et al. (9) observed that they had an increased usage of steroids. More recently, Kwon et al. assessed the association between fetal gender and airway lability among pregnant asthmatic women and found a 10 percent significant reduction in peak expiratory flow rate (PEF) among mothers with a female fetus. Conversely, Baibergenova et al. did not find any significant association between fetal gender and visits to an emergency department (ED) for asthma during pregnancy (84). Among hypotheses put forward to explain the mechanisms behind the association between fetal gender and maternal asthma control during pregnancy, the one related to the regulation of placental glucocorticoid and immune response in asthmatic pregnancies seems the most plausible (8, 10, 84). Indeed, Clifton and Murphy and their research teams have reported that female fetus alters maternal asthma during pregnancy by upregulating maternal inflammatory pathways (85-87, 224) and thus if asthma-associated inflammatory pathways are not treated with inhaled steroids during pregnancy, the mother could suffer asthma exacerbation.

Although studies have reported possible associations between fetal gender and maternal asthma control during pregnancy, methodological issues such as the measure of the outcome and the absence of statistical inference, as well as the questionable clinical

significance of some of the results make it difficult to conclude with a reasonable degree of certainty that women pregnant with a female fetus are more likely to have uncontrolled asthma. Using Canadian administrative databases, we planned a large cohort study to further evaluate the effect of fetal gender on the risk of uncontrolled maternal asthma through the study of exacerbations, use of inhaled short-acting beta$_2$-agonists (SABA) and inhaled corticosteroids (ICS) during pregnancy.

## Materials and Methods

### Source of data

The data for our study came from three administrative databases of the Canadian province of Québec; 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). RAMQ databases provide information on the medical services dispensed to all residents of Québec and on prescribed medications filled in community pharmacies by residents covered by the RAMQ's Public Drug Insurance Plan. Approximately 43% of the population of Quebec is covered by the RAMQ Public Drug Insurance Plan, most notably the elderly and social aid beneficiaries since 1980 and since 1997, 1.7 million of new adherents, mainly workers and their families who have no access to a private drug insurance plan (186). The RAMQ's Prescription Drug Insurance database provides information on dispensed medications – i.e. date of filling, name, dose, quantity, dosage form and duration of the prescription – while the RAMQ's Medical Services database provides information on medical services dispensed in a clinic, an emergency department (ED) or a hospital (date, diagnosis coded with ICD-9, where the service was dispensed, etc.). The RAMQ databases also provide socio-demographic data such as age, gender, social assistance status and where relevant, date of death. Data recorded in the RAMQ Prescription Drug Insurance database and asthma diagnoses recorded in the RAMQ Medical Services database have been formally evaluated and found to be valid (187, 188). The MED-ECHO database is a provincial database which records data on acute care hospitalizations and covers all residents of Quebec. For each hospitalization, data on primary and up to 15 secondary discharge diagnoses, date of entry, duration of hospitalization, and treatments received during the hospitalization are available (187). The *Fichier des événements*

*démographiques* provides information on all births and still births in the province of Québec.

**Study Design and Population**

A large cohort of pregnant asthmatic women and their babies was reconstructed between 1990 and 2002 from the linkage of the three administrative databases. Pregnant women were identified using diagnostic and act codes related to prenatal care, pregnancy complications, abortions and deliveries (189). To be included in our cohort, a women should have had: 1) one or more singleton pregnancy ending in a delivery (life birth or still birth) between January 1, 1990 and December 31, 2002; 2) being between 13-50 years of age at conception; 3) in the two years prior to, or during pregnancy, a diagnosis of asthma ($9^{th}$ international classification of diseases (ICD-9) code 493, except 493.2 which relates to COPD disease) and one or more prescription for an asthma medication (ICS , oral corticosteroids, SABA, long-acting $beta_2$-agonists (LABA), theophyllines, leukotriene-receptor antagonists, inhaled short-acting anticholinergic, cromoglycate or nedocromil) dispensed; 4) coverage with the RAMQ drug insurance plan for at least one year prior to, and throughout the duration of the pregnancy; and 5) no other pregnancy of more than 14 weeks in the year prior to conception. The length of gestation was obtained mainly from the MED-ECHO database, which was calculated based upon the date of the last menstruation. To assess the date of conception, we subtracted the length of gestation from the date of the delivery. The unit of analysis was the pregnancy; a woman could contribute more than one pregnancy in the cohort.

For each included woman, data from RAMQ and MED-ECHO were obtained for the two years preceding conception, and the duration of the pregnancy. This mother-child cohort was then linked with the *Fichier des événements démographiques* databases to obtain information on socio demographic variables for the mothers and the newborns.

**Fetal Gender**

The gender of the baby was extracted from the RAMQ database and was checked for consistency with that recorded in the ISQ and MED-ECHO databases. In case of missing values or inconsistencies, the following algorithm was used to determine the gender: 1)

If the gender of the baby was recorded in the RAMQ database then this value was retained; 2) If the gender of the baby was missing at the RAMQ and recorded at ISQ then the ISQ value was retained; and 3) If the gender of the baby was missing at the RAMQ and ISQ, the value recorded at MED-ECHO was retained. If the gender of the baby was not recorded in any of the three databases, the pregnancy was excluded. Fetal gender has been formally evaluated and found to be highly valid as compared to the information recorded in the medical chart of the mother with specificity and sensitivity higher than 0.97 (195).

**Primary and Secondary Outcomes**

The primary outcome was asthma exacerbations during pregnancy. Based upon the criteria used in the Canadian Asthma Consensus Guidelines, asthma exacerbations were defined as a short ($\leq$ 14 days) course of oral corticosteroids dispensed by a pharmacy, an ED visit for asthma, or a hospitalization for asthma (39). To avoid the overestimation of the number of exacerbations, all the aforementioned events occurring within a 15-day period accounted for one exacerbation. Asthma diagnosis recorded in the RAMQ databases have been formally evaluated and found to be valid (193).

The secondary outcomes included the mean daily dose of ICS and the mean weekly dose of SABA during pregnancy, calculated using data from the RAMQ's database using validated algorithms based upon the name, dose, formulation and quantity of the dispensed medication, duration of the prescription and time intervals between renewals (189, 194). The equivalencies of the mean daily dose of ICS into beclomethasone-CFC were calculated using the equivalency table published in the Canadian Asthma Consensus Guidelines (39). The equivalencies for SABA were established by a pharmacist (MFB); for example, one dose of SABA was equivalent to two inhalations of salbutamol from a metered-dose inhaler (100µg/inhalation) (194).

**Data Analysis**

Descriptive statistics were calculated by fetal gender for socio-demographic variables, antiasthmatic medication use, and health care services use for asthma during pregnancy.

Crude rates of maternal asthma exacerbation during the whole pregnancy and for each trimester separately were compared between pregnancies of a female and male fetus.

Logistic regression models were used to obtain odds ratios of exacerbation adjusted for several potential confounders including socio-demographic variables such as, maternal age at conception (< 18, 18-34, > 34 years), social assistance benefits one year before or during pregnancy (yes/no)**,** area of residency at delivery (rural or urban)**;** pregnancy-related variables such as being primiparous (yes/no), high risk pregnancy (yes/no), gestational diabetes (yes/no), diabetes mellitus (yes/no), pregnancy-induced hypertension (yes/no), chronic hypertension (yes/no), gynecologist or obstetrician visit during pregnancy (yes/no), number of prenatal visits (≤5, 6-14, >14); as well as asthma-related variables such as, a respiratory specialist visit during pregnancy (yes/no), ICS use during pregnancy (yes/no), and asthma severity and control prior to pregnancy. Asthma severity and control were measured with validated database indexes that we developed based on medication use and need for acute care for asthma (196). We used a backward elimination strategy to find final logistic regression models including covariates that changed the odds ratio associated with the gender of the baby by at least 10% and covariates that were found to be statistically associated with the outcome. Adjusted effects of fetal gender were estimated for the whole pregnancy and for each trimester separately. The first, second and third trimesters of pregnancy were defined as periods between 0 to 14 weeks of pregnancy, 15 to 28 weeks of pregnancy and from 29$^{th}$ week up to the end of pregnancy, respectively.

Adjusted differences in the mean daily dose of ICS and mean weekly dose of SABA were estimated between all pregnancies of female and male fetuses using linear regression models and the aforementioned potential confounders. Adjusted differences were estimated for the whole pregnancy and for each trimester separately.

One secondary analysis was performed on the primary outcome. For this analysis, we selected the women who had at least two pregnancies during the study period with fetuses of different sex. For these women, the rate of asthma exacerbations during the whole

pregnancy was compared between pregnancies of a female and male fetus using logistic regression models. All statistical analyses were performed using SAS version 8.02.

## Results

*Study Population Characteristics*

Among the 13 040 pregnancies included in the cohort of asthmatic women, 1774 were excluded because there was another pregnancy of 14 weeks or more in the year prior to conception and 9 pregnancies were excluded because the baby's gender was unknown. The final cohort included 11 257 singleton pregnancies with 5529 female (49.1 %) and 5728 male (50.9 %) fetuses. The rate of concordance for fetal gender between the three databases was 99%.

In Table 1, we present the socio demographic and pregnancy related characteristics of the study women, by fetal gender. The female and male fetus groups showed comparable characteristics. In Table 2, we present the asthma related characteristics in the year before conception and during pregnancy, by fetal gender. All characteristics were distributed similarly among female and male fetus pregnancies for these two periods.

*Maternal Asthma Exacerbation during Pregnancy by Fetal Gender*

In Table 3, we present the proportion of women who had at least one asthma exacerbation within each trimester separately and during the entire pregnancy, by fetal gender. During the first trimester, 6.9% and 6.8% of women carrying a female and male fetus had at least one asthma exacerbation, respectively. In the second trimester, this proportion remained unchanged for the female fetus group, but increased modestly to 7.1% for the male fetus group. During the third trimester, the rate of maternal asthma exacerbations decreased to 4.0% and 3.7% for mothers of female and male fetus, respectively. The final logistic regression models showed no statistically significant differences in the rate of exacerbation both during the entire pregnancy and for each trimester separately between mothers of female and male fetus after adjusting for all potential confounders listed in the data analysis section (adjusted rate ratio=1.02; 95% CI: 0.92-1.14 for the entire pregnancy).

*Maternal SABA Use by Fetal Gender*

In Table 4, we present the results of the analyses performed to compare the use of SABA between women pregnant with female and male fetuses. The mean doses of SABA used per week in each trimester and during the entire pregnancy were similar in both groups. Moreover, the proportion of women who used at least one dose of SABA per week on average during the entire pregnancy was similar between the groups (62.5% for female and 62.6% for male fetuses). No statistically significant adjusted differences were found between mothers of female and male fetuses as to their use of SABA (adjusted mean difference: 0.004 dose/week; 95% CI: -0.23; 0.24 for the entire pregnancy)

*Maternal ICS Use by Fetal Gender*

In Table 5, we present the results of the analysis comparing the mean daily dose of ICS between women pregnant with female and male fetuses. Similar proportions of women used ICS in each trimester and during the entire pregnancy in both groups (41.6% in female and 41.0% in male fetuses during the entire pregnancy). Moreover, the daily doses of ICS were similar between the groups. No statistically significant adjusted differences were found between mothers of female and male fetuses as to their use of ICS (adjusted mean difference: 2.46 μg/day; 95% CI: -4.01; 8.93 for the entire pregnancy).

*Maternal Asthma Exacerbations in Successive Pregnancies with a Different Fetal Gender*

From the cohort of 11 257 asthmatic pregnant women, we identified 1674 women who had more than one pregnancy during the study period. Among them, 874 had one delivery with a girl and one delivery with a boy during the study period. There was no significant difference in the rate of asthma exacerbations during the entire pregnancy between the male and female fetuses (adjusted rate ratio=1.07; 95% CI: 0.81-1.42).

**Discussion**

In this large cohort study of 11 257 pregnancies of asthmatic women, we detected no significant increase in the rate of maternal asthma exacerbations, the use of ICS and SABA during pregnancy among mothers of female fetus, whether examined between or within mothers.

Our results concord with those of Baibergenova et al. who found no difference in ED visits for asthma between pregnancies of male and female fetuses. This study was based on a large cohort of 109 173 live singleton deliveries reconstructed from a hospital and an ambulatory care administrative database provided by the Canadian Institute for Health Information (CIHI). From this cohort, the investigators first identified all patients who visited an ED during pregnancy and then found that 0.49% and 0.48% of those ED visits were for asthma among women pregnant with a female and a male fetus, respectively (p-value > 0.05). However, these results should be interpreted with caution since the authors did not take into account the number of asthmatic women among pregnancies of male and female fetuses.

On the other hand, our results are not in accordance with those of three other smaller studies that found increased markers of uncontrolled asthma among pregnancies of female fetuses (8-10), but the choice of the outcome and the way it was measured can be put forward to explain the differences between studies. In their blind-controlled prospective study (n=34), Beecroft et al. have found that asthmatic women pregnant with a female fetus reported significantly more shortness of breath (72% vs. 31%), nocturnal awakening (55% vs. 37%), and general asthma symptoms (50% vs. 31%) than women pregnant with a male fetus (8). However, these self-reported asthma symptoms might not necessarily reflect asthma exacerbations. Moreover, Dodds et al. have evaluated steroids use during pregnancy among a sample of 817 pregnant asthmatic women without having specific data on asthma severity or symptoms and found that it was higher among mothers of a female fetus as opposed to a male fetus (20% vs. 14%) (9). This outcome is difficult to interpret since it is unclear whether or not it includes only oral corticosteroids or both inhaled and oral formulations, which in the later case would not necessarily reflect uncontrolled asthma. Moreover, we cannot conclude on the statistical significance of this difference since no statistical inference was reported in the article. Finally, Kwon et al. used a prospective cohort design to study an objective outcome among 702 pregnant women with asthma, i.e. PEF measures. The PEF was assessed at enrolment and at 21, 29, and 37 weeks of gestation. The 10% reported difference in log diurnal variation of

PEF between pregnancies of male and female fetuses reached statistical significance, but we question the clinical significance of the observed difference (10).

Our study must be interpreted in light of the following limitations. First, the obtained data from the administrative databases reflect medication dispensing and might not correspond exactly to medication intake. However, there is no reason to believe that the use of dispensed medications differed between mothers of female and male fetus. Secondly, the outcome was evaluated for either trimesters or the entire pregnancy and this precluded us to identify short-term changes in asthma control. Thirdly, we did not have access to clinical data, such as the frequency of asthma symptoms and lung function measures, and this precluded us to evaluate a milder lack of control that could be perceived by the mother.

Our study has also several strengths. One of the biggest strength is its very large sample size, which provided a high power to detect small differences. Indeed, we had a 80% power to detect a relative difference of 16 % (i.e. RR=1.16) in the rate of asthma exacerbations between pregnancies of female and male fetus. Moreover, the data obtained from the databases allowed us to identify moderate to severe asthma exacerbations requiring medical attention, which is an outcome that objectively reflects an important aggravation of asthma symptoms. In addition, our cohort included mothers with pregnancies with alternate fetal gender allowing us to compare the outcome between pregnancies of female and male fetus of the same mother, eliminating inter-patient variability.

In conclusion, we have shown that fetal gender had no significant impact on the rate of maternal moderate to severe asthma exacerbations, use of rescue medications, and ICS during pregnancy. Fetal gender might have a minor impact on maternal asthma symptoms, but this study provides evidence that these changes are not serious enough to lead to a moderate to severe exacerbation. According to our results, it is not recommended to adjust for fetal gender in epidemiologic studies in the field of asthma and pregnancy. Moreover, our results suggest that fetal gender should not be considered to plan the management of asthma

during pregnancy, and that the management should aim at asthma control regardless of the gender of the fetus.

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**COMPETING INTERESTS**

The authors declare no competing interests for the submitted manuscript.

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**Table 1. Socio demographic and pregnancy related characteristics of study women by fetal gender**

| | Pregnancies of female fetus | Pregnancies of male fetus |
|---|---|---|
| **Numbers** | 5529 | 5728 |
| **Age at conception (years), mean ± s.d** | 25.0 ± 5.6 | 24.9 ± 5.6 |
| ***Social assistance, %** | 78.9 | 78.3 |
| **Urban residency at delivery, %** | 80.7 | 81.3 |
| **Primiparous, %** | 36.9 | 37.3 |
| **High risk pregnancy, %** | 35.6 | 36.3 |
| **Gestational diabetes, %** | 8.1 | 7.6 |
| **Chronic diabetes, %** | 2.3 | 2.7 |
| **Pregnancy induced hypertension, %** | 7.0 | 6.7 |
| **Chronic hypertension, %** | 2.6 | 2.3 |
| **Gynecologist or obstetrician visit during pregnancy, %** | 82.2 | 83.3 |
| **Number of prenatal visits, %** | | |
| **≤ 5** | 15.1 | 14.5 |
| **6-14** | 73.3 | 73.0 |
| **> 14** | 11.7 | 12.5 |
| **Season of delivery, %** | | |
| **Winter** | 24.4 | 23.9 |
| **Spring** | 26.2 | 27.2 |
| **Fall** | 24.0 | 23.9 |
| **Summer** | 25.4 | 25.0 |

*Recipient of social assistance in the year prior or during pregnancy

**Table 2. Asthma related characteristics of study women by fetal gender**

| | In the year before conception | | During pregnancy | |
|---|---|---|---|---|
| | **Pregnancies of female fetus N=5529** | **Pregnancies of male fetus N=5729** | **Pregnancies of female fetus N=5529** | **Pregnancies of male fetus N=5729** |
| ***ICS use (µg per day), %** | | | | |
| **0** | 56.0 | 55.3 | 58.4 | 59.0 |
| **0-500** | 40.3 | 41.3 | 37.6 | 37.6 |
| **500-1000** | 2.6 | 2.4 | 3.0 | 2.2 |
| **> 1000** | 1.1 | 0.9 | 1.0 | 1.2 |
| ****SABA use (number of doses per week), %** | | | | |
| **0** | 33.4 | 32.9 | 37.5 | 37.5 |
| **> 0-3** | 34.9 | 34.8 | 32.4 | 32.8 |
| **> 3** | 31.7 | 32.3 | 30.1 | 29.7 |
| *****LABA use, %** | 2.1 | 1.8 | 1.8 | 1.8 |
| **Leukoteriene-receptor antagonists use, %** | 1.0 | 0.8 | 0.4 | 0.2 |
| **Oral corticosteroids use, %** | 12.1 | 12.1 | 7.5 | 7.7 |
| **≥ 1 respiratory physician visit, %** | 6.0 | 7.0 | 5.9 | 5.9 |
| **≥ 1 ED visit for asthma, %** | 13.5 | 13.3 | 12.6 | 12.4 |
| **≥ 1hospitalisation for asthma, %** | 1.2 | 1.2 | 1.5 | 1.5 |
| ******Asthma severity, %** | | | | |
| **Mild** | 81.5 | 82.1 | 82.2 | 82.3 |
| **Moderate** | 13.4 | 12.6 | 12.7 | 12.3 |
| **Severe** | 5.1 | 5.3 | 5.1 | 5.4 |
| ******Asthma control, %** | | | | |
| **Controlled** | 60.6 | 60.1 | 63.2 | 64.0 |
| **Uncontrolled** | 39.4 | 39.9 | 36.8 | 36.0 |

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

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

***LABA**:* long-acting inhaled $beta_2$ -agonist

****Measured with validated database indexes that we developed based on medication use and need for acute care for asthma (196)

**Table 3. Occurrence of maternal moderate to severe asthma exacerbation in each trimester and during the entire pregnancy, by fetal gender**

| | | N Total | At least one exacerbation n (%) | Crude OR F vs M | Adjusted OR(95% CI) F vs M |
|---|---|---|---|---|---|
| **1st trimester** | **F** | 5519 | 378 (6.9) | 1.00 | 1.01 (0.86 to 1.18)* |
| | **M** | 5721 | 391 (6.8) | | |
| **2nd Trimester** | **F** | 5519 | 381 (6.9) | 0.98 | 0.98 (0.84 to 1.14)** |
| | **M** | 5721 | 408 (7.1) | | |
| **3rd Trimester** | **F** | 5474 | 220 (4.0) | 1.02 | 1.03 (0.85 to 1.24)*** |
| | **M** | 5667 | 211 (3.7) | | |
| **During pregnancy** | **F** | 5519 | 846 (15.3) | 1.02 | 1.02 (0.92 to 1.14)**** |
| | **M** | 5721 | 861 (15.1) | | |

F: female fetus, M: male fetus

*Adjusted for respiratory specialist visit, asthma severity and asthma control in the year before pregnancy and ICS use in the first trimester of pregnancy.

**Adjusted for socioeconomic status, gestational diabetes, respiratory specialist visit, asthma severity in the year before pregnancy, and ICS use in the second trimester of pregnancy.

***Adjusted for gestational diabetes, respiratory specialist visit, asthma severity in the year before pregnancy, ICS use in the third trimester of pregnancy.

****Adjusted for socioeconomic status, respiratory specialist visit during pregnancy, asthma severity and asthma control in the year before pregnancy and ICS use during pregnancy.

**Table 4. Use of SABA during the entire pregnancy and within each trimester, by fetal gender**

| | | N Total | At least one dose per week N (%) | Mean number of doses per week | Crude mean difference F vs M | Adjusted mean difference (95% CI) F vs M |
|---|---|---|---|---|---|---|
| **1st trimester** | **F** | 5529 | 3083 (55.8) | 4.4 | 0.09 | 0.07 (-0.17 to 0.31)* |
| | **M** | 5728 | 3200 (55.9) | 4.3 | | |
| **2nd Trimester** | **F** | 5529 | 3058 (55.3) | 4.6 | 0.03 | - 0.003 (-0.27 to 0.26)** |
| | **M** | 5728 | 3172 (55.4) | 4.5 | | |
| **3rd Trimester** | **F** | 5484 | 2864 (52.2) | 4.5 | -0.02 | -0.06 (-0.34 to 0.22)*** |
| | **M** | 5674 | 2972 (52.4) | 4.5 | | |
| **During pregnancy** | **F** | 5529 | 3456 (62.5) | 4.5 | 0.03 | 0.004 (-0.23 to 0.24)**** |
| | **M** | 5728 | 3583 (62.6) | 4.4 | | |

F: female fetus, M: male fetus

*Adjusted for socioeconomic status, high risk pregnancy, and respiratory specialist visit during the first trimester of pregnancy and asthma severity and asthma control in the year before pregnancy

**Adjusted for socioeconomic status and respiratory specialist visit during the second trimester of pregnancy and asthma severity and asthma control in the year before pregnancy

***Adjusted for socioeconomic status, and respiratory specialist visit during the third trimester of pregnancy, and asthma severity and asthma control in the year before pregnancy

****Adjusted for socioeconomic status, high risk pregnancy, pregnancy induced hypertension and respiratory specialist visit during pregnancy, and asthma severity and asthma control in the year before pregnancy

**Table 5. Use of ICS during the entire pregnancy and within each trimester, by fetal gender**

| | N Total | ICS use N (%) | Mean µg per day | Crude mean difference F vs M | Adjusted mean difference (95% CI) F vs M |
|---|---|---|---|---|---|
| **1st trimester** F | 5529 | 1933 (35.0) | 76.5 | 1.55 | 1.17 (-5.33;7.67)* |
| **M** | 5728 | 1995 (34.8) | 74.9 | | |
| **2nd Trimester** F | 5529 | 1933 (35.0) | 87.1 | 4.36 | 3.63 (-3.82 to 11.09)** |
| **M** | 5728 | 1974 (34.5) | 82.8 | | |
| **3rd Trimester** F | 5484 | 1788 (32.6) | 99.3 | 4.36 | 3.01 (-6.28 to12.30)*** |
| **M** | 5674 | 1855 (32.7) | 94.9 | | |
| **During pregnancy** F | 5529 | 2301 (41.6) | 85.7 | 3.17 | 2.46 (-4.01;8.93)**** |
| **M** | 5728 | 2348 (41.0) | 82.5 | | |

F: female fetus, M: male fetus

*Adjusted for maternal age at conception, area of residency at delivery, chronic diabetes, chronic hypertension, number of prenatal visits during the first trimester of pregnancy, respiratory specialist visit during the first trimester and asthma severity and asthma control in the year before pregnancy,

**Adjusted for maternal age at conception, chronic diabetes, chronic hypertension, number of prenatal visit during the second trimester of pregnancy, respiratory specialist visit during the second trimester and asthma severity in the year before pregnancy

***Adjusted for maternal age at conception, chronic diabetes, chronic hypertension, number of prenatal visit during the third trimester of pregnancy, respiratory specialist visit during the third trimester of pregnancy, and asthma severity in the year before pregnancy

****Adjusted for maternal age at conception, area of residency at delivery, gestational diabetes, chronic diabetes, chronic hypertension, number of prenatal visit during pregnancy, respiratory specialist visit during pregnancy and asthma severity and asthma control in the year before pregnancy

## 5.3. Third article

**Titre**: Impact of maternal asthma on perinatal outcomes

**Submitted** to the ERJ.

Included in the present thesis by the permission of the co-authors.

**The role of each author**

Faranak Firoozi, Catherine Lemière, Marie-France Beauchesne, Sylvie Perreault and Lucie Blais participated in the design of the study. Faranak Firoozi and Lucie Blais conducted the study. The cohort original was constructed by Amélie Forget. The statistical analyses were done by Faranak Firoozi. The article was written by Faranak Firoozi and all the authors revised this article.

**Impact of Maternal Asthma on Perinatal Outcomes**

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**Running title:** Asthma in Pregnancy

**Abstract**

**Background/ Objectives**

The literature presents conflicting results concerning the impact of maternal asthma during pregnancy on perinatal outcomes. We investigated the effect of asthma during pregnancy on 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 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 women's life-style habits 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 pregnancies from asthmatic and non-asthmatic women.

**Results**

The cohort (first stage of sampling) included 13,007 pregnancies from asthmatic women 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.

**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 (3-5, 7, 47). 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 (14, 16, 17, 19, 93, 96, 102, 103). However, some other studies do not confirm these results (7, 15, 20, 90, 92, 98-100, 115).

In a recent meta-analysis, conducted by Murphy and 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 (113). 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) (113).

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. To further investigate the potential effect of asthma during pregnancy on adverse perinatal outcomes including SGA infants, LBW infants, and preterm births, 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 the medical services dispensed to all residents of Quebec and on prescribed medications filled in community pharmacies by residents covered by the RAMQ's Public Drug Insurance Plan. Approximately 43% of the population of Quebec is covered by the RAMQ Public Drug Insurance Plan, most notably the elderly and social assistance beneficiaries since 1980. Furthermore, since the enactment of mandatory drug coverage in 1997, the RAMQ's Public Drug Insurance Plan now provides coverage for an additional 1.7 million adherents, mainly workers and their families who have no access to a group drug insurance plan at work (186). The RAMQ Prescribed Medication 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; including information pertaining to date, diagnosis coded with 9$^{th}$ international classification of diseases (ICD-9), where the service was dispensed, etc. Data recorded in the RAMQ Public Prescribed Medication database and asthma diagnoses recorded in the RAMQ Medical Services database have been formally evaluated and found to be valid (187, 188). The MED-ECHO database is a provincial database which records data on acute care hospitalizations and covers all residents of Quebec (187). 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 (184, 185, 190, 225). 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 1$^{st}$, 1990 and December 31$^{st}$, 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 (189). 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 (184, 190). This strategy oversamples women who had a SGA infant, a LBW infant, or a preterm delivery in order to increase the statistical power (184). 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 (226, 227). 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 (195).

**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) (228), 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) (228) 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) (229). **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 (196). 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 (198). 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 (184). 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.

**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 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.

**Discussion**

We have found that asthma during pregnancy was significantly associated with an increased risk of SGA, LBW and preterm births. One of the possible mechanism causing these adverse outcomes is lack of oxygen to the fetus which can lead to intrauterine growth retardation, preterm birth, or neonatal hypoxia (55, 56).

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 (14, 17, 96). 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 (91, 99, 100). 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 and asthma exacerbation on LBW and preterm births through a meta-analysis using data from three and four studies, respectively (113). 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). For LBW, they observed a significantly 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) (113). The differences between these results and those found in our study 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 (230). 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 (195). 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. 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" (231). 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. Finally, our cohort is not representative enough of women in the higher socio-economic level because it included women receiving social assistance and middle class working women. However, the non representativeness of our cohort would be a threat to external validity only if socio-economic status is an effect modifier for the associations under study. But there is no evidence in the literature suggesting that the impact of maternal asthma or its severity or control on newborns differs in different levels of socio-economic status. In fact, there is literature on the association between asthma severity or control and socio-economic status (232, 233), but it is not reported that the relationship between asthma and perinatal outcomes varies between high and low levels of socio-economic status.

The scientific evidence provided by this study showed that asthmatic women are more at risk of having SGA, LBW and preterm infants than non-asthmatic women. Considering the high prevalence of asthma among pregnant women and the fact that uncontrolled asthma has been associated with adverse perinatal outcomes (91, 99, 102), 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.

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**Conflict of interest**

The authors declare no competing interests for the submitted manuscript.

**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.

## Electronic attachment

**Characteristics of asthmatic and non-asthmatic women who responded to the questionnaire (N=2080) and those who did not respond (N=3304)**

| | Asthmatic women N=3168 | | Non-Asthmatic women N=2216 | |
|---|---|---|---|---|
| | **Responding** | **Non-responding** | **Responding** | **Non-responding** |
| | Numbers (%) | | | |
| | 1,274 (40.2) | 1,894 (59.8) | 806 (36.4) | 1,410 (63.6) |
| **Maternal socio-demographic variables** | | | | |
| Age at beginning of pregnancy (years) | | | | |
| **< 18** | 117 (9.2) | 167 (8.8) | 23 (2.8) | 74 (5.3) |
| **18 - 34** | 1,096 (86.0) | 1,627 (85.9) | 703 (87.2) | 1,196 (84.8) |
| **> 34** | 61 (4.8) | 100 (5.3) | 80 (9.9) | 140 (9.9) |
| **Recipient of social Assistance** | 983 (77.2 ) | 1592 (84.0) | 440 (54.6) | 914 (64.8) |
| **Urban residency at Delivery** | 984 (77.2) | 1586 (83.7) | 577 (71.6) | 1130 (80.1) |
| **Pregnancy related variables** | | | | |
| Primiparous | 517 (40.8) | 625 (33.1) | 355 (44.2) | 518 (36.9) |
| High risk pregnancy | 493 (38.7) | 755 (39.9) | 302 (37.5) | 579 (41.1) |
| Gestational diabetes | 107 (8.4) | 128 (6.8) | 51 (6.3) | 110 (7.8) |
| Pregnancy induced hypertension | 98 (7.7) | 105 (5.5) | 77 (9.6) | 133 (9.4) |
| Gynecologist or obstetrician visit during pregnancy | 1,037 (81.4) | 1,614 (85.2) | 671 (83.3) | 1,208 (85.7) |
| Number of prenatal visits | | | | |
| ≤ 5 | 182 (14.3) | 390 (20.6) | 164 (20.4) | 326 (23.1) |
| 6-14 | 950 (74.6) | 1,331 (70.3) | 599 (74.3) | 991 (70.3) |
| > 14 | 142 (11.2) | 173 (9.1) | 43 (5.3) | 93 (6.6) |
| **Maternal co-morbidities** | | | | |
| Chronic diabetes | 27 (2.1) | 49 (2.6) | 10 (1.2) | 25 (1.8) |
| Chronic hypertension | 31 (2.4) | 46 (2.4) | 27 (3.3) | 30 (2.1) |

**Electronic attachment**

**Final odds ratio of perinatal outcomes comparing asthmatic (n=1,274) and non-asthmatic women (n=806) adjusted for variables derived from the databases and the mailed questionnaire**

| | SGA | LBW | Preterm |
|---|---|---|---|
| | Final adjusted OR (95% CI) | | |
| Asthmatic versus non-asthmatic women | 1.27 (1.14-1.41) | 1.41 (1.22-1.63) | 1.64 (1.46-1.83) |
| Recipient of social assistance | 1.22 (0.98-1.52) | 1.27 (0.99-1.65) | 0.82 (0.65-1.02) |
| Primiparous | 0.78 (0.63-0.95) | 0.63 (0.50-0.80) | ---------- |
| High risk pregnancy | ---------- | 1.74 (1.38-2.19) | 1.84 (1.48-2.28) |
| Pregnancy induced hypertension | 1.59 (1.04-2.43) | 1.95 (1.22-3.13) | ---------- |
| Gynecologist or obstetrician visit during pregnancy | ---------- | 1.51 (1.10-2.07) | 1.62 (1.19-2.19) |
| Number of prenatal visits (>14) | 1.75 (1.19-2.59) | 0.26 (0.16-0.44) | 0.25 (0.16-0.41) |
| Number of prenatal visits (5-14) | 1.35 (1.04-1.74) | 0.58 (0.44-0.77) | 0.53 (0.41-0.69) |
| Chronic hypertension | | 2.10 (1.15-3.83) | ---------- |
| Maternal Weight at birth (<2.5 kg) | 1.41 (1.11-1.79) | 2.13 (1.64-2.78) | ---------- |
| Maternal Weight at birth (=>5.0 kg) | 1.16 (0.51-2.61) | 0.81 (0.31-2.12) | ---------- |
| Maternal Weight gain during pregnancy (>16.0 kg) | 0.71 (0.58-0.87) | 0.63 (0.49-0.80) | 0.92 (0.74-1.15) |
| Maternal Weight gain during pregnancy (<8.0 kg) | 1.00 (0.76-1.32) | 1.92 (1.42-2.61) | 1.76 (1.32-2.34) |
| Maternal BMI pre-pregnancy (>24.9) | 0.85 (0.68-1.06) | 0.66 (0.51-0.86) | ---------- |
| Maternal BMI pre-pregnancy (<18.5) | 1.58 (1.21-2.06) | 1.42 (1.05-1.92) | ---------- |
| Preterm birth prior to the current delivery | 0.36 (0.25-0.52) | ---------- | 2.75 (2.12-3.58) |
| LBW infant prior to the current delivery | 2.90 (2.03-4.14) | 3.55 (2.63-4.81) | ---------- |
| Maternal cigarette smoking | 1.92 (1.57-2.35) | 1.31 (1.04-1.65) | ---------- |

## 5.4. Fourth article

**Titre:** Effect of maternal moderate to severe asthma on perinatal outcomes

**Submitted** to the Respiratory Medicine
Included in the present thesis by the permission of the co-authors.

**The role of each author**

Faranak Firoozi, Catherine Lemière, Francine M Ducharme, Marie-France Beauchesne, Sylvie Perreault Anick Bérard, Ema Ferreira, and Lucie Blais participated in the design of the study. Faranak Firoozi, Lucie Blais and Amélie Forget conducted the study. The statistical analyses were done by Faranak Firoozi, and Amélie Forget. The article was written by Faranak Firoozi and all the authors revised this article.

**Effect of Maternal Moderate to Severe Asthma on Perinatal Outcomes**

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**Key words:** Asthma, pregnancy, infant, databases, two stage sampling

**Abstract**

**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% (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.

## Introduction

The prevalence of asthma among pregnant women is estimated to be between 4 and 7% (3-5, 7, 47). Lack of oxygen to the fetus can lead to intrauterine growth retardation (IUGR), preterm birth or neonatal hypoxia (55, 56, 234). Maternal severe or uncontrolled asthma is potentially dangerous to the fetus since it can induce hypoxia combined with potentially an acute respiratory alkalosis that decrease the placental blood flow (54, 235). Moreover, asthmatic women may have minimal symptoms but still have abnormal pulmonary function tests and potentially impaired fetal oxygenation (57). Indeed, adverse fetal outcomes such as preterm birth and low birth weight have been reported as being more prevalent in pregnant asthmatic women than non-asthmatic ones (14, 16, 17, 19, 103). However, scientific evidence is scarce regarding the impact of asthma severity during pregnancy on these perinatal outcomes.

Although studies have reported associations between severe exacerbations requiring hospitalization during pregnancy and adverse perinatal outcomes (18-20), only a few small studies investigated the association between the level of asthma severity during pregnancy and perinatal outcomes and these studies yielded inconsistent results. Bracken et al found that IUGR was more common among infants of mothers with mild to moderate persistent asthma as compared to those with no symptoms or medication use (99). However, Dombrowski et al. found that the rate of preterm birth (≤ 37 weeks) and SGA did not vary according to asthma severity (100). 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 (22).

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 come to a reasonable conclusion. We undertook a population-based cohort study of 13,007 pregnancies of asthmatic women to further investigate the effect of the severity of asthma during pregnancy on the risk of SGA, LBW, and preterm birth.

## Materials and Methods

### Source of data

Our data came from three administrative databases of the province of Quebec, Canada; the *Régie de l'Assurance Maladie du Quebec* (RAMQ), MED-ECHO, and the *Fichier des événements démographiques* (birth and death registries) managed by the *Institut de la statistique du Québec* (ISQ)). These data were supplemented by mailed questionnaires filled by selected mothers. The RAMQ databases provide information on the medical services and on prescribed medications dispensed to residents covered by the RAMQ's Public Drug Insurance Plan (186). Data recorded in the Prescription database and asthma diagnoses recorded in the Medical Services database have been validated (187, 188). The MED-ECHO database records data on acute care hospitalizations of all Quebec residents (187). The *Fichier des événements démographiques* provides information on all births and stillbirths. Additional information regarding siblings and maternal lifestyles during pregnancy which are not included in the 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 (184, 185, 190, 225). The first stage of sampling corresponds to the cohort formed of singleton pregnancies of asthmatic women ending in a delivery between January 1, 1990 and December 31, 2002. Pregnant women and newborns were identified in the RAMQ database using diagnostic and act codes related to prenatal care, pregnancy complications, and deliveries (189). Moreover, to be included, women must have been between 13-50 years of age at the beginning of their pregnancy, have had an asthma diagnosis (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. 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, using a balance sampling strategy (184, 190). This strategy oversamples women with moderate to severe asthma who had a SGA, a LBW, or a preterm baby in order to increase the statistical power (184). A maximum of two pregnancies per woman were selected at this stage of sampling. For all pregnancies selected at this stage, the RAMQ provided us with the current postal addresses and spoken language of the mother.

The questionnaire was used to obtain information on lifestyles, maternal characteristics, and pregnancy-related variables that are not recorded in the administrative databases. The questionnaire was pre-tested by 40 women 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 3,168 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 Quebec* (CAI). This research project was also approved by the ethic committee of the *Hôpital du Sacré-Cœur de Montréal*.

**Exposure**

The main exposure variable is the severity level of maternal asthma during pregnancy measured with an index that we had previously developed and validated (196, 196). This index is based on dispensed prescriptions of asthma medications as well as acute care for

asthma recorded in the RAMQ and MED-ECHO databases. This severity index is based upon the definitions provided in the Canadian Asthma Consensus Guidelines (26) and was validated with lung function measures such as the FEV1 and the FEV1/FVC ratio. It was found that the index correlates well with these clinical measures. Moreover, the frequency distribution of the levels of asthma severity found in the general cohort of asthmatic patients was compared with the distributions obtained using other severity indexes (based on GINA) applied to different populations. 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 < $10^{th}$ percentile for gestational age and gender, using new Canadian standards (226, 236). Preterm birth was defined as a birth before 37 weeks of gestation while LBW was defined as birth weight < 2,500g. Validated algorithms based on data recorded in the RAMQ, MED-ECHO or ISQ databases were used to measure these variables (192).

**Confounding variables**

**Maternal characteristics** i.e. age at beginning of pregnancy (228), receiving social assistance in the year before or during pregnancy, urban residency at delivery, being primiparous, maternal education, annual family income during pregnancy (228) and birth weight**. Pregnancy-related variables** i.e. high risk pregnancies, gestational diabetes, pregnancy-induced hypertension, gynecologist or obstetrician visit during pregnancy, number of prenatal visits, maternal weight gain during pregnancy, maternal body mass index (BMI) at beginning of pregnancy and another preterm or LBW infant prior to the current delivery (237). **Maternal co-morbidities** i.e. diabetes mellitus, and chronic hypertension. **Lifestyles** i.e. maternal & paternal cigarette smoking during pregnancy and maternal alcohol consumption during pregnancy. All potential confounding variables were included in the models however, only some of them remained in the final reduced model.

**Data Analysis**

Descriptive statistics were used to report the characteristics of the pregnancies included in the first and 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 asthma were first estimated for the first stage of sampling using separate Generalized Estimation Equation (GEE) models. The GEE 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.

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 and second stages of sampling. The best reduced models were found using a backward selection strategy, keeping in the model only confounders or covariates that were significantly associated with the outcome ($p<0.05$).

The final adjusted OR estimates were then obtained by correcting the second stage adjusted OR with the second stage sampling fractions and the OR found at the first stage of sampling using the methodology proposed by Collet et al (184). This methodology provides unbiased estimates of the association under study.

**Results**

At the first stage of sampling, the cohort included 13,007 singleton pregnancies from 9925 asthmatic women. From this cohort, a total of 3,347 pregnancies were selected for the second stage of sampling. The RAMQ provided us with the addresses of 3,152 women which corresponded to 3,168 pregnancies. We received 1,274 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). The high prevalence of cigarette smoking among these women 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. 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 1,274 pregnancies of women who answered to the questionnaires with the characteristics of the 1,894 pregnancies of women who did not answer. Overall, there was not notable difference between the responders and non responders (c.f. electronic attachment for details).

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 adverse perinatal

outcomes is much higher at the second stage of sampling since SGA, LBW and premature infants were oversampled.

In Table 4, we present the first stage and final estimates of the ORs for the three perinatal outcomes. 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, the final estimates showed a 25% non significant increased risk of LBW and no significant increased risk of preterm birth among severe as compared to mild asthmatic mothers (OR=1.25; 95% CI: 0.87-1.80).

**Discussion**

Our results show that severe and moderate asthma during pregnancy were significantly associated with an increased risk of SGA babies as compared to mild asthma. We also found a non significant increase in the risk of LBW babies and no increased risk of preterm delivery among severe and moderate asthmatic women.

Some physiologic hypotheses can explain our results. The effects of chronic oxygen deprivation on the fetus are described by several clinicians and were also confirmed by observation of pregnancies at high altitude and in females with congenital heart diseases (50). Maternal asthma can induce hypoxia combined with respiratory alkalosis that decreases the placental blood flow (54, 238). Lack of oxygen to the fetus and the long-term effect of hypoxemia could affect fetal growth (50, 52, 120). Our results support the findings of Schatz et al who reported a significant association between lower maternal mean $FEV_1$ 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 IUGR) ($p<0.05$), but no increased risk of preterm birth and LBW infants (56). These results and our 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 (61, 98) 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 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 (61, 98). 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 (91, 100, 106).

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 (< 10th 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 (99).

Several studies have evaluated the association between markers of severe asthma and the risk of preterm delivery (20, 22, 56, 61, 91, 98, 99, 106). Only Perlow et al. found a significant increased risk of preterm delivery associated with severe asthma that was defined as the mother being corticosteroid dependent during pregnancy (91). This definition is quite restrictive, identifies the most severe asthmatic and corresponds to only a small proportion of women with severe asthma. The other studies have found no significant association between asthma severity and preterm birth but some of them had a small sample size (20, 99) or suffered from the lack of adjustment from confounding variables, including cigarette smoking during pregnancy (20).

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 (91). 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 during pregnancy (53.3% vs. 20.5%; $p<0.01$) (20). Moreover, 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 (61, 106). 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) (22).

Our study has some limitations. Firstly, 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 (231). Moreover, this bias, if present, could not have affected the outcomes and the main exposure since they were measured from databases data that are routinely and prospectively collected. Secondly, the response rate of the mailed questionnaire was about 40%, a participation bias could be present if women who answered the questionnaire are different from women who did not answer the questionnaire on characteristics that are associated with the outcomes under study. However, it is reassuring to observe that it was not the case. Finally, our cohort is less representative of women in the higher socio-economic level. However, 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.

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 (26). 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 (195). Fourthly, we used an SGA definition which is based on new Canadian standards and considers the Canadian growth pattern in its definition (226, 239). Finally, the two-stage sampling design allowed us to obtain information on some variables that are not recorded in the administrative databases.

In conclusion, our study showed an association between asthma severity during pregnancy and the risk of SGA babies, but no significant association with LBW and preterm birth. These results confirm the need to closely follow pregnant women with markers of severe asthma, being those hospitalized for an exacerbation or needing high doses of inhaled corticosteroids to treat their asthma. Our results need to be confirmed in other settings and populations to reinforce the message to be transmitted to pregnant asthmatic women and healthcare professionals.

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**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** **N=**652 (5.0%) | **Pregnancies of moderate asthmatic women** **N=**1618 (12.4) | **Pregnancies of mild asthmatic women** **N=**10737 (82.6) |
|---|---|---|---|
| | Numbers (%) | | |
| **Maternal characteristics** | | | |
| **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) |
| ***Recipient of social assistance** | 541 (83.0) | 1312 (81.1) | 8493 (79.1) |
| **Urban residency at delivery** | 532 (81.6) | 1287 (79.5) | 8709 (81.1) |
| **Primiparous** | 261 (40.0) | 551 (34.1) | 3418 (31.8) |
| **Pregnancy related variables** | | | |
| **High risk pregnancy** | 264 (40.5) | 585 (36.2) | 3851 (35.9) |
| **Gestational diabetes** | 64 (9.8) | 132 (8.2) | 804 (7.5) |
| **Pregnancy induced hypertension** | 55 (8.4) | 115 (7.1) | 676 (6.3) |
| **Gynecologist or obstetrician visit during pregnancy** | 554 (85.0) | 1349 (83.4) | 8810 (82.1) |
| **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) |
| **Asthma related variables measured during pregnancy** | | | |
| ****ICS use (µg per day)** | | | |
| **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) |
| ****SABA use (number of doses per week)** | | | |
| **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) |
| **Leukoteriene-receptor antagonists use** | 14 (2.2) | 14 (0.9) | 6 (0.1) |
| **Oral corticosteroids use** | 384 (58.9) | 260 (16.1) | 336 (3.1) |
| **≥ 1 respiratory physician visit** | 170 (26.1) | 179 (11.1) | 401 (3.7) |
| **≥ 1 ED visit for asthma** | 457 (70.1) | 444 (27.4) | 710 (6.6) |
| **≥ 1 hospitalization for asthma** | 90 (13.8) | 49 (3.0) | 57 (0.5) |
| **Maternal co-morbidities** | | | |
| **Chronic diabetes** | 14 (2.2) | 56 (3.5) | 244 (2.3) |
| **Chronic hypertension** | 23 (3.5) | 43 (2.7) | 238 (2.2) |

*Social assistance status in the year before pregnancy

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

***SABA: short-acting inhaled beta$_2$-agonist

**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** **N=**82 (6.4%) | **Pregnancies of moderate asthmatic women** **N=**189 (14.8%) | **Pregnancies of mild asthmatic women** **N=**1003 (78.7%) |
|---|---|---|---|
| | Numbers (%) | | |
| **Maternal characteristics** | | | |
| **Maternal education (highest level attained)** | | | |
| Elementary school | 12 (14.6) | 7 (3.7) | 86 (8.6) |
| 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) |
| $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) |
| 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) |
| 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) |
| 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) |
| **Preterm birth prior to the current delivery** | 11 (13.4) | 22 (11.6) | 177 (17.7) |
| Unknown | 0 (0.0) | 2 (1.1) | 7 (0.7) |
| **LBW infant prior to the current delivery** | 6 (7.3) | 23 (12.2) | 163 (16.3) |
| Unknown | 0 (0.0) | 0 (0.0) | 9 (0.9) |
| **Life style habits** | | | |
| **Maternal cigarette smoking during pregnancy** | | | |
| Yes | 55 (67.1) | 109 (57.7) | 641 (63.9) |
| 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) |
| 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) |
| 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** (N=13007) | **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** (N=1274) | **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) |

*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

**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)† | 1.30 (1.13-1.49)† |
| **Final estimates*** ** | Adjusted | 1.48 (1.15-1.91)†† | 1.30 (1.10-1.55)†† |
| **LBW** | | | |
| **1st stage** | Crude | 1.11 (0.85-1.45) | 1.10 (0.92-1.31) |
| | Adjusted | 1.04 (0.80-1.37)‡ | 1.08 (0.90-1.29)‡ |
| **Final estimates*** ** | Adjusted | 1.25 (0.87-1.80)‡‡ | 1.04 (0.81-1.34)‡‡ |
| **Preterm birth** | | | |
| **1st stage** | Crude | 0.94 (0.72-1.23) | 0.84 (0.70-1.01) |
| | Adjusted | 0.90 (0.69-1.18)* | 0.82 (0.68-0.99)* |
| **Final estimates*** ** | Adjusted | 0.93 (0.67-1.29) ** | 0.83 (0.65-1.05) ** |

*** Final estimates obtained by adjusting the second stage estimates with the second stage sampling fractions

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

††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

‡ 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,

‡‡ 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

* 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

** 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

**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 beta$_2$-agonist (LABA), theophylline or leukotriene-receptor antagonists dispensed over a 12-month period
**+**SABA**:** Average number of inhaled short-acting beta$_2$-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.

**Electronic attachment**

**Final odds ratio of perinatal outcomes comparing Severe (n=82) and moderate (n=189) asthmatic to mild asthmatic women (n=1003) adjusted for variables derived from the databases and the mailed questionnaire**

| | SGA | LBW | Preterm |
|---|---|---|---|
| | Final adjusted OR (95% CI) | | |
| Severe asthmatic versus mild asthmatic women | 1.48 (1.15-1.91) | 1.25 (0.87-1.79) | 0.93 (0.67-1.29) |
| Moderate asthmatic versus mild asthmatic women | 1.30 (1.10-1.55) | 1.04 (0.81-1.34) | 0.83 (0.65-1.05) |
| Recipient of social assistance | ---------- | 1.71 (1.14-2.55) | ---------- |
| Primiparous | 0.66 (0.51-0.86) | 0.65 (0.47-0.90) | ---------- |
| High risk pregnancy | ---------- | 1.94 (1.44-2.63) | 1.86 (1.38-2.51) |
| Gestational Diabetes | ---------- | ---------- | ---------- |
| Pregnancy induced hypertension | ---------- | ---------- | ---------- |
| Gynecologist or obstetrician visit during pregnancy | ---------- | ---------- | 1.56 (1.02-2.39) |
| Number of prenatal visits (>14) | ---------- | 0.19 (0.10-0.38) | 0.30 (0.17-0.54) |
| Number of prenatal visits (5-14) | ---------- | 0.57 (0.39-0.85) | 0.53 (0.37-0.77) |
| Chronic diabetes | 2.27 (1.10-5.11) | | |
| Chronic hypertension | ---------- | 2.72 (1.23-6.03) | ---------- |
| Maternal Weight at birth (<2.5 kg) | 1.60 (1.19-2.15) | 2.13 (1.52-2.99) | ---------- |
| Maternal Weight at birth (=>5.0 kg) | 1.72 (0.58-5.11) | 0.83 (0.21-3.24) | ---------- |
| Maternal Weight gain during pregnancy (>16.0 kg) | 0.67 (0.52-0.87) | 0.60 (0.43-0.84) | 0.99 (0.72-1.35) |
| Maternal Weight gain during pregnancy (<8.0 kg) | 1.02 (0.71-1.46) | 1.77 (1.18-2.63) | 1.89 (1.28-2.81) |
| Preterm birth prior to the current delivery | 0.35 (0.22-0.54) | ---------- | 3.36 (2.42-4.65) |
| LBW infant prior to the current delivery | 2.62 (1.69-4.08) | 3.24 (2.20-4.77) | ---------- |
| Maternal cigarette smoking | 2.36 (1.82-3.06) | ---------- | ---------- |

# Fifth article

**Titre:** Does Good Asthma Control in Pregnant Women Annihilate the Risk of Perinatal Outcomes?

**Submitted** to Annals of Allergy, Asthma & Immunology

Included in the present thesis by the permission of the co-authors.

**The role of each author**

Faranak Firoozi, Catherine Lemière, Marie-France Beauchesne, Francine M Ducharme, Sylvie Perreault and Lucie Blais participated in the design of the study. Faranak Firoozi and Lucie Blais conducted the study. The cohort original was constructed by Amélie Forget. The statistical analyses were done by Faranak Firoozi. The article was written by Faranak Firoozi and all the authors revised this article.

**Does Good Asthma Control in Pregnant Women Annihilate the Risk of Perinatal Outcomes?**

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**Key words:**
Low birth weight, small for gestational age, preterm birth, two-stage sampling cohort, administrative databases

## Abstract

### Background/Objectives

Adverse perinatal outcomes are more prevalent in pregnant women with asthma as compared to women without asthma. We investigated whether women with adequately controlled asthma during pregnancy are at increased risk of adverse perinatal outcomes than non-asthmatic women.

### Methods

A population-based cohort of 36,115 pregnancies from controlled asthmatic and non-asthmatic women was reconstructed through the linking of three of Quebec's (Canada) administrative databases between 1990 and 2002. A two-stage sampling cohort design was used to collect additional information on the selected women's life-style habits by way of a mailed questionnaire. The degree of asthma control during pregnancy was assessed with a validated database index. A generalized estimation equation model was used to obtain the adjusted odds ratios of small-for-gestational-age (SGA) infants, low-birth-weight (LBW) infants and preterm births comparing women with adequately controlled asthma to non-asthmatic women.

### Results

The cohort included 8,334 pregnancies of women with adequately controlled asthma and 27,781 pregnancies of non-asthmatic women. At the second stage of sampling, we sent 4,066 questionnaires to selected women, with a 38.0% (n=1546) response rate. Final estimates showed that the risk of SGA (OR:1.28, 95%CI: 1.15-1.43), LBW (OR: 1.42, 95%CI:1.22-1.66), and preterm deliveries (OR: 1.63, 95%CI:1.46-1.83) was significantly higher among mother with adequately controlled asthma than non-asthmatic women.

**Conclusions**

Mothers with adequately controlled asthma during pregnancy are at higher risk of adverse perinatal outcomes than non-asthmatic women.

## Introduction

Asthma is known as one of the most frequent chronic diseases encountered during pregnancy with prevalence estimated between 4 and 8% (3-5, 7, 47, 71). The risk of adverse perinatal outcomes, such as preterm birth, low-birth-weight (LBW) infant and small-for-gestational-age (SGA) infant has been reported to be higher among asthmatic than non-asthmatic women (14, 16, 17, 19, 93, 102, 103). It has also been reported that the risk of adverse perinatal outcomes is higher among asthmatic women with uncontrolled asthma than asthmatic women with adequately controlled asthma (20, 93, 106). It has been hypothesized that adverse fetal outcomes could be related to decreased fetal blood oxygen, due to poorly controlled asthma (50, 52, 54, 56, 104, 120).

Knowing that, it would be clinically relevant to evaluate whether the risk of perinatal outcomes of women with adequately controlled asthma is still higher or is similar to the risk observed among non-asthmatic women. To our knowledge, three studies evaluated whether or not women with adequately controlled asthma are at higher risk of perinatal outcomes than non-asthmatic women. In a prospective controlled study comparing women with actively managed asthma during pregnancy and non-asthmatic women, Schatz et al observed relative risks as large as 1.65 for perinatal outcomes, but concluded that there was no difference between the groups since the relative risks were not statistically significant (21). In two other studies, Stenius-Aarniala et al and Jana et al. came to the same conclusion (20, 22). These three studies should however be interpreted with caution since their statistical power was limited.

To further investigate whether or not women with adequately controlled asthma during pregnancy are at increased risk of adverse perinatal outcomes including SGA infant, LBW infant, and preterm birth, we conducted a population-based two-stage sampling cohort study.

## 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 filled by selected mothers.

The RAMQ databases provide information on medical services dispensed to all residents of Quebec and on prescribed medications filled in community pharmacies by residents covered by the RAMQ's Public Prescription Drug Insurance Plan. Approximately 43% of the population of Quebec is covered by the RAMQ Public Prescription Drug Insurance Plan, most notably the elderly and social assistance beneficiaries since 1980. Furthermore, since the enactment of mandatory drug coverage in 1997, the RAMQ's Public Prescription Drug Insurance Plan now provides coverage for an additional 1.7 million adherents, mainly workers and their families who have no access to a group drug insurance plan at work (186). The RAMQ Prescribed Medication 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 include information pertaining to date, diagnosis coded with 9$^{th}$ international classification of diseases (ICD-9), where the service was dispensed, and so on. Data recorded in the RAMQ Prescribed Medication database and asthma diagnoses recorded in the RAMQ Medical Services database have been formally evaluated and found to be valid (187, 188). The MED-ECHO database is a provincial database which records data on acute care hospitalizations and covers all residents of Quebec (187). 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 selected women.

**Study Design and Population**

We performed a two-stage sampling cohort design (balanced selection) (184, 185, 190, 225). The first stage of sampling corresponds to the cohort formed of singleton pregnancies of adequately controlled 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 (189). 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 pregnancy. Women were considered as having asthma if they had a diagnosis of asthma (ICD-9 code 493, except 493.2), and one or more prescriptions for an asthma medication dispensed in the two years prior or during pregnancy. Then, the women with adequately controlled asthma during their pregnancy were identified using an index that we had previously developed and validated, please refer to the section on compared subgroups for more details on the measure of asthma control (196). 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 RAMQ and MED-ECHO databases were obtained one year before and during pregnancy. 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 (184, 190). This strategy oversamples women who had a SGA infant, a LBW infant, or a preterm delivery

in order to increase the statistical power (184). A maximum of two pregnancies per woman were selected at this stage of sampling not to overload a mother with more than two questionnaires to fill. Selected women had to be at least 18 years old at the beginning of the 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 address of the mother as well as her spoken language.

The questionnaire was used to obtain information on life style variables during pregnancy (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 25 years ago. First, we sent 4,066 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).

**Compared groups**

In this study, women with adequately controlled asthma during pregnancy were compared to non-asthmatic women. Asthma control during pregnancy was measured with

an index that we had previously developed and validated (196). This control index is based upon the definition provided in the Canadian Asthma Consensus Guidelines (26). Two levels of asthma control during pregnancy were defined based on the average number of doses of short-acting $beta_2$ agonists (SABA) per week and the presence of markers of moderate-to-severe asthma exacerbations – a filled prescription of oral corticosteroids (less than 14 days), an ED visit for asthma, or a hospitalization for asthma (197). Patients were considered adequately controlled if they had no marker of moderate-to-severe asthma exacerbation and no more than three doses of SABA per week for mild asthma and ten doses of SABA per week for moderate and severe asthma (196). Details of the index of control are provided in the electronic attachment.

**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 (226, 240). 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 outcomes (195).

**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) (228), 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) (228) 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) (241). **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 adequately controlled asthmatic and non-asthmatic women included in the first stage of sampling (cohort) and those selected at the second stage of sampling. Also, the characteristics related to asthma were reported for asthmatic women. The unit of analysis was the pregnancy, since a woman could contribute more than one pregnancy during the study period.

We then calculated the first-stage prevalence of study outcomes for adequately controlled asthmatic and non asthmatic women separately. Crude and adjusted odds ratios (OR) for SGA infants, LBW infants and preterm births comparing pregnancies of adequately controlled asthmatic with non-asthmatic women were then estimated for the first stage of sampling using Generalized Estimation Equation (GEE) models (198). 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 infant, LBW infant 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 based on pregnancies selected at the second stage of sampling with 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 estimates with the second stage sampling fractions and adjusted estimates found at the first stage of sampling using the methodology developed by Collet et al (184).

**Results**

At the first stage of sampling, the cohort included 8,334 singleton pregnancies of adequately controlled asthmatic women and 27,781 singleton pregnancies of non-asthmatic women. At the second stage of sampling, we sent a total of 4,066 questionnaires to selected adequately controlled asthmatic and non-asthmatic women. We received 1,546 completed questionnaires (response rate; 38.0%): 740 questionnaires from adequately controlled asthmatic women (response rate: 40.0%) 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 pregnancies included in the first stage of sampling. When comparing adequately controlled asthmatic to non-asthmatic women, we found a higher prevalence of recipients of social assistance, high risk pregnancy, maternal chronic diabetes and maternal chronic hypertension among pregnancies of adequately controlled asthmatic than those of non-asthmatic women.

Table 2 shows the distribution of variables retrieved from the questionnaires among pregnancies selected at the second stage of sampling. Overall, adequately controlled asthmatic women had a lower education and a lower annual family income than non-asthmatic women. However, the prevalence of several other characteristics was higher among pregnancies of controlled asthmatic than non-asthmatic women: maternal birth weight <2.5 kg, maternal weight gain >16 kg, maternal BMI pre-pregnancy >29.9, preterm birth and LBW infant prior to the current delivery, maternal cigarette smoking, and paternal cigarette smoking. This table also shows that the percentage of missing values was lower than 3.2% for variables retrieved from the questionnaires, except for the maternal weight at birth.

In Table 3, we present the distribution of asthma related variables among pregnancies of adequately controlled asthmatic women included in the first stage of sampling. The use of inhaled corticosteroids (ICS) and SABA during pregnancy among these women was 25.1% and 42.9%, respectively and 51.5% of these women had no asthma medications during pregnancy.

In Table 4, we observe that the first-stage prevalence of SGA babies was higher among pregnancies of adequately controlled asthmatic than those of non-asthmatic women (13.7% vs. 10.6%). The same trend was observed for LBW (9.1% vs. 5.7%) and preterm births (10.5% vs. 6.7%). Adjusted final ORs estimates showed that the risk of the three adverse perinatal outcomes was significantly higher among adequately controlled asthmatic than non-asthmatic women. The highest risk was found for preterm births with an OR of 1.63 (95% CI: 1.46-1.83).

**Discussion**

In this study, women with adequately controlled asthma during pregnancy were found to be at significantly higher risk of delivering SGA, LBW and preterm babies than women without asthma.

We found three studies in the literature that evaluated the impact of appropriate asthma care or asthma control during pregnancy on perinatal outcomes (21). Schatz et al assessed perinatal outcomes in actively managed pregnant asthmatic women as compared with matched non-asthmatic pregnant women. They found a RR of 1.33 for SGA, a RR of 1.64 for LBW, and a RR of 1.65 for preterm births, point estimates that are similar to those found in our study. However, the authors concluded that there was no difference between the groups since these RRs were not found to be statistically sig nificant. It is however, worth noting that this study had only 18% power to detect a RR of 1.33 for SGA (21).

In two other studies, Jana et al. and Stenius-Aarniala et al came to the same conclusion as Schatz (20, 22). Jana et al. compared the risk of adverse perinatal outcomes in 167 women with mild well controlled asthma and 364 non-asthmatic controls (20). They found that incidence of prematurity and LBW were not affected by asthma ($p>0.05$). Since asthma control was not defined in the article and that the study power was limited, it is difficult to interpret the results. Similarly, Stenius-Aarniala et al. found no significant differences in the risk of perinatal outcomes between 109 asthmatic women that were classified in very mild to mild groups (used asthma medication but had no ER or hospital admission for asthma during pregnancy) and 199 non-asthmatic women and concluded that asthmatic women with well controlled asthma have the same risk as non-asthmatic women (22). Again these results should be interpreted with caution due to lack of statistical power.

One of the hypotheses that could explain the results observed in our study is that fetuses of asthmatic women might suffer from abnormal growth and development due to decreased fetal blood oxygen, despite the apparent control of the mother's asthma (120). Indeed, women with asthma may have minimal symptoms, but still have potentially impaired fetal oxygenation (57). Another hypothesis is that asthma per say, whether adequately or poorly controlled, is associated with an unknown pathophysiology of the

placenta that can cause impair fetal development. At last, the observed association might be due, at least in part, to the limits of our measure of asthma control. The index that we used is in part based on filled prescriptions of rescue medications and this might not always reflect exactly the use of medications. Moreover, with this index, we cannot capture women with uncontrolled asthma who might have deprived themselves from rescue medications despite asthma symptoms because of the fear of the potential adverse effects of these medications. However, this should be tempered by the fact that the index of control was also based on other markers of exacerbations such as ED visits and hospitalizations for asthma.

Our study also has other limitations. 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." (231). Secondly, the response rate was low among asthmatic and non-asthmatic women (40% and 36%, respectively). However, it was reassuring to see that the distribution of the database driven variables was similar between responders and non-responders among asthmatic and non-asthmatic women, the data is available in the electronic attachment. Finally, our cohort is less representative of women with a higher socio-economic level, which could be a threat to external validity.

Our study has also several strengths. Firstly, we had a very large sample size, which provided adequate power to detect clinically important differences. Secondly, the measurement of the control of asthma during pregnancy was based on a validated index (26). 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 (195). Fourthly, we used an SGA definition which is based on new Canadian standards and considers the Canadian growth pattern in its definition (226, 242). Finally, the two-stage sampling design allowed us to obtain confounding variables, such as cigarette smoking,

which are not recorded in the administrative databases. 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, we observed that pregnant women with adequately controlled asthma still had an increased risk of having SGA, LBW or preterm infants when compared to non-asthmatic women. Further research are needed to confirm these results and to investigate whether the pathophysiology of asthma, being adequately controlled or not, can induce abnormal fetal growth.

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**Table 1.** Characteristics of study women from the first stage of sampling (database driven variables, n=36115)

| | **Pregnancies of adequately controlled asthmatic women (n=8334)** | **Pregnancies of non-asthmatic women (n=27781)** |
|---|---|---|
| | Number (%) | |
| **Maternal socio-demographic variables** | | |
| **Age at beginning of pregnancy:** | | |
| **< 18 years old** | 576 (6.9) | 987 (3.5) |
| **18 - 34 years old** | 7,286 (87.5) | 24,136 (86.9) |
| **> 34 years old** | 469 (5.6) | 2,658 (9.6) |
| **Recipient of social assistance in the year before pregnancy** | 6,536 (78.4) | 15,970 (57.5) |
| **Urban residency at delivery** | 6,787 (81.5) | 21,407 (77.1) |
| **Pregnancy related variables** | | |
| **Primiparous** | 2,612 (31.4) | 9,611 (34.8) |
| **High risk pregnancy** | 2,955 (35.5) | 8,131 (29.3) |
| **Gestational diabetes** | 591 (7.1) | 1,886 (6.8) |
| **Pregnancy induced hypertension** | 507 (6.1) | 1,437 (5.2) |
| **Gynecologist or obstetrician visit during pregnancy** | 6,848 (82.2) | 2,2453 (80.0) |
| **Number of prenatal visits** | | |
| **≤ 5** | 1,299 (15.6) | 4,831 (17.4) |
| **6-14** | 6,106 (73.3) | 20,577 (74.1) |
| **> 14** | 926 (11.1) | 2,373 (8.5) |
| **Maternal co-morbidity** | | |
| **Chronic diabetes** | 191 (2.3) | 381 (1.4) |
| **Chronic hypertension** | 190 (2.3) | 368 (1.3) |

**Table 2.** Characteristics of women selected at the second stage of sampling (questionnaire driven variables, n=1546)

| | **Pregnancies of adequately controlled asthmatic women (n=740)** | **Pregnancies of non-asthmatic women (n=806)** |
|---|---|---|
| | Number (%) | |
| **Maternal characteristics** | | |
| **Education (highest level attained)** | | |
| Elementary school | 66 (8.9) | 35 (4.3) |
| High school | 554 (74.9) | 527 (65.4) |
| College & University | 101 (13.6) | 226 (28.0) |
| Unknown | 19 (2.6) | 18 (2.2) |
| **Annual family income during pregnancy** | | |
| < $18,000 | 436 (58.9) | 377 (46.8) |
| $18,001 - $46,000 | 249 (33.6) | 323 (40.1) |
| > $46,001 | 38 (5.1) | 90 (11.2) |
| Unknown | 17 (2.3) | 16 (2.0) |
| **Weight at birth** | | |
| < 2.5 kg | 163 (22.0) | 124 (15.4) |
| 2.5 – 5.0 kg | 494 (66.8) | 548 (68.0) |
| > 5.0 kg | 8 (1.1) | 11 (1.4) |
| Unknown | 75 (10.1) | 123 (15.3) |
| **Pregnancy related variables** | | |
| **Maternal weight gain during pregnancy** | | |
| < 8 kg | 112 (15.1) | 115 (14.3) |
| 8 - 16 kg | 313 (42.3) | 423 (52.5) |
| > 16 kg | 291 (39.3) | 245 (30.4) |
| Unknown | 24 (3.2) | 23 (2.8) |
| **Maternal BMI pre-pregnancy** | | |
| < 18.5 | 114 (15.4) | 124 (15.4) |
| 18.5 – 24.9 | 391 (52.8) | 468 (58.1) |
| 25 – 29.9 | 129 (17.4) | 132 (16.4) |
| > 29.9 | 83 (11.2) | 61 (7.6) |
| Unknown | 23 (3.1) | 21 (2.6) |
| **Preterm birth prior to the current delivery** | | |
| Yes | 143 (19.3) | 111 (13.8) |
| No | 593 (80.1) | 692 (85.9) |
| Unknown | 4 (0.5) | 3 (0.4) |
| **LBW infant prior to the current delivery** | | |
| Yes | 135 (18.2) | 119 (14.8) |
| No | 597 (80.7) | 684 (84.9) |
| Unknown | 8 (1.1) | 3 (0.4) |
| **Life style habits (during pregnancy)** | | |
| **Maternal cigarette smoking** | | |
| Yes | 474 (64.1) | 395 (49.0) |
| No | 262 (35.4) | 402 (49.9) |

| | | |
|---|---|---|
| Unknown | 4 (0.5) | 9 (1.1) |
| **Paternal cigarette smoking** | | |
| Yes | 369 (49.9) | 346 (42.9) |
| No | 353 (47.7) | 451 (56.0) |
| Unknown | 18 (2.4) | 9 (1.1) |
| **Maternal alcohol consumption** | | |
| Yes | 125 (16.9) | 148 (18.4) |
| No | 588 (79.5) | 619 (76.8) |
| Unknown | 27 (3.7) | 39 (4.8) |

**Table 3. Asthma related** characteristics of adequately controlled asthmatic women during pregnancy (n=8334)

| During pregnancy | | Number of pregnancies (%) |
|---|---|---|
| * ICS use (μg per day) | 0 | 6,244 (74.9) |
| | 0-500 | 2,013 (24.2) |
| | 500-1,000 | 68 (0.8) |
| | >1,000 | 9 (0.1) |
| **SABA use (number of doses per week) | 0 | 4,763 (57.1) |
| | > 0-3 | 3,521 (42.3) |
| | > 3 | 50 (0.6) |
| Leukoteriene-receptor antagonists use | | 5 (0.1) |
| Long-acting $beta_2$-agonists use | | 69 (0.8) |
| Theophyline use | | 80 (1.0) |
| At least one asthma medication | | 4,054 (48.6) |
| ≥ 1 respiratory physician visit | | 201 (2.4) |
| Oral corticosteroids use | | 0 (0.0) |
| ≥ 1 ED visit for asthma | | 0 (0.0) |
| ≥ 1 hospitalization for asthma | | 0 (0.0) |

***** Inhaled corticosteroids

****** Short-acting $beta_2$-agonists

**Table 4.** The first stage prevalence and crude and adjusted odds ratios of adverse perinatal outcomes comparing pregnancies of adequately controlled asthmatic to non-asthmatic women

| | | SGA | LBW | Preterm birth |
|---|---|---|---|---|
| | | Number (%) | | |
| **1st stage** | **Pregnancies of women with adequately controlled asthma** (N=8,334) | 1,139 (13.7) | 755 (9.1) | 871 (10.5) |
| | **Pregnancies of non-asthmatic women** (N=27,781) | 2,948 (10.6) | 1,575 (5.7) | 1,848 (6.7) |
| | | **OR (95% CI)** | | |
| **1st stage** | Crude | 1.33 (1.24-1.43) | 1.66 (1.51-1.81) | 1.64 (1.50-1.78) |
| | Adjusted | *1.22 (1.13-1.31) | **1.52 (1.38-1.67) | ***1.56 (1.43-1.70) |
| **Final estimates‡** | Adjusted | †1.28 (1.15-1.43) | ††1.42 (1.22-1.66) | †††1.63 (1.46-1.83) |

‡ Final estimates obtained by correcting the second stage adjusted estimates with the second stage sampling fractions

*Adjusted for maternal age at beginning of pregnancy, socio-economic status, primiparous, high risk pregnancy, gestational diabetes, pregnancy induced hypertension, prenatal visits, and chronic diabetes.

** Adjusted for socio-economic status, urban residency at delivery, primiparous, high risk pregnancy, gestational diabetes, pregnancy induced hypertension, gynecologist or obstetrician visit during pregnancy, prenatal visits, and chronic hypertension.

***Adjusted for socioeconomic status, primiparous, high risk pregnancy, pregnancy induced hypertension, gynecologist or obstetrician visit during pregnancy, prenatal visits, chronic diabetes, and chronic hypertension.

†Adjusted for primiparous, 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 during pregnancy.

†† Adjusted for socio-economic status, primiparous, high risk pregnancy, pregnancy induced hypertension, gynecologist or obstetrician visit during pregnancy, prenatal visits, maternal weight at birth, maternal weight gain during pregnancy, maternal BMI pre-pregnancy, and LBW infants prior to the current delivery.

††† Adjusted for primiparous, high risk pregnancy, gestational diabetes, pregnancy induced hypertension, gynecologist or obstetrician visit during pregnancy, prenatal visits, maternal weight gain during pregnancy, maternal BMI pre-pregnancy, preterm births prior to the current delivery, and LBW infants prior to the current delivery.

**Electronic attachment**

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

| Asthma Control | *ICS daily dose (µg) | **Other controller therapy | +SABA doses per week | ++ Marker of moderate to severe exacerbations |
|---|---|---|---|---|
| **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 |
| | 501-1,000 | 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 |
| | 501-1,000 | Yes/No | >10 | No |
| | 501-1,000 | Yes/No | 0-10 | Yes |
| **Severe** | | | | |
| **Controlled** | >1,000 | Yes/No | 4-10 | No |
| **Uncontrolled** | 0-1,000 | Yes/No | >10 | Yes |
| | >1,000 | Yes/No | 0-10 | Yes |
| | >1,000 | 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 beta$_2$-agonist (LABA), theophylline or leukotriene-receptor antagonists dispensed over a 12-month period.
**+**SABA**:** Average number of inhaled short-acting beta$_2$-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.

## Electronic attachment

**Characteristics of adequately controlled asthmatic and non-asthmatic women who answered the questionnaire (N=1546) and those who did not answer (N=2598)**

| | Controlled Asthmatic women | | Non Asthmatic women | |
|---|---|---|---|---|
| | **Responding** | **Non-responding** | **Responding** | **Non-responding** |
| | Numbers (%) | | | |
| | 740 (40.0) | 1,110 (60.0) | 806 (36.4) | 1,410 (63.6) |
| **Age at beginning of pregnancy** | | | | |
| **< 18 years old,** | 54 (7.3) | 82 (7.4) | 23 (2.8) | 74 (5.3) |
| **18 - 34 years old,** | 650 (87.8) | 966 (87.0) | 703 (87.2) | 1,196 (84.8) |
| **> 34 years old,** | 36 (4.9) | 62 (5.6) | 80 (9.9) | 140 (9.9) |
| **Recipient of social assistance,** | 570 (77.0 ) | 914 (82.3) | 440 (54.6) | 914 (64.8) |
| **Urban residency at delivery,** | 579 (78.2) | 928 (83.6) | 577 (71.6) | 1,130 (80.1) |
| **Primiparous,** | 273 (37.1) | 339 (30.6) | 355 (44.2) | 518 (36.9) |
| **High risk pregnancy,** | 294 (39.7) | 452 (40.7) | 302 (37.5) | 579 (41.1) |
| **Gestational diabetes,** | 51 (6.9) | 78 (7.0) | 51 (6.3) | 110 (7.8) |
| **Chronic diabetes,** | 22 (3.0) | 22 (2.0) | 10 (1.2) | 25 (1.8) |
| **Pregnancy induced hypertension,** | 61 (8.2) | 65 (5.9) | 77 (9.6) | 133 (9.4) |
| **Chronic hypertension,** | 21 (2.8) | 28 (2.5) | 27 (3.4) | 30 (2.1) |
| **Gynecologist or obstetrician visit during pregnancy,** | 605 (81.8) | 949 (85.5) | 671 (83.3) | 1208 (85.7) |
| **Number of prenatal visits,** | | | | |
| **≤ 5** | 108 (14.6) | 247 (22.3) | 164 (20.4) | 326 (23.1) |
| **6-14** | 545 (73.7) | 777 (70.0) | 599 (74.3) | 991 (70.3) |
| **> 14** | 87 (11.8) | 86 (7.8) | 43 (5.3) | 93 6.6) |

**Electronic attachment**

**Final odds ratio of perinatal outcomes comparing adequately controlled asthmatic (n=740) and non-asthmatic women (n=806) adjusted for variables derived from the databases and the mailed questionnaire**

| | SGA | LBW | Preterm |
|---|---|---|---|
| | Final adjusted OR (95% CI) | | |
| Adequately controlled asthmatic versus non-asthmatic women | 1.28 (1.15-1.43) | 1.42 (1.22-1.66) | 1.63 (1.46-1.83) |
| Recipient of social assistance | ---------- | 1.36 (1.05-1.78) | ---------- |
| Primiparous | 0.77 (0.61-0.97) | 0.59 (0.46-0.77) | 0.81 (0.64-1.04) |
| High risk pregnancy | ---------- | 1.73 (1.35-2.21) | 1.68 (1.33-2.13) |
| Gestational Diabetes | ---------- | ---------- | 1.26 (0.82-1.94) |
| Pregnancy induced hypertension | 1.70 (1.05-2.76) | 1.83 (1.09-3.09) | 1.29 (0.79-2.10) |
| Gynecologist or obstetrician visit during pregnancy | ---------- | 1.52 (1.09-2.12) | 1.62 (1.17-2.23) |
| Number of prenatal visits (>14) | 1.59 (1.02-2.49) | 0.31 (0.18-0.53) | 0.28 (0.17-0.46) |
| Number of prenatal visits (5-14) | 1.24 (0.93-1.64) | 0.63 (0.46-0.85) | 0.57 (0.43-0.75) |
| Maternal Weight at birth (<2.5 kg) | 1.38 (1.05-1.81) | 2.03 (1.52-2.71) | ---------- |
| Maternal Weight at birth (=>5.0 kg) | 1.38 (0.54-3.54) | 0.93 (0.34-2.56) | ---------- |
| Maternal Weight gain during pregnancy (>16.0 kg) | 0.73 (0.58-0.92) | 0.61 (0.47-80) | 0.88 (0.69-1.12) |
| Maternal Weight gain during pregnancy (<8.0 kg) | 1.02 (0.75-1.40) | 1.83 (1.31-2.56) | 1.55 (1.13-2.13) |
| Maternal BMI pre-pregnancy (>24.9) | 0.82 (0.64-1.06) | 0.59 (0.45-0.79) | 0.84 (0.65-1.10) |
| Maternal BMI pre-pregnancy (<18.5) | 1.56 (1.15-2.11) | 1.31 (0.94-1.81) | 0.81 (0.59-1.11) |
| Preterm birth prior to the current delivery | 0.29 (0.19-0.44) | ---------- | 3.05 (2.08-4.47) |
| LBW infant prior to the current delivery | 3.53 (2.32-5.37) | 3.77 (2.71-5.24) | 0.76 (0.51-1.12) |
| Maternal cigarette smoking | 1.72 (1.38-2.15) | ---------- | ---------- |

# General discussion

Considering the high prevalence of asthma among pregnant women and the fact that expectant mother and health professionals might underestimate the impact of a sub-optimal treatment of asthma during pregnancy, we considered that evaluation of the consequences of maternal asthma on the health of the newborn would be necessary. We conducted a large population-based cohort study to further investigate the reciprocal effect of asthma and pregnancy.

In the first methodological study related to the development and validation of database indexes of asthma severity and control, we have demonstrated that our database indexes correlate well with lung function measures, such as the $FEV_1$ and the $FEV_1$/FVC ratio, which are reliable indices reflecting asthma severity and control (39, 118). Moreover, the application of our database severity index to a population-based cohort of asthmatic patients led to a distribution of asthma severity similar to that found with other severity indexes. These database indexes were used to measure exposure in the study 4 and 5. Moreover, we used the indexes to describe the study population (exposed and non-exposed) in the study 2 and the asthma-related characteristics of the exposed women during pregnancy in the study 3.

In the second study, we evaluated the impact of pregnancy on maternal asthma. No significant differences were found between mothers of a female and male fetus as to the occurrence of asthma exacerbations (adjusted rate ratio=1.02; 95% CI: 0.92 to 1.14), the daily dose of ICS (adjusted mean difference (AMD): 2.46 µg; 95% CI: -4.01 to 8.93), and the weekly dose of SABA (AMD: 0.004 dose; 95% CI: -0.23 to 0.24). Based on these results, we concluded that fetal gender is unlikely to affect maternal asthma during

pregnancy to the point where acute care and medications are more often required among women pregnant with a female fetus. Thus, although pregnancy could influence the course of asthma but at least fetal gender could not have a serious impact on maternal asthma during pregnancy.

To understand better the impact of asthma in pregnancy, we conducted three last studies. In the third study, the cohort (first stage of sampling) included 13,007 pregnancies from asthmatic women and 27,781 pregnancies from non-asthmatic women. In this study, we have found that asthma during pregnancy was significantly associated with an increased risk of SGA (OR: 1.27, 95% CI: 1.14-1.41), LBW (OR: 1.41, 95% CI:1.22-1.63) and preterm births (OR: 1.64, 95%CI:1.46-1.83). Knowing that, we considered that it would be clinically relevant to evaluate whether the risk of perinatal outcomes of women with moderate and severe asthma is still higher or is similar to the risk observed among mild asthmatic women.

In the fourth study, our results show that the proportions of women with mild, moderate and severe asthma were 82.5%, 12.5% and 5.0%, respectively. 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. 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. Some physiologic hypotheses can explain at least in part these findings. Maternal asthma can induce hypoxia combined with respiratory alkalosis that decreases the placental blood flow (54, 243) and as a result chronic oxygen deprivation of the fetus could affect fetal growth (50, 52, 120).

The remaining question was whether the risk of perinatal outcomes of women with adequately controlled asthma is similar to the risk observed among non-asthmatic women, so we conducted the fifth study. In this study, the cohort included 8,334 pregnancies of women with adequately controlled asthma and 27,781 pregnancies of non-asthmatic women. Final estimates showed that the risk of SGA (OR:1.28, 95%CI: 1.15-1.43), LBW (OR: 1.42, 95%CI:1.22-1.66), and preterm deliveries (OR: 1.63, 95%CI:1.46-1.83) was significantly higher among mother with adequately controlled asthma than non-asthmatic women.

## 5.5. Contribution of our results to the literature in the field of asthma in pregnancy

### 5.5.1. Impact of feminine sex hormones on asthma

Some data suggest that feminine sex hormones could play a role in the modulation of immunological inflammation in asthma (244). Serum levels of feminine sex hormones have been directly correlated with the clinical and functional features of asthma (244). In peri- menopausal and post-menopausal period, asthma may worsen in women with prior disease (245). Knowing this characteristic of asthma, the question has raised whether feminine sex of the fetus might influence the maternal asthma. We investigated this question in our second study among 11,257 pregnancies of asthmatic women. Although, three other smaller studies have found increased markers of poorly controlled asthma among pregnancies of female fetuses (8-10), we detected no significant increase in the

rate of maternal asthma exacerbations, the use of ICS and SABA during pregnancy among mothers of female fetus, whether examined between or within mothers.

### 5.5.2. Impact of asthma on adverse perinatal outcomes

In our last three studies, we evaluated the impact of maternal asthma, and its severity and control during pregnancy on three adverse perinatal outcomes. Comparing to the findings reported in the literature on the impact of asthma on adverse perinatal outcomes (113), our results are much more precise (narrow confidence interval) because of our large study population. The same precision was also observed in the study 4 and 5 comparing to the results found in the literature. Moreover, most of the studies in the field of asthma in pregnancy, evaluated the impact of maternal asthma on other adverse perinatal outcomes rather than SGA infant. However, our results suggest that the effect of maternal asthma and more precisely severe maternal asthma is more likely to be captured by the SGA measure than the weight at birth alone or the timing of the delivery. These results are in concordance with the results found by Schatz et al. (56).

### 5.5.3. Smoking during pregnancy

While the percentage of women who smoked was higher in our cohort than general population, smoking was not found to be a confounder for the associations under study in the three last studies. As found in other studies (125, 142, 155, 159-161), we observed that smoking during pregnancy was significantly associated with increased risk of adverse perinatal outcomes but this co-variable did not act as a confounder for the association between asthma, its severity and control during pregnancy and adverse perinatal outcomes. One of the possible explanations of this phenomenon is the presence of several other confounding variables along with smoking in multivariate regression

models. Although smoking is a risk factor for adverse perinatal outcomes and it is associated with maternal asthma but it is possible that smoking is simultaneously associated with other confounding variables, included in the model, such as "receiving social assistance benefits". In this case, removing the associated confounding variable in backward selection eliminates the effect of smoking. Moreover, as it was shown in study 4, the percentage of women who smoked during pregnancy does not vary a lot according to the level of asthma severity.

## 5.6. Strengths of the study

### 5.6.1. Databases

One of the strengths of our studies is using the databases. Using three Quebec's administrative databases to measure exposures and outcomes presents many advantages over other means of data collection, such as personal interview or self-administered questionnaires. First, we avoid recall bias and we capture real patient's filling of medications and use of clinical practice. Second, it is usually difficult for patients to report the medications they are taking when details, such as the exact name, dose and quantity, are required (220-222, 246, 247) and they tend to overestimate their adherence (219). Third, the use of computerized databases allows us to capture drug history over a long period of time (one year before and during pregnancy) and for a very large number of subjects in a standardized format. Fourth, one of the most important advantages of using data recorded prospectively in administrative databases is that we could study a large number of pregnant women (generally understudied population) in a reasonable time frame and budget. Fifth, the high quality of personal identifier in Quebec's administrative databases helps correct linkage between databases. Sixth, it has been shown that data recorded in Quebec's administrative databases has good internal quality (good validity, and reliability of data) (188, 192, 230, 248).

### 5.6.2. Questionnaire

Another strength of our studies is that database data was coupled with questionnaire data in order to obtain confounding variables such as parental smoking and lifestyle of the mother during pregnancy not recorded in the databases. The short and simple questions of our questionnaire made it possible to use self-administered questionnaire method to collect data in the second stage of sampling of the last three studies. This method of data collection has some advantages over interview-administered questionnaire. First, self-administered questionnaire generally cost less than interview-administered questionnaire (249). Second, this method of data collection may yield more accurate data on embarrassing topics such as illicit drug use or smoking during pregnancy. Third, self-administered questionnaire provide greater confidentiality than interview-administered questionnaire and may increase the subject's willingness to answer the questions (249). Fourth, the less educated subjects are more willing to answer a self-administered questionnaire rather than an interview-administered questionnaire (249). Fifth, with this method of data collection, there is always a possibility to ask the responders for more clarification by telephone if it is needed (249).

## 5.7. Limits of the study

### 5.7.1. Biases in the study design

Two types of error threat epidemiologic studies; random error and systematic error (250). Random error is the variability in the data and represents the precision of the study (250). It could be reduced by increasing the sample size (increasing the power of the study). A small p-value and a narrow confidence interval imply a great precision and

small random error. Systematic error or bias is a result of an error in the way that the study has been carried out and can influence the internal validity of the study i.e. the result is a difference between the estimated association and the real association value in the population. The bias could occur in the design, in the conduct or in the analysis of a study.

## Selection Bias

### *Participation Bias*

Participation bias or self-selection bias is a systematic error in a study which stems from the procedures used to select subjects and factors that influence study participation (250). This bias occurs when the participants are not representative of the general population and they are different from the persons who did not accept to participate (250). The self-selection bias could be a threat to the validity of the study if the reasons for self-selection are associated with the outcome under study (249). In summary, the association between exposure and outcome differs for those who participated and those who did not participate in the study. If bias occurs, the interpretation of the study findings is getting complicated.

In the second stage of sampling of the last three studies, the risk of participation bias could have been present, if women who answered the questionnaire were different from women who did not answer. However, the bias is present only if the differences in the characteristics between two groups of responders and non-responders are associated with the outcomes under study. To verify the possibility of participation bias in our studies, we compared the characteristics (driven from databases, i.e. the first stage of sampling) of the pregnancies of women who answered the questionnaire with the

characteristics of the pregnancies of women who did not answer in each of the three studies separately. Overall, responders and non-responders were quite similar for the variables retrieved from the administrative databases (maternal socio-demographic variables, pregnancy-related variables and maternal co-morbidities). The tables presenting the details of the comparisons are available in the three last articles included in the present thesis. Considering the similarity of two groups of responders and non-responders for the characteristics retrieved from the administrative databases, there is less chance that they differ in other characteristics to the point that the selection bias affects our studies, however, if it happened, we do not know in which direction the selection bias might operate and how it might affect the study results.

**Confounding Bias**

Confounding is a distortion of the association between the exposure and the outcome of interest because the effect of some extraneous risk factors is mixed with the effect of the exposure of interest (250). Confounding could occur if the extraneous risk factors of the outcome are unevenly distributed between the compared populations. In this case, extraneous risk factor would be an alternative explanation for the relationship observed between exposure and outcome (183). To handle the problem of confounding in our studies, we used multivariate regression models to adjust the ORs by controlling simultaneously for several confounding variables (see section of Confounding variables). However, knowing the difficulty to measure some of the confounding variables such as maternal socio-economic status, cigarette smoking and alcohol consumption during pregnancy, we cannot be sure entirely of the efficacy of the adjustment. Moreover, although we tried to include all the known risk factors of the adverse perinatal outcomes in the regression models, we cannot be assured that we considered all the risk factors. We suppose that we took into account all confounding variables that could affect the interpretation of our results; however, considering that observational studies do not have

the same efficacy as clinical trials to control for all confounding variables, we cannot eliminate the possibility of confounding bias. If we failed to control some unknown confounding variables, the conclusion of the studies could be biased.

## Information Bias

This systematic error occurs in assessing the association between exposure and outcome as a result of error in measurement of exposure or outcome status (250). The information bias occurs, when the misclassification happens which can be differential or non-differential (250).

### *Recall Bias*

A common type of information bias is recall bias which occurs in retrospective studies due to differentials in memory capabilities of sample subjects to recall the past events or experiences (250). The recall of exposures or events may differ in two compared groups. Subjects with the outcome are more likely to carefully consider whether or not an exposure occurred.

The most important bias that could occur with data collection via a mailed questionnaire is recall bias. However, in our studies, the results of the pre-testing of the questionnaire was reassuring and a study published in the literature showed that women had no problem to recall pregnancy related variables for pregnancies that happened as far as 15 years ago (231).

Moreover, the questionnaire data were not used to measure the outcome and the main exposure variables. Via the mailed questionnaire we only collected some potential confounders that were not recorded in the administrative databases. The outcomes and main exposure variables were measured with data recorded in the administrative databases. In these databases there is no potential for recall bias since the data are routinely and prospectively collected, independently of the outcome under study. The recall bias, if present, could have affected only the confounding variables, not the outcomes and the main exposure variables. If misclassification of confounding variables occurred, it could be differential for some of confounding variables because it is possible that women with asthma were more concerned about their health and reporting the details about smoking or other variables than non-asthmatic women or they prefer to under-report some of their characteristics intentionally. Then, the recall bias could be present more in the exposed group than in non-exposed group but we are unable to predict that. However, remembering the pregnancy-related characteristics could be as difficult (if so) for asthmatic women as non-asthmatic ones. As a result, recall bias could be present in both exposed and unexposed group and its direction is not predictable (183).

*Other information bias*

In historical cohort studies, in which information is obtained from past records, information bias can be introduced if the quality and extent of information obtained is different for exposed persons than for non-exposed persons (183). In our studies, the outcome assessment for exposed and non-exposed persons was made through data obtained from administrative databases. As a result, if there is any inaccuracy in outcome measurement, it will not be related to exposure status and only a non-differential misclassification can be introduced. The usual effect of non-differential misclassification is that the effect tends to be diluted, and it will produce an underestimation of the OR (towards 1.0) (183).

The indexes that we used in our studies to measure asthma severity and control are in part based on filled prescriptions of asthma medications. However, data regarding asthma medications recorded in RAMQ databases represents the filled prescriptions and might not always reflect exactly the use of medications. Then, a misclassification of exposure can be introduced in studies 4 and 5. However, the asthma severity and control measurement is not only based on the medication use but also on the medical care services use. Moreover, a recent article showed that only 6% of drugs dispensed to pregnant women were not used (231). Then, although the adherence to asthma treatment could be different between severe asthmatic and mild asthmatic patients, there is little chance that exposure misclassification occurred. But, in the case of misclassification, there is a higher risk that a severe asthmatic patient misclassified as mild asthmatic one than the contrary case. The result of a differential misclassification bias is either an association even if one does not really exist or an association when one does in fact exist and we cannot predict the direction of bias (183). In the case of our study, the misclassification bias, if occurred, would probably result in an underestimation of the association; because as it was explained, most likely, the severe asthmatic patients would be misclassified as mild asthmatics.

Also, there is a potential of non-differential misclassification of asthmatic women due to possible inaccurate diagnosis of asthma entered into the databases. Aaron et al. have shown that about one-third of individuals with physician-diagnosed asthma did not have asthma when objectively assessed (251). However, in our studies, asthma during pregnancy is defined as having at least one diagnosis of asthma and at least one dispensed prescription for an asthma medication. Having the second source of data (filled asthma prescriptions) may improve the validity of our operational definition of asthma and reduce the risk of misclassification. Moreover, the asthma diagnostic codes recorded in the RAMQ database were validated by comparing the database values to medical chart

values and were found to be valid (230). Although Aaron et al. have shown that there is a risk of over-diagnosis of asthma, it has been reported that there is a risk of under-diagnosis of asthma too (252). Then, if the misclassification occurred, it would probably be non-differential which result in an under detection of an association even if one really exists (183). However, if we consider that the misclassification was mostly among asthmatic than non-asthmatics, then the misclassification will be differential.

### 5.7.2. External Validity

The external validity of a study refers to the appropriateness by which its results can be applied to non-study patients or populations (its generalizability) (183). Our cohort is not representative enough of women in the higher socio-economic level because it included women receiving social assistance and middle class working women. However, the non representativeness of our cohort would be a threat to external validity only if socio-economic status is an effect modifier for the associations under study. But there is no evidence in the literature suggesting that the impact of maternal asthma or its severity or control on newborns differs in different levels of socio-economic status. In fact, there is literature on the association between asthma severity or control and socio-economic status (232, 233), but it is not reported that the relationship between asthma and perinatal outcomes varies between high and low levels of socio-economic status.

## 5.8. Clinical implication of our results

The knowledge provided by our studies is transferable immediately to health professionals and asthmatic women. First, the results of the second study suggest that fetal gender should not be considered to plan the management of asthma during pregnancy, and that the management should aim at asthma control regardless of the

gender of the fetus. Second, our results in the three last studies will help health professionals and asthmatic women to realise that all asthmatic women even those with adequately controlled asthma should be closely monitored during pregnancy, because they are at increased risk of adverse perinatal outcomes. Third, the scientific evidence provided by our studies will help health professionals and decision makers to develop preventive, therapeutic and health care strategies to ensure an optimal treatment of asthma during pregnancy that will improve maternal care by reducing the frequency of asthma exacerbations and as a result improving asthma control during pregnancy and improve perinatal outcomes by preventing SGA, LBW and premature birth.

## 5.9. Further research

Further research is needed to answer some other questions in the field of asthma during pregnancy. There is a real need to know better the factors that can yield to poorly controlled asthma during pregnancy. Although, it is reported that adherence to prescribed medications for chronic diseases reduces during pregnancy (253-256), there are certainly other factors that can induce poorly controlled asthma. Moreover, further research is needed to clarify the pathophysiology of asthma in inducing abnormal fetal growth even in women with adequately controlled asthma. Another interesting question that comes up from the results of our fourth study is why severe maternal asthma during pregnancy does affect SGA but not LBW and preterm birth. Also, there is a lack of knowledge regarding how to treat better asthma during pregnancy and it will be helpful to develop and evaluate different interventions during pregnancy on this regard.

# 6. Conclusion

The five studies of this thesis were conducted to achieve an ultimate objective; knowing better the reciprocal effect of asthma and pregnancy. The database indexes developed and validated in the first study were used in the other studies included in the present thesis to measure the control and the severity of asthma. These database indexes can be used in epidemiologic studies using administrative databases that record data on dispensed prescriptions and medical services for asthma to correctly assess the severity and control of asthma in currently treated asthmatic patients. The results of the second study helped us to conclude that fetal gender is unlikely to affect maternal asthma during pregnancy to the point where acute care and medications are more often required among women pregnant with a female fetus. The results of the three last studies provided us with a better understanding of the impact of maternal asthma on adverse perinatal outcomes. The third study showed that the risk of SGA, LBW and preterm delivery was significantly higher among asthmatic than non-asthmatic women. The results of the fourth study showed that severe and moderate asthma during pregnancy were significantly associated with an increased risk of SGA babies as compared to mild asthma. And results of the fifth study helped us to conclude that women with adequately controlled asthma during pregnancy are significantly at higher risk of delivering SGA, LBW and preterm babies than women without asthma. The scientific evidence provided by these studies can help health professionals and women to develop preventive, therapeutic and health care strategies to ensure an optimal treatment of asthma during pregnancy. All asthmatic women even those with adequately controlled asthma should be closely monitored during pregnancy, because they are at increased risk of adverse perinatal outcomes.

Reference List


(1) Statistic Canada. Hospital Statistics: Annual Report, 2000-2001. 2002 Jan 1.

(2) The National Asthma Control Task Force. The prevention and management of Asthma in Canada: a major challenge now and in the future. 2000.

(3) 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.

(4) 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.

(5) 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.

(6) Rey E, Boulet LP. Pregnancy plus - Asthma in pregnancy 2. British Medical Journal 2007 Mar 17;334(7593):582-5.

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

(8) Beecroft N, Cochrane GM, Milburn HJ. Effect of sex of fetus on asthma during pregnancy: blind prospective study. British Medical Journal 1998 Sep 26;317(7162):856-7.

(9) Dodds L, Armson BA, Alexander S. Use of asthma drugs is less among women pregnant with boys rather than girls [letter; comment]. BMJ 1999 Apr 10;318(7189):1011.

(10) Kwon HL, Belanger K, Holford TR, Bracken MB. Effect of fetal sex on airway lability in pregnant women with asthma. American Journal of Epidemiology 2006 Feb 1;163(3):217-21.

(11) Derbes V. Reciprocal influences of bronchial asthma and pregnancy. The American Journal of Medecine 1946;1(4):367-75.

(12) Beckmann CA. A descriptive study of women's perceptions of their asthma during pregnancy. MCN Am J Matern Child Nurs 2002 Mar;27(2):98-102.

(13) Finnell RH. Teratology: general considerations and principles. J Allergy Clin Immunol 1999 Feb;103(2 Pt 2):S337-S342.

(14) 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.

(15) 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.

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

(17) 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.

(18) Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. Thorax 1996 Apr;51(4):411-4.

(19) 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.

(20) 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.

(21) Schatz M, Zeiger RS, Hoffman CP, Harden K, Forsythe A, Chilingar L, et al. Perinatal outcomes in the pregnancies of asthmatic women: a prospective controlled analysis. Am J Respir Crit Care Med 1995 Apr;151(4):1170-4.

(22) Stenius-Aarniala B, Piirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. Thorax 1988 Jan;43(1):12-8.

(23) Murphy A. Asthma in Focus. First ed. London: Pharmaceutical Press; 2007.

(24) Martindale S. The Complete Drug Reference. 35 ed. London: Pharmaceutical Press; 2007. p. 997-9.

(25) Kumar V, Cotran R, Robbins S. The Respiratory System. Basic Pathology. Fifth ed. W. B. Saunders Company; 1992. p. 385-436.

(26) Lemiere C, Bai T, Balter M, Bayliff C, Becker A, Boulet LP, et al. Adult Asthma Consensus Guidelines Update 2003. Can Respir J 2004 May;11(Suppl A):9A-18A.

(27) Tattersfield AE, Knox AJ, Britton JR, Hall IP. Asthma. Lancet 2002 Oct 26;360(9342):1313-22.

(28) Rubin R, Strayer D. The respiratory system. Rubin's Pathology. 5th ed. Wolters Kluwer, Lippincott Williams & Wilkins; 2007. p. 483-548.

(29) Hallberg J, Anderson M, Wickman M, Svartengren M. Sex influences on lung function and medication in childhood asthma. Acta Paediatrica 2006 Oct;95(10):1191-6.

(30) Tsoukleris MG, Katona BG. Asthma and Chronic Obstructive Pulmonary Diseases. In: Shargel L, Mutnick AH, Souney PF, Swanson LN, editors. Comprehensive Pharmacy Review. 4th ed. Lippincott Williams& Wilkins; 2001. p. 892-923.

(31) Statistics Canada. Persons with asthma, by age and sex. CANSIM, tables 104-0001, 105-0001, ed. 2003.

(32) Manfreda J, Becklake MR, Sears MR, Chan-Yeung M, mich-Ward H, Siersted HC, et al. Prevalence of asthma symptoms among adults aged 20-44 years in Canada. CMAJ 2001 Apr 3;164(7):995-1001.

(33) Statistics Canada. National Population Health Survey, 1994/95, 1996/97 and 1998/99, cross sectional sample, health file; Statistics Canada, National Longitudinal Survey of Children and Youth. 2007 Aug 3.

(34) Manfreda J, Becklake MR, Sears MR, Chan-Yeung M, mich-Ward H, Siersted HC, et al. Prevalence of asthma symptoms among adults aged 20-44 years in Canada. CMAJ 2001 Apr 3;164(7):995-1001.

(35) Sears MR. Descriptive epidemiology of asthma. Lancet 1997 Oct;350 Suppl 2:SII1-SII4.

(36) Simpson BM, Custovic A, Simpson A, Hallam CL, Walsh D, Marolia H, et al. NAC Manchester Asthma and Allergy Study ((NAC)MAAS): risk factors for asthma and allergic disorders in adults. Clinical and Experimental Allergy 2001 Mar;31(3):391-9.

(37) Platts-Mills TA, Rakes G, Heymann PW. The relevance of allergen exposure to the development of asthma in childhood. J Allergy Clin Immunol 2000 Feb;105(2 Pt 2):S503-S508.

(38) Strachan D. Family size, infection and atopy: the first decade of the "hygiene hypothesis". Thorax 2000;55:2-10.

(39) Boulet LP, Becker A, Berube D, Beveridge R, Ernst P. Canadian Asthma Consensus Report, 1999. Canadian Asthma Consensus Group. CMAJ 1999 Nov 30;161(11 Suppl):S1-61.

(40) Pocket guide for asthma management and prevention - A pocket guide for physicians and nurses. 2005.

(41) Williams DM, Self TH. Asthma. In: Berardi RR, editor. Handbook of nonprescription drugs. 14th ed. American Pharmacists association; 2002. p. 287-313.

(42) Alcock SM, Mamun M, Prescott RJ, Connolly CK. Symptoms and pulmonary function in asthma. Respiratory Medicine 1998 Jun;92(6):849-57.

(43) Global Initiative for asthma. Global strategy for asthma management and prevention. 2002. Report No.: NIH Pub No.: 02-3659.

(44) McCormack DG. Adult asthma. In: Gray D, editor. Therapeutic Choices. 3rd ed. Canadian Pharmacists Association; 2000. p. 312-9.

(45) Régie de l'assurance maladie du Quebec. Liste de médicaments. 17 ed. 2007.

(46) Ducharme FM. Inhaled glucocorticoids versus leukotriene receptor antagonists as single agent asthma treatment: systematic review of current evidence. British Medical Journal 2003 Mar 22;326(7390):621-3.

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

(48) Kwon HL, Triche EW, Belanger K, Bracken MB. The epidemiology of asthma during pregnancy: Prevalence, diagnosis, and symptoms. Immunology and Allergy Clinics of North America 2006 Feb;26(1):29-+.

(49) Nelson-Piercy C. Asthma in pregnancy. Thorax 2001 Apr;56(4):325-8.

(50) Liccardi G, D'Amato M, D'Amato G. Asthma in pregnant patients: pathophysiology and management. Monaldi Arch Chest Dis 1998 Apr;53(2):151-9.

(51) Schatz M. Asthma during pregnancy: interrelationships and management. Ann Allergy 1992 Feb;68(2):123-33.

(52) Cousins L. Fetal oxygenation, assessment of fetal well-being, and obstetric management of the pregnant patient with asthma. J Allergy Clin Immunol 1999 Feb;103(2 Pt 2):S343-S349.

(53) Guy ES, Kirumaki A, Hanania NA. Acute asthma in pregnancy. Crit Care Clin 2004 Oct;20(4):731-45, x.

(54) Guy ES, Kirumaki A, Hanania NA. Acute asthma in pregnancy. Crit Care Clin 2004 Oct;20(4):731-45, x.

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

(56) 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.

(57) Working group on asthma and pregnancy. National asthma education program (NAEP) report of the working group on asthma and pregnancy: management of asthma during pregnancy. 1993. Report No.: PB96-141593 (at the US Dpt of Commerce) (Report# 93-3279 is the reference number at NIH).

(58) Norjavaara E, de Verdier MG. Normal pregnancy outcomes in a population-based study including 2968 pregnant women exposed to budesonide. Journal of Allergy and Clinical Immunology 2003 Apr;111(4):736-42.

(59) Briggs GB, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation. Seventh ed. Lippincott Williams&Wilkins; 2005.

(60) Blais L, Beauchesne M-F, Rey É, Malo JL, Forget A. Use of inhaled corticosteroids during the first trimester and the risk of congenital malformations among asthmatic pregnant women. Pharmacoepidemiology and drug safety 2004;13:S125.

(61) Fitzsimons R, Greenberger PA, Patterson R. Outcome of pregnancy in women requiring corticosteroids for severe asthma. J Allergy Clin Immunol 1986 Aug;78(2):349-53.

(62) Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000 Dec;62(6):385-92.

(63) Olesen C, Thrane N, Nielsen GL, Sorensen HT, Olsen J. A population-based prescription study of asthma drugs during pregnancy: changing the intensity of asthma therapy and perinatal outcomes. Respiration 2001;68(3):256-61.

(64) Campbell LA, Klocke RA. Implications for the pregnant patient. Am J Respir Crit Care Med 2001 Apr;163(5):1051-4.

(65) Hansen WF, Yankowitz J. Pharmacologic therapy for medical disorders during pregnancy. Clin Obstet Gynecol 2002 Mar;45(1):136-52.

(66) Greenberger PA, Patterson R. Beclomethasone diproprionate for severe asthma during pregnancy. Ann Intern Med 1983 Apr;98(4):478-80.

(67) Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. Teratology 1997 Nov;56(5):335-40.

(68) Tamasi L, Somoskovi A, Muller V, Bartfai Z, Acs N, Puho E, et al. A population-based case-control study on the effect of bronchial asthma during pregnancy for congenital abnormalities of the offspring. Journal of Asthma 2006;43(1):81-6.

(69) Tata L, Lewis S, McKeever T, Smith C, Doyle P, Smeeth L, et al. A Comprehensive Analysis of Adverse Obstetric and Pediatric Complications in Women with Asthma. Am J Respir Crit Care Med 2007;175:991-7.

(70) Jadad AR, Sigouin C, Mohide PT, Levine M, Fuentes M. Risk of congenital malformations associated with treatment of asthma during early pregnancy [letter]. Lancet 2000 Jan 8;355(9198):119.

(71) NAEPP Expert Panel Report. Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment-2004 Update. Journal of Allergy and Clinical Immunology 2005;115:34-46.

(72) Tan KS, Thomson NC. Asthma in pregnancy. Am J Med 2000 Dec 15;109(9):727-33.

(73) American College of Obstetricians and Gynecologist, American College of Allergy AaI. The use of newer asthma and allergy medications during pregnancy. Annals of Allergy, Asthma & Immunology 2000 May 1;84:475-80.

(74) Clark SL. Asthma in pregnancy. National Asthma Education Program Working Group on Asthma and Pregnancy. National Institutes of Health, National Heart, Lung and Blood Institute [see comments]. Obstet Gynecol 1993 Dec;82(6):1036-40.

(75) Belanger K, Triche EW, Leaderer BP, Hellenbrand K, Bracken MB. Asthma treatment during pregnancy: Are National Guidelines Being Met? 2002.

(76) Chambers K. Asthma education and outcomes for women of childbearing age. Case Manager 2003 Nov;14(6):58-61.

(77) Schatz M, Harden K, Forsythe A, Chilingar L, Hoffman C, Sperling W, et al. The course of asthma during pregnancy, post partum, and with successive pregnancies: a prospective analysis. J Allergy Clin Immunol 1988 Mar;81(3):509-17.

(78) Gluck LC. The change of asthma course during pregnancy. Clinical Reviews in Allergy & Immunology 2004 Jun;26(3):171-80.

(79) Schatz M. Interrelationships between asthma and pregnancy: a literature review. J Allergy Clin Immunol 1999 Feb;103(2 Pt 2):S330-S336.

(80) Kwon HL, Belanger K, Bracken MB. Effect of pregnancy and stage of pregnancy on asthma severity: A systemic review. American Journal of Obstetrics and Gynecology 2004;190(5):1201-10.

(81) Gluck JC, Gluck P. The effects of pregnancy on asthma: a prospective study. Ann Allergy 1976 Sep;37(3):164-8.

(82) White RJ, Coutts II, Gibbs CJ, MacIntyre C. A prospective study of asthma during pregnancy and the puerperium. Respir Med 1989 Mar;83(2):103-6.

(83) Holbreich M. Asthma and other allergic disorders in pregnancy. Am Fam Physician 1982 Mar;25(3):187-92.

(84) Baibergenova A, Thabane L, Akhtar-Danesh N, Levine M, Gafni A. Is fetal gender associated with emergency department visits for asthma during pregnancy? Journal of Asthma 2006 May;43(4):293-9.

(85) Murphy VE, Gibson PG, Giles WB, Zakar T, Smith R, Bisits AM, et al. Maternal asthma is associated with reduced female fetal growth. American Journal of Respiratory and Critical Care Medicine 2003 Dec 1;168(11):1317-23.

(86) Clifton VL, Murphy VE. Maternal asthma as a Model for examining fetal sex-specific effects on maternal physiology and placental mechanisms that regulate human fetal growth. Placenta 2004;18(Supplement A, Trophoblast Research):S45-S52.

(87) Murphy VE, Gibson PG, Smith R, Clifton VL. Asthma during pregnancy: mechanisms and treatment implications. Eur Respir J 2005 Apr;25(4):731-50.

(88) Clifton VL. Sexually dimorphic effects of maternal asthma during pregnancy on placental glucocorticoid metabolism and fetal growth. Cell and Tissue Research 2005 Oct;322(1):63-71.

(89) Lehrer S, Stone J, Lapinski R, Lockwood CJ, Schachter BS, Berkowitz R, et al. Association between pregnancy-induced hypertension and asthma during pregnancy. Am J Obstet Gynecol 1993 May;168(5):1463-6.

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

(91) 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.

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

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

(94) Minerbi-Codish I, Fraser D, Avnun L, Glezerman M, Heimer D. Influence of asthma in pregnancy on labor and the newborn. Respiration 1998;65(2):130-5.

(95) Sheiner E, Mazor M, Levy A, Wiznitzer A, Bashiri A. Pregnancy outcome of asthmatic patients: A population-based study. Journal of Maternal-Fetal & Neonatal Medicine 2005 Oct;18(4):237-40.

(96) 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.

(97) Kallen B, Otterblad OP. Use of anti-asthmatic drugs during pregnancy. 2. Infant characteristics excluding congenital malformations. Eur J Clin Pharmacol 2007 Apr;63(4):375-81.

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

(99) 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.

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

(101) Clark JM, Hulme E, Devendrakumar V, Turner MA, Baker PN, Sibley CP, et al. Effect of maternal asthma on birthweight and neonatal outcome in a British inner-city population. Paediatric and Perinatal Epidemiology 2007 Mar;21(2):154-62.

(102) 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.

(103) 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.

(104) SteniusAarniala BSM, Hedman J, Teramo KA. Acute asthma during pregnancy. Thorax 1996 Apr;51(4):411-4.

(105) Schatz M, Zeiger RS, Harden KM, Hoffman CP, Forsythe AB, Chilingar LM, et al. The safety of inhaled beta-agonist bronchodilators during pregnancy. J Allergy Clin Immunol 1988 Oct;82(4):686-95.

(106) Greenberger PA, Patterson R. The outcome of pregnancy complicated by severe asthma. Allergy Proc 1988 Sep;9(5):539-43.

(107) Schatz M, Patterson R, Zeitz S, O'Rourke J, Melam H. Corticosteroid therapy for the pregnant asthmatic patient. JAMA 1975 Aug 18;233(7):804-7.

(108) Stenius-Aarniala B, Riikonen S, Teramo K. Slow-release theophylline in pregnant asthmatics [published erratum appears in Chest 1996 Jun;109(6):1668]. Chest 1995 Mar;107(3):642-7.

(109) Mihrshahi S, Belousova E, Marks GB, Peat JK. Pregnancy and birth outcomes in families with asthma. Journal of Asthma 2003;40(2):181-7.

(110) Schatz M. The efficacy and safety of asthma medications during pregnancy. Seminars in Perinatology 2001 Jun;25(3):145-52.

(111) Dombrowski MP, Bottoms SF, Boike GM, Wald J. Incidence of preeclampsia among asthmatic patients lower with theophylline. Am J Obstet Gynecol 1986 Aug;155(2):265-7.

(112) Sobande AA, Archibong EI, Akinola SE. Pregnancy outcome in asthmatic patients from high altitudes. Int J Gynaecol Obstet 2002 May;77(2):117-21.

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

(114) Corchia C, Bertollini R, Forastiere F, Pistelli R, Perucci C. Is maternal asthma a risk factor for low birth weight? Results of an epidemiologic survey. European Journal of Epidemiology 1995 Dec;11(6):627-31.

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

(116) Acs N, Puho E, Banhidy F, Czeizel AE. Association between bronchial asthma in pregnancy and shorter gestational age in a population-based study. J Matern Fetal Neonatal Med 2005 Aug;18(2):107-12.

(117) Combescure C, Chanez P, Saint-Pierre P, Daures JP, Proudhon H, Godard P. Assessment of variations in control of asthma over time. European Respiratory Journal 2003 Aug;22(2):298-304.

(118) National Asthma Education and Prevention Program Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. 1997 Apr 1. Report No.: 97-4051.

(119) Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. Thorax 1996 Apr;51(4):411-4.

(120) Braems G. Fetal hypoxemia on a molecular level: adaptive changes in the hypothalamic-pituitary-adrenal (HPA) axis and the lungs. European Journal of Obstetrics Gynecology and Reproductive Biology 2003 Sep 22;110:S63-S69.

(121) Schatz M, Dombrowski MP, Wise R, Momirova V, Landon M, Mabie W, et al. Spirometry is related to perinatal outcomes in pregnant women with asthma. American Journal of Obstetrics and Gynecology 2006 Jan;194(1):120-6.

(122) Bakhireva LN, Schatz M, Jones KL, Chambers CD. Asthma control during pregnancy and the risk of preterm delivery or impaired fetal growth. Ann Allergy Asthma Immunol 2008 Aug;101(2):137-43.

(123) Murphy VE, Gibson P, Talbot PL, Clifton VL. Severe asthma exacerbations during pregnancy. Obstetrics and Gynecology 2005 Nov;106(5):1046-54.

(124) Weiss JL, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH, et al. Threatened abortion: A risk factor for poor pregnancy outcome, a population-based screening study. American Journal of Obstetrics and Gynecology 2004 Mar;190(3):745-50.

(125) 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.

(126) Meis PJ, Michielutte R, Peters TJ, Wells HB, Sands RE, Coles EC, et al. Factors Associated with Preterm Birth in Cardiff, Wales .2. Indicated and Spontaneous Preterm Birth. American Journal of Obstetrics and Gynecology 1995 Aug;173(2):597-602.

(127) Odegard RA, Vatten LJ, Nilsen ST, Salvesen KA, Austgulen R. Preeclampsia and fetal growth. Obstetrics and Gynecology 2000 Dec;96(6):950-5.

(128) Cheng CJ, Bommarito K, Noguchi A, Holcomb W, Leet T. Body mass index change between pregnancies and small for gestational age births. Obstetrics and Gynecology 2004 Aug;104(2):286-92.

(129) Kramer MS, Platt R, Yang H, McNamara H, Usher RH. Are all growth-restricted newborns created equal(ly)? Pediatrics 1999 Mar;103(3):599-602.

(130) Miller HC, Jekel JF. Associations Between Unfavorable Outcomes in Successive Pregnancies. American Journal of Obstetrics and Gynecology 1985;153(1):20-4.

(131) Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, GilstrapIII LC, Wenstrom KD. Williams Obstetrics. Twenty-Second ed. McGraw-Hill; 2005.

(132) Fraser AM, Brockert JE, Ward RH. Association of Young Maternal Age with Adverse Reproductive Outcomes. New England Journal of Medicine 1995 Apr 27;332(17):1113-7.

(133) Klebanoff MA, Graubard BI, Kessel SS, Berendes HW. Low-Birth-Weight Across Generations. Jama-Journal of the American Medical Association 1984;252(17):2423-7.

(134) 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.

(135) Cnattingius S, Bergstrom R, Lipworth L, Kramer MS. Prepregnancy weight and the risk of adverse pregnancy outcomes. N Engl J Med 1998 Jan 15;338(3):147-52.

(136) Hickey CA, Cliver SP, Mcneal SF, Hoffman HJ, Goldenberg RL. Prenatal Weight-Gain Patterns and Spontaneous Preterm Birth Among Nonobese Black-And-White Women. Obstetrics and Gynecology 1995 Jun;85(6):909-14.

(137) Kleijer ME, Dekker GA, Heard AR. Risk factors for intrauterine growth restriction in a socio-economically disadvantaged region. Journal of Maternal-Fetal & Neonatal Medicine 2005 Jul;18(1):23-30.

(138) Kharrazi M, DeLorenze G, Kaufman FL, Eskenazi B, Bernert JT, Graham S, et al. Environmental tobacco smoke and pregnancy outcome. Epidemiology 2004;15(6):660-70.

(139) Windham GC, Eaton A, Hopkins B. Evidence for an association between environmental tobacco smoke exposure and birthweight: a metaanalysis and new data. Paediatric and Perinatal Epidemiology 1999 Jan;13(1):35-57.

(140) Hanke W, Sobala W, kalinka J. Environmental tobacco smoke exposure among pregnant women: impact on fetal biometry at 20-24 weeks of gestation and newborn child's birth weight. Int Arch Occup Environ Health 2004;77:47-52.

(141) Dejmek J, Solansky I, Podrazilova K, Sram RJ. The exposure of nonsmoking and smoking mothers to environmental tobacco smoke during different gestational phases and fetal growth. Environmental Health Perspectives 2002 Jun;110(6):601-6.

(142) 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.

(143) 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.

(144) Peacock JL, Bland JM, Anderson HR. Preterm Delivery - Effects of Socioeconomic-Factors, Psychological Stress, Smoking, Alcohol, and Caffeine. British Medical Journal 1995 Aug 26;311(7004):531-5.

(145) Lieberman E, Gremy I, Lang J, Chen A. Low birthweight at term and the timing of fetal exposure to maternal smoking. Am J Pub Hlth 1994;84(7):1127-31.

(146) 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.

(147) 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.

(148) Lundsberg LS, Bracken MB, Saftlas AF. Low-to-moderate gestational alcohol use and intrauterine growth retardation, low birthweight, and preterm delivery. Annals of Epidemiology 1997 Oct;7(7):498-508.

(149) Hoffman, Jodi D. Genetic factors in preterm delivery. Obstetrical and gynecological survey 1999;54(3):203-10.

(150) 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.

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

(152) Shankaran S, Das A, Bauer CR, Bada HS, Lester B, Wright LL, et al. Association between patterns of maternal substance use and infant birth weight, length, and head circumference. Pediatrics 2004 Aug;114(2):226-34.

(153) Eyler FD, Behnke M, Conlon M, Woods NS, Wobie K. Birth outcome from a prospective, matched study of prenatal crack/cocaine use: I. Interactive and dose effects on health and growth. Pediatrics 1998 Feb;101(2):229-37.

(154) Bandstra ES, Morrow CE, Anthony JC, Churchill SS, Chitwood DC, Steele BW, et al. Intrauterine growth of full-term infants: Impact of prenatal cocaine exposure. Pediatrics 2001 Dec;108(6):1309-19.

(155) 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.

(156) 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.

(157) Bloom SL, Yost NP, McIntire DD, Leveno KJ. Recurrence of preterm birth in singleton and twin pregnancies. Obstetrics and Gynecology 2001 Sep;98(3):379-85.

(158) Meis PJ, Michielutte R, Peters TJ, Wells HB, Sands RE, Coles EC, et al. Factors Associated with Preterm Birth in Cardiff, Wales .1. Univariable and Multivariable Analysis. American Journal of Obstetrics and Gynecology 1995 Aug;173(2):590-6.

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

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

(161) 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.

(162) Rawlings JS, Rawlings VB, Read JA. Prevalence of Low-Birth-Weight and Preterm Delivery in Relation to the Interval Between Pregnancies Among White and Black-Women. New England Journal of Medicine 1995 Jan 12;332(2):69-74.

(163) Zhu BP, Rolfs RT, Nangle BE, Horan JM. Effect of the interval between pregnancies on perinatal outcomes. New England Journal of Medicine 1999 Feb 25;340(8):589-94.

(164) Lasker JN, Coyle B, Li K, Ortynsky M. Assessment of risk factors for low birth weight deliveries. Health Care Women Int 2005 Mar;26(3):262-80.

(165) Valero De BJ, Soriano T, Albaladejo R, Juarranz M, Calle ME, Martinez D, et al. Risk factors for low birth weight: a review. Eur J Obstet Gynecol Reprod Biol 2004 Sep 10;116(1):3-15.

(166) Tierney-Gumaer R, Reifsnider E. Risk factors for low birth weight infants of Hispanic, African American, and White women in Bexar County, Texas. Public Health Nurs 2008 Sep;25(5):390-400.

(167) Valero De BJ, Soriano T, Albaladejo R, Juarranz M, Calle ME, Martinez D, et al. Risk factors for low birth weight: a review. Eur J Obstet Gynecol Reprod Biol 2004 Sep 10;116(1):3-15.

(168) Lund R, Modvig J, Hilden J, Rosdahl N, Kure L, Schmidt K. Risk of low birthweight in social districts of Copenhagen. Scand J Public Health 1999 Jun;27(2):89-93.

(169) Valero De BJ, Soriano T, Albaladejo R, Juarranz M, Calle ME, Martinez D, et al. Risk factors for low birth weight: a review. Eur J Obstet Gynecol Reprod Biol 2004 Sep 10;116(1):3-15.

(170) Valero De BJ, Soriano T, Albaladejo R, Juarranz M, Calle ME, Martinez D, et al. Risk factors for low birth weight: a review. Eur J Obstet Gynecol Reprod Biol 2004 Sep 10;116(1):3-15.

(171) McIntosh LJ, Roumayah NE, Bottoms SF. Perinatal outcome of broken marriage in the inner city. Obstet Gynecol 1995 Feb;85(2):233-6.

(172) Lasker JN, Coyle B, Li K, Ortynsky M. Assessment of risk factors for low birth weight deliveries. Health Care Women Int 2005 Mar;26(3):262-80.

(173) Lasker JN, Coyle B, Li K, Ortynsky M. Assessment of risk factors for low birth weight deliveries. Health Care Women Int 2005 Mar;26(3):262-80.

(174) Lasker JN, Coyle B, Li K, Ortynsky M. Assessment of risk factors for low birth weight deliveries. Health Care Women Int 2005 Mar;26(3):262-80.

(175) Levy A, Fraser D, Katz M, Mazor M, Sheiner E. Maternal anemia during pregnancy is an independent risk factor for low birthweight and preterm delivery. Eur J Obstet Gynecol Reprod Biol 2005 Oct 1;122(2):182-6.

(176) Levy A, Fraser D, Katz M, Mazor M, Sheiner E. Maternal anemia during pregnancy is an independent risk factor for low birthweight and preterm delivery. Eur J Obstet Gynecol Reprod Biol 2005 Oct 1;122(2):182-6.

(177) Dasanayake AP. Poor periodontal health of the pregnant woman as a risk factor for low birth weight. Ann Periodontol 1998 Jul;3(1):206-12.

(178) Markson LE, Turner BJ, Houchens R, Silverman NS, Cosler L, Takyi BK. Association of maternal HIV infection with low birth weight. J Acquir Immune Defic Syndr Hum Retrovirol 1996 Nov 1;13(3):227-34.

(179) French JI, McGregor JA, Draper D, Parker R, McFee J. Gestational bleeding, bacterial vaginosis, and common reproductive tract infections: risk for preterm birth and benefit of treatment. Obstet Gynecol 1999 May;93(5 Pt 1):715-24.

(180) Noble A, Ning Y, Woelk GB, Mahomed K, Williams MA. Preterm delivery risk in relation to maternal HIV infection, history of malaria and other infections among urban Zimbabwean women. Cent Afr J Med 2005 May;51(5-6):53-8.

(181) Valero De BJ, Soriano T, Albaladejo R, Juarranz M, Calle ME, Martinez D, et al. Risk factors for low birth weight: a review. Eur J Obstet Gynecol Reprod Biol 2004 Sep 10;116(1):3-15.

(182) Ehrenberg HM, Dierker L, Milluzzi C, Mercer BM. Low maternal weight, failure to thrive in pregnancy, and adverse pregnancy outcomes. Am J Obstet Gynecol 2003 Dec;189(6):1726-30.

(183) Gordis L. Epidemiology. Third ed. Elsevier Saunders; 2004.

(184) 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.

(185) 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.

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

(187) 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.

(188) 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.

(189) 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.

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

(191) 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):35.

(192) Vilain A, Otis S, Forget A, Blais L. Agreement between administrative databases and medical charts for pregnancy-related variables among asthmatic women. Pharmacoepidemiology and drug safety 2008 Apr;17(4):345-53.

(193) Blais L, Lemière C, Menzies D, Berbiche D. Validity of asthma diagnoses recorded in the Medical Services database of Quebec. Pharmacoepidemiology and drug safety 2005 Dec 23;15 :245-52.

(194) Blais L, Beauchesne M-F, Lévesque S. Socioeconomic status and medication prescription partterns in pediatric asthma in Canada. Journal of Adolescent Health 2006;38(5):607 e9-607 e16.

(195) 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.

(196) 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.

(197) Cockcroft DW, Swystun VA. Asthma control versus asthma severity. Journal of Allergy and Clinical Immunology 1996 Dec;98(6):1016-8.

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

(199) Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986 Mar;42(1):121-30.

(200) Hosmer DW, Lemeshow S. Applied Logistic Regression. 2nd ed. John Wiley & Sons, Inc.; 2000.

(201) Kleinbaum DG, Klein M. Statistics for Biology and Health. 2nd ed. Springer; 2002.

(202) Blais L, Desgagne A, LeLorier J. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the risk of cancer: a nested case-control study. Arch Intern Med 2000 Aug 14;160(15):2363-8.

(203) Garbe E, LeLorier J, Boivin J-F, Suissa S. Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. Lancet 1997;350:979-82.

(204) Blais L, Suissa S, Boivin JF, Ernst P. First treatment with inhaled corticosteroids and the prevention of admissions to hospital for asthma. Thorax 1998 Dec;53(12):1025-9.

(205) Blais L, Ernst P, Boivin JF, Suissa S. Inhaled corticosteroids and the prevention of readmission to hospital for asthma. Am J Respir Crit Care Med 1998 Jul;158(1):126-32.

(206) Eisner MD, Ackerson LM, Chi F, Kalkbrenner A, Buchner D, Mendoza G, et al. Health-related quality of life and future health care utilization for asthma. Ann Allergy Asthma Immunol 2002 Jul;89(1):46-55.

(207) Ungar WJ, Chapman KR, Santos MT. Assessment of a medication-based asthma index for population research. Am J Respir Crit Care Med 2002 Jan 15;165(2):190-4.

(208) Atta JA, Nunes MPT, Fonseca-Guedes CHF, Avena LA, Borgiani MT, Fiorenza RF, et al. Patient and physician evaluation of the severity of acute asthma exacerbations. Brazilian Journal of Medical and Biological Research 2004 Sep;37(9):1321-30.

(209) Vollmer WM, Markson LE, O'Connor E, Sanocki LL, Fitterman L, Berger M, et al. Association of asthma control with health care utilization and quality of life. Am J Respir Crit Care Med 1999 Nov;160(5 Pt 1):1647-52.

(210) Lee S, Kirking DM, Erickson SR. Methods of measuring asthma severity and influence on patient assignment. Ann Allergy Asthma Immunol 2003 Nov;91(5):449-54.

(211) Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999 Oct;14(4):902-7.

(212) Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol 2004 Jan;113(1):59-65.

(213) Blais L, Lemière C, Berbiche D. Validation of asthma diagnostic codes in the administrative health databases of Québec, Canada. Pharmacoepidemiology and drug safety 2004;13 :S32.

(214) Blais L, Beauchesne MF. Use of inhaled corticosteroids following discharge from an emergency department for an acute exacerbation of asthma. Thorax 2004 Nov;59(11):943-7.

(215) Blais L, Beauchesne M-F, Lévesque S. Socio-economic status and medication patterns in pediatric asthma in Canada. Journal of Adolescent Health 2006;under publication.

(216) Liard R, Leynaert B, Zureik M, Beguin FX, Neukirch F. Using Global Initiative for Asthma guidelines to assess asthma severity in populations. Eur Respir J 2000 Oct;16(4):615-20.

(217) Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. J Allergy Clin Immunol 2004 Jul;114(1):40-7.

(218) Fuhlbrigge AL. Asthma severity and asthma control: symptoms, pulmonary function, and inflammatory markers. Curr Opin Pulm Med 2004 Jan;10(1):1-6.

(219) Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben Joseph RH. Inhaled corticosteroids for asthma therapy - Patient compliance, devices, and inhalation technique. Chest 2000 Feb;117(2):542-50.

(220) Paganini-Hill A, Ross RK. Reliability of recall of drug usage and other health-related information. Am J Epidemiol 1982 Jul;116(1):114-22.

(221) Van den Brandt PA, Petri H, Dorant E, Goldbohm RA, Van de CS. Comparison of questionnaire information and pharmacy data on drug use. Pharm Weekbl [Sci ] 1991 Apr 26;13(2):91-6.

(222) West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. Am J Epidemiol 1995 Nov 15;142(10):1103-12.

(223) Metlay JP, Hardy C, Strom BL. Agreement between-patient self-report and a Veterans Affairs national pharmacy database for identifying recent exposures to antibiotics. Pharmacoepidemiology and drug safety 2003 Jan;12(1):9-15.

(224) Clifton VL. Sexually dimorphic effects of maternal asthma during pregnancy on placental glucocorticoid metabolism and fetal growth. Cell and Tissue Research 2005 Oct;322(1):63-71.

(225) 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.

(226) 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.

(227) 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).

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

(229) 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.

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

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

(232) Almqvist C, Pershagen G, Wickman M. Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. Clinical and Experimental Allergy 2005 May;35(5):612-8.

(233) Lynd LD, Sandford AJ, Kelly EM, Pare PD, Bai TR, FitzGerald M, et al. A cross-sectional study of the relationship between socioeconomic status and the magnitude of short-acting beta-agonist use in asthma. Chest 2004 Oct;126(4):1161-8.

(234) Schatz M, Dombrowski M. Outcomes of pregnancy in asthmatic women. Immunology and Allergy Clinics of North America 2000 Nov;20(4):715-+.

(235) Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. Thorax 1996 Apr;51(4):411-4.

(236) 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).

(237) 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.

(238) Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. Thorax 1996 Apr;51(4):411-4.

(239) 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).

(240) 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).

(241) 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.

(242) 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).

(243) Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. Thorax 1996 Apr;51(4):411-4.

(244) Balzano G, Fuschillo S, Melillo G, Bonini S. Asthma and sex hormones. Allergy 2001 Jan;56(1):13-20.

(245) Prudhomme A. Influence du sexe féminin sur l'asthme. Rev Pneumol Clin 1999 Oct;55(5):296-300.

(246) Rothman KJ, Greenland S. Precision and Validity in Epidemiologic Studies. Modern Epidemiology. second ed. Philadelphia: Lippincott-Raven; 1998. p. 115-34.

(247) Tilley BC, Barnes AB, Bergstralh E, Labarthe D, Noller KL, Colton T, et al. A comparison of pregnancy history recall and medical records. Implications for retrospective studies. Am J Epidemiol 1985 Feb;121(2):269-81.

(248) McKnight J, Scott A, Menzies D, Bourbeau J, Blais L, Lemiere C. A cohort study showed that health insurance databases were accurate to distinguish chronic obstructive pulmonary disease from asthma and classify disease severity. J Clin Epidemiol 2005 Feb;58(2):206-8.

(249) Rothman KJ, Greenland S. Modern epidemiology. Second ed. Lippincott Williams & Wilkins; 1998.

(250) Rothman KJ. Epidemiology, an Introduction. Oxford University press; 2002.

(251) Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, FitzGerald JM, Hernandez P, et al. Overdiagnosis of asthma in obese and nonobese adults. CMAJ 2008 Nov 18;179(11):1121-31.

(252) Stupka E, deShazo R. Asthma in seniors: Part 1. Evidence for underdiagnosis, undertreatment, and increasing morbidity and mortality. Am J Med 2009 Jan;122(1):6-11.

(253) Einarson A, Selby P., Koren G. Abrupt discontinuation of psychotropic drugs during pregnancy: fear of teratogenic risk and impact of counselling. Journal of Psychiatry & Neuroscience 2001 Jan;26(1):44-8.

(254) Williams J, Myson V, Steward S, Jones G, Wilson JF, Kerr MP, et al. Self-discontinuation of antiepileptic medication in pregnancy: Detection by hair analysis. Epilepsia 2002 Aug;43(8):824-31.

(255) Einarson A. Rate of antidepressant discontinuation during pregnancy: cause of concern. 2002.

(256) Marcus M S, Flynn HA, Barry KL, Blow FC. Antidepressant Medication Discontinuation in pregnancy: weighing the risks. 2002.

# Appendix A

## Questionnaires

# Appendix B

## List of asthma medications

### 1. Bronchodilatateurs beta-agoniste inhalés à courte durée d'action

*3380* épinéphrine (bitartrate d')

2639 Suspension Aérosol avec applicateur

*3406* épinéphrine (chlorhydrate d')

1856 Solution Aérosol

*3419* épinéphrine racémique (chlorhydrate d')

1972 Solution pour Inhalation

*6721* orciprénaline (sulfate d')

1972 Solution pour Inhalation

2610 Suspension Aérosol

*10530* salbutamol

1856 Solution Aérosol

5584 Aérosol oral

*33634* salbutamol (sulfate de)

1305 Poudre Aérosol

1334 Poudre Aérosol avec applicateur

1972 Solution pour Inhalation

5563 Poudre pour inhalation avec applicateur

5564 Poudre pour inhalation

5619 Poudre pour inhalation applicateur

*34180* terbutaline (sulfate de)

1334 Poudre Aérosol avec applicateur

5563 Poudre pour inhalation avec applicateur

5564 Poudre pour inhalation

5619 Poudre pour inhalation applicateur

*38548* fénotérol (bromhydrate de)

1305 Poudre Aérosol

1972 Solution pour Inhalation

*46299* pirbutérol (acétate de) 46299 *

5584 Aérosol oral

*46737* salbutamol (sulfate de) 46737 *

1305 Poudre Aérosol

1334 Poudre Aérosol avec applicateur

1972 Solution pour Inhalation

5563 Poudre pour inhalation avec applicateur

5564 Poudre pour inhalation

5619 Poudre pour inhalation applicateur

*47153* pirbutérol (acétate de)

5584 Aérosol oral

**2. Bronchodilatateurs beta-agoniste inhalés à longue durée d'action**

*46247* salmétérol (xinafoate de) 46247 *

5563 Poudre pour inhalation avec applicateur

5564 Poudre pour inhalation

5584 Aérosol oral

5619 Poudre pour inhalation applicateur

*46430* formoterol (fumarate dihydraté de) 46430 *

5564 Poudre pour inhalation

*47112* salmétérol (xinafoate de)

5563 Poudre pour inhalation avec applicateur

5564 Poudre pour inhalation

5584 Aérosol oral

5619 Poudre pour inhalation applicateur

*47231* formoterol (fumarate de)

5564 Poudre pour inhalation

*47271* formoterol (fumarate dihydrate de)

5564 Poudre pour inhalation

**3. Bronchodilatateurs anticholinergique à courte durée d'action**

*43124* ipratropium (bromure d')

1885 Solution Aérosol avec applicateur

1972 Solution pour Inhalation

5584 Aérosol oral

*46640* ipratropium (bromure d') 46640 *

1885 Solution Aérosol avec applicateur

1972 Solution pour Inhalation

5584 Aérosol oral

**4. Bronchodilatateurs théophylline**

*364* aminophylline

203 Comprimé

435 Comprimé Longue Action

2117 Solution Injectable I.V.

2262 Solution Orale

*9464* théophylline

116 Capsule

145 Capsule Longue Action

203 Comprimé

435 Comprimé Longue Action

754 Elixir

1827 Sirop

2262 Solution Orale

5075 Solution sans Alcool

5555 Solution sans sucre

5606 Solution orale sans sucre

5607 Elixir sans sucre

5611 Capsule longue action

*9490* théophylline (aminoacétate calcique de)

203 Comprimé

*9503* théophylline (aminoacétate sodique de)

203 Comprimé

*43475* oxtriphylline

203 Comprimé

435 Comprimé Longue Action

754 Elixir

1827 Sirop

*46428* aminophylline 46428 *

203 Comprimé

435 Comprimé Longue Action

2117 Solution Injectable I.V.

2262 Solution Orale

*46847* théophylline

116 Capsule

145 Capsule Longue Action

203 Comprimé

435 Comprimé Longue Action

754 Elixir

1827 Sirop

2262 Solution Orale

5075 Solution sans Alcool

5555 Solution sans sucre

5606 Solution orale sans sucre

5607 Elixir sans sucre

5611 Capsule longue action

**5. Bronchodilatateurs beta-agonistes oral à courte durée d'action**

*6721* orciprénaline (sulfate d')

203 Comprimé

1827 Sirop

*33634* salbutamol (sulfate de)

203 Comprimé

2262 Solution Orale

*34180* terbutaline (sulfate de)

203 Comprimé

*38548* fénotérol (bromhydrate de)

203 Comprimé

*46737* salbutamol (sulfate de) 46737 *

203 Comprimé

2262 Solution Orale

**6. Corticostéroïdes inhalé**

*780* béclométhasone (dipropionate de)

1305 Poudre Aérosol

1334 Poudre Aérosol avec applicateur

1856 Solution Aérosol

5563 Poudre pour inhalation avec applicateur

5564 Poudre pour inhalation

5584 Aérosol oral

5619 Poudre pour inhalation applicateur

***Catégorie dencom forme***

*9737* triamcinolone (acétonide de)

1856 Solution Aérosol

5584 Aérosol oral

*38730* flunisolide

1856 Solution Aérosol

5584 Aérosol oral

*45499* budésonide

1856 Solution Aérosol

1972 Solution pour Inhalation

5563 Poudre pour inhalation avec applicateur

5564 Poudre pour inhalation

5619 Poudre pour inhalation applicateur

*46345* fluticasone (propionate de) 46345 *

5564 Poudre pour inhalation

5584 Aérosol oral

*47050* fluticasone (propionate de)

5564 Poudre pour inhalation

5584 Aérosol oral

*47213* flunisolide *

1856 Solution Aérosol

5584 Aérosol oral

**7. Anti-allergiques cromoglycate**

*2223* cromoglycate disodique

1305 Poudre Aérosol

1334 Poudre Aérosol avec applicateur

1972 Solution pour Inhalation

5563 Poudre pour inhalation avec applicateur

5564 Poudre pour inhalation

5584 Aérosol oral

5619 Poudre pour inhalation applicateur

*39419* cromoglicate sodique

1305 Poudre Aérosol

1334 Poudre Aérosol avec applicateur

1972 Solution pour Inhalation

5563 Poudre pour inhalation avec applicateur

5564 Poudre pour inhalation

5584 Aérosol oral

5619 Poudre pour inhalation applicateur

*47315* cromolyn *

1305 Poudre Aérosol

1334 Poudre Aérosol avec applicateur

1972 Solution pour Inhalation

5563 Poudre pour inhalation avec applicateur

5564 Poudre pour inhalation

5584 Aérosol oral

5619 Poudre pour inhalation applicateur

**8. Anti-allergiques nédocromil**

*45563* nédocromil sodique *

2610 Suspension Aérosol

5584 Aérosol oral

*46463* nédocromil sodique 46463 *

2610 Suspension Aérosol

5584 Aérosol oral

*47033* nédocromil sodique

2610 Suspension Aérosol

5584 Aérosol oral

**9. Antileucotriènes zafirlukast**

*46401* zafirlukast 46401 *

203 Comprimé

*47266* zafirlukast

203 Comprimé

**10. Antileucotriènes montelukast**

*46467* montélukast sodique 46467 *

203 Comprimé

464 Comprimé Masticable

*47302* montélukast sodique *

203 Comprimé

464 Comprimé Masticable

*47303* montélukast sodique

203 Comprimé

464 Comprimé Masticable

X

**11. Autres agents inhalés**

*5070* isoprotérénol (sulfate d')

2639 Suspension Aérosol avec applicateur

*5083* isoprotérénol (chlorhydrate d')

1856 Solution Aérosol

1972 Solution pour Inhalation

5584 Aérosol oral

*5096* isoprotérénol (chlorhydrate d')/ phényléphrine (bitartrate de)

2639 Suspension Aérosol avec applicateur

*5109* isoprotérénol (chlorhydrate d')/ phényléphrine (chlorhydrate de)

1856 Solution Aérosol

*45547* procatérol hémihydraté (chlorhydrate de)

1856 Solution Aérosol

5584 Aérosol oral

**12. Autres agents par voie orale**

*5083* isoprotérénol (chlorhydrate d')

493 Comprimé Sub-lingual

*45555* kétotifène (fumarate de)

203 Comprimé

1827 Sirop

*46752* kétotifène (fumarate de) 46752 *

203 Comprimé

1827 Sirop

**13. Produit de combinaison Bronchodilatateurs (beta-agoniste CA et antichol.)**

*46302* ipratropium (bromure d')/ salbutamol (sulfate de) 46302 *

1972 Solution pour Inhalation

5584 Aérosol oral

X

*47186* ipratropium (bromure d')/ salbutamol (sulfate de)

1972 Solution pour Inhalation

5584 Aérosol oral

**14. Produit de combinaison Bronchodilatateurs (beta-agoniste LA et CSI)**

*46597* salmétérol (xinafoate de)/ fluticasone(propionate de) 46597 *

5564 Poudre pour inhalation

5584 Aérosol oral

*46800* budésonide/formoterol(fumara- te dihydrate de) 46800 *

5564 Poudre pour inhalation

*47335* salmétérol (xinafoate de)/ fluticasone (propionate de)

5564 Poudre pour inhalation

5584 Aérosol oral

*47428* formotérol (fumarate dihydraté de)/budésonide

5564 Poudre pour inhalation

**15. Bronchodilatateurs beta-agoniste oral à longue durée d'action**

*33634* salbutamol (sulfate de)

435 Comprimé Longue Action

*46737* salbutamol (sulfate de) 46737 *

435 Comprimé Longue Action

# Appendix C

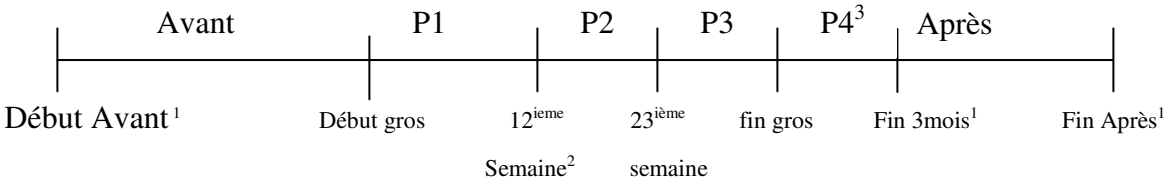
## VCF07_Diabète

**VCF= Variable confondante fixe dans le temps.**

### *BUT*

Création d'une variable indiquant pour chaque grossesse si la femme souffrait de diabète mellitus ou de diabète de grossesse.

### *Algorithme*




P1 = [ début de la grossesse, fin de la 12ième semaine de grossesse[2] ]

P2 = [ début de la 13ième semaine de grossesse, fin de la 23ième semaine de grossesse ]

P3 = [ début de la 24ième semaine de grossesse, fin de grossesse]

P4[3] = ] fin de la grossesse, *Fin 3mois*[1] ]

Après = ] *Fin 3mois*[1], *Fin Après*[1]]

## Diabète mellitus :

Si

1. Au moins un Rx[7] ou Dx[8] (DM/DG)[4] durant «avant» ou durant P1
   **ou**
2. Au moins un Rx ou Dx (DM/DG) durant P2 ou P3 **et** au moins un Dx (DM/DG) durant «après»[6]
   **ou**
3. Au moins un Dx (DM/DG) durant P4[5-6] **et** au moins un Dx (DM/DG) durant «après»

**alors DM=1.**

## Diabète gestationnel:

Si DM=0 et

1. Au moins un Rx ou Dx (DM/DG) durant P3 ou durant P2

ou

2. Au moins un Dx (DM/DG) durant P4

alors DG=1.

**********ATTENTION**********

Si au moins un code de syndrome des ovaires poly kystiques (code ICD-9 256.4) avant ou pendant la grossesse nous effectuerons ce même algorithme sans tenir compte des Rx

**********ATTENTION**********

## *NOTES*

[1] S'il existe une grossesse précédente (GP), nous établirons une borne supérieure à cette grossesse.

$$\textit{Borne GP} = \begin{cases} \text{fin de la GP} + 1 + 3 \text{ mois} & \text{si durée GP} \geq 12 \text{ semaines complètes} \\ \text{fin de la GP} + 1 & \text{si durée GP} < 12 \text{ semaines complètes} \end{cases}$$

Si *borne GP* est supérieure au début de la grossesse actuelle nous remplacerons Borne GP par le début de la grossesse actuelle.

Une fois cette borne trouvée nous choisirons la date maximale entre la borne de la grossesse précédente et un an avant la grossesse.

*Début Avant* = MAX (début de la grossesse-365 jours, *borne GP*)

ET

*Fin 3mois* = MIN (fin de la grossesse + 91 jours, début gros suivante - 1 )

*Fin Après* = MIN (fin gros +365 jours, début gros suivante - 1 )

[2] Habituellement le test de diabète gestationnel s'effectue entre la 24ième et la 28ième semaine de grossesse. Mais il peut aussi avoir lieu à la12 ième ou encore à la 20 ième semaine s'il y a des facteurs de risque important ( ex une femme qui pèserait 130 kg)

[3] Le diabète gestationnel prend généralement 6 semaines pour se résorber. Une minorité cependant peut prendre jusqu'à 3 mois avant que la glycémie ne redevienne normale. C'est pourquoi nous devons attendre 3 mois avant de vérifier si la maladie persiste.

[4] Tous les codes sont considérés comme un code de diabète peu importe s'il s'agit d'un code de diabète mellitus ou de diabète gestationnel. C'est plutôt le moment où ce code à été émis qui décidera s'il s'agit de diabète mellitus ou de diabète gestationnel.

[5] S'il n'y a eu aucun code et aucun rx durant la grossesse mais qu'il y a néanmoins un code durant la période 1-3 mois inclusivement après la grossesse, cela signifie qu'il y a eu quelques chose puisque qu'on lui fait passer le test pour voir si tout redevient normal après la grossesse. En effet, le test de diabète gestationnel n'est pas fait systématiquement après la grossesse. Il est effectué seulement chez celles qui ont eu du diabète gestionnel ou du diabète mellitus qui se serait développé après les 12 premières semaines de grossesse.

[6] Pour les périodes P4 et «Après» nous ne considérons pas les Rx puisque nous n'avons pas exigé que ces périodes soient couvertes par la RAMQ pour le remboursement des médicaments.

[7-8] Voir l'annexe pour les listes de médicaments et de codes pertinents.

## *Annexes*

# DX : Codes diagnostiques pour le diabète (Codes ICD-9)

- **DX(DM)**
  250.0 à 250.9 - Diabète mellitus
  648.0 - Diabète mellitus (code spécifique à la grossesse)

- **DX(DG)**
  648.8 - Diabète de gestationnel

## Rx : Prescription d'un médicaments pour le diabète

| *classe* | *dencom* | *forme* | |
|---|---|---|---|
| *Analogues méglitinide* | | | |
| 46810 | nateglinide | 203 | Comprimé |
| 47357 | répaglinide | 203 | Comprimé |
| 46568 | repaglinide 46568 * | 203 | Comprimé |
| *Biguanides* | | | |
| 47208 | metformine | 203 | Comprimé |
| 46862 | metformine ( chlorhydrate de)/ rosiglitazone (maléate de) | 0 | |
| 5824 | metformine (chlorhydrate de) | 203 | Comprimé |
| *Inh. alpha-glucosidose* | | | |
| 47151 | acarbose | 203 | Comprimé |
| 46300 | acarbose 46300 * | 203 | Comprimé |
| *Insulines* | | | |
| 47424 | insuline aspart | 2146 | Solution Injectable S.C. |
| 46798 | insuline aspart 46798 * | 2146 | Solution Injectable S.C. |
| 4823 | insuline globine zinc | 0 | |
| 46603 | insuline injectable(humaine) | 0 | |
| 39133 | insuline isophane (boeuf et porc) | 2755 | Suspension Injectable S.C. |
| 46537 | insuline isophane (boeuf et porc) 46537 * | 2755 | Suspension Injectable S.C. |

| | | | |
|---|---|---|---|
| 18348 | insuline isophane (boeuf) | 0 | |
| 39458 | insuline isophane (boeuf) * | 0 | |
| 18335 | insuline isophane (porc) | 2755 | Suspension Injectable S.C. |
| 44164 | insuline isophane bio-synthétique de séquence humaine | 2755 | Suspension Injectable S.C. |
| 44151 | insuline isophane semi-synthétique de séquence humaine | 2755 | Suspension Injectable S.C. |
| 46602 | insuline isophane(humaine) | 0 | |
| 46592 | insuline isophane(humaine)/ insuline injectable(humaine) | 0 | |
| 39120 | insuline lente (boeuf et porc) | 2755 | Suspension Injectable S.C. |
| 46538 | insuline lente (boeuf et porc) 46538 * | 2755 | Suspension Injectable S.C. |
| 41655 | insuline lente (porc) | 2755 | Suspension Injectable S.C. |
| 45415 | insuline lente bio-synthétique de séquence humaine | 2755 | Suspension Injectable S.C. |
| 44476 | insuline lente semi-synthétique de séquence humaine | 2755 | Suspension Injectable S.C. |
| 47206 | insuline lispro | 2146 | Solution Injectable S.C. |
| 47426 | insuline lispro / insuline lispro protamine | 2755 | Suspension Injectable S.C. |
| 46322 | insuline lispro 46322 * | 2755 | Suspension Injectable S.C. |
| 46607 | insuline lispro/insuline isophane (humaine) 46607 | 0 | |
| 39146 | insuline protamine zinc (boeuf et porc) | 2755 | Suspension Injectable S.C. |
| 18309 | insuline protamine zinc (boeuf) | 0 | |
| 39484 | insuline protamine zinc (boeuf) * | 0 | |
| 18322 | insuline protamine zinc (porc) | 0 | |
| 39497 | insuline protamine zinc (porc) * | 0 | |
| 39159 | insuline semilente (boeuf et porc) | 2755 | Suspension Injectable S.C. |
| 4888 | insuline sulfatée | 2755 | Suspension Injectable S.C. |

| *classe* | *dencom* | *forme* | |
|---|---|---|---|
| 39172 | insuline ultralente (boeuf et porc) | 2755 | Suspension Injectable S.C. |
| 45483 | insuline ultralente bio-synthétique de séquence humaine | 2755 | Suspension Injectable S.C. |
| 44996 | insuline ultralente semi-synthétique de séquence humaine | 2755 | Suspension Injectable S.C. |
| 39185 | insuline zinc cristalline (boeuf et porc) | 2146 | Solution Injectable S.C. |

| | | | |
|---|---|---|---|
| 46536 | insuline zinc cristalline (boeuf et porc) 46536 * | 2755 | Suspension Injectable S.C. |
| 43735 | insuline zinc cristalline (boeuf) | 0 | |
| 39523 | insuline zinc cristalline (boeuf) * | 0 | |
| 18296 | insuline zinc cristalline (porc) | 2146 | Solution Injectable S.C. |
| 18296 | insuline zinc cristalline (porc) | 2755 | Suspension Injectable S.C. |
| 47004 | insuline zinc cristalline (porc) * | 2146 | Solution Injectable S.C. |
| 47004 | insuline zinc cristalline (porc) * | 2755 | Suspension Injectable S.C. |
| 43033 | insuline zinc cristalline (porc)/insuline isophane (porc) | 2755 | Suspension Injectable S.C. |
| 44489 | insuline zinc cristalline bio-synthétique de séquence humaine | 2146 | Solution Injectable S.C. |
| 44502 | insuline zinc cristalline semi-synthétique de séquence humaine | 2146 | Solution Injectable S.C. |
| 45511 | insulines isophane et zinc cristalline bio-synthétique de séquence humaine | 2755 | Suspension Injectable S.C. |
| 45405 | insulines isophane et zinc cristalline semi-synthétiques de séquence humaine | 2755 | Suspension Injectable S.C. |
| 45531 | insulines zinc cristalline et isophane bio-synthétiques de séquence humaine | 2755 | Suspension Injectable S.C. |
| 45535 | insulines zinc cristalline et isophane de séquence humaine | 0 | |
| 45534 | insulines zinc cristalline et isophane semi-synthétiques de séquence humaine | 0 | |

### *Matériel médical*

| | | | |
|---|---|---|---|
| 43995 | réactif quantitatif du glucose dans le sang | 3828 | Bandelette |
| 43995 | réactif quantitatif du glucose dans le sang | 87 | Bâtonnet |
| 47350 | réactif quantitatif du glucose dans le sang ( one touch) | 3828 | Bandelette |
| 47350 | réactif quantitatif du glucose dans le sang ( one touch) | 87 | Bâtonnet |

### *Sulfonylurée*

| | | | |
|---|---|---|---|
| 91 | acétohexamide | 203 | Comprimé |
| 1937 | chlorpropamide | 203 | Comprimé |
| 47329 | gliclazide | 203 | Comprimé |
| 47329 | gliclazide | 435 | Comprimé Longue Action |
| 46056 | gliclazide 46056 * | 203 | Comprimé |
| 46056 | gliclazide 46056 * | 435 | Comprimé Longue Action |
| 47427 | glimépiride | 203 | Comprimé |

| | | | |
|---|---|---|---|
| 46799 | glimepiride 46799 * | 203 | Comprimé |
| 4264 | glyburide | 203 | Comprimé |
| 9672 | tolbutamide | 203 | Comprimé |
| 15184 | tolbutamide sodique | 203 | Comprimé |

### *Thiazolidinédiones*

| | | | |
|---|---|---|---|
| 47392 | pioglitazone (chlorhydrate de) | 203 | Comprimé |
| 46678 | pioglitazone (chlorhydrate de) 46678 * | 203 | Comprimé |
| 47371 | rosiglitazone (maléate de) | 203 | Comprimé |
| 46642 | rosiglitazone (maléate de) 46642 * | 203 | Comprimé |

# Appendix D

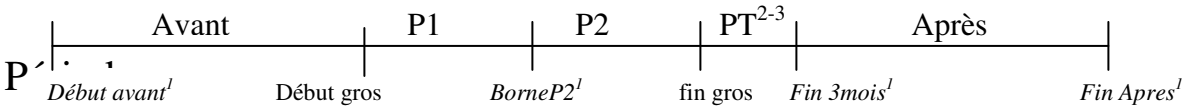
## VCF09_Hypertension

**VCF= Variable confondante fixe dans le temps.**

### *BUT*

Création d'une variable indiquant pour chaque grossesse si la femme souffrait d'hypertension chronique, d'hypertension de grossesse, de prééclampsie ou d'éclampsie.

### *Algorithme*




Avant = [ *début avant*[1], début de la grossesse [

P1 = [ début de la grossesse, *BorneP2*[1]]

P2 = ] *BorneP2*[1], fin de la grossesse [

PT[2-3] = ] fin de la grossesse, *Fin 3mois*[1] ]

Après = ] *Fin 3mois*[1], *Fin Après*[1]]

## Hypertension chronique

Si

1. Au moins Rx[7] ou Dx[8] (HC/HG)[4] durant « Avant »
   **ou**
2. Au moins Rx ou Dx (HC/HG) durant P1
   **ou**
3. Au moins Rx ou Dx (HC/HG) durant P2 **et a**u moins Dx (HC/HG) durant « Apres » [5-6]

Alors HC=1

# Hypertension de grossesse

**Si au moins Rx ou Dx (HC/HG) durant « Avant » ou durant P1:**

- Au moins Dx (HG) durant P2 (Hypertension Sur ajoutée)

**Sinon,**

- Au moins Rx ou Dx (HG/HC) durant P2

Alors HG=1

**********ATTENTION**********

S'il y a au moins un code ou une prescription d'exclusion[9] avant ou pendant la grossesse nous effectuerons ce même algorithme sans tenir compte des Rx.

**********

# Pré-éclampsie

Si au moins un DX (PE) durant P2 alors PE=1;

# Éclampsie

Si au moins un DX (ECL) durant P2 alors ECL=1;

**NOTES :**

[1] S'il existe une grossesse précédente (GP), nous établirons une borne supérieure à cette grossesse.

$$\textit{Borne GP} = \begin{cases} \text{fin de la GP + 1 + 3 mois} & \text{si durée GP} \geq 12 \text{ semaines complètes} \\ \text{fin de la GP + 1} & \text{si durée GP} < 12 \text{ semaines complètes} \end{cases}$$

Si *borne GP* est supérieure au début de la grossesse actuelle nous remplacerons Borne GP par le début de la grossesse actuelle.

Une fois cette borne trouvée nous choisirons la date maximale entre la borne de la grossesse précédente et un an avant la grossesse.

$$\textit{Début Avant} = \text{MAX (début de la grossesse-365 jours , } \textit{borne GP}\text{ )}$$

De façon générale, l'hypertension de grossesse se déclare après la fin de la 20$^{ième}$ semaine. S'il s'agit d'une grossesse multiple, l'hypertension peut déclarer dès la fin de la 15$^{ième}$ semaine. Nous considèrerons donc se fait dans le choix de la *BorneP2*.

$$\textit{Borne P2} = \begin{cases} \text{fin de la 20}^{ième}\text{ semaine de grossesse} & \text{si grossesse « simple »} \\ \text{fin de la 15}^{ième}\text{ semaine de grossesse} & \text{si grossesse multiple} \end{cases}$$

ET

$$\textit{Fin 3mois} = \text{MIN ( fin de la grossesse + 91 jours , début gros suivante - 1 )}$$

$$\textit{Fin Après} = \text{MIN ( fin gros +365 jours , début gros suivante - 1 )}$$

[2] L'hypertension de grossesse prend généralement 6 semaines pour se résorber. Une minorité cependant peut prendre jusqu'à 3 mois avant que la tension ne redevienne normale. C'est pourquoi nous devons attendre 3 mois avant de vérifier si la maladie persiste.

[3] Ici on ne peut analyser la période PT (période tampon) comme on l'a fait pour le diabète gestationnel puisqu'il n'y a pas de test particulier pour identifier l'hypertension de grossesse, il s'agit seulement d'une prise de tension généralement effectuer à chaque visite. Donc si une femme n'a aucun rx ou dx avant et pendant sa grossesse mais qu'il y a néanmoins un code durant la période 1-3 mois inclusivement après la grossesse, on ne peut l'interpréter comme de l'hypertension (chronique ou de grossesse) car il peut seulement s'agir d'une mauvaise lecture de la tension.

[4] Tous les codes sont considérés comme un code d'hypertension peu importe s'il s'agit d'un code d'hypertension chronique ou d'hypertension de grossesse. C'est plutôt le moment où ce code à été émis qui décidera s'il s'agit d'hypertension chronique ou d'hypertension de grossesse

[5]Attention, si HG après 21 semaines et HC entre 4-12 mois il peut y avoir HC+HG et non seulement HC. Toutefois, nous ne sommes pas en mesure de décider s'il s'agit d'hypertension surajoutée ou seulement d'hypertension chronique avec les informations que nous possédons. Nous conclurons donc pour ces grossesses qu'il s'agit d'hypertension chronique.

[6] Pour la période «Après» nous ne considérons pas les Rx puisque nous n'avons pas exigé que cette période soient couvertes par la RAMQ pour le remboursement des médicaments.

## [7]RX : prescription d'un médicaments pour l'hypertension :

| Classe pharmacologique | Noms génériques | Dénomination commune |
|---|---|---|
| **Antagonistes α-adrénergiques*** | Doxazosine | 45625 |
| | Prazocin | 37742, 46831 |
| | Térazosine | 45520 |
| **Agonistes α-adrénergiques** | Clonidine | 10751 |
| | Méthyldopa | 06136, 46389 |

*α-blockers

[8] DX : Codes Diagnostiques pour l'hypertension ( codes ICD-9)

- **DX(HC)**
  - pour l'hypertension chronique:
    - 401 Essential Hypertension
    - 402 Hypertensive Heart Disease
    - 403 Hypertensive Renal Disease
    - 404 Hypertensive Heart and Renal Disease
    - 405 Secondary Hypertension
  - pour l'hypertension chronique spécifique à la grossesse :
    - 642.0 Hypertension essentielle ou chronique
    - 642.1 Maladie hypertensive associée à des problèmes rénaux
    - 642.2 Autre hypertension préexistante compliquant la grossesse
    - 642.7 Hypertension super-imposée -autres hypertensions chroniques

- **DX(HG)**
  - pour l'hypertension de grossesse:
    - 642.3 Hypertension de grossesse (gestationnelle)
    - 642.9 Hypertension de novo – nouvellement hypertendue et sans protéinurie

- **DX(PE)**
  - pour la pré-éclampsie:

    642.4 Pré-éclampsie

    642.5 Pré-éclampsie grave

- **DX(ECL)**
  - pour l'éclampsie:

    642.6 Éclampsie