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Association between timing of asthma diagnosis and medication use during pregnancy

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Ce mémoire intitulé

Association between timing of asthma diagnosis and medication use during pregnancy

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A été évalué par un jury composé des personnes suivantes

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Résumé

L'utilisation de médicaments contre l'asthme pendant la grossesse est recommandée par les lignes directrices internationales pour maintenir le contrôle des symptômes puisqu'il a été démontré qu'un mauvais contrôle de l'asthme augmente le risque d'effets périnataux indésirables. À ce jour, aucune étude n'a évalué l'association entre le moment du diagnostic d'asthme et l'utilisation des médicaments antiasthmatiques pendant la grossesse. L'objectif de cette étude est d'évaluer si l'utilisation des médicaments antiasthmatiques pendant la grossesse diffère chez les femmes souffrant d'asthme diagnostiqué au cours des 19 premières semaines de grossesse par rapport à celles diagnostiquées deux ans avant la grossesse.

Nous avons mené une étude de cohorte rétrospective en utilisant la base de données québécoise sur l'asthme et la grossesse. L'issue principale était l'utilisation de corticostéroïdes inhalés (CSI), CSI/ß2-agonistes à longue durée d'action (BALA) et ß2-agonistes à courte durée d'action (BACA) pendant la grossesse définie comme le nombre d'ordonnances remplies dès 20 semaines de grossesse (entrée à la cohorte – EC –) jusqu'à l'accouchement. L'utilisation de corticostéroïdes oraux (CSO) pendant la grossesse a été définie comme le nombre de jours d'ordonnances remplies d'EC jusqu'à l'accouchement. Des modèles de régression de Poisson ont été utilisés pour comparer les taux d'utilisation des médicaments contre l'asthme entre les femmes diagnostiquées avant et au début de la grossesse, tout en ajustant pour les facteurs de confusion potentiels. Les issues secondaires étaient le traitement rempli au moment du diagnostic, défini comme les médicaments antiasthmatiques dispensés à la pharmacie au cours du mois précédent et du mois suivant la date du diagnostic d'asthme et l'adhésion aux CSI pendant la période de suivi, estimée avec la proportion de jours couverts (PDC).

La cohorte comprenait 1 731 femmes souffrant d'asthme diagnostiqué avant la grossesse et 359 au début de la grossesse. Les femmes diagnostiquées en début de grossesse étaient plus susceptibles d'utiliser les CSI [aRR 1.9, IC à 95 % 1.6–2.3] et les SABA [aRR 2.0, IC à 95 % 1.7–2.4] que les femmes diagnostiquées avant la grossesse. Pas de différence au niveau de l'utilisation des CSI/BALA [aRR 0.9, IC à 95 % 0.7–1.3] et des CSO [aRR 0.8, IC à 95 % 0.6–1.2]. Les médicaments de contrôle et de secours les plus couramment dispensés étaient les CSI et BACA au cours du mois précédant le diagnostic et le mois suivant le diagnostic, respectivement, pour les deux sous-cohortes. Le PDC moyen pendant la période de suivi chez les utilisatrices de contrôleurs basés sur les CSI parmi les femmes diagnostiquées avant la grossesse était assez similaire à celui des femmes diagnostiquées en début de grossesse (27,7%; IC 95% 25,3–30,1 vs 24,5%; IC 95% 21,3–27,8). En ce qui concerne l'adhésion, le modèle de régression linéaire a révélé que la différence ajustée de l'adhésion aux CSI n'était pas statistiquement significative (-3,6; IC à 95 % - 7,9 à 0,6).

L'asthme diagnostiqué en début de grossesse pourrait suggérer un asthme plus persistant de nature en raison des changements hormonaux nécessitant une plus grande utilisation des CSI et des BACA. Compte tenu de la faible adhésion et utilisation des médicaments antiasthmatiques pendant la grossesse, ces résultats supportent un suivi médical étroit des femmes asthmatiques nouvellement diagnostiquées avant ou au début de le grossesse en fournissant aux patientes des ressources éducatives sur la gestion de l'asthme pour maintenir l'asthme sous contrôle et prévenir des conséquences périnatales graves.

Mots-clés : Asthme; Utilisation des médicaments antiasthmatiques; Asthme maternel; Adhésion; Grossesse; Épidémiologie; Bases de données sur l'asthme et la grossesse au Québec.

Abstract

Asthma medication use during pregnancy is recommended by international guidelines to maintain control of symptoms since poor control has been shown to increase the risk of adverse perinatal outcomes. To date, no studies have evaluated the association between the timing of new-onset asthma and the use of asthma medications during pregnancy. The objective of this study is to assess whether asthma medication use during pregnancy differs in women with asthma diagnosed during the first 19 weeks of pregnancy compared to those diagnosed 2 years before pregnancy.

We conducted a retrospective cohort study using the Quebec asthma and pregnancy database. The primary outcome was the use of inhaled corticosteroids (ICS), ICS/long-acting ß2-agonists (LABA) and short-acting ß2-agonists (SABA) during pregnancy defined as the number of filled prescriptions from 20 weeks of pregnancy (Cohort entry – CE –) until delivery. Oral corticosteroids (OCS) use during pregnancy was defined as the number of days of filled prescriptions from CE until delivery. Poisson regression models were used to compare the rates of asthma medication use between women diagnosed before and early in pregnancy, while adjusting for potential confounders. The secondary outcomes were the treatment dispensed at diagnosis defined as asthma medications filled at the pharmacy in the month prior and the month following the date of asthma diagnosis and adherence to ICS during follow-up estimated with the proportion of days covered (PDC).

The cohort included 1 731 women with asthma diagnosed before and 359 early in pregnancy. Women diagnosed early in pregnancy were more likely to use ICS [aRR 1.9, 95% CI 1.6–2.3]

and SABA [aRR 2.0, 95% CI 1.7–2.4] than women diagnosed pre-pregnancy. No difference in the use ICS/LABA [aRR 0.9, 95% CI 0.7–1.3] and OCS [aRR 0.8, 95% CI 0.6–1.2]. The most common asthma controller and reliever dispensed in the month prior to diagnosis and the month after diagnosis were ICS and SABA, respectively, for both sub-cohorts. The mean PDC over the study follow-up among users of ICS-based controllers in women diagnosed pre-pregnancy was quite similar to those diagnosed early in pregnancy (27.7%; 95% CI 25.3–30.1 vs 24.5%; 95% CI 21.3–27.8). With respect to adherence, the linear regression model revealed that the adjusted difference in ICS adherence was not statistically significant (-3.6; 95% CI -7.9 to 0.6).

Asthma diagnosed early in pregnancy might suggest a more persistent asthma in nature due to hormonal changes requiring more use of ICS and SABA. Taking into consideration low asthma medication use and adherence during pregnancy, these results support a closer medical follow-up of asthmatic women newly diagnosed before or early in pregnancy by providing patients with educational resources about asthma management to maintain asthma under control and prevent serious perinatal outcomes.

Keywords: Asthma; Asthma medication use; Maternal asthma; Adherence; Pregnancy; Epidemiology; Quebec Asthma and Pregnancy database.

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Abbreviations

aOR – Adjusted odds ratio

CASP – Critical Appraisal Skills Program

CI – Confidence interval

CTS – Canadian Thoracic Society

ED – Emergency department

ICD – International Classification of Diseases

ICS – Inhaled corticosteroid

LABA – Long-acting beta2-agonist

LBW – Low birth weight

LMP – Last menstrual period

LTRA – Leukotriene receptor antagonist

GINA – Global Initiative for Asthma

MED-ECHO – Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière

MPR – Medication possession ratio

OCS – Oral corticosteroids

OR – Odds ratio

PDC – Proportion of days covered

QAPD – Quebec Asthma and Pregnancy Database

RAMQ – Régie de l'Assurance Maladie du Québec

RR – Rate ratio

Rx – Prescription

SAAC – Short-acting anticholinergic

SABA – Short-acting beta2-agonist

SGA – Small gestational age

THEO – Theophylline

WHO – World Health Organization

To my beloved family, my lovely angel and my dearest friends

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I am really grateful to my supervisor, Dr. Lucie Blais, for giving me the opportunity to join her team. I truly appreciate her valuable experience in the field of asthma and pregnancy, rigorous scientific knowledge and guidance throughout my masters. I particularly acknowledge her great availability, yet so loaded with responsibilities, and her continuous encouragement and support in attending national and international conferences to disseminate the study results.

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CHAPTER 1: INTRODUCTION

1. Introduction

According to WHO estimates, asthma affects 235 million individuals worldwide. (1) The proportion of Canadians diagnosed with asthma increased by 67% from 2.1 million (6.7%) in 2000–2001 to 3.8 million (11.0%) in 2011–2012. An increase in the prevalence of asthma could be due to a greater case detection of asthma or an increase in the frequency of risk factors for asthma. (2) Therefore, asthma is considered a serious health burden in terms of loss of productivity and health care costs. (3) In the past decades, asthma has been shown to be the most frequent chronic disease and a serious medical complication during pregnancy. (4-6) The disease affects about 3.4% to 12.4% of pregnant women and shows an increase in its prevalence over time. (6, 7) During pregnancy, asthma symptoms improve in approximately one third of women, remain the same in one third, and worsen in one third, which suggests the importance of frequent re-assessment of asthma control and medication requirements. (8-10)

Several studies showed an association between uncontrolled asthma during pregnancy and perinatal outcomes including low birth weight, prematurity and congenital malformations. (6, 11-14) Poorly controlled and severe asthma might lead to respiratory alkalosis that will decrease fetal blood oxygen and will be potentially dangerous to the growth and development of the fetus. (15) According to the Global Initiative for Asthma (GINA) and the Canadian Thoracic Society (CTS) guidelines, the use of asthma medications during pregnancy is highly recommended to maintain asthma control since the benefits outweigh the potential risks of asthma medication use. (1, 16, 17) The ultimate goal of asthma therapy in pregnancy is to achieve and maintain asthma control and improve the quality of life by preventing symptoms and minimizing future risk of exacerbations. (1, 17) Treatment and control of asthma could be achieved by using several

medications. Asthma medications are categorized in two classes: 1) reliever medications (e.g. short-acting beta2-agonists (SABA), oral corticosteroids (OCS)); and 2) long-term controller medications (e.g. inhaled corticosteroids (ICS) and long-acting beta2-agonists (LABA)). (1, 17) ICS are considered the cornerstone in the management of moderate to severe persistent asthma during pregnancy while SABA are widely used for quick relief of asthma symptoms during pregnancy. LABA are used for patients with moderate to severe persistent asthma not fully controlled with ICS alone. LABA have limited studies on their safety and use during pregnancy compared to SABA and ICS due to their precedence on the market. (1, 17)

Non-adherence to ICS medications during pregnancy has been shown to range between 27% and 40% (18-20) in women with prevalent asthma, with poor control linked to a higher risk of adverse perinatal outcomes. (21-23) Baarnes et al. (18) reported that ICS self-reported and documented adherence using the Medication Possession Ratio (MPR) were significantly higher during pregnancy compared to prior to pregnancy in women with asthma diagnosed prior to pregnancy.

According to the literature, women with pre-existing asthma had a decrease in asthma medication use during pregnancy compared to pre-pregnancy. (24-27) Only one cohort study assessed asthma medication use during pregnancy between prevalent cases of asthma diagnosed during or prior to pregnancy. (28) A significant lower ICS use (27.7% vs 97.0%, $p < 0.001$) and higher use of SABA (34.8% vs 9.7%, $p < 0.001$), ICS/LABA (28.0% vs 10.5%, $p < 0.001$), LTRA (Leukotriene receptor antagonists (LTRA); 20.3% vs 7.1%, $p < 0.001$) and OCS (27.5% vs 7.4%, $p < 0.001$) during pregnancy in women with asthma diagnosis code during pregnancy compared to women with evidence of asthma prior to pregnancy. (28) Nevertheless, these results should be

interpreted with caution since the follow-up period was not clearly defined for both groups and asthma medication use was measured in the entire pregnancy for all women, giving by design, differential periods to assess asthma medication use in women diagnosed during pregnancy. Moreover, asthma diagnosed during pregnancy was reported to be a new asthma diagnosis, without implementing a lookback period to exclude prevalent cases of asthma, and asthma diagnosed pre-pregnancy did not necessarily occur within a fixed period before pregnancy and could have occurred several years before, making the comparison difficult. (28)

In women with pre-existing asthma, the fear of harmful effects of asthma medications on the fetus (7) and consequently treatment nonadherence are known underlying causes of exacerbations and poor asthma control during pregnancy. (11-13) As diagnosing asthma during pregnancy can be challenging due to pregnancy-induced hormonal changes (8, 29-32), whether pregnancy-onset asthma leads to similar trend in asthma medication use and adherence during pregnancy has yet to be investigated. We suspect that women newly diagnosed with asthma prior to pregnancy would be more likely to use and adhere to their medication than those newly diagnosed during pregnancy. While no other studies have assessed the timing of asthma diagnosis in relation with asthma medication use during pregnancy and to overcome the aforementioned methodological limitations, we conducted a retrospective population-based cohort study of pregnant women selected from the Quebec Asthma and Pregnancy Database (QAPD). Therefore, the general objective of this large retrospective cohort study was to assess whether the use and adherence to asthma medications during pregnancy differ in women with asthma newly diagnosed during the first 19 weeks of pregnancy compared to women with asthma newly diagnosed 2 years prior to pregnancy.

CHAPTER 2: REVIEW OF THE LITERATURE

2. Review of the literature

This chapter will introduce the definition of asthma including asthma severity and control. I will also discuss the prevalence and treatment of asthma during pregnancy as well as the impact of asthma disease and asthma medications on perinatal outcomes. Moreover, I will cover the association between the timing of asthma diagnosis and asthma medication use and adherence during pregnancy.

2.1 Asthma during pregnancy

2.1.1 Asthma definition

According to the GINA guidelines, asthma is defined as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness and coughing particularly at night or in the early morning. These episodes are usually associated with wide spread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment". (1) Asthma symptoms are triggered by factors such as exercise, exposure to environmental allergens, obesity, medications like nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin, stress and pregnancy. It might cause limitation of activity and flare-ups that require urgent health care and might be fatal. (1)

2.1.2 Asthma prevalence

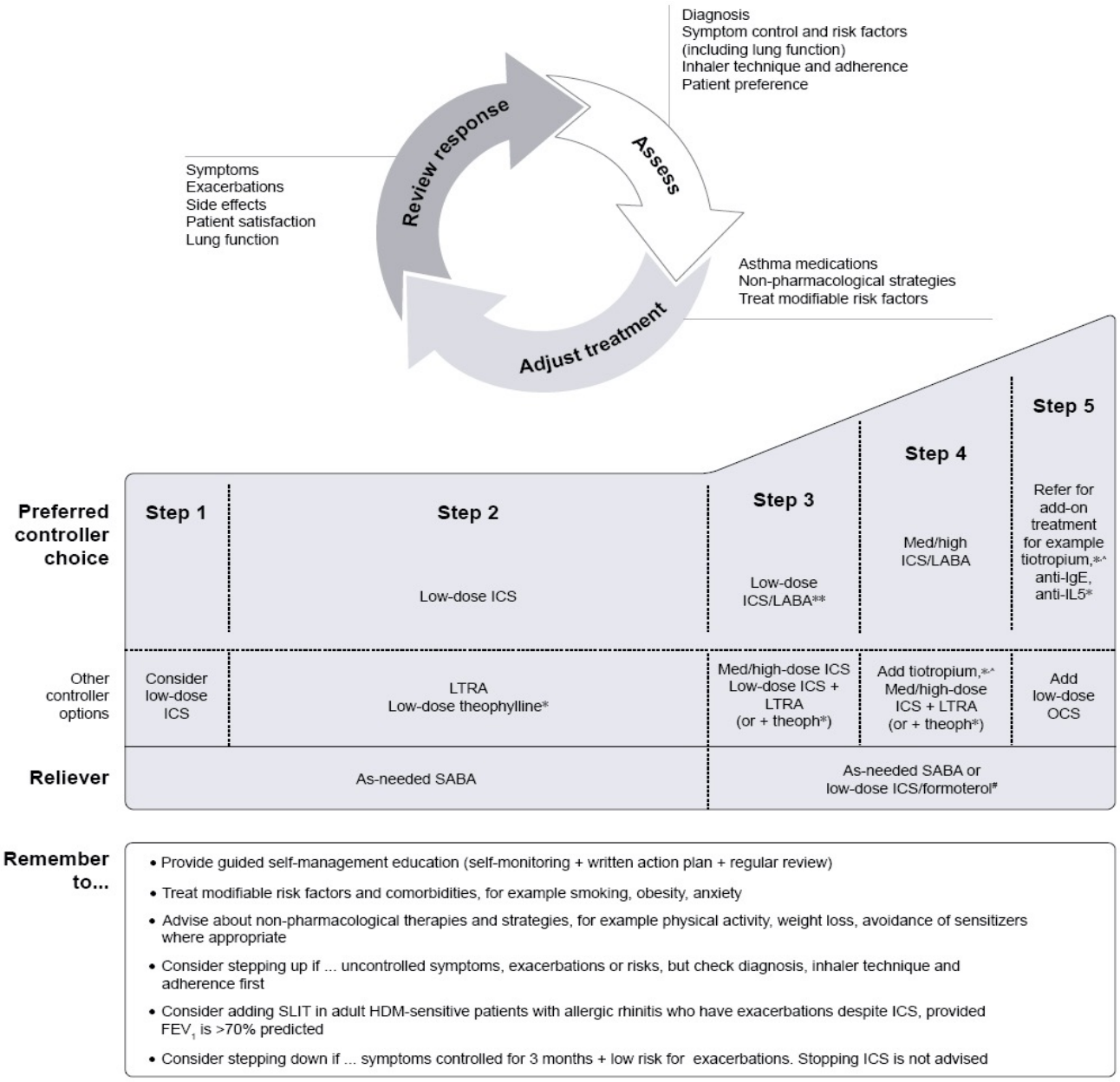
According to WHO estimates, asthma is affecting 235 million individuals worldwide. (3) The number of Canadians living with diagnosed asthma increased by 67% from 2.1 million (6.7%) in

2000–2001 to 3.8 million (11.0%) in 2011–2012. The causes of the increase in prevalence could be due to a greater case detection of asthma or an increase in the risk factors for asthma. (2) However, Canadians diagnosed with asthma who needed medical attention declined by 18% from 908 000 in 2000–2001 to 820 000 in 2011–2012. (1) In the past decades, asthma has been shown to be the most frequent chronic disease that can complicate pregnancy, with a prevalence ranging between 3.4% and 12.4%. (6, 7)

2.1.3 Asthma severity and control

During pregnancy, asthma symptoms improve in approximately one third of women, remain the same in one third, and worsen in one third. (8-10) According to the GINA guidelines, asthma severity is assessed once the patient has reached the level of treatment needed to control asthma symptoms and exacerbations. It might vary over months or years requiring treatment adjustment to find the patient's most appropriate therapy. (1) Asthma severity is classified into three categories based on the intensity of the treatment required to achieve asthma control: mild asthma (Step 1 or 2), moderate asthma (Step 3), and severe asthma (Step 4 or 5). (1, 3) A stepwise approach is then used to manage asthma in each patient according to his/her level of asthma severity (Please see Figure 2.1). (1) The GINA guidelines defined asthma control as the degree to which the manifestations of asthma can be observed in the patient, or have been minimized by therapeutic intervention. Asthma control is assessed based on symptom control and future risk of adverse outcomes measured at asthma diagnosis and periodically thereafter. (1) Asthma control is classified into controlled, partly controlled, and uncontrolled (Please see Table 2.1). (1)

Figure 2.1 Stepwise approach to control symptoms and minimize future risk



Source: Global Initiative for Asthma guidelines for asthma management and prevention, Executive summary report, 2018

*Not for children <12 years. **For children 6-11 years, the preferred Step 3 treatment is medium dose ICS. ^Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years. #Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclomethasone/formoterol maintenance and reliever therapy. ICS: inhaled corticosteroids; LABA: long-acting beta2-agonists; IgE: immunoglobulin E; IL5: interleukin-5; LTRA: leukotriene receptor antagonists; OCS: oral corticosteroids; SABA: short-acting beta2-agonists; HDM: house dust mite; SLIT: sublingual immunotherapy.

able 2.1 Classification of asthma control according to the GINA guidelines

Asthma symptom control			
Characteristic	Controlled (all of the following)	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less per week)	More than twice a week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None (twice or less per week)	Any	Three or more features of partly controlled asthma present in any week
Nocturnal symptoms/ awakening	None	Any	Three or more features of partly controlled asthma present in any week
Need for reliever/ rescue treatment *	None (twice or less per week)	More than twice a week	Three or more features of partly controlled asthma present in any week
Risk factors for poor asthma outcomes			
Having uncontrolled asthma symptoms is an important risk factor for exacerbations Additional potentially modifiable risk factors for flare-ups (exacerbations) even in patients with few symptoms † - High SABA use (with increased mortality if > 1 x 200-dose canister/month) - Inadequate ICS: not prescribed ICS; poor adherence; incorrect inhaler technique - Low FEV1, especially if <60% predicted - Higher bronchodilator reversibility - Major psychological or socioeconomic problems - Exposures: smoking; allergen exposure if sensitized - Comorbidities: obesity; chronic rhinosinusitis; confirmed food allergy - Sputum or blood eosinophilia - Elevated FENO (in adults with allergic asthma taking ICS) - Pregnancy Other major independent risk factors for flare-ups (exacerbations) - Ever intubated or in intensive care unit for asthma - ≥ 1 severe exacerbation in last 12 months **Risk factors for developing fixed airflow limitation** - Preterm birth, low birth weight and greater infant weight gain - Lack of ICS treatment - Exposures: tobacco smoke; noxious chemicals; occupational exposures - Low initial FEV1; chronic mucus hypersecretion; sputum or blood eosinophilia **Risk factors for medication side-effects** - *Systemic*: frequent OCS; long-term, high dose and/or potent ICS; also taking P450 inhibitors - *Local*: high-dose or potent ICS; poor inhaler technique			

ource: Global Initiative for Asthma guidelines for asthma management and prevention, Executive summary report, 2018

Excludes reliever taken before exercise. †Independent risk factors are those that are significant after adjustment for the level of mptom control. SABA: short-acting beta2-agonists; ICS: inhaled corticosteroids; FEV1: forced expiratory volume in one second; FENO: actional exhaled nitric oxide; P450 inhibitors: cytochrome P450 inhibitors such as ritonavir, ketoconazole, itraconazole; OCS: oral rticosteroids.

2.2 Asthma treatment during pregnancy

The goal of asthma treatment is to achieve and maintain asthma control by preventing symptoms, functional and psychological morbidity and minimizing risk factors for future poor outcomes such as exacerbations and limitation of physical activity. According to the GINA, CTS and National Asthma Education and Prevention Program guidelines (1, 6, 17), the use of controller medications for asthma during pregnancy is recommended since the benefit of active treatment to maintain asthma control and prevent exacerbations outweighs the potential risks of asthma medication use. Nevertheless, the fear of harmful effects on the fetus may be a barrier to the use of asthma treatments, potentially leading to complications associated with uncontrolled asthma during pregnancy. (7) Asthma medications are categorized in two classes: 1) reliever medications provided to patients for as-needed quick relief of symptoms (e.g. SABA and OCS); 2) long-term controller medications (e.g. ICS, LABA and LTRA) are used as regular maintenance therapy to reduce airway inflammation and avoid loss of lung function. During pregnancy, monthly monitoring of asthma is recommended. If the patient is not controlled while taking controller medications and has persistent symptoms, step up in treatment is recommended after checking for adherence, and comorbid conditions. (1, 6)

2.2.1 Controller medications

Controller medications should be taken daily on a long-term basis to control symptoms and avoid exacerbations. The most effective maintenance medications are anti-inflammatory drugs since the main cause of symptoms are due to airway inflammation in asthmatic patients. (1)

- **ICS:** ICS are considered the primary drug of choice in all levels of persistent asthma and the most potent and effective anti-inflammatory medication available. ICS, especially budesonide, is the cornerstone therapy in the management of persistent asthma during pregnancy (1, 3, 6) based on more available data related to safety during pregnancy compared to other ICS. (33-36)

- **LABA:** Salmeterol and formoterol are used during pregnancy in combination with ICS. Although limited safety data is available for LABA use during pregnancy, they have been used concomitantly with ICS for a sustained control of symptoms, especially nocturnal symptoms, in moderate and severe persistent asthma. (1, 3, 6)

- **LTRA:** Zafirlukast or montelukast are less effective than ICS and can be used during pregnancy as alternative therapy in women with mild persistent asthma or patients not sufficiently controlled on ICS. (1, 3, 6)

- **Methylxanthines:** Theophylline is a sustained-release bronchodilator used during pregnancy as alternative treatment in mild persistent asthma or as adjunctive with ICS, in moderate or persistent asthma. This agent is not used often due to the frequent need of drug level monitoring. (1, 3, 6)

- **Cromolyn sodium and Nedocromil:** These agents can be used during pregnancy as an alternative treatment, but not preferred, for women with mild persistent asthma. They have limited effectiveness compared to ICS. (1, 3, 6, 37, 38)

2.2.2 Reliever medications

Quick-relief medications are usually prescribed on as needed basis for immediate relief of respiratory symptoms. (1, 3) They provide rapid reversibility of acute airway obstruction and relief of bronchoconstriction. (1)

- **SABA:** SABA are the agents of choice in rescue therapy used as needed during pregnancy. They act as bronchodilators in acute asthmatic symptoms, exacerbations and prevent exercise-induced bronchoconstriction by relaxing the smooth muscles of the bronchi. Albuterol is the preferred agent due to its proven safety profile during pregnancy. (1, 3, 6)

- **OCS:** OCS are generally used for a short-term period to treat and provide a rapid control of the disease since it decreases the inflammation by reversibly increasing the capillary permeability. In severe persistent uncontrolled asthma, short courses of prednisone may be prescribed during pregnancy until asthma control is regained. (1, 3, 6)

2.3 Impact of asthma during pregnancy on perinatal outcomes

Pregnant women with asthma are at a higher risk of adverse perinatal outcomes, requiring interventions to minimize the risk for substantial morbidity. (39) Preterm birth (< 37 weeks of gestation) occurs in about 8% of pregnancies in Canada, low birth weight – LBW – (< 2500 g) in about 6% and small gestational age – SGA – (birth weight below the 10^{th} percentile for gestational age) in about 9% and are associated with high mortality and morbidity rates that substantially affect infants, their families and the healthcare system. (40) Approximately 1 in 25 Canadian infants are diagnosed with 1 or more congenital anomalies every year. (41) Although it could be difficult to separate the effect of the disease, severity, and associated levels of control from the

effects of asthma medications, many studies (42-53) have documented that maternal asthma could significantly increase the risk of preterm birth (odds ratio [OR] 1.27, 95% CI 1.10–1.40, $p < 0.001$ (43); adjusted odds ratio [aOR] 2.37, 95% CI 1.15–4.88 (42); rate ratio [RR] 1.41, 95% CI 1.23–1.62 (45); RR 1.16, 95% CI 1.08-1.24 (53)), LBW (OR 1.23, 95% CI 1.10–1.40, $p = 0.001$ (43); RR 1.46, 95% CI 1.22–1.75 (45)), SGA (RR 1.22, 95% CI 1.14–1.31 (45); aOR 1.31, 95% CI 1.12–1.55 (44); RR 1.06, 95% CI 1.01-1.11 (53)) and congenital malformations (RR 1.11, 95% CI 1.02–1.21, $p < 0.1$ (52)).

2.3.1 Asthma diagnosed prior to pregnancy

Maternal asthma diagnosed prior to pregnancy was found to be associated with preterm delivery and LBW in two studies (42, 43). Sorensen et al. (42) showed that asthmatic women experienced a 2-fold increased risk of preterm delivery compared to women with no history of asthma, while controlling for maternal age, race, parity and smoking during pregnancy (aOR 2.37, 95% CI 1.15–4.88). (42) Shaked et al. (43) reported that preterm delivery and LBW were more common in pregnant women with asthma compared to pregnant women without asthma (OR 1.27, 95% confidence interval [CI] 1.10– 1.40, $p < 0.001$; OR 1.23, 95% CI 1.10–1.40, $p = 0.001$, respectively).

2.3.2 Asthma diagnosed during pregnancy

The risk of preterm delivery, SGA and LBW in women with asthma diagnosed during pregnancy were examined in only one prospective cohort study. (44) Compared to non-asthmatic women, maternal asthma diagnosed during pregnancy was associated with a significantly increased risk of SGA (aOR 1.31, 95% CI 1.12–1.55). No significant associations were found

between maternal asthma and preterm delivery (aOR 0.96, 95% CI 0.69–1.34) or LBW (aOR 1.11, 95% CI 0.77–1.59). Of note, these results were adjusted for potential confounders including maternal age, maternal BMI, parity, smoking, ethnicity and marital status. (44)

2.3.3 Asthma diagnosed either prior to or during pregnancy

Pregnancy outcomes of women with asthma diagnosed either during or prior to pregnancy compared to non-asthmatic women were examined in several studies and results have shown increased risks in perinatal outcomes among asthmatic mothers.

Murphy et al. (45) conducted a meta-analysis including 11 prospective and 15 retrospective cohort studies that reported at least one perinatal outcome in pregnant women with asthma diagnosed either before or during pregnancy and in pregnant non-asthmatic women. Maternal asthma was found to be associated with a significantly increased risk of LBW (RR 1.46, 95% CI 1.22–1.75), SGA (RR 1.22, 95% CI 1.14–1.31) and preterm delivery (RR 1.41, 95% CI 1.23–1.62). (45) These significant associations between maternal asthma and preterm birth, LBW and SGA are also in accordance with other studies. (46-51) Furthermore, Murphy et al. (11) conducted another systematic review and meta-analysis to examine the risk of congenital malformations, among other outcomes, in pregnant women with and without asthma. This study reported that infants of asthmatic pregnant women are 11% more likely to have congenital malformations compared with infants of women without asthma (RR 1.11, 95% CI 1.02–1.21, $p < 0.1$). Following the meta-analysis, another study also supported the association between congenital malformations and maternal asthma. (52)

2.3.4 Asthma newly diagnosed during pregnancy vs prior to pregnancy

Only one retrospective cohort study (53) assessed whether women with newly asthma newly diagnosed during pregnancy are at an increased risk of preterm birth, SGA and major congenital malformations compared to women with asthma newly diagnosed prior to pregnancy. Longo et al. (53) reported that the risk of prematurity is higher among women diagnosed during the second (RR 1.34, 95% CI 1.08–1.65) and third (RR 1.93, 95% CI 1.62–2.29) trimesters compared to pre-pregnancy (RR 1.06, 95% CI 0.98–1.15). This study also showed a trend toward an increased risk of major congenital malformations among women newly diagnosed during the first trimester (RR 1.18, 95% CI 0.94–1.49) relatively to those diagnosed pre-pregnancy (RR 0.99, 95% CI 0.92–1.07). No significant associations were found between the timing of asthma diagnosis and SGA. Irrespective of the timing of asthma diagnosis, women with incident asthma were more likely to have preterm birth (RR 1.16, 95% CI 1.08–1.24) and SGA RR 1.06, 95% CI 1.01–1.11) compared to those without asthma; however, it was not found to be associated with an increased risk of major malformations (RR 1.04, 95% CI 0.97–1.11). (53)

Overall, there is a well-documented consistency in the association between adverse perinatal outcomes and maternal asthma, in studies that combined women diagnosed prior and during pregnancy. Yet, these studies vary in terms of sample size, study design, adjustment for confounders and examination of specific outcomes (prematurity, LBW, SGA and congenital malformations). Optimal preventive and healthcare strategies should be implemented to improve asthma control during pregnancy and prevent exacerbations, with the aim of reducing perinatal outcomes. (45)

2.4 Impact of asthma medication use during pregnancy on perinatal outcomes

Multiple studies (13, 33-36, 54-68) found an association between the use of asthma medications during pregnancy and the risk of adverse perinatal outcomes including preterm delivery, LBW, SGA and major or any congenital malformations. However, it is difficult to interpret these associations as causal because part of this risk might be attributable to the severity of asthma. Asthmatic women using asthma medications during pregnancy were documented to be at a higher risk of perinatal outcomes. (13, 33-36, 55, 56, 58, 59, 62-68)

2.4.1 ICS

Many studies examined the association between maternal ICS use during pregnancy and the risk of major congenital malformations, preterm birth, LBW and SGA but only two studies reported an increased risk of perinatal outcomes. (54, 57, 60, 61, 63, 68) Kallen et al. reported that ICS users during pregnancy have a significantly increased risk of major malformations (aOR 1.08, 95% CI 1.01–1.16) compared to asthmatic non-users. (63) Moreover, Blais et al. found that asthmatic users of high ICS doses during the first trimester of pregnancy had a significantly increased risk of congenital malformations (aRR 1.63, 95% CI 1.02–2.60) compared to asthmatic non-users. (68)

2.4.2 Beta2-agonists

Although LABA and SABA are considered key medications in the treatment of maternal asthma, there are evidence of perinatal outcomes increased risk. (33-36, 55, 56, 62-67)

2.4.2.1 LABA

Recently, Eltonsy et al. (62) conducted a systemic review including six studies that examined the association between LABA use during pregnancy and major congenital malformations. Among those six studies, only one reported that maternal LABA users were found to be associated with a significantly increased risk of major cardiac malformations (aOR 2.38, 95% CI 1.11–5.10), genital malformations (aOR 6.84, 95% CI 2.58–18.10), major "other unspecified malformations" (aOR 3.97, 95% CI 1.29–12.20) and any "other and unspecified malformations" (aOR 3.43, 95% CI 1.39–8.45) compared to asthmatic and non-asthmatic non-users. (55) However, an important limitation should be considered in the interpretation of these results since the authors used non-asthmatics as a reference group. Although it may be difficult to separate the effect of asthma as a disease (i.e. asthma control and asthma severity) from the effects of asthma medications, many studies suggested that maternal asthma could significantly increase the risk of perinatal outcomes as compared to women without asthma. (11, 13, 14, 45, 69) Therefore, including non-asthmatic women in the reference group might overestimate the adverse effects of asthma medications. The authors could have compared asthmatic users against asthmatic non-users, decreasing the possibility of confounding by indication (i.e. asthma itself) and by severity. However, following this systemic review, further studies reported no significant association between maternal LABA use and congenital malformations, preterm delivery, LBW and SGA. (54, 57, 63)

2.4.2.2 SABA

In the systemic review conducted by Eltonsy et al. (62), 13 studies reported an increased risk of major or any congenital malformations in asthmatic women exposed to SABA. Among

those studies, two reported a significantly increased risk of any cardiac defect (aOR 1.38, 95% CI 1.12–1.70), cleft lip (aOR 1.79, 95% CI 1.07–2.99), cleft palate (aOR 1.65, 95% CI 1.06–2.58) and any malformations (aOR 1.11, 95% CI 1.04–1.19) in asthmatic users compared to the general population of asthmatic (users and non-users) and non-asthmatic women. (56, 66) Moreover, one more study reported that maternal SABA use was found to be associated with a significantly increased risk of any malformations (crude OR 1.6, 95% CI 1.3–2.0) compared to asthmatic non-users. (64) These significant associations between maternal use of SABA and congenital malformations are also in accordance with other studies. (63, 65) As mentioned in the previous section, these results should be interpreted with caution due to the likelihood of indication bias caused by the use of non-asthmatics in the reference groups. Nevertheless, another study included in this systemic review found a significantly decreased risk of major malformations (aOR 0.68, 95% CI 0.48–0.95) among asthmatic users of high dose of SABA per week (> 10 doses) compared to asthmatic women unexposed to SABA during pregnancy. (55)

2.4.2.3 SABA and/or LABA

In their systemic review, Eltonsy et al. (62) included six studies that examined the association between the maternal exposure to beta2-agonists and major congenital malformations. From the six studies, four reported a significantly increased risk of congenital heart defects (aOR 2.20, 95% CI 1.05–4.61), gastroschisis (aOR 2.06, 95% CI 1.19–3.59), cleft lip (aOR 1.77, 95% CI 1.08–2.88) and other selected birth defects (aOR 2.39, 95% CI 1.23–4.66) among asthmatic users compared to a mixed population of asthmatic non-users and non-asthmatics. (33, 34, 66, 67) Nevertheless, these study results might prevent drawing a solid conclusion, considering the potential risk of confounding by indication and severity. Further

studies confirmed the association between congenital malformations and SABA and/or LABA use during pregnancy. (35, 36, 63, 65) Notwithstanding, these results were not conclusive since SABA and LABA cannot be considered as a combined beta2-agonists therapy due to their different indications in asthma management. In fact, this confounding by indication can be minimized in these studies by comparing two treatment regimens with the same indication such as comparing ICS/LABA in low or medium doses to high doses of ICS.

2.4.3 ICS/LABA

Despite being used for many years in the treatment of asthma during pregnancy, ICS/LABA combination therapy is one of the least studied treatment regimens. An explanation for this limited knowledge can be due to the fact that researchers have focused on ICS and LABA separately to examine the effect of each medication on perinatal outcomes. To the best of our knowledge, two studies examined the association between ICS/LABA use during pregnancy and the risk of perinatal outcomes. (35, 61) Garne et al. (35) reported a significantly increased risk of esophageal atresia (aOR 3.63, 95% CI 1.26–10.42) among asthmatic users compared to asthmatic women unexposed to this combination therapy during pregnancy. Blais et al. (61) found no significant difference in the risk of major congenital malformations among women using low-dose ICS plus LABA compared to those using medium-dose ICS (aOR 1.1, 95% CI 0.6–1.9) and also among women using medium-dose ICS plus LABA compared to those using high-dose ICS (aOR 1.2, 95% CI 0.5–2.7). Hence, the risk of major congenital malformations did not differ among asthmatic women treated with either ICS/LABA combination therapy or ICS at higher doses, suggesting that both treatments can be considered during pregnancy.

2.4.4 OCS

Namazy et al. (13) conducted a meta-analysis including two prospective studies that reported perinatal outcomes in asthmatic women using OCS during pregnancy. Maternal OCS use during pregnancy was found to be associated with a significantly increased risk of preterm delivery (RR 1.51, 95% CI 1.15–1.98), LBW (RR 1.41, 95% CI 1.04–1.93). (13) These significant associations between asthmatic women exposed to OCS during pregnancy and adverse perinatal outcomes are also in accordance with other studies. (58, 59, 65)

In summary, evidence on maternal ICS and SABA use during pregnancy has demonstrated sufficient fetal safety for the management of asthma during pregnancy while OCS use during pregnancy was found to be associated with adverse perinatal outcomes. Despite their use among asthmatic women, especially in combination with ICS, LABA have very small body of evidence of perinatal outcomes increased risk in the literature. Further studies and meta-analyses are required to achieve the power needed to make conclusions about the effects of LABA on congenital malformations.

2.5 Use and adherence to asthma medications during pregnancy

This section is the most important section of the literature review since it will summarize the whole body of evidence on the general objective of our study (i.e. the association between the timing of asthma diagnosis and asthma medication use during pregnancy). I will discuss in details the search strategy used and the studies evaluating asthma medication use and adherence during pregnancy.

2.5.1 Literature review methods

A librarian was consulted to develop a search strategy to answer the following literature review question: What do we know in the literature about the association between the timing of asthma diagnosis (i.e. prior vs during pregnancy) and the use and/or adherence to asthma medication during pregnancy. It included three concepts about asthma, pregnancy and drug therapy that were combined in order to generate results from 2 databases: i) Medline (549 studies); and ii) Embase (1 110 studies), for a total of 1 659 studies (Please see Figure 2.4). From the total, 202 duplicates were excluded, 1 457 were evaluated at first by title (1 274 excluded), and then by abstract (80 excluded) for relevance to asthma guidelines, timing of asthma diagnosis and measurement of medication use and adherence before or during pregnancy. From the remaining 103 studies, 99 were excluded as they were not relevant to our study objectives since they did not assess the use or adherence to asthma medications, and they were either evaluating asthma management strategies or safety of asthma medications during pregnancy.

To ensure the inclusion of moderate-to-good quality studies in my literature review, I appraised the quality of the remaining eight studies with the Critical Appraisal Skills Program (CASP) cohort study checklist, which includes 12 items. I excluded two studies as it failed to meet five of the CASP quality appraisal items because of poor quality methods used and unclear results. From the final six studies included in this literature review, one study assessed adherence to asthma medications during pregnancy in women with asthma diagnosed prior to pregnancy (18) and five studies investigated the use of asthma medications during pregnancy among women with asthma diagnosed either prior to or during pregnancy. (24-28) In the five studies assessing timing of asthma diagnosis relative to pregnancy-onset, two included women with asthma

diagnosed either during or prior to pregnancy (24, 25), two included women with asthma diagnosed prior to pregnancy (26, 27) and one study considered women with asthma diagnosed prior to pregnancy and those with asthma newly diagnosed during pregnancy separately (28).

2.5.2 Studies evaluating asthma medication use and adherence during pregnancy

Six studies – four cohort studies (18, 24, 26, 28), one ecological study (27) and one survey (25) – included pregnant women with asthma diagnosed either prior to or during pregnancy. The studies included were mostly published during the last 14 years and conducted in different countries including USA, France, Denmark, Korea, Australia and Canada. Sawicki et al. (25) included women who self-reported asthma diagnosis during their 36th week antenatal visit at an outpatient clinic, while the remaining five studies defined asthma as having a physician-confirmed asthma diagnosis and/or received at least 1 prescription for an asthma medication prior or during pregnancy (Please see Table 2.4.A). (18, 24, 26-28) Five out of six studies measured asthma medication use during pregnancy including one ecological and three cohort studies using prescription claims data and one survey using a questionnaire. (24-28) The sixth study measured adherence to asthma medication in pregnant women via the medication possession ratio (MPR) and self-reported adherence. (18)

Five studies assessed the use of ICS (24-28) and one study assessed the adherence to ICS in pregnant women (18). Moreover, four studies assessed SABA use (24, 25, 27, 28), one study assessed the use of LABA, LTRA, ICS/LABA and xanthine derivatives (28), two studies assessed OCS

use (27, 28), one study assessed ICS + SABA use (25), and one study assessed the overall use of LABA, LTRA and mast cell stabilizers without reporting the use of each drug class separately (24).

2.5.2.1 Asthma medication use during pregnancy in women with asthma diagnosed prior to pregnancy

We identified two studies, including one cohort and one survey, that assessed the use of asthma medications during pregnancy in women with asthma diagnosed prior to pregnancy. (24, 25)

Schatz et al. (24) enrolled 334 women with asthma diagnosed prior to pregnancy to examine health care and asthma medication use including SABA and controller medications (ICS, LABA, LTRA and mast cell stabilizers) 6 months prior to pregnancy and during the first 6 months of pregnancy. However, patients were not followed until delivery. (8) Asthma was defined as having received at least one prescription for any asthma medication in the 6 months preceding pregnancy. Asthma medication use was defined as patients who filled at least one asthma medication 6 months prior to pregnancy or the first 6 months of pregnancy using a database of US managed care organization (PharMetrics Patient-Centric Database). Of note, no information regarding asthma severity was reported in the study. (24)

The findings demonstrated that ICS, SABA and any other asthma controllers (LABA, LTRA, or mast cell stabilizers) use decreased during the first 6 months of pregnancy when compared to 6 months prior to pregnancy (19.5% vs 30.2%, 41.0% vs 84.7%, 8.7% vs 12.3% respectively) (Please see Table 2.4.B). (24) According to the authors, the change in asthma medication use during pregnancy might be due to pregnancy-related or seasonal changes in asthma severity or symptoms. (24)

While the data was collected prospectively, eliminating the possibility of recall bias, the study suffered from the following limitations: 1) small sample size reducing statistical power; and 2) absence of statistical analyses to determine whether or not the observed differences in use during and prior to pregnancy were statistically significant. (24)

Sawicki et al.'s survey (25) included 102 pregnant women attending an Australian pregnancy clinic at their 36th week who self-reported asthma diagnosis prior to pregnancy. They were asked to complete a questionnaire regarding their asthma symptoms and management in general and, more specifically, to recall the change in their asthma medication use (controllers or relievers alone or in combination) during pregnancy as compared to before pregnancy. The period of recall about their asthma medication use prior to pregnancy was not specified. (25) The survey showed that the overall self-reported use of any asthma medication has significantly decreased from 92.2% before pregnancy to 75.5% during pregnancy (p < 0.001). Specifically, the self-reported ICS use alone or in combination with SABA decreased during the first 36th weeks of gestation compared to prior to pregnancy (2.0% vs 5.9%, p < 0.001; 5.9% vs 12.7%, p = 0.012 respectively). The use of LABA alone decreased from 1.0% before pregnancy to 0.0% during the first 36th weeks of gestation (p < 0.001). It is worth noting that ICS/LABA combination use remained unchanged prior to and during pregnancy (2.9%). Furthermore, this survey concluded a significant increase in self-reported SABA use during the first 36th weeks of gestation compared to prior to pregnancy (57% vs 54%, p = 0.004) (Please see Table 2.4.B). (25) In addition, asthma medication use during pregnancy was not associated with asthma severity and asthma symptoms. (25)

The study results were not conclusive due to several major drawbacks. Self-reporting of maternal medication use might not be highly accurate, leading to a non-differential misclassification and a recall bias that underestimates or overestimates asthma medication use. (70, 71) For instance, the authors were not able to distinguish between patients' non-adherence to therapy from prescribed reduction in medications use since the responses were not verified against data records. Moreover, the study results are only limited to patients attending one Australian maternal clinic and cannot be generalized to the whole Australian population. Further surveys should have been conducted in other Australian maternity hospitals to enhance the external validity of these study results. (25)

2.5.2.2 Adherence to asthma medications during pregnancy in women with asthma diagnosed prior to pregnancy

Baarnes et al.'s (18) cohort study evaluated if enrolment in an asthma management program improves ICS adherence during pregnancy and 3 months post-pregnancy. This study included 114 women with prevalent asthma diagnosed at any time prior to pregnancy. Information regarding the duration of asthma, treatment, and smoking history of women were available; however, the time frame with respect to asthma diagnosis prior to pregnancy was not specified. Asthma diagnosis was defined by a physician-confirmed asthma diagnosis (International Classification of Disease, Tenth Revision [ICD–10]; J45) and having filled an ICS prescription at any time prior to pregnancy. Pregnant women were asked to grade their adherence to the prescribed daily dose of ICS at the initial medical visit during the 9 months prior to pregnancy as good, moderate or low. Follow-up visits were scheduled every 4 weeks during pregnancy to assess the level of adherence to ICS. The results were compared to those obtained

from the 9 months prior to pregnancy. Self-reported adherence was compared to documented adherence measured using the MPR. The MPR was calculated as the total number of days supplied, using prescription refill records, over the number of days of observation multiplied by 100 in both the 9 months prior to and during pregnancy. For the MPR, the following cut-off values were used: non-adherence (0%), poor adherence (< 40%), moderate adherence (41-79%) and good adherence (> 80%). (18)

Baarnes et al. (18) identified that women enrolled in this study were mainly prescribed budesonide (69%) followed by fluticasone (15%) and beclomethasone (3%). Self-reported adherence to ICS was higher during pregnancy (73%) compared to 9 months prior to pregnancy (52%, $p < 0.001$). The MPR was higher during pregnancy (moderate adherence: 46%) compared to 9 months prior to pregnancy (poor adherence: 28%, $p < 0.0001$). It is worth mentioning that 71% of women with a low pre-pregnancy MPR had moderate to good adherence during pregnancy. Moreover, self-reported adherence was significantly correlated with the MPR during pregnancy ($p = 0.004$) but not during the 9 months prior to pregnancy ($p = 0.46$) (Please see Table 2.4.C). According to the authors, adherence to asthma medications during pregnancy was significantly higher than prior to pregnancy due to the extensive follow-up and close monitoring every 4 weeks during pregnancy. (18)

Nevertheless, this study suffered from some limitations. Self-reporting is not a valid measurement of actual adherence compared to MPR with a tendency to overestimate adherence. (70, 71) Another key weakness is the lack of a control group to confirm or infirm if the improvement of ICS adherence during pregnancy was due to the pregnancy itself and not to the close monitoring during follow-up visits. (18)

2.5.2.3 Asthma medication use during pregnancy in women with asthma diagnosed either during or prior to pregnancy

One cohort and one ecological study assessed the use of asthma medications during pregnancy in women with asthma diagnosed either during or prior to pregnancy. (26, 27) A cohort study conducted by Blais et al. (26) assessed the change in ICS use and markers of uncontrolled asthma during pregnancy in 4 434 women with asthma diagnosed at any time during pregnancy or prior to pregnancy, contributing a total of 4 920 pregnancies to the analysis. Asthma was defined as at least one asthma diagnosis (ICD-9; 493) as well as filling at least one prescription for any asthma medication at any point in time in the 2 years prior to or during pregnancy and at least one ICS prescription 9 months prior to pregnancy. The study comprised data from three health administrative databased in Quebec including The Régie de l'Assurance Maladie du Québec (RAMQ) and the Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (MED-ECHO) and the Institut de la statistique du Québec databases. (26) Blais et al. (26) described the average daily ICS dose (expressed in beclomethasone–chlorofluorocarbon equivalent) 9 months prior to pregnancy compared to during pregnancy using an algorithm developed in previous studies (68, 72). This algorithm is based on the name of the drug and equivalences between the different inhaled corticosteroid products as recognized by the Canadian Asthma Consensus guidelines (73, 74), dose prescribed, date and duration of the prescription and rate of renewals. (75, 76) The change in ICS use was then categorized as discontinuation (reduction of ≥ 75%), reduction (26–75% reduction), no change (± 25% change) and increase (increase > 25%). (26)

This study reported that among 4 920 pregnancies of women with asthma diagnosed either during or prior to pregnancy, 29.5% discontinued their ICS therapy during pregnancy while taking lower daily doses of ICS (8 ± 28.4 μg) during pregnancy when compared to 9 months prior to pregnancy (179.5 ± 187.5 μg). Moreover, 19.0% of enrolled women reduced their daily ICS doses from 325.6 ± 408.7 μg 9 months prior to pregnancy to 158.2 ± 219.3 μg during pregnancy. Furthermore, 22.7% did not change their daily doses of ICS during versus prior to pregnancy (218.4 ± 320.9 μg vs 228.7 ± 331.3 μg), whereas 28.8% of women increased their ICS daily dose to 290 ± 330.5 μg during pregnancy from 125.2 ± 181.7 μg 9 months prior to pregnancy (Please see Table 2.4.B). Overall, the mean daily doses of ICS were below the recommended doses according to international guidelines for 9 months prior to and during pregnancy. (1, 6, 17) Of note, the study findings were adjusted for maternal sociodemographic variables, pregnancy-related and maternal chronic conditions, asthma related variables and markers of asthma severity and control. (26)

Strengths of this study include its large sample size and the use of prescription refills, as opposed to questionnaires, to ascertain medication use. However, the discontinuation of ICS use during pregnancy might be related to an improvement in asthma control leading to confounding bias. (26)

Enriquez et al. (27) conducted an ecological study of 8 149 women with asthma diagnosed either during or prior to pregnancy to determine the change in asthma medication use (ICS, SABA and OCS) starting 20 weeks prior to pregnancy and during pregnancy. Women were included in the study if they had a physician-confirmed asthma diagnosis (ICD–9; 493) with/without having filled 2 prescriptions of SABA or a single prescription for any other asthma medication from the

180 days prior to last menstrual period (LMP) through delivery. Using the Tennessee Medicaid database and vital record files, women were categorized as follows: ICS or SABA users in the week if the days' supply of their prescription included at least 1 day in that week; OCS users were defined as women filling a single prescription of at least 3 days' supply, with each course of OCS prescription separated by at least 7 days. Weekly asthma medication use was computed by dividing the total number of users by the total number of enrolled women for the corresponding week and was assessed at 3 times: from 20 weeks prior to LMP through 5 weeks after LMP, at 13 weeks after LMP and at 26 weeks after LMP. When assessing change in medication use during pregnancy, women contributing to the 'pre-pregnancy' group may have been different from those contributing to the 'during pregnancy' group, as this was an ecological study rather than a cohort study. (27)

Enriquez et al. (27) reported that ICS use significantly decreased by 23% (95% CI 13.9–31.0, $p < 0.0005$) at 13 weeks of pregnancy (3.7%) compared to 20 weeks prior to pregnancy through 5 weeks after LMP (4.7%). The results of ICS use between 14 weeks and 26 weeks of pregnancy were not reported. SABA use decreased by 13% (95% CI 9.0–17.2, $p < 0.0001$) at 13 weeks of pregnancy (15.4%) compared to 20 weeks prior to pregnancy through 5 weeks after LMP (17.7%). This significant decline in SABA use during the first trimester was followed by an increase of 7% between 14 weeks and 26 weeks of pregnancy (95% CI 1.6–12.4, $p = 0.01$) but it is still considered lower than the pre-pregnancy level. Furthermore, OCS use has significantly decreased by 54% (95% CI 41.6–64.2, $p < 0.0001$) at 13 weeks of pregnancy (0.8%) compared to 20 weeks prior to pregnancy through 5 weeks after LMP (1.7%). The results of OCS use between 14 weeks and 26 weeks of pregnancy were not reported (Please see Table 2.4.B). (27)

According to the authors, prescribers may have some concerns about the safety of asthma medications. However, they will encourage women to continue their appropriate asthma therapy, preferably using SABA, to ensure asthma control. This study had a large sample size allowing a high statistical power and had no recall bias by using claims databases. However, it suffered from some limitations: 1) lack of adjustment for confounding variables such as maternal sociodemographic characteristics, maternal chronic conditions or asthma-related variables might have led to ecological fallacy; 2) the time intervals used for the comparison of asthma medication use were unequal prior to pregnancy and during pregnancy. The longer the time interval, the more opportunity women would have to pick up their prescriptions. (27)

2.5.2.4 Asthma medication use during pregnancy in women with asthma diagnosed during pregnancy vs prior to pregnancy

Kim et al. (28) is the only study to date that compared the use of asthma medications (ICS, LABA, ICS/LABA, SABA, LTRA, OCS and xanthine derivatives) during pregnancy between women with an asthma diagnosis code during pregnancy (n = 483) and those with evidence of asthma prior to pregnancy (n = 3 357). Of note, the timing of asthma diagnosis prior to pregnancy (could be shortly before pregnancy or during infancy) and during pregnancy was not specified. Physician-confirmed asthma was operationally defined as having a recorded asthma diagnosis (ICD–10; J45.x – J46.x) during or prior to pregnancy in the Korean National Health Insurance (NHI) claim database along with at least one asthma medication claim or a positive lung function test. Asthma medication use was defined as patients who filled at least one asthma medication during pregnancy. It is worth mentioning that some patients were using more than one class of asthma medications. (28)

Kim et al.'s (28) study showed a significant lower ICS use (27.7% vs 97.0%, $p < 0.001$) and higher use of SABA (34.8% vs 9.7%, $p < 0.001$), ICS/LABA (28.0% vs 10.5%, $p < 0.001$), LTRA (20.3% vs 7.1%, $p < 0.001$), LABA (8.3% vs 3.0%, $p < 0.001$), OCS (27.5% vs 7.4%, $p < 0.001$) and xanthine derivatives (15.5% vs 4.7%, $p < 0.001$) during pregnancy in women diagnosed during pregnancy compared to women diagnosed prior to pregnancy. Additionally, the findings demonstrated that LABA alone had the lowest overall percentage of use during pregnancy of all asthma medication classes studied (Please see Table 2.4.D). (28)

The strength of this study is that it had no recall bias and can be generalized on the national level since Korea has a unique NHI system covering almost the entire population. On the other hand, the study had some methodological limitations: 1) asthma diagnosed during pregnancy was reported to be a new asthma diagnosis (without implementing a lookback period to exclude prevalent cases of asthma) whereas asthma diagnosed prior to pregnancy might be either a prevalent or a new asthma diagnosis; 2) the use of medication was measured in the entire pregnancy for all women, giving by design, a different period to ascertain asthma medication use in women diagnosed during pregnancy; and 3) estimates might be susceptible to bias related to unmeasured confounders due to the lack of information in claim databases on maternal characteristics and asthma severity or control.

2.5.3 Summary of literature review and knowledge gap

In the above sections, we aimed to summarize the existing literature on the use and adherence to asthma medications during pregnancy. Women with asthma diagnosed prior to pregnancy or during pregnancy had a decrease in asthma medication use during pregnancy

compared to before pregnancy. (24-27) Additionally, women with asthma diagnosed prior to pregnancy had a higher self-reported and documented adherence (MPR) to ICS during pregnancy compared to before pregnancy. (18)

Kim et al.'s (28) study evaluated the association between prevalent cases of asthma and asthma medication use during pregnancy. A lower use of ICS and higher use of other asthma medication classes during pregnancy were reported in women diagnosed during pregnancy compared to women diagnosed prior to pregnancy. Nevertheless, these results should be interpreted in the light of major methodological limitations mentioned earlier.

In fact, the GINA, CTS and National Asthma Education and Prevention Program guidelines (1, 6, 17) recommend the use of asthma medications during pregnancy to achieve disease control. The appropriate use of ICS and SABA, as first-line therapy, does not cause harm to the developing fetus or pregnant women since the risk of adverse effects associated with using them during pregnancy appears to be substantially less than the risk related to poorly controlled asthma. (1, 6) Recently, Longo et al. (53) found that the risk of preterm birth was higher in women with asthma newly diagnosed later in pregnancy compared to women with asthma newly diagnosed before or in the first trimester of pregnancy, hypothesizing that asthma diagnosed later in pregnancy might be latent or new asthma symptoms triggered by hormonal fluctuations, and thus difficult to treat in a timely manner. Moreover, non-adherence is considered to be a major problem in achieving optimal asthma control, with poor control linked to a higher risk of adverse perinatal outcomes. (21-23)

Despite the believed association between asthma diagnosis and asthma medication use/adherence during pregnancy (18, 24-28), we found no study that evaluated whether women with new-onset asthma prior to pregnancy are more likely to use and adhere to their medications than those with new-onset asthma during pregnancy. To address this gap in knowledge and the limitations of Kim et al. (28), we performed the first retrospective cohort study to assess whether the use and adherence to asthma medications during pregnancy differ in women with asthma newly diagnosed during the first 19 weeks of pregnancy compared to women with asthma newly diagnosed 2 years prior to pregnancy.

Figure 2.4 Flow chart of selected articles

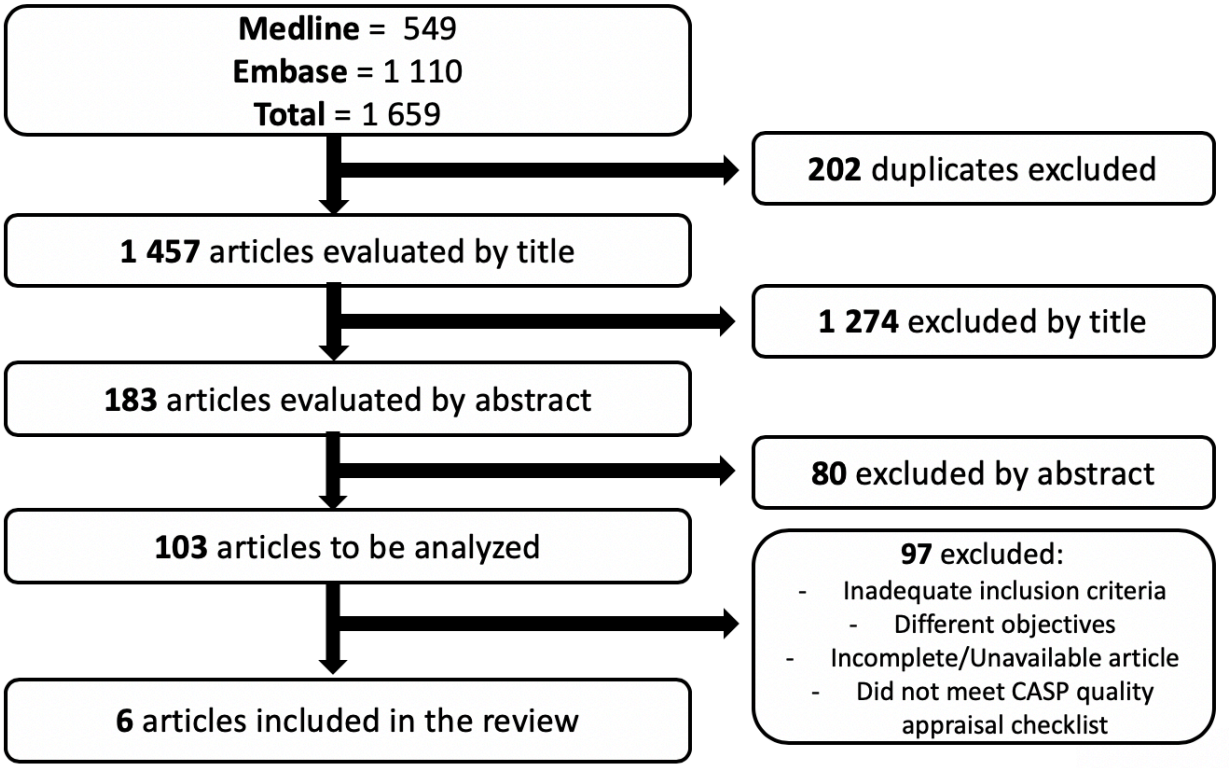


Table 2.4.A Studies investigating the association between asthma medication use or adherence and asthma diagnosis

Study	Design	Study population	Exposure timing	Asthma Dx definition	Outcome definition
Outcome: Asthma medication use during pregnancy					
Kim et al. (2015)[28]	Cohort study	Women with asthma Dx prior to pregnancy (n =3 357) vs Women with new asthma Dx during pregnancy (n = 483)	During pregnancy	Asthma Dx prior to pregnancy with ≥ 1 filled asthma Rx or positive lung function test (same definition for both groups)	≥ 1 filled asthma Rx 1 year prior to and during pregnancy
Blais et al. (2012)[26]	Cohort study	Women with asthma Dx either prior to or during pregnancy (n = 4 434 women with 4 920 pregnancies)	9 months prior vs during pregnancy	Asthma Dx with ≥ 1 filled asthma Rx in 2 years prior to or during pregnancy and ≥ 1 filled ICS Rx 9 months prior to pregnancy	Change in ICS use between 9 months prior to pregnancy and during pregnancy based on the average daily ICS dose
Sawicki et al. (2012)[25]	Survey	Women with asthma Dx prior to pregnancy attending a pregnancy clinic at their 36th week (n = 102)	Diagnosis at any point in time prior to pregnancy vs during pregnancy	Self-reported asthma	Questionnaire about asthma medication use regarding the change in asthma medication use during pregnancy as compared to before pregnancy
Enriquez et al. (2006)[27]	Ecological study	Women with asthma Dx either prior to or during pregnancy (n = 8 149) *(women contributing to the 'pre-pregnancy' group may have been different from those contributing to the 'during pregnancy' group)*	20 weeks prior to LMP through 5 weeks after LMP vs 13 weeks after LMP vs 26 weeks after LMP	Asthma Dx with/without: - ≥ 2 filled Rx SABA or - ≥ 1 filled Rx of ICS or OCS starting 20 weeks prior to LMP through delivery	- ICS or SABA users in the week defined by if the day's supply of their prescription included at least 1 day in that week - OCS users defined by single prescription of at least 3 days' supply with each course of OCS separated by at least 7 days
Schatz et al. (2005)[24]	Cohort study	Women with asthma Dx at any point in time prior to pregnancy (n = 334)	6 months prior vs during the first 6 months of pregnancy	≥ 1 filled Rx in 6 prior to pregnancy	≥ 1 filled Rx 6 months prior to pregnancy and 6 months during pregnancy
Outcome: Adherence to asthma medication during pregnancy					
Baarnes, et al. (2016)[18]	Cohort study	Women with asthma Dx at any point in time prior to pregnancy (n = 114)	9 months prior vs during pregnancy	Asthma Dx and ≥ 1 filled Rx of ICS in 9 months prior to pregnancy	Self-reported vs documented adherence (MPR) calculated based on the number of filled prescriptions

LMP: Last menstrual period; ICS: Inhaled Corticosteroids; SABA: Short-acting beta-2 agonists; OCS: Oral corticosteroids; MPR: Medication Possession Rate.

Table 2.4.B Results of studies investigating the association between asthma medication use or adherence and asthma diagnosis

Treatment	Study	Outcome: Asthma medication use				Statistical results
		Prior to pregnancy	During pregnancy			
			1st trimester	2nd trimester	3rd trimester	
ICS	**Sawicki et al. (2012)[25]**	6.0%	2.0%			$p < 0.001$
	Enriquez et al. (2006)[27]	4.7%	3.7% *(by 23.0%)*	∅		$p < 0.0005$
	Schatz et al. (2005)[24]	30.2%	19.5% *(by 36.0%)*		∅	*p*-value not reported
	Blais et al. (2012)[26]	**Mean daily dose ± SD** (beclomethasone–chlorofluorocarbon equivalent)	**Mean daily dose ± SD** (beclomethasone–chlorofluorocarbon equivalent)			**Comparison during vs prior to pregnancy**
		179.5 µg ± 187.5 µg	8.0 µg ± 28.4 µg			Discontinuation (29.5%)
		325.6 µg ± 408.7 µg	158.2 µg ± 219.3 µg			Reduction (19.0%)
		228.7 µg ± 331.3 µg	218.4 µg ± 320.9 µg			No change (22.7%)
		125.2 µg ± 181.7 µg	290.0 µg ± 330.5 µg			Increase (28.8%)
SABA	**Sawicki et al. (2012)[25]**	54.0%	57.0%			$p = 0.004$
	Enriquez et al. (2006)[27]	17.7%	15.4% *(by 13.0%)*	Increase by 7.0% $p = 0.01$	∅	$p < 0.0001$
	Schatz et al. (2005)[24]	85.0%	41.0% *(by 52.0%)*		∅	*p*-value not reported
ICS + SABA	**Sawicki et al. (2012)[25]**	13.0%	6.0%			$p = 0.012$
OCS	**Enriquez et al. (2006)[27]**	1.7%	0.8% *(by 54.0%)*	∅		$p < 0.0001$
Others (LABA, LTRA and mast cell stabilizers)	**Schatz et al. (2005)[24]**	12.0%	9.0% *(by 25.0%)*		∅	*p*-value not reported

ICS: inhaled corticosteroids; SABA: short-acting beta-2 agonists; OCS: oral corticosteroids; LABA: long-acting beta-2 agonists; LTRA: leukotriene receptor antagonists.

Table 2.4.C Results of a study investigating ICS adherence during versus prior to pregnancy among women with asthma diagnosed pre-pregnancy

Treatment	Study	Outcome: Adherence to asthma medication			Statistical results
			Prior to pregnancy	During pregnancy	
ICS	**Baarnes et al. (2016)[18]**	Self-reported	52.0%	73.0%	$p < 0.001$
		Documented	28.0%	46.0%	$p < 0.0001$

ICS: Inhaled Corticosteroids.

able 2.4.D Results of the only study investigating the association between asthma medication use during pregnancy and the timing of asthma diagnosis

Treatment	Study	Outcome: Asthma medication use during pregnancy		
		Asthma newly diagnosed during pregnancy	Asthma diagnosed prior to pregnancy	Statistical results
ICS	**Kim et al. (2015)[28]**	27.7%	97.0%	$p < 0.001$
LABA		8.3%	3.0%	$p < 0.001$
SABA		34.8%	9.7%	$p < 0.001$
ICS/LABA		28.0%	10.5%	$p < 0.001$
LTRA		20.3%	7.1%	$p < 0.001$
OCS		27.5%	7.4%	$p < 0.001$
Xanthines derivatives		15.5%	4.7%	$p < 0.001$

ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonists; SABA: short-acting beta-2 agonists; LTRA: leukotriene receptor antagonists; OCS: oral corticosteroids.

CHAPTER 3: OBJECTIVES

3. Objectives

The objectives and hypotheses of our study are listed below.

3.1 Primary objective

3.1.1 To compare the use of ICS, ICS/LABA, any controller medication (ICS, ICS/LABA, LTRA, and THEO) and SABA use during pregnancy between women with asthma newly diagnosed during the first 19 weeks of pregnancy and women with asthma newly diagnosed 2 years prior to pregnancy.

3.1.2 To compare the use of OCS during pregnancy between women with asthma newly diagnosed during the first 19 weeks of pregnancy and women with asthma newly diagnosed 2 years prior to pregnancy.

3.2 Secondary objectives

3.2.1 To compare the asthma medications dispensed in the month prior and the month following the date of asthma diagnosis between women with asthma newly diagnosed during the first 19 weeks of pregnancy and those newly diagnosed 2 years prior to pregnancy.

3.2.2 To compare the level of ICS adherence to asthma medications during pregnancy between women with asthma newly diagnosed during the first 19 weeks of pregnancy and women with asthma newly diagnosed 2 years prior to pregnancy.

3.3 Hypotheses

We hypothesized that asthma diagnosed early in pregnancy may have a more persistent phenotype than asthma diagnosed prior to pregnancy due to hormonal fluctuations or to an

asthma present prior to pregnancy but undiagnosed yet and consequently untreated. Another possible underlying mechanism for the association between asthma medication use and the timing of asthma diagnosis could be that women with asthma diagnosed prior to pregnancy might be more likely to use their asthma medications and persist even after becoming pregnant than those diagnosed early in pregnancy.

CHAPTER 4: METHODS

4. Methods

This chapter encompasses the methods presented in the manuscript more comprehensively including sources of data, study design, exposure assessment, outcomes definition, potential confounders and statistical analyses.

4.1 Sources of data

To conduct this study, we used the QAPD database constructed by linking two administrative health databases from the province of Quebec (Canada): RAMQ and MED-ECHO databases.

4.1.1 Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (MED-ECHO)

The MED-ECHO database is the Quebec universal hospital discharge summary database that is used in the planning, organization and evaluation of services provided in health and social service sectors. MED-ECHO database contains data on acute care hospitalizations (i.e. health care insurance number, date of admission, date of delivery, primary and secondary diagnoses coded according to the ICD–9 before 2006 or the ICD–10 since 2006, length of hospitalization and treatments received during hospitalization) and covers all residents of Quebec. By using gestational age at birth and date of birth of the newborns, we retrospectively identified the date of the first day of the last menstrual period and the date of delivery for each pregnancy using validated algorithms. (77)

4.1.2 Régie de l'assurance maladie du Québec (RAMQ)

The RAMQ database contains data on medical services (i.e. health care insurance number, nature of the medical act, date of service; site of practice [outpatient clinic, emergency department (ED), or inpatient clinic] and the treating physician's specialty) provided on a fee for service basis to all residents of Quebec as well as data on prescription medications (i.e. date of filling, name, dose, dosage form, quantity and duration of prescriptions, new or refill prescriptions, encrypted identification and the prescribing physician's specialty) dispensed in community pharmacies for residents covered by the RAMQ's Public Drug Insurance Plan and on the admissibility to the Public Drug Insurance Plan (i.e. the date of the beginning and end of the admissibility). According to the RAMQ annual report 2010, 41.7% of the population in Quebec were covered by the Public Drug Insurance Plan, including residents receiving social assistance, approximately 90% of the elderly and residents aged <65 years who have no access to a private drug insurance plan provided by their spouse or employers. (7, 8) RAMQ also provided socioeconomic data including date of birth of mothers, receipt of social assistance and area of residence.

Moreover, the prescription data recorded in the RAMQ Medication Prescription database and the medical diagnosis of asthma recorded in the RAMQ Medical Services database were formally evaluated and found to be valid and precise (78, 79) with data shown to have 83% correct identification of the patients and drugs dispensed from the prescriptions (79) and a positive predictive value of 75% and a negative predictive value of 96% for asthma diagnoses. (77) These prospectively gathered and interlinked databases to identify the exposures and outcomes had

several advantages over other methods of data collection such as self-administered questionnaires or maternal interviews. (80-83)

4.1.3 Quebec asthma and pregnancy database (QAPD)

The QAPD includes all women who delivered in a hospital between January 1, 1990, and March 31, 2010, and had at least 1 asthma diagnosis recorded in the RAMQ or MED-ECHO database up to 2 years before 1 or more of their deliveries, plus a 4-fold larger random sample of other women who delivered during the same period. (84) The recorded prescription data and the medical diagnosis of asthma were evaluated and found to be reliable. (78, 79) Moreover, the QAPD has been previously used by the research team of Dr. Lucie Blais in collaboration with other researchers to study the impact of asthma medications, asthma control and drug insurance plans on the prevalence of congenital malformations, as well as to study the impact of having asthma diagnosed during pregnancy on perinatal outcomes. (53, 61, 85, 86)

4.2 Ethics approval

This research project was approved by the *Ethics Committee of the Centre intégré universitaire de santé et de services sociaux du Nord-de-l'Île-de-Montréal*. Authorization was obtained from the *Commission d'Accès à l'Information du Québec* before accessing and linking information from the MED-ECHO and RAMQ databases.

4.3 Study design

To achieve our goal, a population-based retrospective cohort design was used. A cohort comprising pregnant women was selected from the QAPD (Please see the selection process in

Figure I of the manuscript) and included women if they: (1) had a delivery between January 1, 1998, and March 31, 2010, to ensure a lookback period of 8 years to exclude women with a history of asthma. We kept only the first pregnancy recorded in QAPD; (2) had 20 to 45 weeks of gestation at delivery; (3) were aged between 15 and 45 years at the beginning of pregnancy; (4) were newly diagnosed with asthma within 2 years before or during the first 19 weeks of pregnancy (i.e. did not have asthma in the 8 year lookback period); and (5) were covered by RAMQ's Public Drug Insurance Plan from 3 months prior to asthma diagnosis until delivery. We kept only the first recorded pregnancy in the QAPD to avoid potential overlaps between the pre-pregnancy and early pregnancy periods in women with less than 2 years between successive pregnancies. Using a previously validated definition, asthma was defined as at least one asthma diagnosis (ICD–9 code 493, except 493.2, or ICD–10 code J45) at any point in time within 2 years before or during the first 19 weeks of pregnancy as recorded in the QAPD. (78) We excluded women with a history of chronic obstructive pulmonary disease (ICD–9 491, 492, 496; ICD–10 J41–J44) and cystic fibrosis (ICD–9 277.0; ICD–10 E84) during the 8-year lookback period since these diseases might share similar symptoms or treatments with asthma and women with quadruplet being rare pregnancies in our cohort.

Because pregnancies that terminated before week 20 of gestation were not included in the QAPD since they are considered to be spontaneous/elective abortions in the province of Quebec (87), we defined our cohort entry as the first day of week 20 of gestation to avoid selection bias (88), particularly if being diagnosed with asthma during pregnancy is associated with miscarriage. (89, 90) Women were followed from cohort entry until delivery.

4.4 Maternal exposure to asthma diagnosis

Hormonal fluctuations and more intense medical follow-up are likely to contribute to the diagnosis of asthma during pregnancy. It is well recognized that female sex hormones have a role in the development and severity of asthma, with asthma developing later in women's life likely to be more severe or difficult to treat. (13) Despite such high incidence of asthma diagnosed during pregnancy, no studies have evaluated whether asthma newly diagnosed during pregnancy is of a different phenotype and whether it is more likely to be difficult to treat compared to asthma newly diagnosed pre-pregnancy. Asthma diagnosis was identified using ICD–9 code 493 (except 493.2) or ICD–10 code J45. Women diagnosed with asthma during an 8-year lookback period from 2 years prior to pregnancy were excluded to select only women with asthma newly diagnosed at any time in the 2 years prior to pregnancy or during the first 19 weeks of pregnancy. We used 2 years prior to maximize our sample size in the comparison group – going too far back would have led to confounding by severity and too soon to pregnancy would have led to smaller numbers.

4.5 Outcomes definition

4.5.1 Asthma medication use during pregnancy

To assess our primary outcome, the use of asthma medications during pregnancy was measured as mentioned in the corresponding section of the manuscript. It is worth mentioning that we had to reconstruct the ICS and LABA prescriptions especially that the first ICS/LABA combination (salmeterol/fluticasone) was released on the market on September 24, 1999 (91) and our cohort included women who delivered between January 1, 1998, and March 31, 2010. At

first, we applied correction factors to the days' supply of ICS in order to overcome data entry mistakes in pharmacy files. (92) Briefly, ICS are provided in canisters containing a fixed number of puffs, hence the canister's lifespan may vary depending on the prescribed number of puffs per day. The correction factors were derived from the most frequent dosages and corresponding days' supply obtained from the original prescriptions for specific ICS product and canister size. (92) Ultimately, after applying the correction factors, we reconstructed ICS and LABA prescriptions as follows: 1- prescriptions filled on the same day were assigned a new duration of treatment as follows: two prescriptions of ICS alone or two prescriptions of LABA alone were deemed as one prescription with a duration corresponding to the addition of both prescriptions' durations recorded in the RAMQ database. For instance, a woman filled on the same day two ICS prescriptions with a duration of 25 days. The estimated duration of the new ICS prescription would be 50 days; two prescriptions of ICS/LABA combination were deemed as one prescription with a duration corresponding to the least duration of treatment, recorded in the RAMQ database, among both prescriptions. For instance, a woman filled on the same day an ICS prescription with a duration of 30 days and a LABA prescription with a duration of 20 days. The estimated duration of the combined ICS/LABA prescription would be 20 days, corresponding to the prescription with the least duration of treatment. 2- two prescriptions of ICS and LABA filled separately on different days with a duration of treatment overlapping for at least 15 days were considered as one prescription of ICS/LABA combination therapy. The start day of this combined prescription would be the date when the second prescription was filled and the prescription's duration corresponds to the least duration of treatment among both prescriptions. Otherwise, if two prescriptions of ICS and LABA were filled separately on different days with a duration of

treatment overlapping for less than 15 days, ICS and LABA prescriptions were not combined. In addition, the reimbursement criteria for ICS/LABA prescriptions changed during the period where the cohort was selected and the outcomes were measured (i.e. between January 1, 1998 and March 31, 2010). Since their market entry from September 24, 1999 until January 28, 2004, ICS/LABA therapy was reimbursed by the RAMQ without an exception. However, starting January 28, 2004, this combination was transferred to the exceptional drug list to promote their optimal use, meaning that it was reimbursed by the RAMQ only for patients with insufficient disease control despite the use of ICS. Of note, patients covered by the RAMQ who have already received a reimbursement for ICS/LABA prior to January 28, 2004, were still eligible for continued treatment. (93)

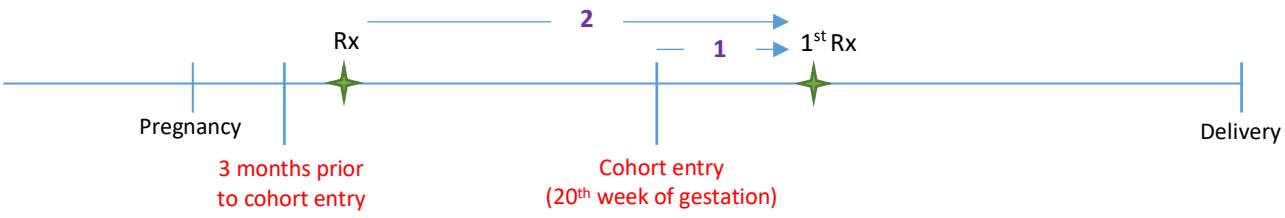
4.5.2 Treatment dispensed at asthma diagnosis

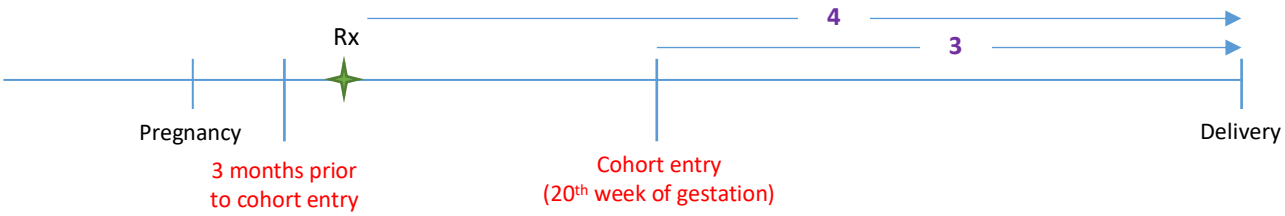
Treatment dispensed at diagnosis was defined as all asthma medications filled at the pharmacy in the month prior and the month following the date of asthma diagnosis. Treatments were analyzed in two separate categories as controllers (alone or in combination with other controllers) and relievers (alone or in combination with other relievers), while excluding those that were too low to assess, therefore not of a clinical interest. Of note, prescriptions filled on the same day of as the asthma diagnosis were included with the prescriptions filled in the month following asthma diagnosis.

4.5.3 Asthma medication adherence during pregnancy

According to international guidelines, ICS are the cornerstone therapy in the management of asthma during pregnancy. ICS are needed to be administered as prescribed on a daily basis, which

increases the risk of poor adherence compared to asthma relievers prescribed as needed. (1, 6, 17) Moreover, ICS were the most prescribed asthma controllers in our cohort. We estimated adherence to ICS during follow-up with the proportion of days covered (PDC). The PDC was calculated as the ratio of the number of days' supply of ICS dispensed after cohort entry over the number of days between cohort entry and delivery × 100 and was capped at 100%. (18) The number of days' supply dispensed is obtained by summing the duration of all filled prescriptions (new and refills) of ICS and ICS/LABA combination therapy recorded in the RAMQ Prescription Medications file during follow-up. Moreover, if a prescription of ICS was filled in the 3 months prior to cohort entry, a proportion of its days' supply was added to the numerator of the PDC, assuming that those days' supply were used after cohort entry. The proportion of days' supply was obtained as follows: we estimated the number of days between cohort entry and the first filled prescription during follow-up, if any, (arrow 1) or the date of delivery (arrow 3). Then, we divided this number by the number of days between the prescription filled in the 3 months prior to cohort entry and the first filled prescription during follow-up, if any, (arrow 2) or the date of delivery (arrow 4) to obtain a proportion. Finally, we multiplied this proportion by the duration of the filled prescription recorded in the RAMQ database during the 3 months prior to cohort entry. The purpose of this adjustment is that women might not refill their prescriptions as prescribed and use the same inhaler for more than one month (with an approximate 3–4 refills/year). (94)





4.6 Sensitivity analysis

Because the results of the PDC analysis were discordant with those of asthma medication use during pregnancy, we conducted a post-hoc analysis to assess ICS medication use during pregnancy among ICS users for both sub-cohorts. Users were defined as women who received at least one ICS or ICS/LABA prescription during follow-up or in the 3 months prior to cohort entry. ICS use was defined as the number of filled prescriptions during pregnancy since asthma diagnosis. We estimated the rates of users of ICS or ICS/LABA who filled a prescription during the first 19 weeks of pregnancy and after cohort entry (≥ 20 weeks) until delivery (per 100 women-months), separately.

4.7 Confounding variables

The potential confounders mentioned in the corresponding section of the manuscript were found in the literature to be associated with asthma medication use and/or adherence. Of note, the Romano comorbidity score (95) is an adapted form of the Charlson Comorbidity Index, the most widely used comborbidity index that was validated first in a cohort of breast cancer patients (96) and in several other studies thereafter (97-103) by evaluating the ability of scores to predict mortality. The Romano Comorbidity score is a weighted index using ICD-9-CM codes derived from all hospital discharges and all diagnoses associated with ambulatory physician services during the

baseline year. Each condition was assigned a weight from 1 to 6 based on the strength of their association with mortality (Please see Table 4.6). (95) These weights were summed to produce the Romano comorbidity score for a patient. Other determinants of asthma medication use and adherence such as education level (104-107), body mass index (105, 108-110), smoking habits (105, 108, 111, 112) and alcohol consumption (105, 110) were not recorded in the Quebec administrative databases. Therefore, these factors were not included in our models leading to a potential residual confounding.

Table 4.6 Romano weighted index of comorbidity

Assigned weights for diseases	**Conditions**
1	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS
Assigned weights for each condition that a patient has. The total equals the score (eg. chronic pulmonary (1) and lymphoma (2) = total score (3))	

Source: Charlson, M., Pompei, P., Ales, K., & MacKenzie, C. (1987).

4.8 Statistical analyses

The detailed statistical analyses were reported in the corresponding section of the manuscript. Furthermore, we conducted a sensitivity analysis adjusting for the same confounding variables mentioned earlier (age at asthma diagnosis, area of residence in the year prior to asthma diagnosis, receipt of social assistance 3 months before asthma diagnosis and maternal comorbidities in the 2 years before asthma diagnosis), while modifying the lookback period to measure the variable 'number of hospitalizations, ED visits and ambulatory medical visits **in the year prior to 1 year before asthma diagnosis**'. The purpose of this analysis was to adjust for the likelihood of getting diagnosed with asthma by measuring the number of contacts with the healthcare system. The more a woman was exposed to the healthcare system (i.e. more hospitalizations, visits to an ED and ambulatory medical visits), the higher the chance to detect an asthma diagnosis if she had a latent asthma and to be prescribed an asthma therapy, consequently leading to more asthma medication use. (113, 114) All analyses were performed using SAS v9.4 software (SAS Institute, Cary, NC).

CHAPTER 5: RESULTS – MANUSCRIPT

5. Results – Manuscript

5.1 Manuscript

Association between timing of asthma diagnosis and medication use during pregnancy

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This article is included in the current thesis by the permission of the co-authors.

ABSTRACT

Background: Asthma medication use during pregnancy is recommended by international guidelines to maintain control of symptoms since poor control has been shown to increase the risk of adverse perinatal outcomes.

Objective: To assess whether asthma medication use during pregnancy differs in women with asthma diagnosed during the first 19 weeks of pregnancy compared to those diagnosed 2 years before pregnancy.

Methods: We conducted a retrospective cohort study using the Quebec asthma and pregnancy database. Use of inhaled corticosteroids (ICS), ICS/long-acting ß2-agonists (LABA) and short-acting ß2-agonists (SABA) during pregnancy was defined as the number of filled prescriptions from 20 weeks of pregnancy (Cohort entry – CE –) until delivery. Use of oral corticosteroids (OCS) during pregnancy was defined as the number of days of filled prescriptions from CE until delivery. Poisson regression models were used to compare the rates of asthma medication use between women diagnosed before and early in pregnancy.

Results: The cohort included 1 731 women with asthma diagnosed before and 359 early in pregnancy. Women diagnosed early in pregnancy were more likely to use ICS [aRR 1.9, 95% CI 1.6–2.3] and SABA [aRR 2.0, 95% CI 1.7–2.4] than women diagnosed before pregnancy. No difference in the use of ICS/LABA [aRR 0.9, 95% CI 0.7–1.3] and OCS [aRR 0.8, 95% CI 0.6–1.2]

Conclusion: Women with asthma diagnosed early in pregnancy use more ICS and SABA than those diagnosed before pregnancy, which could suggest a more persistent phenotype due to hormonal changes triggered by pregnancy.

HIGHLIGHTS BOX

What is already known about this topic? No study to date evaluated the use and adherence to asthma medications during pregnancy among women with asthma newly diagnosed early in pregnancy compared to women newly diagnosed before pregnancy.

What does this article add to our knowledge? Women newly diagnosed in early pregnancy were significantly more likely to use asthma controllers and SABA than those newly diagnosed before pregnancy, which could suggest a more persistent phenotype that develops and/or re-initiates during pregnancy.

How does this study impact current management guidelines? These results support a close medical follow-up of asthmatic women newly diagnosed before or early in pregnancy to improve medication use and adherence and consequently keep asthma under control during pregnancy.

KEY WORDS

Asthma; Asthma medication use; Maternal asthma; Adherence; Pregnancy; Epidemiology; Quebec Asthma and Pregnancy database.

Introduction

Asthma affects approximately 13% of pregnant women worldwide and is one of the most common chronic diseases during pregnancy. (1, 2) Despite international guidelines recommending the use of asthma medications during pregnancy to achieve disease control, women with asthma are often concerned about the harmful side effects of asthma treatments on the fetus, leading to a reduction in their use during pregnancy. (3-5) Non-adherence to asthma medications during pregnancy has been shown to range between 27% and 40% (6-10) and is considered to be a major problem in achieving optimal asthma control, with poor control linked to a higher risk of adverse perinatal outcomes. (9-11)

Recently, Longo et al. (12) showed that women with asthma diagnosed in the second and third trimesters of pregnancy were at a significantly higher risk of preterm birth than those diagnosed in the first trimester or within 2 years prior to pregnancy. They hypothesized that latent or new asthma symptoms later in pregnancy triggered by hormonal fluctuations and that led to a diagnosis, likely increased the preterm birth risk when compared to those diagnosed in the first trimester or prior to pregnancy. (12) Kim et al.'s study (13) evaluated the association between prevalent cases and asthma medication use during pregnancy and reported a lower use of inhaled corticosteroids (ICS) and higher use of ICS in combination with long-acting β2 agonists (LABA), short-acting β2 agonists (SABA) and oral corticosteroids (OCS) during pregnancy in women newly diagnosed during pregnancy compared to women diagnosed pre-pregnancy. Nevertheless, these results should be interpreted with caution since asthma medication use was measured between different study populations and over the entire pregnancy for all women. The

period for ascertaining medication use in women diagnosed during pregnancy would necessarily be shorter when compared to those with previous asthma, which could lead to biased results. (13)

While we hypothesized that women with asthma newly diagnosed prior to pregnancy might be more likely to use and adhere to their medications than those newly diagnosed during pregnancy, no studies have evaluated the impact of the timing of asthma diagnosis on asthma medication use during pregnancy. Therefore, the primary objective of this retrospective cohort study was to assess whether asthma medication use from week 20 of gestation until delivery differs in women newly diagnosed during the first 19 weeks of pregnancy compared to women newly diagnosed within 2 years prior to pregnancy. Our secondary objectives were to compare the asthma treatment dispensed at diagnosis and ICS adherence from week 20 of gestation until delivery between women diagnosed early in pregnancy and pre-pregnancy.

Methods

Data sources

The Quebec Asthma and Pregnancy Database (QAPD) was used and constructed by linking two administrative health databases from the province of Quebec (Canada): The *Régie de l'Assurance Maladie du Québec* (RAMQ) and the *Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière* (MED-ECHO) databases. The MED-ECHO database contains data on acute care hospitalizations, including deliveries, and covers all residents of Quebec. The RAMQ database contains data on medical services provided on a fee for service basis to all residents of Quebec as well as data on prescription medications dispensed in community pharmacies for

residents covered by the RAMQ's Public Drug Insurance Plan. According to the RAMQ annual report 2010, 41.7% of the population in Quebec were covered by this drug plan, including residents receiving social assistance, approximately 90% of the elderly and residents aged <65 years who have no access to a private drug insurance plan provided by their spouse or employers. (14, 15)

The QAPD includes all women who delivered from January 1990 to March 2010 and had at least one asthma diagnosis recorded in the RAMQ database or the MED-ECHO database up to 2 years preceding a delivery and all pregnancies of a 4-fold larger random sample of other women who delivered during the same period. (16) We retrospectively identified the date of the first day of the last menstrual period and the date of delivery for each pregnancy using the gestational age at birth and the date of birth of the newborns recorded in the MED-ECHO database using validated algorithms. (17) We had access to RAMQ and MED-ECHO data between January 1988 and March 2010 for all the pregnant women. Moreover, the recorded prescription data and the medical diagnosis of asthma were evaluated and found to be reliable. (18, 19) The QAPD was previously used to study the impact of asthma medications, asthma control and drug insurance plans on the prevalence of congenital malformations, as well as to study the impact of having asthma diagnosed during pregnancy on perinatal outcomes. (12, 20-22)

This research project was approved by the *Ethics Committee of the Centre intégré universitaire de santé et de services sociaux du Nord-de-l'Île-de-Montréal*. Authorization was obtained from the *Commission d'Accès à l'Information du Québec* before accessing and linking information from the MED-ECHO and RAMQ databases.

Study design

We conducted a retrospective population-based cohort study of pregnant women selected from the QAPD who: (1) delivered between January 1, 1998, and March 31, 2010, to ensure a lookback period of 8 years to exclude women with a history of asthma; (2) were 20 to 45 weeks of gestation at delivery; (3) were aged between 15 and 45 years at the beginning of pregnancy; (4) were newly diagnosed with asthma within 2 years before or during the first 19 weeks of pregnancy (i.e. did not have asthma in the 8 year lookback period); and (5) were covered by the RAMQ's Public Drug Insurance Plan from 3 months prior to asthma diagnosis until delivery. We kept only the first recorded pregnancy in the QAPD to avoid potential overlaps between the pre-pregnancy and early pregnancy periods in women with less than 2 years between successive pregnancies. Using a previously validated definition, asthma was defined as at least one asthma diagnosis (International Classification of Disease, Ninth Revision [ICD–9] code 493, except 493.2, or ICD–10 code J45) at any point in time within 2 years before or during the first 19 weeks of pregnancy as recorded in the QAPD. (18) We excluded women with a history of chronic obstructive pulmonary disease (ICD–9 491, 492, 2496; ICD–10 J41–J44) and cystic fibrosis (ICD–9 277.0; ICD–10 E84) in the 8-year lookback period and with quadruplet pregnancies.

Cohort entry was defined as the first day of week 20 of gestation, since pregnancies that terminated before week 20 were not included in the QAPD and are considered to be spontaneous abortions in the province of Quebec. (23) We then identified two sub-cohorts of interest: (1) women with asthma diagnosed within 2 years prior to pregnancy (referred to as 'asthma diagnosed pre-pregnancy') and (2) women with asthma diagnosed during the first 19 weeks of

pregnancy (referred to as 'asthma diagnosed early in pregnancy'). Women were followed from cohort entry until delivery.

Outcomes

Primary Outcome: Asthma medication use in pregnancy

The use of ICS, ICS/LABA, any controller medication (ICS, ICS/LABA, leukotriene-receptor antagonists (LTRA) and theophylline (THEO)) and SABA from week 20 of gestation until delivery was measured as the number of filled prescriptions recorded in the RAMQ prescription claims database during follow-up. Since women might not refill their prescriptions as prescribed and use the same inhaler for more than one month, (with an approximate 3–4 refills/year) (24), we also counted the last filled prescription in the 3 months prior to cohort entry. (25) The use of LTRA and THEO, separately, and the use of short-acting anticholinergics (SAAC) were not reported due to their low proportion of use (ranging between 0.1% – 0.3%) during follow-up. OCS use was defined as the number of days' supply dispensed during follow-up. OCS prescriptions filled prior to cohort entry with a duration that overlaps cohort entry were also considered, counting only the number of days' supply remaining after cohort entry.

Secondary Outcomes: Treatment at diagnosis and medication adherence

Treatment dispensed at diagnosis was defined as all asthma medications filled at the pharmacy in the month prior and the month following the date of asthma diagnosis. Common treatments were classified in two categories as controllers (alone or in combination with other controllers) and relievers (alone or in combination with other relievers).

Adherence to ICS during follow-up was estimated with the proportion of days covered (PDC). The PDC was calculated as the ratio of the number of days' supply of ICS dispensed after cohort entry over the number of days between cohort entry and delivery × 100. (6) If an ICS prescription was filled in the 3 months prior to cohort entry and the timing between successive refills suggested spillover of the previous ICS prescription during the follow-up period, a proportion of its leftover days' supply was added to the numerator of the PDC, assuming that those days' supply were used after cohort entry (see online supplement for more details).

Confounding variables

Maternal sociodemographic variables such as age (13–18, >18–34, >34 years) (26-28) at asthma diagnosis, area of residence (rural/urban) (26, 28, 29) in the year prior to asthma diagnosis, receipt of social assistance (yes/no) (26, 28, 30) 3 months before asthma diagnosis, number of hospitalizations, emergency department visits and ambulatory medical visits for any cause (0, 1–5, >5) (31, 32) up to 1 year before asthma diagnosis and maternal comorbidities (26, 33, 34) within 2 years before asthma diagnosis using Romano comorbidity score (0, ≥1) (35, 36) were considered as potential confounders since they were found in the literature to be associated with asthma medication use.

Statistical analyses

Descriptive statistics were used to report the characteristics of women for each sub-cohort separately. We also estimated the proportions of women who filled any controller medication, ICS, ICS/LABA, SABA and OCS during follow-up. In addition, we calculated the crude rates of use of any controller medication, ICS, ICS/LABA and SABA defined as the number of prescriptions

filled in addition to the last prescription filled in the 3 months prior to cohort entry, if applicable, per 100 women–months. The rate of OCS use was defined as the number of days' supply after cohort entry per 100 women–months.

To address the main objective, crude rate ratios (RRs) and adjusted RRs (aRRs) of asthma medication use during follow-up comparing both sub-cohorts were estimated using Poisson regression models, after verifying that overdispersion did not exist for each outcome, and an offset for varying follow-up durations as a result of different delivery times. (37) All potential confounders were included in all adjusted models.

To assess the treatment dispensed at diagnosis, we estimated the proportion of women who filled prescriptions of controllers (any controller, ICS and ICS/LABA) and relievers (any reliever, SABA and SAAC) and OCS in the month prior and the month following the date of asthma diagnosis, separately, for both sub-cohorts. We also estimated the mean (± standard deviation) PDC for ICS during follow-up for each sub-cohort. A linear regression model was used to compare the level of adherence to ICS between sub-cohorts while adjusting for confounding variables. To better understand the discordance between the analyses of asthma medication use and PDC, we conducted a post-hoc analysis to assess ICS medication use following diagnosis in the first 19 weeks of gestation and during the follow-up period among ICS users, i.e. those who received at least one ICS or ICS/LABA from 3 months prior to cohort entry or during follow-up, for both sub-cohorts. All analyses were performed using SAS v9.4 software (SAS Institute, Cary, NC).

Results

Of the 583 071 pregnant women in the QAPD, 2 090 pregnant asthmatic women were included in this study with 359 (17.2%) women with asthma diagnosed early in pregnancy and 1 731 (82.8%) women with asthma diagnosed pre-pregnancy (Figure 1). Women with asthma diagnosed early in pregnancy were more likely to be older than 18 years, deliver prematurely, receive social assistance, live in an urban area, have at least one hospitalization, emergency department visit and ambulatory medical visit in the year prior to the asthma diagnosis and suffer from other chronic diseases than those diagnosed pre-pregnancy (Table 1). In addition, the proportion of women who filled at least one asthma medication during follow-up was low for both sub-cohorts (asthma diagnosed early in pregnancy compared to pre-pregnancy): ICS (29.3% vs 13.8%), ICS/LABA (2.2% vs 1.4%), SABA (41.5% vs 20.6%) and OCS (1.7% vs 1.4%).

Compared to women diagnosed pre-pregnancy, women diagnosed early in pregnancy had higher rates (per 100 women–months) of use of any controller (9.9, 95% CI 8.4–11.5 vs 5.5, 95% CI 4.9–6.0), ICS (9.1, 95% CI 7.6–10.6 vs 4.6, 95% CI 4.1–5.1) and SABA (14.9, 95% CI 13.0–16.8 vs 7.4, 95% CI 6.8–8.0) later in pregnancy; however ICS/LABA and OCS rates of use were quite similar. With respect to the rate of medication use, we found that women diagnosed early in pregnancy were more likely to use any controller [aRR 1.8, 95% CI 1.5–2.1], ICS [aRR 1.9, 95% CI 1.6–2.3], and SABA [aRR 2.0, 95% CI 1.7–2.4] and, on average, less likely to use ICS/LABA [aRR 0.9, 95% CI 0.7–1.3] and OCS [aRR 0.8, 95% CI 0.6–1.2], although not statistically significant, during follow-up than women diagnosed pre-pregnancy (Table 2).

Approximately 30% of women filled asthma controllers and about 40% filled relievers in the month after asthma diagnosis, whereas about 5% filled asthma controllers and about 7% filled asthma relievers in the month before asthma diagnosis (Table 3). The most common asthma controller and reliever dispensed within the month prior and after diagnosis among women diagnosed early in pregnancy were ICS (5.3% vs 4.9%; 29.3% vs 30.2%) and SABA (7.2% vs 7.5%; 41.5% vs 39.3%), respectively, compared to those diagnosed pre-pregnancy. Very few women filled a combination therapy. In both sub-cohorts, about 10% of women filled OCS in the month after diagnosis whereas about 2% filled OCS in the month prior to diagnosis.

With respect to adherence, the mean PDC during follow-up for all women using ICS-based controllers was 24.5% (95% CI 21.3–27.8) in women diagnosed early in pregnancy and 27.7% (95% CI 25.3–30.1) in those diagnosed pre-pregnancy. The linear regression model revealed that the adjusted difference in ICS adherence was not clinically relevant (-3.6; 95% CI -7.9 to 0.6). The post-hoc analysis showed that ICS users with asthma diagnosed early in pregnancy were more likely to fill an ICS prescription during the first 19 weeks of pregnancy [crude rates 22.8 vs 18.7] but less likely to fill an ICS prescription from cohort entry until delivery [crude rates 13.7 vs 23.5] than users with pre-pregnancy asthma (Table 4).

Discussion

Our findings suggest a higher use of any controller, ICS and SABA and similar use of ICS/LABA and OCS from week 20 of gestation until delivery in women with asthma diagnosed early in pregnancy compared to women with asthma diagnosed pre-pregnancy. The overall asthma medication use during follow-up was low ranging approximately between 2% for OCS and 42% for SABA.

Prescription of asthma therapy at diagnosis was low, with ICS and SABA being the most commonly prescribed asthma controller and reliever, respectively. Although, the rate of ICS use was considerably higher in women diagnosed early in pregnancy, we found no clinically relevant difference in mean ICS adherence between both sub-cohorts. This might be due to the fact that ICS users with asthma diagnosed early in pregnancy were more likely to fill an ICS prescription immediately upon their asthma diagnosis (i.e. during the first 19 weeks of pregnancy) and less likely to refill it regularly during follow-up, as compared to users diagnosed pre-pregnancy.

While no other studies have assessed the timing of incident asthma diagnosis in relation to asthma medication use during pregnancy, one retrospective cohort study assessed asthma medication use during pregnancy among 483 women with asthma diagnosis code during pregnancy and 3 357 women with asthma diagnosis code at some point prior to pregnancy. (13) The authors reported significant lower proportions of ICS use (27.7% vs 97.0%, $p < 0.001$) and significant higher use of ICS/LABA (28.0% vs 10.5%, $p < 0.001$), SABA (34.8% vs 9.7%, $p < 0.001$) and OCS (27.5% vs 7.4%, $p < 0.001$) during pregnancy in women diagnosed during pregnancy compared pre-pregnancy (13) whereas our study reported higher use of ICS (29.3% vs 13.8%), ICS/LABA (2.2% vs 1.4%), SABA (41.5% vs 20.6%) and OCS (1.7% vs 1.4%) during follow-up in women diagnosed early in pregnancy compared to pre-pregnancy. This divergence in findings could be due to different study populations and follow-up periods. Because there was a lack of a lookback period to exclude potential prevalent asthma cases, we cannot be certain that these women were newly diagnosed as was the case in our study. Moreover, medication use was assessed during the entire pregnancy (follow-up period) for all women, giving by design, differential periods to ascertain asthma medication use in women who may have been diagnosed

during pregnancy versus those with asthma prior to pregnancy. (13) In our study, the follow-up period was defined as the first day of week 20 of gestation until delivery for all women. (23)

Our finding that the most dispensed treatments upon asthma diagnosis were ICS and SABA comes in concordance with asthma management guidelines. (38, 39) As a matter of fact, ICS have been advocated as the first-line controller therapy while SABA are the agents of choice in rescue therapy used during pregnancy for mild asthma to gain prompt control of symptoms and reduce exacerbations risk. (38-40)

While our study, to our knowledge, was the first to assess adherence to ICS-based therapy from week 20 of gestation until delivery in women with newly diagnosed asthma, only one prospective cohort study of 114 prevalent asthma cases evaluated ICS adherence 9 months prior to pregnancy and during pregnancy. (6) This study reported high ICS adherence during pregnancy using self-reported adherence (73%) and another pharmacy-based adherence measure, the medication possession ratio – MPR – (46%) (6), whereas we observed low adherence during follow-up using PDC (27.7%) among users diagnosed pre-pregnancy. This difference in results could be due to different study populations as they included women with prevalent asthma while we included women with new-onset asthma. Moreover, self-reporting subjective measures of adherence have been shown to severely overestimate true adherence. (41, 42) The PDC definition adapted in our study measured a more accurate adherence level compared to MPR (43-45), assuming that the days' supply of filled prescriptions prior to cohort entry were used after cohort entry.

While guidelines stress the importance of maintaining asthma medication use during pregnancy to keep asthma under control, we found low use and adherence to asthma medications, representing a significant problem in asthma management and increased risk of adverse perinatal and maternal outcomes. (38, 39) Our results do not support our initial hypothesis, which suggested that women diagnosed pre-pregnancy may be more likely to use and adhere to their medication during pregnancy. The elevated use of ICS and SABA during pregnancy in those diagnosed during versus pre-pregnancy could suggest a persistent pregnancy-onset asthma phenotype; this could be due to substantial hormonal fluctuations that have been shown to impact lung inflammation (3, 46), requiring more asthma medication use during pregnancy than asthma diagnosed pre-pregnancy. While our results might be explained by fluctuations in asthma course with pregnancy, they support other studies showing similar patterns of decreased asthma medication use during pregnancy compared to before pregnancy in women diagnosed pre-pregnancy. (27, 47) and low adherence during pregnancy ranging between 27% and 40% in women with prevalent asthma. (6-8)

The current study has some important strengths. Our study was the first to assess asthma medication use and ICS adherence from week 20 of gestation until delivery among women with asthma newly diagnosed prior to and early in pregnancy. It also comprised a large sample of women with asthma diagnosed either during or pre-pregnancy. However, there are also some limitations to be considered when interpreting our results. First, filled prescriptions used to identify asthma medication use and adherence might not always represent the actual use, leading to a nondifferential outcome misclassification, which could underestimate the associations between asthma medication use and the timing of asthma diagnosis. Second, since

our databases did not include pregnancies terminated before week 20, being considered as abortions in the province of Quebec (23), we suspected a potential selection bias. In fact, if women diagnosed in early pregnancy relative to pre-pregnancy were more likely to have spontaneous or elective abortions (48, 49) and would have been more likely to use their medications, our estimates would be biased toward the null. (50, 51) Third, smoking habits were not recorded in the QAPD database, which were found to be associated with both asthma diagnosis and asthma medication use/adherence during pregnancy. (52-56) In Canada (2010), the reported maternal smoking rate was lower than the smoking rate pre-pregnancy (12.3% vs 17.4%) (57, 58). Smokers might seek medical attention more than nonsmokers because of health concerns from smoking, increasing the likelihood of getting diagnosed with asthma. (52); hence not adjusting for this variable might overestimate the studied association. Finally, the generalizability of our results might be reduced since women with higher socioeconomic status are underrepresented in our cohort as prescription data is only available for Quebec residents with low socioeconomic status covered by public drug insurance.

Despite guideline recommendations, the overall asthma medication use and adherence during pregnancy were considerably low. Women diagnosed early in pregnancy might have a more persistent or more symptomatic asthma requiring higher use of controllers and SABA later in pregnancy than women diagnosed pre-pregnancy, although more research needs to be considered to confirm these findings. Our results support an ongoing collaboration between prescribers and patients by providing educational resources focusing on the safety and importance of medication use and adherence to optimize asthma control and increase the likelihood of healthy pregnancies and newborns.

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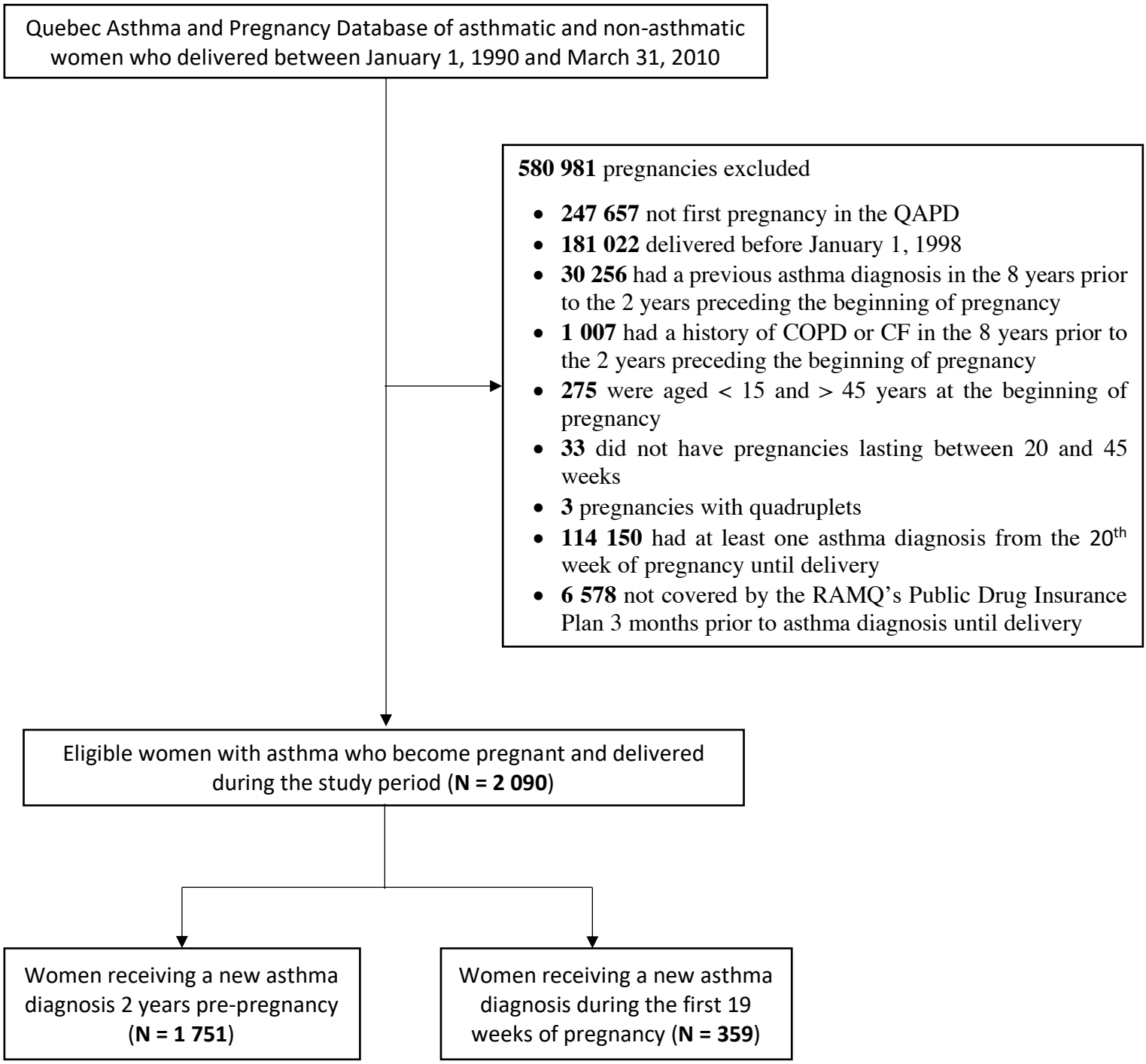
Figure I: Population flowchart



QAPD: Quebec Asthma and Pregnancy Database; CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; RAMQ: *Régie de l'Assurance Maladie du Québec.*

Table I: Pregnancy characteristics and duration of follow-up

Characteristics	Asthma diagnosed early in pregnancy (n=359)	Asthma diagnosed pre-pregnancy (n=1 731)
Maternal age at asthma diagnosis (years), n (%)		
13–18	35 (9.8)	341 (19.7)
> 18–34	293 (81.6)	1 274 (73.6)
> 34–45	31 (8.6)	116 (6.7)
Gestational age (weeks), n (%)		
20–31	6 (1.7)	31 (1.8)
> 31–36	38 (10.6)	143 (8.3)
> 36	315 (87.7)	1 557 (89.9)
Receipt of social assistance 3 months prior to asthma diagnosis, n (%)	118 (32.9)	522 (30.2)
Urban area of residence in the year prior to asthma diagnosis, n (%)	312 (86.9)	1 432 (82.7)
Number of hospitalizations, ED and ambulatory medical visits 1 year prior to asthma diagnosis, n (%)		
0	13 (3.6)	98 (5.7)
1–5	151 (42.1)	798 (46.1)
≥ 6	195 (54.3)	835 (48.2)
Romano comorbidity score 2 years prior to asthma diagnosis, n (%)		
0	332 (92.5)	1 616 (93.4)
1	19 (5.3)	79 (4.6)
2	7 (1.9)	25 (1.4)
3	0 (0.0)	2 (0.1)
4	1 (0.3)	2 (0.1)
6	0 (0.0)	7 (0.4)
Days of follow-up, mean [SD]	130.5 [15.4]	131.0 [16.5]
Asthma medication use from 20th week of gestation until delivery, n (%)		
Any controller*	110 (30.6)	256 (14.8)
ICS	105 (29.3)	239 (13.8)
ICS/LABA	8 (2.2)	25 (1.4)
SABA	149 (41.5)	357 (20.6)
OCS	6 (1.7)	24 (1.4)

***** Including ICS, ICS/LABA, LTRA and THEO. ED: emergency department; SD: standard deviation; ICS: inhaled corticosteroids; LABA: long-acting β_2 agonists; SABA: short-acting β_2 agonists; OCS: oral corticosteroids; LTRA: leukotriene-receptor antagonists; THEO: theophylline.

Table II. Crude rate and crude and adjusted RR of asthma medication use from the 20th week of gestation until delivery

Asthma medications	Crude rate* (95% CI)		Rate ratio (Asthma diagnosed early in pregnancy vs pre-pregnancy)	
	Asthma diagnosed early in pregnancy (n=359)	Asthma diagnosed pre-pregnancy (n=1 731)	Crude RR (95% CI)	Adjusted§ RR (95% CI)
Any controller**	9.9 (8.4 – 11.5) †	5.5 (4.9 – 6.0) †	1.8 (1.5 – 2.2)	1.8 (1.5 – 2.1)
ICS	9.1 (7.6 – 10.6) †	4.6 (4.1 – 5.1) †	2.0 (1.7 – 2.4)	1.9 (1.6 – 2.3)
ICS/LABA	0.8 (0.3 – 1.2) †	0.8 (0.6 – 1.0) †	1.0 (0.7 – 1.4)	0.9 (0.7 – 1.3)
SABA	14.9 (13.0 – 16.8) †	7.4 (6.8 – 8.0) †	2.0 (1.7 – 2.4)	2.0 (1.7 – 2.4)
OCS	1.8 (1.1 – 2.4) ‡	2.0 (1.7 – 2.3)‡	0.9 (0.6 – 1.3)	0.8 (0.6 – 1.2)

* per 100 women per month.

† Defined as number of filled prescriptions during follow-up.

‡ Defined as number of days of filled prescriptions during follow-up.

§ Adjusted for maternal age, area of residence, social assistance, Romano comorbidity score and number of hospitalizations, emergency department or ambulatory medical visits.

** Including ICS, ICS/LABA, LTRA and THEO.

RR: rate ratio; CI: confidence interval; ICS: inhaled corticosteroids; LABA: long-acting β_2 agonists; SABA: short-acting β_2 agonists; OCS: oral corticosteroids; LTRA: leukotriene-receptor antagonists; THEO: theophylline.

Table III. Asthma treatment dispensed in the month prior and the month following the date of asthma diagnosis

	1 month prior diagnosis†			1 month after diagnosis		
	Asthma diagnosed early in pregnancy (n=359), n (%)	**Asthma diagnosed pre-pregnancy (n=1 731), n (%)**	***p*-value**	**Asthma diagnosed early in pregnancy (n=359), n (%)**	**Asthma diagnosed pre-pregnancy (n=1 731), n (%)**	***p*-value**
Asthma controllers						
Any controller*	19 (5.3)	91 (5.2)	.4772	112 (31.0)	562 (32.6)	.1581
ICS	19 (5.3)	85 (4.9)	.7621	105 (29.3)	522 (30.2)	.7327
ICS + LABA	0 (0.0)	4 (0.2)	**.0455**	6 (1.7)	27 (1.6)	.8775
Asthma relievers						
Any reliever**	26 (7.2)	129 (7.5)	.4581	150 (41.8)	694 (40.0)	.0587
SABA	26 (7.2)	126 (7.3)	.9806	149 (41.5)	681 (39.3)	.4462
SABA + SAAC	0 (0.0)	3 (0.2)	.0833	1 (0.3)	11 (0.6)	.2910
OCS	4 (1.1)	28 (1.6)	.5068	35 (9.8)	165 (9.5)	.4387

† Excluding the day of asthma diagnosis.

* Including ICS, ICS/LABA, LTRA and THEO.

** Including SABA and SAAC.

ICS: inhaled corticosteroids; THEO: theophylline; LTRA: leukotriene-receptor antagonists; LABA: long-acting β_2 agonists; SABA: short-acting β_2 agonists; SAAC: short-acting anticholinergic; OCS: oral corticosteroids.

Table IV. Crude rate of ICS filled prescriptions during pregnancy among users

Variables	Rate per 100 users of ICS per month (95% CI)	
	Asthma diagnosed early in pregnancy (n=110)	Asthma diagnosed pre-pregnancy (n=255)
ICS prescriptions filled during the first 19 weeks of pregnancy	22.8 (18.7 – 26.9)	18.7 (16.2 – 21.1)
ICS prescriptions filled between week 20 of pregnancy and delivery	13.7 (10.4 – 17.0)	23.5 (20.7 – 26.3)

ICS: inhaled corticosteroids; CI: confidence interval

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ICS were the most prescribed asthma controllers in our cohort. We estimated adherence to ICS during follow-up using the PDC. The PDC was calculated as the ratio of the number of days' supply of ICS dispensed after cohort entry over the number of days between cohort entry and delivery × 100 and was capped at 100%. (E1)

Prior to calculating the numerator of the PDC, we applied validated correction factors to the days' supply in order to overcome possible data entry errors within pharmacy files. (E2) The number of days' supply dispensed is obtained by summing the duration of all filled prescriptions (new and refills) of ICS and ICS/LABA combination therapy recorded in the RAMQ Prescription Medications file during follow-up. Moreover, if a prescription of ICS was filled in the 3 months prior to cohort entry, a proportion of its days' supply was added to the numerator of the PDC, assuming that those days' supply were used after cohort entry. The proportion of days' supply was obtained as follows: we estimated the number of days between cohort entry and the first filled prescription during follow-up, if any, (arrow 1) or the date of delivery (arrow 3). Then, we divided this number by the number of days between the prescription filled in the 3 months prior to cohort entry and the first filled prescription during follow-up, if any, (arrow 2) or the date of delivery (arrow 4) to obtain a proportion. Finally, we multiplied this proportion by the duration of the filled prescription recorded in the RAMQ database during the 3 months prior to cohort entry. The purpose of this adjustment is that women might not refill their prescriptions as prescribed and use the same inhaler for more than one month (with an approximate 3–4 refills/year). (E3)

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E3. Stempel DA, Stoloff SW, Carranza Rosenzweig JR, Stanford RH, Ryskina KL, Legorreta AP. Adherence to asthma controller medication regimens. Respir Med. 2005;99(10):1263-7.

5.2 Unpublished sensitivity analysis

Due to space limitation, the results of the additional sensitivity analysis were not included in the manuscript submitted for publication. The analysis consisted in comparing the association measures by modifying the lookback period to measure the variable 'number of hospitalizations, ED visits and ambulatory medical visits **in the year prior to 1 year before asthma diagnosis**'.

Unlike the corresponding results in the main analyses, women with asthma diagnosed early in pregnancy were less likely to have at least one hospitalization, an ED visit or an ambulatory medical visit for any cause in the year prior to 1 year before asthma diagnosis than women with asthma diagnosed pre-pregnancy. This difference in results between both analyses can be explained by the fact that in the 1 year prior to asthma diagnosis, women diagnosed early in pregnancy might have been more in contact with the healthcare system simply as a consequence of their prenatal visit compared to prior to pregnancy.

In table 5.2, we found that women with asthma diagnosed early in pregnancy were more likely to use any controller (aRR 1.7, 95% CI 1.4–2.1), ICS (aRR 1.9, 95% CI 1.6–2.3), and SABA (aRR 2.0, 95% CI 1.7–2.3) and less likely to use ICS/LABA (aRR 0.8, 95% CI 0.6–1.1) and OCS (aRR 0.9, 95% CI 0.6–1.2) during follow-up than women diagnosed pre-pregnancy. The linear regression model revealed that the adjusted difference in ICS adherence was not statistically significant (-3.5; 95% CI -7.7 to 0.7). These results were similar to those found with the main analyses, indicating that the number of hospitalizations, ED visits and ambulatory medical visits, measured

up to 2 years prior to asthma diagnosis did not have a sizeable impact on the association between asthma medication use and the timing of asthma diagnosis.

able 5.1 Pregnancy characteristics and duration of follow-up

Characteristics	Asthma diagnosed early in pregnancy (n=359)	Asthma diagnosed pre-pregnancy (n=1 731)
Maternal age at asthma diagnosis (years), n (%)		
13–18	35 (9.8)	341 (19.7)
> 18–34	293 (81.6)	1 274 (73.6)
> 34–45	31 (8.6)	116 (6.7)
Gestational age (weeks), n (%)		
20–31	6 (1.7)	31 (1.8)
> 31–36	38 (10.6)	143 (8.3)
> 36	315 (87.7)	1 557 (89.9)
Receipt of social assistance 3 months prior to asthma diagnosis, n (%)	118 (32.9)	522 (30.2)
Urban area of residence in the year prior to asthma diagnosis, n (%)	312 (86.9)	1 432 (82.7)
Number of hospitalizations, ED and ambulatory medical visits in the year prior to 1 year before asthma diagnosis, n (%)		
0	75 (20.9)	230 (13.3)
1–5	162 (45.1)	819 (47.3)
≥ 6	122 (34.0)	682 (39.4)
Romano comorbidity score 2 years prior to asthma diagnosis, n (%)		
0	332 (92.5)	1 616 (93.4)
1	19 (5.3)	79 (4.6)
2	7 (1.9)	25 (1.4)
3	0 (0.0)	2 (0.1)
4	1 (0.3)	2 (0.1)
6	0 (0.0)	7 (0.4)
Days of follow-up, mean [SD]	130.5 [15.4]	131.0 [16.5]
Asthma medication use from the 20th week of gestation until delivery, n (%)		
Any controller*	110 (30.6)	256 (14.8)
ICS	105 (29.3)	239 (13.8)
ICS/LABA	8 (2.2)	25 (1.4)
SABA	149 (41.5)	357 (20.6)
OCS	6 (1.7)	24 (1.4)

Including ICS, ICS/LABA, LTRA and THEO. ED: emergency department; SD: standard deviation; ICS: inhaled corticosteroids; LABA: long-acting β_2 agonists; SABA: short-acting β_2 agonists; OCS: oral corticosteroids; LTRA: leukotriene-receptor antagonists; THEO: theophylline.

Table 5.2 Crude rate and crude and adjusted RR of asthma medication use from the 20th week of gestation until delivery

Asthma medications	Crude rate* (95% CI)		Rate ratio (Asthma diagnosed early in versus pre-pregnancy)	
	Asthma diagnosed early in pregnancy (n=359)	Asthma diagnosed pre-pregnancy (n=1 731)	Crude RR (95% CI)	Adjusted§ RR (95% CI)
Any controller**	9.9 (8.4 – 11.5) †	5.5 (4.9 – 6.0) †	1.8 (1.5 – 2.2)	1.7 (1.4 – 2.1)
ICS	9.1 (7.6 – 10.6) †	4.6 (4.1 – 5.1) †	2.0 (1.7 – 2.4)	1.9 (1.6 – 2.3)
ICS/LABA	0.8 (0.3 – 1.2) †	0.8 (0.6 – 1.0) †	1.0 (0.7 – 1.4)	0.8 (0.6 – 1.1)
SABA	14.9 (13.0 – 16.8) †	7.3 (6.8 – 8.0) †	2.0 (1.7 – 2.4)	2.0 (1.7 – 2.3)
OCS	1.8 (1.1 – 2.4) ‡	2.0 (1.7 – 2.3) ‡	0.9 (0.6 – 1.3)	0.9 (0.6 – 1.2)

* per 100 women per month.

† Defined as number of filled prescriptions during follow-up.

‡ Defined as number of days of filled prescriptions during follow-up.

§ Adjusted for maternal age, area of residence, social assistance, Romano comorbidity score and number of hospitalizations, emergency department or ambulatory medical visits.

** Including ICS, ICS/LABA, LTRA and THEO.

RR: rate ratio; CI: confidence interval; ICS: inhaled corticosteroids; LABA: long-acting β_2 agonists; SABA: short-acting β_2 agonists; OCS: oral corticosteroids; LTRA: leukotriene-receptor antagonists; THEO: theophylline.

CHAPTER 6: DISCUSSION

6. Discussion

This chapter presents a discussion of the results included in the thesis. In addition, this section will illustrate the contribution of the results in the field of asthma during pregnancy. Finally, we will present the strengths and weaknesses of the study and the future perspectives of research.

6.1 General discussion

Our study results reported an overall low asthma medications use during pregnancy regardless of the timing of asthma diagnosis. More specifically, we found that women newly diagnosed early in pregnancy were more likely to use asthma controllers and SABA from week 20 of pregnancy until delivery than women newly diagnosed pre-pregnancy. While our study was the first to evaluate this association, one retrospective cohort study (28) assessed asthma medication use in women with prevalent asthma and found a significant lower use of ICS (27.7% vs 97.0%, $p < 0.001$) and significant higher use of ICS/LABA (28.0% vs 10.5%, $p < 0.001$), SABA (34.8% vs 9.7%, $p < 0.001$) and OCS (27.5% vs 7.4%, $p < 0.001$) during pregnancy in women with asthma diagnosis codes during pregnancy compared to those with evidence of asthma pre-pregnancy. Concerns about the methodologies and conduct of this study have been raised. Indeed, the follow-up period was not clearly defined for both groups and asthma medication use was measured over the entire pregnancy for all women, giving by design, differential periods to ascertain asthma medication use in women diagnosed during pregnancy. Furthermore, since no lookback period was implemented to exclude prevalent asthma cases, we cannot be certain that these women had a new-onset asthma, making the comparison difficult. (28)

We also found that prescription of asthma therapy within one month prior and one month after asthma diagnosis was low, with ICS and SABA being the most commonly prescribed asthma controller and reliever, respectively. In fact, International guidelines highly recommend the use of ICS and SABA at recommended doses, as first-line therapy, does not cause harm to the fetus or pregnant women since the risk of adverse effects associated with using them during pregnancy appears to be less than the risk of poorly controlled asthma. (1, 6, 16)

Our study was also the first to assess adherence to ICS-based therapy from week 20 of gestation until delivery in women with newly diagnosed asthma. Although, the rate of ICS use was higher in women diagnosed early in pregnancy, we found no clinically relevant difference in mean adherence among users in both sub-cohorts. This might be explained by the fact that ICS users with asthma diagnosed early in pregnancy were more likely to fill an ICS prescription directly upon their asthma diagnosis and less likely to refill it regularly later in pregnancy, compared to users diagnosed pre-pregnancy. Baarnes's et al. study (18) reported high adherence during pregnancy using self-reported adherence (73%) and MPR (46%), whereas our study found low adherence during follow-up using PDC (27.7%) among ICS users diagnosed prior to pregnancy. This difference in results could be due to different study populations as they included women with prevalent asthma while we included those with new-onset asthma. Self-reported adherence might lead to social desirability bias which could alter the study results by overestimating adherence. (70, 71) The PDC definition adapted in our study measured a more accurate adherence level compared to MPR , assuming that the days' supply of filled prescriptions prior to cohort entry were used after cohort entry. (115-117)

As mentioned earlier, starting January 28, 2004, ICS/LABA prescriptions were reimbursed by the RAMQ only for patients with insufficient asthma control despite ICS use. (93) This change in the reimbursement criteria during our study period might have altered ICS/LABA use and ICS-based controllers adherence during follow-up. However, according to the GINA guidelines published since 2004 until 2010 (i.e. last year of our study period), this combination therapy was the preferred option for the management of moderate persistent asthma (step 3) if the patient was not controlled on a low dose of ICS. Moreover, these guidelines recommended the use of ICS and SABA during pregnancy as first-line treatments upon asthma diagnosis. (118, 119) To this end, knowing that our study included women with newly diagnosed asthma, it seems unlikely that these reimbursement changes had a sizeable impact on our study results.

We also performed a sensitivity analysis while modifying the lookback period to measure the variable 'number of hospitalizations, ED visits and ambulatory medical visits **in the year prior to 1 year before asthma diagnosis**'. This analysis did not affect the regression models regarding asthma medication use and adherence during pregnancy compared to those of the main analyses.

6.2 Contribution of our results to the literature in the field of asthma during pregnancy

Looking into the literature, no study to date evaluated our research question regarding the association between the timing of asthma diagnosis and asthma medication use/adherence during pregnancy. The aforementioned studies shared several methodological limitations, preventing the inferring of solid conclusions. Our study addressed these limitations by measuring

asthma medication use over the same follow-up period to allow equal opportunity for newly diagnosed women to fill their prescriptions in both sub-cohorts. With respect to the rates of asthma medication use, our study could suggest that asthma diagnosed early in pregnancy might be either a new-onset asthma with a more persistent phenotype triggered by hormonal changes (32) or a latent disease that was present prior to pregnancy, but was left undiagnosed and consequently untreated, requiring more use of asthma controllers and SABA, compared to asthma diagnosed pre-pregnancy. (39) Recently, Longo et al. (53) found that the risk of preterm birth was higher in women with asthma diagnosed in the second and third trimesters of pregnancy compared to women with asthma diagnosed prior to or early in pregnancy. They hypothesized that asthma diagnosed later in pregnancy might be of a different phenotype and more likely to be severe due to hormonal fluctuations (8, 32) or to a latent disease present prior to pregnancy but not diagnosed yet and untreated, when compared to women diagnosed and subsequently treated prior to or early in pregnancy. In fact, several studies have reported an association between asthma and hormonal changes throughout the female life-span. For instance, it was found that estrogen levels have a role in the development and severity of asthma. Low estrogen levels may cause airway inflammation leading to a more severe asthma in nature or even difficult to treat. (29-31) Our results also support other studies showing similar patterns of decreased asthma medication use (24-27) and adherence (6-8) during pregnancy in women with prevalent asthma.

Our study also added evidence to the use of ICS and SABA during pregnancy upon asthma diagnosis being considered as the first-line asthma therapy during pregnancy to prevent complications associated with uncontrolled asthma. (1, 6, 16)

In addition, our study was the first to assess ICS-based controllers adherence from week 20 of gestation until delivery among women with new-onset asthma. Adherence was measured using an adapted definition of the PDC as an objective measurement tool compared to self-reported adherence to limit the social desirability that might have biased our results. (68, 69) While guidelines stress the importance of maintaining asthma medication use during pregnancy to keep asthma under control, we found low ICS adherence, representing a significant problem in asthma management and increased risk of adverse perinatal and maternal outcomes. (40, 41)

Although these results support poor asthma medication use and adherence during pregnancy in a representative population-based cohort, more research is warranted to provide additional information regarding the association between the timing of asthma diagnosis and the use of asthma medications during pregnancy.

6.3 Strengths of the study

6.3.1 Databases

Among the major strengths of this study is the use of the Quebec Asthma and Pregnancy Database. It is considered one of the largest administrative-linked pregnancy databases in Canada with 583 071 pregnancies, spanning over 20 years (i.e. from 1990 until 2010). The QAPD database was constructed by linking two large administrative health databases from the province of Quebec, the RAMQ and MED-ECHO databases. Both databases – MED–ECHO and RAMQ – have been used by the research team of Dr. Lucie Blais and other researchers to study the impact of having asthma diagnosed during pregnancy, asthma medications, asthma control and drug insurance plans on the prevalence of congenital malformations with many articles published in

renowned medical journals. (55, 68, 84, 120-122) Pregnancy variables (i.e. maternal age, length of gestation, date of delivery, and date of last menstruation) recorded in the RAMQ and MED-ECHO databases or derived from data recorded in those databases and used in our analysis were evaluated and found to be highly valid. The validity of the variables was assessed by calculating Pearson correlation coefficient between the values obtained from the databases and patients' medical charts, and the correlations were found to be high for all variables ranging from 0.920 to 0.999. (77) First, data on asthma diagnosis were prospectively collected independently of the outcome, avoiding the possibility of any recall bias. Second, the use of two large administrative databases allowed us to establish the largest sample size to date and assess our outcomes while measuring several potential confounders to reflect the population of pregnant asthmatic women. Third, administrative databases also provide the ability to study large number of pregnant women with newly diagnosed asthma with a reasonable budget and time frame.

6.3.2 Study design

A retrospective cohort was a suitable study design to assess our objectives since it is highly efficient in terms of cost-effectiveness and time frame. Our study was the first to evaluate the association between timing of new-onset asthma and asthma medication use during pregnancy among a cohort of women with newly diagnosed asthma either 2 years prior to pregnancy or during the first 19 weeks of pregnancy. We also excluded pregnancies that terminated before the 20^{th} week of gestation since these are considered as abortions in the province of Quebec. (87) Consequently, the follow-up period was standardized for all women in our study, starting the first day of the 20^{th} week of gestation until delivery, to allow for equal opportunity for women to fill their prescriptions in both groups. (88)

6.3.3 Outcomes measurement

Asthma medication use was assessed over the same follow-up period, defined as the first day of week 20 of gestation until delivery, for all women in the two sub-cohorts regardless of when they were diagnosed with asthma. In addition, our study was the first to investigate the adherence to ICS from the 20th week of gestation until delivery among women with asthma diagnosed early in pregnancy. Adherence was measured using PDC as an objective measurement tool to limit the social desirability compared to self-reported adherence that might not be highly accurate (70, 71), leading to a non-differential misclassification and a recall bias that underestimates asthma medication use.

6.4 Limitations of the study

Bias is a systematic error resulting from errors in the methods the study was conducted such as the way the subjects were selected, errors in the measurement of variables, or any confounding factor that were simply unmeasured. Therefore, it might influence the internal validity of the study. Generally, biases can be classified into selection bias, information bias, and confounding bias. (80-83)

6.4.1 Selection bias

Selection bias refers to any error that arises in the process of selecting the study population and in a cohort study it is usually related to losses to follow-up. (80-83) Since our databases did not include the pregnancies terminated before week 20, being considered as abortions in the province of Quebec (87), we suspect a potential selection bias. In fact, if being diagnosed with asthma is associated with early pregnancy termination (89, 90), exposure

misclassification would likely be nondifferential, which could generally result in estimates biased toward the null. (88, 123) Moreover, if asthma medication use were measured before week 20, there might be unmeasured variables (e.g., smoking, obesity or alcohol consumption) associated with both pregnancy termination and medication use. (124-126) Therefore, the association between the timing of asthma diagnosis and asthma medication use measured before week 20 could have been biased by these unmeasured variables, leading to a collider bias. For instance, if a woman did not have an abortion, she is less likely to have risk factors for abortion which may also affect asthma medication use. However, it is difficult to predict the impact of a collider bias on the association between asthma diagnosis and asthma medication use during pregnancy.

6.4.2 Information bias

Information bias occurs as a result of differences in the way the exposure, outcomes, or potential confounders were measured. Misclassification is one of the common forms of information bias, which can be differential or non-differential. (80-83)

In our study, the exposure assessment (i.e. asthma diagnosis) was identified using diagnoses codes recorded in the RAMQ and MED-ECHO databases which were not specifically validated for this study, but validation was performed earlier in a separate study. (78) However, asthma diagnosis was not confirmed using spirometry or lung function. Asthma misdiagnoses due to the presence of comorbidities with asthma-like symptoms such as gastroesophageal reflux disease, may have led to nondifferential misclassification of the exposure (i.e. dilutes the true effect toward the null) resulting in an underestimation of the observed results. Moreover, other comorbidities associated with pregnancy and that might mimic asthma symptoms, such as

pregnancy-related dyspnea, may have led to more cases of false positive asthma diagnosed early in pregnancy using more asthma medications and resulting in a differential misclassification of the exposure and an underestimation of the measured relative risks.

Regarding the outcomes' assessment, the use and adherence to asthma medications were measured using medication claims data, which might not reflect their actual intake. Consequently, if there was any inaccuracy in the measurement of outcomes, it will not be related to the exposure because our outcomes are equally misclassified among women diagnosed pre-pregnancy and those diagnosed early in pregnancy, leading to a non-differential information bias and an underestimation of the association measured. (127)

6.4.3 Confounding bias

Confounding results in an observed association different from the true effect with an extraneous factor associated with the exposure, an independent risk factor for the disease, and not in the causal pathway between exposure and disease. (80-83) In order to reduce the impact of confounding in our study, we used multivariate regression models to adjust the RRs for several confounding covariables at the same time (see potential confounders and statistical analysis sections in the manuscript). We included the majority of known risk factors that were found to be associated with the exposure (i.e. asthma diagnosis) and the study outcomes in our models. However, there was a possibility of residual confounding due to our inability to adjust for smoking habits. The reasons for poorer asthma control during pregnancy among smokers may be related the direct effect of smoking on asthma status or asthma medication use and nonadherence. Smokers might seek medical attention more than nonsmokers because of concerns about health

effects of smoking (such as bronchitis), increasing the likelihood of getting diagnosed with asthma. (128) We also suspect that the more a woman was in contact with the healthcare system during pregnancy, the higher the chance to detect an asthma diagnosis if she had a latent asthma. In Canada, even though the reported maternal smoking rate decreased from 21.9% in 1993–1996 to 12.3% in 2010 (129), the smoking rate pre-pregnancy was considerably higher with 17.4% in 2010. (130) If the latter is the case, these women are more likely to be diagnosed. Moreover, smokers were found to be less likely to use asthma medications during pregnancy. (131) To this end, we expect that not adjusting for these variables might possibly overestimate the association between the timing of asthma diagnosis and asthma medication use during pregnancy.

6.5 External validity

External validity refers generally to which extent a study's findings could be applied to other non-study populations (i.e. generalizability). (80, 82, 83, 132) Under the Quebec Universal Drug Insurance program, all Quebec residents must be covered by either a private insurer or by the RAMQ Public Drug Insurance Plan (with or without social assistance). Our cohort included only women covered by the RAMQ Public Drug Insurance Plan which involved residents receiving social assistance and residents aged < 65 years who have no access to a private drug insurance plan provided by their spouse or employers. (133, 134) The prevalence of women publicly insured with social assistance was very similar among women with asthma diagnosed early in pregnancy (32.9%) compared to women with asthma diagnosed pre-pregnancy (30.2%). Nevertheless, the generalizability of our results might be reduced since women with higher socioeconomic status

were underrepresented in our cohort as prescription data is only accessible for Quebec residents with public drug insurance. (26, 135-137)

6.6 Clinical implications of the results

In the field of asthma during pregnancy, there is still considerable lack of knowledge that need to be answered in proper means regarding the association between asthma medication use during pregnancy and the timing of asthma diagnosis. The overall asthma medication use and adherence from the 20th week of gestation until delivery was considerably low in both sub-cohorts. Despite the recommendations of international guidelines, prescribers and patients might be worried about the potential harm of asthma medication on the fetus, resulting in reluctance to use and adhere to asthma therapies during pregnancy. (1, 6, 17) This could be because only some women have a persistent phenotype require more use of ICS and SABA compared to those with episodic asthma. Women newly diagnosed during pregnancy seem to be more likely to have this persistent phenotype relatively to those newly diagnosed pre-pregnancy, although more research needs to be conducted to confirm these findings. The findings in our study add essential evidence-based knowledge that could be part of a larger therapeutic strategy endorsed by healthcare professionals. Pregnant asthmatic women should have a closer medical follow-up and be provided with educational resources advising that the benefit of asthma treatment outweighs the potential risks of asthma medication use . This strategy might minimize the risk of exacerbations and keep asthma under control throughout pregnancy increasing the likelihood of healthy pregnancies and newborns. Since asthma diagnosis can be challenging due to hormonal changes during pregnancy, family physicians might want to refer women planning

to become pregnant or at their first prenatal visit to a pulmonologist for asthma screening if they present asthma like symptoms.

6.7 Further research

Our results are highly valuable for other researchers in the field of asthma especially since our study is the first to compare asthma medication use and adherence during pregnancy in women with asthma newly diagnosed early in and pre-pregnancy. In fact, part of the observed results in women diagnosed early in pregnancy could be attributable to an asthma more severe in nature due to hormonal fluctuations or that was present prior to pregnancy but undiagnosed yet and consequently untreated. Thus, we recommend future studies to assess the average daily doses of ICS and number of weekly doses of SABA during pregnancy, being markers of asthma control and severity, to better understand the underlying mechanism of the association between the timing of asthma diagnosis and asthma medication use during pregnancy. Moreover, it might be interesting to assess the type of health care used in both sub-cohorts, in the year before pregnancy (currently presented as a grouped variable in the thesis), around asthma diagnosis or during follow-up, whether it was associated with respiratory-related causes (i.e. visits to respiratory specialists or lung-related health care use).

Ultimately, our results could assist in guiding future research studies to uncover more reasons behind this association while avoiding the encountered limitations. For instance, studies that adjust for the confounders that were not measured in our administrative databases are encouraged to investigate the effect of these confounders on the association between the timing of asthma diagnosis and asthma medication use during pregnancy. Furthermore, future studies

might also consider including women with private drug insurance to enhance the generalizability of the results covering all pregnant asthmatic women.

CHAPTER 7: CONCLUSION AND PERSPECTIVES

7. Conclusion and Perspectives

The work presented in this thesis aimed at examining the association between the timing of new-onset asthma and asthma medication use during pregnancy. Briefly, our study showed a higher use of any controller, ICS and SABA and a similar use of ICS/LABA and OCS from the 20th week of gestation until delivery among women with asthma diagnosed early in pregnancy compared to women with asthma diagnosed pre-pregnancy. It is important to realize that although the rate of ICS use was considerably higher in women with asthma diagnosed early in pregnancy, we found no significant difference in the adherence level from the 20th week of gestation until delivery between the two sub-cohorts. These results were explained by the fact that ICS users diagnosed early in pregnancy were more likely to fill an ICS prescription upon their asthma diagnosis and less likely to refill it regularly thereafter compared to those diagnosed pre-pregnancy. Moreover, consistent with the literature, our study adds evidence to the use of ICS and SABA during pregnancy upon asthma diagnosis, and that comes in concordance with asthma management guidelines. (6, 16)

While guidelines stress the importance of maintaining asthma medication use during pregnancy to maintain asthma under control, we found low use and adherence to controller medications, representing a significant problem in asthma management and increased risk of adverse perinatal and maternal outcomes. (6, 16) In light of the aforementioned results, it would be recommended screening for preconception and/or prenatal asthma to initiate the appropriate asthma therapy among women with asthma-like symptoms. It will also support a closer monitoring of women once the diagnosis of asthma is made to encourage women to be adherent

to their prescribed therapy, keep asthma under control during pregnancy and prevent serious perinatal outcomes. Therefore, our study carries major clinical relevance for the healthcare professionals.

To this end, the major knowledge gaps that we addressed – on asthma medication use and adherence from the 20th week of gestation until delivery – provided a constructive knowledge that could assist in guiding future epidemiological research in other provinces on asthma drug use and adherence during pregnancy.

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