Université de Montréal

Beta$_2$-agonists use during pregnancy and the risk of congenital malformations

par
Sherif Eltonsy

Médicaments et Santé des Populations
Faculté de Pharmacie

Mémoire présenté à la Faculté des études supérieures
en vue de l'obtention du grade de Maîtrise
en Sciences Pharmaceutiques
option Médicaments et Santé des Populations

Décembre 2010

Université de Montréal
Faculté des études supérieures et postdoctorales

Ce mémoire intitulé:

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Présenté par :
Sherif Eltonsy

a été évaluée évalué par un jury composé des personnes suivantes :

Anick Bérard PhD, président-rapporteur
Lucie Blais PhD, directeur de recherche
Sylvie Perreault PhD, membre du jury

Résumé

Selon les lignes directrices de traitement de l'asthme pendant la grossesse, les beta$_2$-agonistes inhalés à courte durée d'action (SABA) sont les médicaments de choix pour tous les types d'asthme [intermittent, persistant, léger, modéré et sévère] comme médicaments de secours rapide et dans la gestion des exacerbations aiguës. D'autre part, les beta$_2$-agonistes inhalés à longue durée d'action (LABA) sont utilisés pour les patients atteints d'asthme persistant, modéré à sévère, qui ne sont pas entièrement contrôlés par des corticostéroïdes inhalés seuls. Malgré que plusieurs études aient examinées l'association entre les LABA, les SABA et les malformations congénitales chez les nouveau-nés, les risques réels restent controversés en raison de résultats contradictoires et des difficultés inhérentes à la réalisation d'études épidémiologiques chez les femmes enceintes. L'objectif de cette étude était d'évaluer l'association entre l'exposition maternelle aux SABA et LABA pendant le premier trimestre de grossesse et le risque de malformations congénitales chez les nouveau-nés de femmes asthmatiques.

Une cohorte de grossesses de femmes asthmatiques ayant accouchées entre le 1er janvier 1990 et le 31 décembre 2002 a été formée en croisant trois banques de données administratives de la province de Québec (Canada). Les issues principales de cette étude étaient les malformations congénitales majeures de touts types. Comme issues secondaires, nous avons considéré des malformations congénitales spécifiques. L'exposition principale était la prise de SABA et/ou de LABA au cours du premier trimestre de grossesse. L'exposition secondaire étudiée était le nombre moyen de doses de SABA par semaine au cours du premier trimestre.

L'association entre les malformations congénitales et la prise de SABA et de LABA a été évaluée en utilisant des modèles d'équations généralisées (GEE) en ajustant pour plusieurs variables confondantes reliées à la grossesse, l'asthme de la mère et la santé de la

mère et du fœtus.

Dans la cohorte formée de 13 117 grossesses de femmes asthmatiques, nous avons identifié 1 242 enfants avec une malformation congénitale (9,5%), dont 762 avaient une malformation majeure (5,8%). Cinquante-cinq pour cent des femmes ont utilisé des SABA et 1,3% ont utilisé des LABA pendant le premier trimestre. Les rapports de cotes ajustées (IC à 95%) pour une malformation congénitale associée à l'utilisation des SABA et des LABA étaient de 1,0 (0,9-1,2) et 1,3 (0,9-2,1), respectivement. Les résultats correspondants étaient de 0,9 (0,8-1,1) et 1,3 (0,8-2,4) pour les malformations majeures. Concernant le nombre moyen de doses de SABA par semaine, les rapports de cotes ajustées (IC à 95%) pour une malformation congénitale était de 1.1 (1.0-1.3), 1.1 (0.9-1.3), et 0.9 (0.7-1.1) pour les doses >0-3, >3-10, and >10 respectivement. Les résultats correspondants étaient de 1.0 (0.8-1.2), 0.8 (0.7-1.1), et 0.7 (0.5-1.0) pour les malformations majeures. D'autre part, des rapports de cotes (IC à 95%) statistiquement significatifs ont été observés pour les malformations cardiaques (2.4 (1.1-5.1)), les malformations d'organes génitaux (6.8 (2.6-18.1)), et d'autres malformations congénitales (3.4 (1.4 à 8.5)), en association avec les LABA pris pendant le premier trimestre.

Notre étude procure des données rassurantes pour l’utilisation des SABA pendant la grossesse, ce qui est en accord avec les lignes directrices de traitement de l’asthme. Toutefois, d'autres études sont nécessaires avant de pouvoir se prononcer sur l’innocuité des LABA pendant la grossesse.

Mots-clés : asthme, grossesse, malformations congénitales, beta$_2$-agonistes, étude de cohorte.

Abstract

According to asthma management guidelines during pregnancy, short-acting β_2-agonists (SABA) are the drug of choice in all types of asthma [intermittent or persistent, mild, moderate and severe] as a quick reliever medication and in the management of acute exacerbations or emergency hospitalizations. On the other hand, long-acting β_2-agonists (LABA) are used for patients with moderate and severe persistent asthma not fully controlled with inhaled corticosteroids alone. While many studies examined their associations with congenital malformations in newborns, the actual risks remain controversial due to the discordance between different risk reports and the difficulties in performing epidemiological studies on pregnant women. The objective of this study is to investigate the association between maternal exposure to SABA and LABA during the first trimester of pregnancy and the risk of congenital malformations in the newborns among asthmatic women.

Through the linkage of three administrative databases from Québec, a cohort of pregnancies from asthmatic women insured by the RAMQ drug insurance plan was formed between January 1, 1990 and December 31, 2002. The primary outcomes were major and any congenital malformations and the secondary outcomes were specific malformations. The primary exposure was the separate exposure to SABA and LABA during the first trimester, while the secondary exposure was the average number of doses of SABA per week taken during the first trimester. The association between congenital malformations and SABA and LABA exposure was assessed using generalized estimating equation models while adjusting for sociodemographic, asthma, maternal and fetal variables.

We identified 1242 infants with a congenital malformation (9.5%), 762 of which had a major malformation (5.8%) within the cohort formed of 13117 pregnancies. Fifty-five percent of the women used SABA during the first trimester, and 1.3% used LABA. The adjusted odds ratio (95% CI) for any malformation associated with the use of SABA and

LABA were 1.0 (0.9-1.2) and 1.3 (0.9-2.1), respectively. The corresponding figures were 0.9 (0.8-1.1) and 1.3 (0.8-2.4) for major malformations. Regarding the average number of doses of SABA per week, the adjusted odds ratio (95% CI) for any malformation were 1.1 (1.0-1.3), 1.1 (0.9-1.3), and 0.9 (0.7-1.1) for doses >0-3, >3-10, and >10 respectively. The corresponding figures were 1.0 (0.8-1.2), 0.8 (0.7-1.1), and 0.7 (0.5-1.0) for major malformations. On the other hand, significant increased risks, odds ratio (95% CI), of cardiac malformations 2.4 (1.1-5.1), genital organ malformations 6.8 (2.6-18.1), and other congenital malformations 3.4 (1.4-8.5) were observed with LABA use in the 1st trimester.

Our study adds evidence, in concordance with asthma management guidelines, to the safety of SABA during pregnancy. However, more research is needed before we can decide on the safety of LABA during pregnancy.

Keywords: asthma, pregnancy, congenital malformations, beta$_2$-agonists, cohort study.

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To my beloved family, and to the dearest of all; Salma and Farah

Preface

This Msc thesis consists of six chapters including an introduction, a review of the literature, the objectives of the study, the methods, the manuscript of an article submitted for publication, and a discussion section. These chapters are followed by a bibliography section.

The introduction chapter provides the rationale and general objectives of the study we performed. The review of the literature covers different aspects on the subject of our study and provides an overview on the results relevant to our project with focus on asthma during pregnancy. The objectives chapter presents the general, primary, and secondary objectives of our research project. The methodology chapter comprehends the information presented under the "Methodology" section in the manuscript more comprehensively. The manuscript chapter contains an article reporting the results of our study on the use of SABA and LABA during pregnancy and the risk of congenital malformations. This manuscript was submitted to Birth defects research: part A. The discussion chapter presents the strengths and limitations of our project, the contribution of our results to the literature in the field of asthma during pregnancy, the clinical implications of our results, further research recommendations and it ends with an overall conclusion. The bibliography section contains all articles, books, and reports cited in this thesis, however the manuscript includes its own bibliography.

Acknowledgements

First of all, I am truly grateful to my supervisor, Dr Lucie Blais, for giving me the opportunity to join her great team, and for providing me with support, advices, and knowledge during my study period. Her guidance throughout my program and her goal oriented advices helped me gain a rich experience which I really appreciate. I would like to thank all the jury members for accepting the evaluation of this project.

I wish to thank Amélie Forget for her exceptional technical help throughout the whole project, and her constructive and precious advices.

I also wish to thank Marie-Christyne Cyr for sharing her knowledge and experience, and her supporting spirit. I wish to acknowledge also the whole team of Dr Blais for their magnificent spirit and great friendship.

Lastly, I would like to thank my wife Salma for her continuous support, advices, and encouragement through my endeavours. Thanks for my beautiful daughter Farah whose presence gave me tremendous energy to complete this project. I would like also to thank my parents, whose care and encouragement throughout my whole years of study have been my dearest assets, my brother Mohamed for his advices and support during my study, my brother Abdallah, and my sisters Esraa and Yomna for being precious gifts in my life.

Abbreviations

ACQ = Asthma Control Questionnaire

ACT = Asthma Control Test

aOR: Adjusted Odds Ratio

ATAQ = Asthma Therapy Assessment Questionnaire

CAMP: Cyclic Adenosine Monophosphate

CBP: CAMP response element binding protein (CREB) binding protein

CI: Confidence Interval

cOR: Crude Odds Ratio

cRR: Crude Relative Risk

ED: Emergency Department

FDA: Food and Drug Administration

FEV_1 = Forced Expiratory Volume in 1 second.

GEE: Generalized Estimating Equations

GINA: Global Initiative for Asthma

GR: Glucocorticoid Receptor

ICD: International Classification of Disease

ICS: Inhaled Corticosteroids

INCS: Intranasal Corticosteroids

ISQ: Institut Statistique de Québec

IUGR: Intrauterine Growth Retardation

LABA: Long Acting $Beta_2$-Agonists

LTRAs: Leukotriene Receptor Antagonists

NAEPP: National Asthma Education and Prevention Program

OCS: Oral Corticosteroids

OR: Odds Ratio

PKA: Protein Kinase A

pOR: Prevalence Odds Ratio

RAMQ: Régie de l'Assurance Maladie du Québec

SABA: Short Acting $Beta_2$-Agonists

TERIS: Teratogen Information System

U.S.: United States

CHAPTER 1: INTRODUCTION

Introduction

Asthma has been recognized as one of the most common chronic pulmonary diseases and a serious medical complication in pregnancy.[1-3] The disease affects about 3.7% to 8.4% of pregnant women and shows an increasing prevalence over time.[1;2]

Pregnancy outcomes of asthmatic women compared to non-asthmatic women were examined in many studies, and have shown increased risks of both maternal and fetal outcomes among asthmatic mothers.[1;4] From the maternal outcomes that were reported to increase among asthmatic women versus non-asthmatic women were preeclampsia, antepartum hemorrhage, hypertensive disorders, cesarean delivery, placenta previa, and postpartum bleeding. While the adverse fetal outcomes include small for gestational age infants, low birth weight, preterm labor, transient tachypnea of the newborn, neonatal hypoxia, and neonatal hyperbilirubinemia. [4;5]

More specifically, uncontrolled and severe asthma during pregnancy has been shown to have potential harmful effects.[1;4;6;7] Most studies suggest that more severe asthma during pregnancy is associated with increased fetal and maternal risks [1;4], while better-controlled asthma is associated with decreased risks.[5] Therefore benefit-risk comparisons often favor the use of asthma medications during pregnancy to maintain asthma under control.[3]

From the adverse effects of uncontrolled maternal asthma is the association with intra uterine growth restriction (IUGR), prematurity, and congenital malformations that may lead to compromised fetal growth.[1;8-11] Two main potential mechanisms have been hypothesized to explain these observations :(1) fetal hypoxia due to poor maternal asthma control and (2) asthma medications used to treat asthma.[12]

Treatment and control of asthma could be achieved by using several medications. Even if some of them are accepted and widely used during pregnancy, none has been classified as completely safe for use during pregnancy or located in category “A” in the FDA classification of medications used during pregnancy.[3;13] Asthma medications can

be categorized into two classes, the first class includes the quick relief medications, i.e. the short-acting beta$_2$-agonists (SABA). The second class includes long-term controller medications, i.e. inhaled corticosteroids, long-acting beta$_2$-agonists (LABA), mast cell stabilizers, methylxanthines, and leukotriene receptors antagonists.

SABA have been widely used for years to relief asthma symptoms during pregnancy, which is not the case for LABA. More data on the safety of SABA than LABA during pregnancy are available in the literature due to their precedence in the markets.[3;14] According to the US National Asthma Education and Prevention Program guidelines for managing asthma during pregnancy, SABA are the drug of choice in all types of asthma [intermittent or persistent, mild, moderate and severe] as a quick reliever medication and in the management of acute exacerbations or emergency hospitalizations. On the other hand, LABA are used for patients with moderate and severe persistent asthma not fully controlled with inhaled corticosteroids alone.[3]

Congenital malformations are present in approximately 3% of live births,[15] and they are considered the leading cause of infants mortality in the USA and Canada.[16;17] Major congenital malformations are considered as one of the primary outcomes when studying the safety of medications used during pregnancy. Congenital malformations put children at risk of developmental delay and morbidities in both childhood and adulthood. Children with malformations are more susceptible to health problems and lifelong disabilities, besides having a shorter life expectancy than their healthy peers.[18-20] Beside its direct effect on the population health, congenital malformations are considered a heavy economic burden for both the family and society. [18;19]

Moreover, we can't neglect the psychological impact of birth defects on parents and families. The presence of negative pregnancy experiences and infants with disabilities are related with a higher risk of mental health problems for mothers, especially depression.[18;21] Also from the psychological disorders that affect the parents are excessive parenting stress, distress and hopelessness, resulting in lower quality of life.[22-25]

The association between the use of SABA and LABA during pregnancy and the risk of congenital malformations was the object of 15 different studies [14;26-39]: 8 studies investigated the risk of congenital malformations associated with the use of SABA and LABA separately.[14;26;27;33-36] From these 8 studies, 4 used a control group of asthmatic women,[14;35;36;39] with only one of them reporting a significant increased risk of congenital malformations with Fenoterol (SABA) use (pOR=1.6, 95% CI=1.3-2.0).[36]

Nevertheless, it is not possible to conclude on the safety of these medications during pregnancy since there were many important methodological limitations in most of these studies. The interpretation of the study results is often difficult due to low statistical power, timing of the exposure during pregnancy, and incomplete adjustment for asthma severity/control and other important confounders.[14;35;36;39] While investigating SABA and LABA and their association with congenital malformations, important potential confounders should be taken into consideration, including socio-demographic variables, maternal and fetal conditions, and asthma related variables. Due to the difficulty of drawing valuable and explicit conclusions about the safety of SABA and LABA in pregnancy, we performed a study with primary objectives of evaluating the association between maternal exposure to SABA and LABA during the first trimester of pregnancy and major and any congenital malformations. Moreover, the secondary objective of our study was to examine the same associations with specific congenital malformations.

CHAPTER 2: REVIEW OF THE LITERATURE

Review of the literature

2.1 Asthma and its prevalence

Asthma is a complex disorder characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper-responsiveness, and an underlying inflammation.[40] According to the Global Initiative for Asthma (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".[41]

Asthma is considered one of the most common chronic diseases affecting an estimated 300 million people worldwide.[40;41] Moreover, considerably higher estimates can be obtained with less conservative criteria for the diagnosis of clinical asthma.[40] The prevalence of asthma increased very markedly over the last 50 years of the past century, especially in westernized societies, where it now poses a considerable burden on individuals and economic disease burden on healthcare systems and society.[42;43] The prevalence of asthma in Canada and the United States is amongst the highest in the world for both children and adults, reaching about 10% to 11.2%.[42;44]

2.2 Asthma severity and control

While being complementary notions in the management of asthma, asthma severity and control may overlap in their ways of assessment and each has its distinguished clinical importance.[40;41]

2.5.1 Asthma severity

According to the US National Asthma Education and Prevention Program guidelines for the diagnosis and management of asthma, asthma severity is defined as the intrinsic intensity of the disease process.[40] Severity is most easily and directly measured in a patient who is not receiving long-term control therapy.[45] Severity can also be measured, once asthma control is achieved, by the step of care (i.e., the amount of medication) required to maintain control.[40] According to US National Asthma Education and Prevention Program guidelines for the diagnosis and management of asthma and in common daily practice, asthma severity is measured taking into account many factors which include the level of asthma symptoms, night-time symptoms, use of SABA for quick relief, pulmonary function and airway limitation, rate of exacerbations, and limitations to normal activities.[40] Using these factors, asthma severity level according to US National Asthma Education and Prevention Program guidelines was classified into four categories; intermittent, mild persistent, moderate persistent, and severe persistent (see Table 1 and 2).[40] The stepwise approach for managing asthma in adults is then used to manage asthma in each patient according to his severity level (see Figure 1). On the other hand, according to the recent Global Initiative for Asthma (GINA) guidelines, asthma severity is classified according to the intensity of the treatment required to achieve efficient asthma control.[41]

Table 1. Classification of asthma severity measured before treatment is started according to US National Asthma Education and Prevention Program guidelines

	Clinical features before treatment[#]		
	Symptoms[¶]	**Night-time symptoms**	**Lung function**
Severe persistent	Continual symptoms Limited physical activity Frequent exacerbations	Frequent	FEV_1 or PEF ≤60% pred PEF variability >30%
Moderate persistent	Daily symptoms Daily use of inhaled SABA Exacerbations affect activity Exacerbations more than twice per week; may last days	More than once per week	FEV_1 or PEF >60 and ≤80% pred PEF variability >30%
Mild persistent	Symptoms more than twice per week but no more than once per day Exacerbations may affect activity	More than twice per month	FEV_1 or PEF ≥80% pred PEF variability 20–30%
Intermittent	Symptoms no more than twice per week Asymptomatic and normal PEF between exacerbations Exacerbations are brief (from a few hours to a few days); intensity may vary	No more than twice per month	FEV_1 or PEF ≥80% pred PEF variability <20%

Asthma severity was classified by clinical characteristics before treatment. FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow; % pred: % predicted; SABA: short-acting β_2-agonist. [#]: the presence of one of the features of severity is enough to place the patient in that category. An individual should be assigned to the most severe grade in which any feature occurs. An individual's classification may change over time. [¶]: Patients at any level can have mild, moderate or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms.

From US National Asthma Education and Prevention Program guidelines for the diagnosis and management of asthma, Expert Panel Report 3, 2007

Table 2. Classifying severity in patients after asthma becomes well controlled, by lowest level of treatment required to maintain control.

Classification of Asthma Severity			
Intermittent	**Persistent**		
	Mild	Moderate	Severe
Step 1	Step 2	Step 3 or 4	Step 5 or 6

From US National Asthma Education and Prevention Program guidelines for the diagnosis and management of asthma, Expert Panel Report 3, 2007

3.5.1 Asthma control

According to the US National Asthma Education and Prevention Program guidelines for the diagnosis and management of asthma,[40] asthma control is defined as the degree to which the manifestations of asthma are minimized by therapeutic intervention and the goals of therapy are met.[40] The assessment of asthma control is done through measuring the components of control which include level of asthma symptoms, night-time awakenings, interference with normal activities, SABA use for quick relief of symptoms, pulmonary function (FEV_1 or peak flow), exacerbations, the progressive loss of lung function, and the treatment

related side-effects[40] According to the US National Asthma Education and Prevention Program guidelines for the diagnosis and management of asthma, asthma control is classified into three classes; well controlled, not well controlled and very poorly controlled (see Table 3).[40] The Global Initiative for Asthma (GINA) guidelines uses similar aspects for measuring asthma control, and classifies it into controlled, partly controlled, and uncontrolled.[41]

Table 3. Classification of asthma control in adults according to US National Asthma Education and Prevention Program guidelines

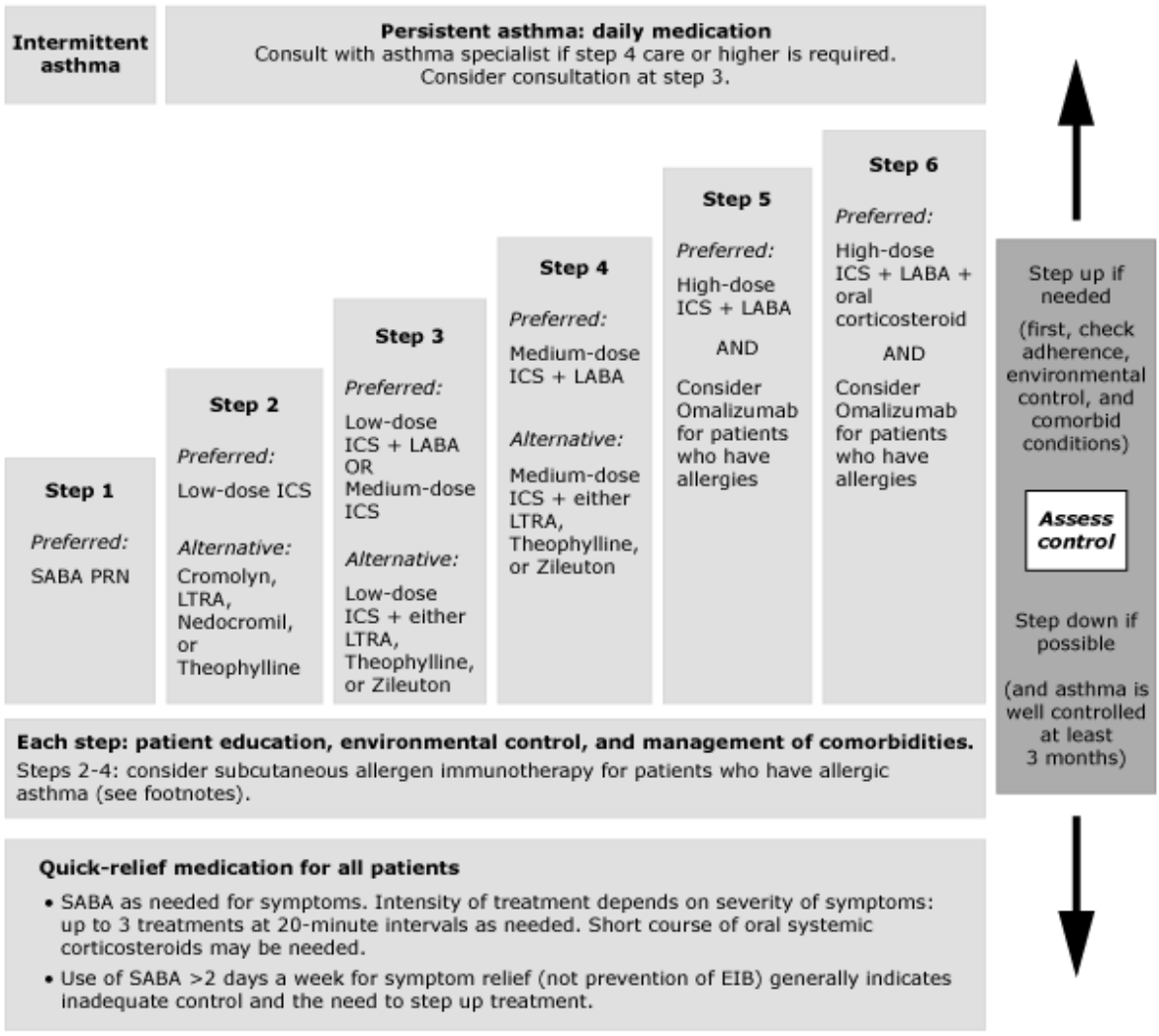
COMPONENTS OF CONTROL	**CLASSIFICATION OF ASTHMA CONTROL**		
	WELL CONTROLLED	**NOT WELL CONTROLLED**	**VERY POORLY CONTROLLED**
Impairment			
Symptoms	≤ 2 days/week	> 2 days/week	Throughout the day
Night-time awakenings	≤ 2 times/month	1–3 times/week	≥ 4 times/week
Interference with normal activity	None	Some limitation	Extremely limited
Short-acting beta-2- agonist use for symptom control (not prevention of exercise-induced bronchospasm)	≤ 2 days/week	> 2 days/week	Several times/day

FEV_1 or peak flow	> 80% predicted or personal best	60%–80% predicted or personal best	< 60% predicted or personal best
Validated questionnaires			
ATAQ	0	1–2	3–4
ACQ	≤ 0.75	≥ 1.5	NA
ACT	≥ 20	16–19	≤ 15
Risk			
Exacerbations requiring oral systemic corticosteroids	0–1/year	2–3/year	> 3/year
	Consider severity and interval since last exacerbation.		
Progressive loss of lung function	Evaluation requires long-term follow-up care.		
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		

ATAQ = Asthma Therapy Assessment Questionnaire, ACQ = Asthma Control Questionnaire, ACT = Asthma Control Test, FEV_1 = forced expiratory volume in 1 second.

From US National Asthma Education and Prevention Program guidelines for the diagnosis and management of asthma, Expert Panel Report 3, 2007

Figure 1. Stepwise approach for managing asthma in adults according to US National Asthma Education and Prevention Program guidelines



Source: US National Asthma Education and Prevention Program guidelines for the diagnosis and management of asthma, Expert Panel Report 3, 2007

2.3 Asthma management and treatment

Asthma treatment goal is to prevent and control asthma symptoms, reduce the frequency and severity of asthma exacerbations, and reverse airflow obstruction.[40] Recommendations in the treatment choices reflect the scientific fact that asthma is a chronic disorder with episodes of airflow limitation, cough, and mucus production.[45] Asthma medications are thus categorized into two classes: *quick-relief* medications which are taken to achieve prompt reversal of acute pulmonary obstruction and relief of the accompanying broncho-constriction (these medications are also known as acute rescue or reliever medications) and *long-term-control* medications which are taken daily on a long-term basis to achieve and maintain control of persistent asthma (these medications are also known as long-term preventive, maintenance, or controller medications). Patients with persistent asthma are in need of both classes of medication. [3;40;41]

2.3.1 Controller medications

Controller medications should be taken daily on a long-term basis in order to keep asthma under control. The most effective are those that attenuate the underlying inflammation characteristic of asthma.[40;41]

- **Corticosteroids**: Most potent and effective anti-inflammatory medication currently available. Inhaled corticosteroids (ICS) have fewer side effects than oral or systemic corticosteroids, and are used in the long-term control of asthma. [40;41] From the commonly used ICSs: Beclomethasone dipropionate, Budesonide, Ciclesonide, Flunisolide, Fluticasone propionate, Mometasone furoate, Triamcinolone acetonide.[40;41] ICSs are the most effective long-term controller medications in all levels of persistent asthma, and they have superiority over any other single long-term controller medication.[40] Systemic corticosteroids are often used to gain prompt control of the disease.[40;41] Long-term oral corticosteroids therapy (tablets or syrup) are

used only if needed in cases of severe persistent uncontrolled asthma (see Figure 1), with favouring their discontinuation as soon as asthma control is regained.[40;41]

- **Cromolyn sodium and Nedocromil**: Mild to moderate anti-inflammatory medications. They are recommended as an alternative, but not preferred, medication for patients at step 2 in asthma management (mild persistent asthma) (see Figure 1). They also can be used as preventive treatment prior to exercise or unavoidable exposure to known allergens.[40]
- **Leukotriene modifiers**: Zafirlukast or Montelukast may be considered an alternative therapy to low doses of inhaled corticosteroids or Cromolyn or Nedocromil for patients with mild persistent asthma. Also as add-on therapy in patients not sufficiently controlled by ICSs (see Figure 1). [40]
- **Methylxanthines**: Sustained-release Theophylline is a mild-to-moderate bronchodilator used principally as adjuvant to inhaled corticosteroids for prevention of nocturnal asthma symptoms.[40]
- **Long-acting beta$_2$-agonists (LABA)**: Long-acting bronchodilators (Salmeterol and Formoterol) are used concomitantly with ICS for long-term control of symptoms, especially nocturnal symptoms. LABA have duration of bronchodilator of at least 12 hours after a single dose. These medications should not be taken alone in asthma as they don't have enough effect on the airway inflammation of asthma. [40] LABA are recommended in combination with ICSs for long-term control in moderate and severe persistent asthma (step 3 to 6 in the stepwise approach for managing asthma, see Figure 1).[40] The combination of LABA and ICS is the recommended and preferred choice when a medium dose of ICS fails to achieve the efficient control of asthma.[41]

2.3.2 Relievers

Those are quick-relief medications which are used to treat acute symptoms and exacerbations. [40;41]

- **Short-acting beta$_2$-agonists (SABA)**: Including Salbutamol, Terbutaline, Fenoterol, Levalbuterol, Metaproterenol, and Pirbuterol, SABAs are considered therapy of choice for relief of acute asthma symptoms, acute exacerbations and pre-treatment of exercise-induced broncho-constriction (see Figure 1). [40;41]
- **Anticholinergics**: Ipratropium bromide provides additive benefit to inhaled beta$_2$-agonists in severe exacerbations. May act as alternative bronchodilator for patients intolerant to inhaled beta$_2$-agonists. [40;41]
- **Systemic corticosteroids**: Short courses of oral corticosteroids or parenteral corticosteroid solutions are used for moderate to severe exacerbations to speed recovery and prevent recurrence of exacerbations.[40] They include Prednisone, Prednisolone, and Methylprednisolone.[40]

2.4 Asthma during pregnancy

Asthma is considered as one of the most frequent chronic diseases that affects pregnant women.[3;9] Asthma has a prevalence of 3.7 to 8.4% among pregnant women.[2;9;29] Moreover, a study showed a presence of an overall increasing prevalence of asthma during pregnancy over time.[46]

2.4.1 Impact of pregnancy on asthma

The rule of thirds applies to asthmatic pregnant women, where approximately one third of the patients suffer from worsening of their asthma symptoms, one third experience

improvement, while one third of the pregnant women have their asthma symptoms remaining unchanged.[47;48] In a meta-analysis of 14 studies, the distribution of changes in asthma symptoms during pregnancy was in agreement with the rule of thirds, however in some studies, the distribution may be still population-dependant.[49]

It has also been suggested by many studies that the more severe the asthma, the more likely it is to worsen during pregnancy.[4;50;51] The fewest symptoms occur after week 37, nearly 75% of women return to their pre-pregnancy status within 3 months after delivery, the change in course of asthma tends to be consistent during successive pregnancies and exacerbations during delivery are rare.[3;4;51;52] The unsolved issue in this subject is determining the mechanism behind these changes. Asthma is an extremely variable disease, and a number of physiologic changes occur during pregnancy which could worsen or improve asthma.[4;51] The most important recommendation that should be followed is that since the course of asthma can change during pregnancy, therefore pregnant women need to be followed up more closely, and their therapy should be adjusted to achieve control of symptoms.[3;4;52]

2.4.2 Impact of asthma on pregnancy

Pregnancy outcomes of asthmatic women compared to non-asthmatic women were examined in many studies, and have shown increased risks of both adverse maternal and fetal outcomes among asthmatic mothers.[53] From the maternal outcomes that were reported to increase among asthmatic women versus non-asthmatic women were preeclampsia, antepartum hemorrhage, hypertensive disorders, cesarean delivery, placenta previa, and postpartum bleeding. While the adverse fetal outcomes include: small for gestational age infants, low birth weight, preterm delivery, congenital malformations, transient tachypnea of the newborn, neonatal hypoxia, and neonatal hyperbilirubinemia.[53-55]

The critical effect of asthma during pregnancy on the fetal development is demonstrated through the possibility of inducing hypoxia combined with acute or compensated respiratory acidosis, besides an acute respiratory alkalosis that decreases the placental blood flow, increases systemic and pulmonary vascular resistance, and decreases cardiac output.[56;57] In cases of fetal lack of oxygen, the oxygen extraction rate by fetal tissues increases and could lead to long term effects of hypoxia as intrauterine growth retardation, preterm birth, neonatal hypoxia or perinatal morbidity and mortality.[57-60]

Severe or uncontrolled asthma is associated with adverse fetal outcomes including perinatal mortality, IUGR, preterm birth, low birth weight, and congenital malformations.[3;11;47;55;61] On the other hand, it has been shown that women with well controlled asthma and proper treatment have little or no increased risk of adverse fetal outcomes.[3;47;62;63]

An acute exacerbation of asthma is commonly referred to as an asthma attack. Some patients could have stable asthma for months and then suddenly suffer from an episode of acute asthma.[40] The symptoms of an attack are dyspnoea, wheezing, cough, and chest tightness. The cough in an acute attack may sometimes produce clear sputum. The onset may be sudden, with a feeling of constriction in the chest, breathing becomes difficult, and wheezing occurs.[40;41]

Due to its potential risks on the fetal development and the severe problems they could contribute to,[11;64-66] exacerbations in pregnancy should be managed as soon as their signs and symptoms are recognized.[3] Exacerbations are potentially dangerous to the fetus as it can provoke maternal hypoxia combined with respiratory alkalosis, which could decrease the placental blood flow.[11;67] Hypoxia resulting from exacerbations could cause abnormal development of the fetus,[68] and they have been found to be associated

with an increased risk of cleft lip and palate in mice.[69] Exacerbations are common during pregnancy, reaching about 30% among pregnant women with severe asthma.[70] Asthma exacerbations have been found to be associated with adverse perinatal outcomes in some studies e.g. low birth weight and congenital malformations.[11;71]

2.4.3 Pharmacologic treatment of asthma during pregnancy

According to the US National Asthma Education and Prevention Program guidelines for managing asthma during pregnancy, the pharmacologic management of asthma during pregnancy postulates that the safer for the pregnant patients is to be treated with asthma medications than to have asthma symptoms or exacerbations and reduced lung function which could affect the fetal oxygen supply.[3;45] The type and amount of medications required to manage each patient are determined according to the severity of the patient's asthma.

According to the US National Asthma Education and Prevention Program guidelines for managing asthma during pregnancy,[3] asthma control is defined as minimizing the chronic asthma symptoms during the day or night, minimizing asthma exacerbations, achieving no limitations on daily activities, maintenance of normal pulmonary function, minimal use of SABA, and minimizing the medications side effects.[3] While they both aim to achieve asthma control, the difference in the treatment goal between asthmatic pregnant women and other non pregnant patients is that the optimal therapy should maintain control of asthma not only for the health and the quality of life of the patient, but also for the normal fetal development throughout gestation.[3;40] According to US National Asthma Education and Prevention Program guidelines, there is not much differences between the treatment of asthma in pregnant and non pregnant patients, apart from the fact that the stepwise approach for the pregnant patients is classified into 4 steps, while it is classified into 6 steps for non pregnant patients (see Figure 1 and

Table 4). The main differences between the two stepwise approaches are; 1) the use of Zileuton in steps 3 and 4 (moderate persistent asthma) among non pregnant patients (see Figure 1) , 2) use of Omalizumab for patients who have allergies in steps 5 and 6 (severe persistent asthma) among non pregnant patients (see Figure 1), and 3) the recommendations for making repeated attempts to reduce systemic corticosteroid levels in pregnant patients suffering from severe persistent asthma (step 4) (see Table 4).

Asthma medications used during pregnancy are categorized into 2 classes, the first class is the quick relief medications that are taken as needed in order to treat asthma symptoms and exacerbations.[3;40] This class includes SABA, anticholinergics and short-courses of systemic corticosteroids. The second class includes long-term controllers which are ICS, long-term systemic corticosteroids, LABA, cromones, methylxanthines, and leukotriene modifiers.

The principal action of $beta_2$-agonists is to relax airway smooth muscle by stimulating $beta_2$-receptors, thus increasing cyclic AMP and producing functional antagonism to broncho-constriction. Both SABA and LABA are believed to have similar mechanism of actions when taken by inhalation; the only difference with LABA is that their broncho-dilating effect could last for 12 hours after a single inhalation.[3;40;72] Therefore, the positioning of SABA and LABA in the stepwise approach of managing asthma during pregnancy is crucial in understanding their use, effect and their importance.[3]

Another great concern that faces the endeavors to achieve optimal asthma control is the non-adherence of asthmatic pregnant women to their asthma medications due to their fears of a potential harm to their fetus.[47] In an online survey asking pregnant women aged 18 to 44 years old about their attitudes toward medication use, 39 % of the women reported having discontinued or reduced it, and one third of them did so without their physician consultation.[73] Another analysis showed that among women using asthma

medications before pregnancy, SABA claims were reduced by 52% during pregnancy and ICS by 36%.[74] Moreover, it is believed that the actual proportion of pregnant women that are non-adherent to asthma medications are even higher than these reported percentages.[47]

According to the US National Asthma Education and Prevention Program guidelines for managing asthma during pregnancy,[3] asthma clinical severity is classified into the following classes; 1) mild intermittent, 2) mild persistent, 3) moderate persistent, and 4) severe persistent (same classification as the one presented for adult asthmatic presented in table 1). However, the stepwise approach for managing asthma during pregnancy classifies asthma in 4 steps only and not into 6 as the stepwise approach for managing asthma in adults. (see Figure 1 and table 4). In order to achieve the desired clinical control of asthma symptoms, the stepwise approach is used to manage asthma during pregnancy (see table 4).[3] In cases of mild intermittent asthma, a SABA is used on an as-needed basis to treat asthma symptoms, and it is usually enough for this type of asthma. The recommendations imply that if the patient's symptoms are relieved and the pulmonary functions are normalized, SABA can be continued on an as-needed basis but not more than 2 times per week.[3] Moreover, for patients experiencing exercise-induced bronchospasm, SABA should be used shortly before exercise (see Table 4).[3;45] In cases of mild intermittent asthma and exercise induced bronchospasm, Salbutamol (Albuterol) is the preferred SABA due to the safety profile for both pregnant and non-pregnant women (see Table 4). Also the greatest amount of efficacy and safety data during pregnancy could be found with Salbutamol.[3]

Regarding persistent asthma, it is classified into mild, moderate and severe (see Table 4). SABA are used in all those types of persistent asthma as quick relief medications, with salbutamol as the drug preferred and the intensity of the treatment depending on the severity of asthma exacerbations. However, the use of SABA more than 2 times a week in

intermittent asthma (on a daily basis or increasing use in persistent asthma) may indicate the need to initiate or increase controller therapy (see Table 4).[3]

Table 4. Stepwise Approach for Managing Asthma during pregnancy and lactation: Treatment

Classify Severity: Clinical Features Before Treatment or Adequate Control		**Medications Required To Maintain Long-Term Control**
Symptoms/Day **----------** **Symptoms/Night**	**PEF or FEV_1** **----------** **PEF Variability**	**Daily Medications**
Step 4 Severe Persistent		
Continuous ---------- Frequent	$\underline{\leq}$60% ---------- >30%	Preferred treatment: - High-dose inhaled corticosteroid AND - Long-acting inhaled $beta_2$-agonist AND, if needed, - Corticosteroid tablets or syrup long term (2 mg/kg per day, generally not to exceed 60 mg per day) (Make repeat attempts to reduce systemic corticosteroid and maintain control with high-dose inhaled corticosteroid.*) Alternative treatment: - High-dose inhaled corticosteroid* AND - Sustained release theophylline to serum concentration of 5–12 micrograms/mL

Step 3 Moderate Persistent		
Daily --- >1 night/week	>60%-<80% --- >30%	Preferred treatment: EITHER - Low-dose inhaled corticosteroid* and long-acting inhaled beta$_2$-agonist OR - Medium-dose inhaled corticosteroid* If needed (particularly in patients with recurring severe exacerbations): - Medium-dose inhaled corticosteroid* and long-acting inhaled beta$_2$-agonist. Alternative treatment: - Low-dose inhaled corticosteroid* and either theophylline or leukotriene receptor antagonist** If needed: - Medium-dose inhaled corticosteroid* and either theophylline or leukotriene receptor antagonist**
Step 2 Mild Persistent		
>2 days/week but <daily --- >2 nights/month	≥80% --- 20 to 30%	Preferred treatment: - Low-dose inhaled corticosteroid* Alternative treatment (listed alphabetically): cromolyn, leukotriene receptor antagonist** OR sustained-release theophylline to serum concentration of 5–12 micrograms/mL.
Step 1 Mild Intermittent		
≤2 days/week --- ≤2 nights/month	≥80% --- <20%	No daily medication needed. Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroid is recommended.

Quick Relief All Patients
Short-acting bronchodilator: 2-4 puffs **short-acting inhaled beta$_2$-agonist***** as needed for symptoms
Intensity of treatment will depend on severity of exacerbation; up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed. Course of systemic corticosteroid may be needed.
Use of short-acting inhaled beta$_2$-agonist*** >2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term-control therapy.

Step Down

Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.

Step up

If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.

Goals of Therapy: Asthma Control

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/work missed
- Maintain (near) normal pulmonary function
- Minimal use of short-acting inhaled beta$_2$- agonist***
- Minimal or no adverse effects from medications

* There are more data on using budesonide during pregnancy than on using other inhaled corticosteroids.

** There are minimal data on using leukotriene receptor antagonists in humans during pregnancy, although there are reassuring animal data submitted to FDA.

*** There are more data on using albuterol during pregnancy than on using other short-acting inhaled beta$_2$-agonists.

Source: National Asthma Education and Prevention Program. Managing asthma during pregnancy: recommendations for pharmacologic treatment; National Heart, Lung, and Blood Institute; 2005

While SABA are indicated in all asthma types as a reliever medication, and ICS being the cornerstone therapy in the management of persistent asthma during pregnancy, LABA (Salmeterol and Formoterol) are used in cases of moderate and severe persistent asthma (see table 4), in combination with low or medium dose inhaled corticosteroids. Due to the limited number of studies on LABA during pregnancy, guidelines and practitioners commonly expect them to have a safety profile similar to Salbutamol.[3;41] Moreover, the choice between Salmeterol and Formoterol is not supported with enough data, but Salmeterol is preferred as it has been available in the markets for a longer period of time than Formoterol.[3;41;72]

Beside their potential role in the pharmacologic management of asthma symptoms, SABA have a crucial role in the management of acute exacerbations during pregnancy, both home managed and hospital or clinic managed.[40;75] For the home management, the pregnant women are recommended to use inhaled Salbutamol. In the hospital and clinic management, Salbutamol also is the recommended drug during pregnancy used through a nebulizer.[3]

The U.S. Food and Drug Administration (FDA) introduced in 1979 the Drugs in Pregnancy category system in which one of five letters (A, B, C, D, X) and their corresponding definition texts are used to summarize pregnancy information and safety of a certain drug. Both SABA and LABA are categorized in risk category C, [13;47] which stipulate that risk cannot be ruled out, animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.[13] However, criticism have been raised against the FDA rating system as these categories are based on experimental animal and human gestational data submitted to the

FDA and not necessarily published, also a consideration was raised on whether the risk-benefit comparisons would favor the use of certain drugs during pregnancy.[3;47]

No asthma medication is placed in category A, [3;13] and that could be due to the requirement of well-controlled studies in pregnant women, which is ethically very difficult. Moreover, the FDA categorization does not take into account all published human or animal gestational studies, the route of administration, the distinction of the level of risk between trimesters, or the drug efficacy.[3;47] Therefore they became of limited usefulness for clinical decision making in pregnant women who need medical attention.[76] The FDA is currently revising its pregnancy labeling system to replace the letter categorization with texts that are complete and accurately offer the available information.[3]

In order to avoid some of the cons of the FDA rating system, other rating systems were proposed like the Teratogen Information System (TERIS) rating system, which gives a drug summary on each drug, where each summary is "based on a thorough review of published data identified through MEDLINE, TOXLINE, and DART bibliographic searches. References provided in the Catalog of Teratogenic Agents [77], Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risks [13], and Chemically Induced Birth Defects [78] are also used extensively".[79] A potential advantage in the TERIS rating system is being based on the reproducibility, consistency, and biological plausibility of available clinical, epidemiologic, and experimental data.[47;79] In order to precisely cover the potential risk of a drug and to provide complete hazard information, the TERIS rating system gives 2 aspects for each exposure; the magnitude of teratogenic risk to a newborn after exposure, and the quality and quantity of data on which risk estimate was based. [79]

Not all SABA are rated by the TERIS system. The categorized SABA in the recent TERIS review which are Salbutamol, Levalbuterol, Metaproterenol and Pirbuterol are defined as having undetermined magnitude of risk to newborns, even Salbutamol which is considered the most trusted and used SABA. Also the quality and quantity of data on SABA are considered limited in the TERIS system. [47;79] LABA also have similar categorizations in TERIS system. Salmeterol has an undetermined magnitude of risk and very limited quality and quantity of data on it. Formoterol, being new in markets is still not rated by TERIS (not enough data for evaluation in the 2007 edition). [47;79]

The risk of asthma symptoms during pregnancy, and the necessity of using asthma medications with unproven safety profiles during pregnancy has been a worrying issue in the past years until these days. Physicians managing asthma during pregnancy nowadays are placed in a substantial dilemma due to the difficulty of assessing the benefit-risk comparison in the pharmacologic therapy of asthma, especially when presently no asthma medication - as it is the case with every other medication - can be considered absolutely safe.[3;13;52;80] For that reason, asthma guidelines mostly recommend the use of all available information on a certain medication, rather than using its category in the different rating systems.[3]

The endorsement of the use of SABA in the management of asthma during pregnancy came because of 3 facts; first, the known selectivity of $beta_2$-agonists, second, their minimal systemic effects, and third, their well known safety profile in non-pregnant patients. [3;14] Salbutamol is considered the most important drug in this class. It has been used for many years in the management of asthma symptoms and exacerbations during pregnancy. Due to its efficacy, proven safety in pregnancy,[3;14;81;82] and precedence in market, Salbutamol offered the chance for other SABA agents to be tried in pregnancy i.e. Fenoterol and Pirbuterol.[3]

LABA have been introduced in the 1990s as a breakthrough in asthma therapy. Their introduction has been considered as a major therapeutic development, and has lead to basic relocations of beta$_2$-agonists use in the management of asthma.[72] Salmeterol and Formoterol are considered two highly selective LABA and the only prescribed in Canada. [3;72] According to guidelines of management of asthma during pregnancy,[3] there is only limited observational data on the use of LABA during pregnancy. However, they justified their recommendation for their use on the expected similar safety profiles between SABA and LABA.[3;40] Both Salmeterol and Formoterol are available in markets in separate forms or in combinations with ICS. Salmeterol has a longer history of use due to its precedence over Formoterol (since 1990), while Formoterol was approved by the FDA and Health Canada in 2001. Besides having limited human data on their safety during pregnancy,[3] both Salmeterol and Formoterol have shown fetal risk in animal models, with delayed fetal ossification and other adverse outcomes at high doses [83], and those may have contributed to their positioning in class C in the FDA category system. The recommendations of the guidelines do not elaborate on which LABA is preferred, however they mentioned the longer history of salmeterol in the markets as a point of advantage.[3]

2.5 Beta$_2$-agonists and Congenital Malformations

To this date, we identified 15 studies which examined the association between beta$_2$-agonists and congenital malformations (see Table 5).[14;26-39] Among them, nine examined beta$_2$-agonists as a group (SABA and LABA),[28-34;37] seven examined SABA separately,[14;26;27;33-36] and six examined LABA separately (see Table 5).[26;27;33;35;36;39] One of the major factors that could affect the strength of any of these studies is the type of the reference group used as a comparison group. Comparing beta$_2$-agonists pregnant users against a group of non-asthmatics could potentially affect the results of a study since the observed relation will be confounded by the effect of asthma disease itself. Therefore, better conclusions could always be withdrawn from studies that

compared beta$_2$-agonists users with asthmatic non-users in order to separate as much as possible the effect of the medications and the disease. Another potential benefit that could be withdrawn through using an asthmatic non-users reference group is the reduction in the effect of the indication bias. Most of studies examining asthma medications are susceptible to indication bias due to asthma severity/control level, and using a reference group of asthmatic patients could relatively decrease the magnitude of such bias. Examining the fetal adverse effects of SABA and LABA combined as a group (beta$_2$-agonists) may not be as informative and conclusive as separating SABA and LABA alone due to their different nature and different indications. However some important safety results could be obtained from such studies when separating both groups is unachievable.

2.5.1 Short acting beta$_2$-agonists (SABA)

From the 7 studies that examined SABA separately from LABA, three studies used a reference group of asthmatic non-users.[14;35;36] A matched case-control study by Tamasi et al.[36] using self-reported questionnaires found a significant increased risk of any malformation with Fenoterol exposure compared to asthmatic pregnant women who were not exposed to Fenoterol anytime during pregnancy (pOR, 1.6; 95% CI, 1.3-2.0) (see Table 5). The authors classified the cases and controls according to the type of medication used during pregnancy, and the sample size (511 cases and 757 controls) helped to acquire relatively high statistical power in most groups (98% with Fenoterol exposure). The authors selected two or three newborns without congenital malformations and matched them with every case according to sex, birth week, and district of parent's residence. Even if the authors compared asthmatic SABA users against a group of asthmatic non-users of SABA, the study has other limitations: (1) non adjustment for asthma severity, (2) neglecting potential confounders such as other maternal diseases or medications use during pregnancy, (3) the exposure to SABA was defined as anytime during pregnancy, and (4) selection bias possibility due to the inability to follow up non-respondent control mothers (75%)

Two other studies examined SABA use during pregnancy and the risk of major malformations using a reference group of asthmatic pregnant women which is considered a substantial advantage over other studies. [14;35] Schatz et al. assessed the safety of any SABA during pregnancy in relation to fetal development.[14] Major and minor congenital malformations, among other outcomes, were analyzed and reported separately for anytime use during pregnancy and 1st trimester use (see Table 5). The authors in the study controlled for asthma severity based on medication requirement, smoking, use of other asthma medications, and the data were prospectively gathered for the SABA group and the asthmatic control group. For anytime and first trimester use of SABA during pregnancy, they found a cOR of 0.6 and 0.73 respectively, with a p-value > 0.05 for both (see Table 5). However, this study had some limitations: (1) the sample size was small and the study had only 9.7% power to detect the observed cOR of 0.73 in the 1st trimester and (2) the asthma severity aspect was assessed based on a medication requirement scale which is incomplete since many other factors could also indicate severity, such as asthma exacerbations and the need for acute care. The authors suggested the safe use of SABA during pregnancy but that conclusion needs more ascertainment.

Tata et al. in a matched case control study examined the risk of major malformations with the maternal use of any SABA anytime during pregnancy and in the 1st trimester.[35] The authors used a reference cohort of asthmatic pregnant non-users. The study found an aOR of 1.06 (p-value 0.336) with SABA exposure anytime during pregnancy, and 1.01 (p-value 0.941) in the 1st trimester (see Table 5). The sample size of the study was relatively high but the statistical power to detect the aOR of 1.01 was low (17%). The study suffered a major limitation of using general population as a reference group.

Other studies were identified and found using a reference group of non-asthmatic pregnant women or a mixed group of asthmatics and non- asthmatics. [26;27;33;34] Kallen and Olausson, in a retrospective cohort study based on the Swedish Medical Birth Register,[26] reported a slight increased risk of all types of congenital malformation with

maternal use of Terbutaline (SABA) (aOR 1.11, 95% CI 1.04-1.19), while no significant increased risk was found with Salbutamol (aOR 1.09, 95% CI 0.97-1.75) comparing users of the medication against non-users or general population (see Table 5). However, the study included the general population in the reference group. Restricting analysis on any cardiovascular defects, only Salbutamol had a significant increased risk (OR=1.38, 95% CI=1.12-1.70). The study has some limitations including (1) use of the general population as a reference group, and (2) the accurate time of exposure during pregnancy wasn't adequately determined.

Another 2 studies by Shao Lin et al.[33;34] reported an increased risk of major malformations with SABA use; however the reported ORs in both studies were non-statistically significant. Shao Lin et al.[33] examined the risk of gastroschisis, a major para-umbilical abdominal wall defect, due to maternal asthma drug use in a case-control study and found an increased risk with Salbutamol and/or Pirbuterol (cOR 1.62, calculated using provided data in the study) (see Table 5). However SABA users were compared to non-users, whether or not they had asthma. Also due to the interview methods drawbacks as being completed 6 weeks to 2 years after the delivery, recall bias may have occurred since mothers of affected children may be more likely to report their exposures than mothers of controls.

Shao Lin et al. in another study [34], examined the association between asthma medications and the risk of congenital heart defects. The study was a matched case-control. The authors examined the risk of heart malformations due to maternal exposure to salbutamol and metaproterenol. An aOR of 2.37 with 95% CI 0.9-6.23 was found with salbutamol exposure in the 1st trimester. The power to detect this OR was 51% (see Table 5). With metaproterenol exposure, a cRR of 1.35 was found. However the study suffered from some limitations: (1) the unexposed group was a group of non asthmatic women (2) non controlling for frequency of medication use or dose, (3) inaccurate reporting of exposure time during pregnancy, (4) possibility of recall bias due to the prior knowledge of

the presence of a major congenital malformations among cases, and (5) possibility of selection bias as the response rate was below 60%.

Kallen and Olausson in another study examined the risk of any malformations with maternal use of SABA during pregnancy using the Swedish Medical Birth Register.[27] The authors examined the risk of any cardiovascular defect with maternal use of salbutamol and terbutaline anytime during pregnancy, the reported aOR were 0.93 (95% CI 0.64-1.36) with salbutamol and 1.14 (95% CI 0.93-1.38) with terbutaline (see Table 5). Yet the study suffered some limitations: (1) using a reference group of non-users (asthmatic and non-asthmatic pregnant women), (2) the timing of exposure was not precise (anytime during pregnancy), (3) little information were gathered on the doses of SABA used during pregnancy, (4) low statistical power with the reported aORs (3.7% and 24%) and (6) multiple comparison tests problem.

2.5.2 Long acting beta$_2$-agonists (LABA)

Six studies examined the association between LABA use during pregnancy and congenital malformations in newborns. Only three of them used a reference group of asthmatic pregnant women in order to separate the effect of LABA from asthma disease itself.[35;36;39] However, neither one of the six studies that investigated LABA found a significant increased risk of malformations with their use (see Table 5).

Tata et al. in a matched case-control study using a reference group of asthmatic pregnant non-users reported an aOR of 1.12 with the use of any LABA anytime during pregnancy and aOR of 1.09 in the first trimester (see Table 5),[35] however both results were non-significant, and the study suffered some limitations which were discussed above. Shao Lin et al. in a case-control study found a non-significant cOR of 1.97 with Salmeterol use during the first trimester of pregnancy, compared to a group of asthmatic pregnant non-users of LABA.[33] Kallen and Olausson in a retrospective cohort study reported no increased risk of any malformations with maternal use of Salmeterol and Formoterol during

the first trimester of pregnancy (aOR 1.02 95%CI 0.83-1.25) and (aOR 1.06 95%CI 0.80-1.40) respectively (see Table 5).[26] The same authors in another study reported a non-statistically significant increased risk of any cardiovascular defect with Salmeterol use in early pregnancy (aOR 1.50 95%CI 0.90-2.53) comparing Salmeterol users with non-users asthmatic and non-asthmatic women.[27] The limitations of these studies were discussed earlier.

Tamasi et al. in a matched case-control study found no increased risk of any malformations with Clenbuterol use at anytime during pregnancy (pOR 0.7, 95%CI 0.50-1.20) (see Table 5).[36] The authors compared Clenbuterol users to a group of asthmatic pregnant non-users. It is worth noting that Clenbuterol is not commonly used for controlling asthma symptoms as Salmeterol or Formoterol. The limitations of this study and the matching criteria were discussed earlier. Jones et al. investigated the adverse maternal and fetal risks due to exposure to LABA during pregnancy, mainly Salmeterol. Since only an abstract is available, few data could be obtained.[39] The authors compared a group of asthmatic pregnant women using Salmeterol (126 patients) with a group of pregnant women who used SABA only (91 patients), and another group of non-asthmatic pregnant women (115 patients) (see Table 5). There were no statistically significant differences observed in the prevalence of major congenital malformations between the three groups, with 4.7% in Salmeterol group, 3.9% in SABA group, and 1.9% in non-asthmatic group. The power of the study was 5.6% for the SABA group, and 22% for the non-asthmatic group compared to Salmeterol users group. The authors suggested that Salmeterol is not a human teratogen, but we need more data about the study procedures, conducting and analysis to be able to judge the adequacy of the conclusion.

Three different prescription-based observational studies (Prescription-Event Monitoring) reported some cases of congenital malformations after maternal exposure to Salmeterol or Formoterol.[84-86] Wilton et al. reported two cases of congenital malformations among 25 births after maternal exposure to formoterol (see Table 5).[84] Wilton et al. in another study and Mann et al. reported 1 case of malformation among 47

babies and 1 case of congenital malformations among 65 pregnancies respectively, for mothers who have been exposed to Salmeterol (see Table 5).[85;86]

2.5.3 SABA & LABA

Nine studies examined SABA and LABA together as one group and their association with increased risk of congenital malformations. Shao Lin et al. reported in two studies a significant increased risk of major malformations with maternal use of beta$_2$-agonists in the first trimester comparing beta$_2$-agonists users with non-asthmatic pregnant women (see Table 5).[33;34] In the first study, the authors found an increased risk of various heart defects with maternal use of any beta$_2$-agonists during the first trimester of pregnancy, with an aOR of 2.2 (95% CI 1.05-4.61).[34] The authors examined in the second study the association between beta$_2$-agonists and the risk of gastroschisis, which is a major para-umbilical abdominal wall defect (see Table 5).[33] The authors found an increased risk of gastroschisis in newborn of women reported using beta$_2$-agonists during the first trimester with aOR 2.06 (95%CI 1.19-3.59) as compared to asthmatic and non-asthmatic non-users of beta$_2$-agonists. However, both studies suffered from indication bias and other limitations that were discussed earlier.

Four studies among the 9 that investigated beta$_2$-agonists used a reference group of asthmatic pregnant women (see Table 5).[29-32] Bakhireva et al. in a prospective cohort study examined the association between maternal use of beta$_2$-agonists and fetal outcomes, including major malformations (see Table 5).[31] Comparing beta$_2$-agonists users against asthmatic ICS users, the authors didn't find any increased risk of malformations (cRR 0.95). The prospective cohort design used limited the possibility of participation, selection, and recall bias and only 5% of the participants were lost in the follow-up. However, the use of self-reporting medication use method in this study has a minor limitation. Due to the recruitment of patients from different multiple geographic areas with different types of

insurance coverage and multiple prescription sources, the supplementation of patient report information with pharmacy records was unachievable. Also self-reports were validated against medical records only for the portion of patients with available data.

Schatz et al. in an observational cohort study examined the association between $beta_2$-agonists use anytime during pregnancy and adverse perinatal outcomes including major congenital malformations.[30] The authors didn't find an increased risk of malformations with $beta_2$-agonists use (cRR 1.0) compared to asthmatic non-users (see Table 5). The study reflected the contemporary use of $beta_2$-agonists nowadays, and asthma severity and control together with other potential covariables were adjusted for in the study. However the sample size was insufficient to guarantee high statistical power. Alexander et al. in a retrospective cohort study examined the association between $beta_2$-agonists use during pregnancy and perinatal outcomes (see Table 5).[29] The authors compared $beta_2$-agonists users against a group of asthmatics taking no medications, and another group of asthmatics using ICS. The study didn't find an increased risk of any malformations with $beta_2$-agonists use with aOR 0.9 (95%CI: 0.6-1.4) and aOR 0.8 (95%CI: 0.4-1.7). Yet the study suffered some limitations: (1) no adjustment for asthma severity and control, (2) small sample sizes and limited power (12% for both comparisons), (3) the exposure was not specific to the first trimester and was measured during the entire pregnancy, and (4) no information on the doses of medication use. Clark et al. in a prospective cohort study examined the association between $beta_2$-agonists use during pregnancy and neonatal outcomes, including any malformations (see Table 5).[32] The authors compared $beta_2$-agonists users with a group of asthmatic ICS users, and another group of asthmatics using both types of medications. The study didn't find any increased risk of malformation with $beta_2$-agonists use anytime during pregnancy. The authors however didn't adjust for asthma severity/control, the sample sizes were insufficient to obtain high statistical power, the exposure was not specific to the first trimester and was measured during the entire

pregnancy, and the data were gathered from participants of one center which may affect the generalizability of the study results.

Schatz et al. in a prospective cohort study examined the safety of beta$_2$-agonists among other asthma and allergy medications.[28] The study compared beta$_2$-agonists users with non-asthmatic pregnant women. No increased risk of major congenital malformations was found with maternal use of beta$_2$-agonists anytime during pregnancy or during the first trimester (cRR 0.6, p-value >0.05) and (cRR 0.76, p-value >0.05) respectively (see Table 5). The use of a non-asthmatic reference group prevented from separating the medication effect alone, and the small sample sizes resulted in low statistical power for the study (17%). Lao et al. in a retrospective cohort study examined the association between beta$_2$-agonists and any malformations.[37] The study didn't find any increased risk with beta$_2$-agonists use anytime during pregnancy comparing asthmatic beta$_2$-agonists users with non-asthmatic pregnant women. However, the sample sizes in the study were very small, and the exposure was not specific to the first trimester and was measured during the entire pregnancy. Olesen et al. in a population-based prescription study examined the risk of congenital malformations among other adverse neonatal outcomes with maternal exposure to different asthma medications including beta$_2$-agonists.[38] Data on the exact numbers and results were not shown in the study; however the risk of malformations was assessed for asthmatic beta$_2$-agonists users receiving prescriptions for beta$_2$-agonists 30 days prior to conception until 8 weeks of gestation. The authors used a reference group of women who didn't purchase any prescription drug during pregnancy. The authors reported no deviations from the expected values regarding the risk of malformations with maternal use of beta$_2$-agonists. The study suffered some limitations, including; (1) no available data on hospital admission medications, and (2) no adjustment for other maternal diseases and conditions during pregnancy.

From the former illustration, it is obvious that drawing rightful and precise conclusions from the literature on the risk of congenital anomalies due to $beta_2$-agonists use during pregnancy is difficult and requires carefulness and assertion. The former studies suffered from common limitations; (1) using a reference group of non-asthmatic pregnant women, (2) inadequate adjustment for asthma severity and control, (3) inaccurate defining of exposure time during pregnancy, and (4) small sample sizes and low statistical power. Hence, for the previously mentioned reasons, we aimed to conduct a large population-based study in order to assess the association between $beta_2$-agonists and congenital malformations, while trying to avoid the limitations of other studies.

Table 5. Description of the studies that examined beta$_2$-agonists and their association with major and any malformation

Non specified (Both SABA and LABA)														
Study	Design	Data collection	Exposure Time	ß$_2$ agonist users			Control			Effect		Power (%) for study's effect size	Power (%) for RR =1.5
				ß$_2$ agonist	No*	Outcome (% or mean)	Type of exposure	No*	Outcome (% or mean	OR or RR	(95% CI) or (P Value)		
Outcomes													
Major Malformations													
Bakhireva et al. 2005 (31)	Prospective Cohort	Org.of teratology inf. Services(tel.interviews+records) 1998-2003	Any time	Any	103	3.9	Non Asthmatic	303	0.3	cRR 13	NA	72.5	8
				Any	103	3.9	Asthamtic ICS users [£]	438	4.1	cRR 0.95	NA	4.8	16.7
Schatz et al. 2004 (30)	Observational Cohort + RCT	Maternal/Fetal medical centers(patient history+monthly visit+postportum reviews) 1994-2000	Any time	Any	1828	2.0 [Ω]	ß$_2$ agonist non users [§₸¥]	295	2.0 [Ω]	cRR 1.0	(p>0,05)	5	12.2
Schatz et al. 1997 (28)	Prospective Cohort	Medical care program(Questionnaire/daily cards) 1978-1989	Any time	Any [‡]	667	3.7	Non Asthmatic Non user	823	6.2	cRR 0.6	(p>0,05)	59.1	53.9
			1st trimester	Any [‡]	488	4.3		1000	5.6	cRR 0.76	(p>0,05)	17.5	47.6
Case Control Studies													
					Cases		Controls		NE Pop. type				
					Exp.	NE	Exp	NE					
Shao lin et al. 2009 (34)	Matched Case Control 2:1	NY state congenital malform. Registry+medical records+tel.interviews 1988-1991	1st trimester	Any [¢]	22	443	22	965	Non Asthmatic, No asthma Med	aOR 2.2	(1.05,4.61)	60	19.4
Shao Lin et al. 2008 (33)	Case Control	National birth defects prevention study(clinics)+tel.intervews+prescription database 1997-2002	1st trimester	Any [µ]	17	358	96	3932	Non user [µ] (asthmatic/non asthmatic)	cOR 1.94	(1.14,3.29)	71	28
										aOR 2.06	(1.19, 3.59)	___	___

SHORT ACTING (SABA)													
Study	Design	Data collection	Exposure Time	ß2 agonist users			Control			Effect		Power (%) for study's effect size	Power (%) for RR=1.5
				ß2 agonist	No.*	Outcome (% or mean)	Type of exposure	No*	Outcome (% or mean	OR or RR	(95% CI) or (P Value)		
Outcomes													
Major Malformations													
Schatz et al. 1988 (14)	Prospective Cohort	Medical care program(Questionnaire:history of asthma)+medical records 1978-1984	Any time	Any S.A. §¢#	259	3.9	Non Asthmatic	295	6.4	cOR 0.6	(p> 0,05)	25.8	24.9
			1st trimester	Any S.A. §¢#	180	3.9		295	6.4	cOR 0.6	(p> 0,05)	25.8	22.3
			Any time	Any S.A. §¢#	259	3.9	Asthamtic non users µ	101	6	cOR 0.65	(p>0,05)	16.2	11.9
			1st trimester	Any S.A. §¢#	180	3.9		172	5.3	cOR 0.73	(p> 0,05)	9.7	15.1
			Any time	Any S.A. §¢#	259	3.5	General population	1999254	3.0	NA	NA	9.6	31
Case Control Studies													
					Cases		Controls		NE Pop. type				
					Exp.	NE	Exp	NE					
Shao lin et al. 2009 (34)	Matched Case Control	NY state congenital malform. Registry+medical records+tel.interviews 1988-1991	1st trimester	Vent.µ	15	443	14	965	Non Asthmatic No asthma Med.	aoR 2.37	(0.9,6.23)	51	14.5
			Early pregnancy		17	15	18	25	Non Asthmatic No asthma Med.	cRR 1.3	(p>0,05)	—	—
			1st trimester	Alupent (Metaproterenol)µ	1	31	1	42	Non Asthmatic No asthma Med.	cRR 1.35	NA	—	—
				Terbutalin µ	1	31	0	43	Non Asthmatic No asthma Med.	—	NA	—	—
Shao Lin et al. 2008 (33)	Case Control	National birth defects prevention study(clinics)+tel.intervews+prescription database 1997-2002	1st trimester	Albut./Pirbuterol µ	13	368	88	4033	Non user µ (asthmatic/non asthmatic)	cOR 1.62	NA	91	26
Tata et al. 2008 (35)	Matched Case Control 1:6	Health improvement Database 1988-2004	Any time	Any S.A.	375	4420	2085	26235	Asthmatic non users	aOR 1.06	p (0.336) (0.94,1.19)	16.9	100
			1st trimester		NA	NA	NA	NA	NA	aOR 1.01	p (0.941) (0.86-1.18)	NA	NA

LONG ACTING (LABA)														
Study	Design	Data collection	Exposure Time	ß2 agonist users			Control			Effect		Power(%) for study's effect size	Power (%) for RR=1.5
				ß2 agonist	No.*	Outcome (% or mean)	Type of exposure	No*	Outcome (% or mean	OR or RR	(95% CI) or (P Value)		
Outcomes													
Major Malformations													
Jones et al. 2002 (39)	Prospective cohort	Org. of teratology Inf. Services 1998-2001	Any time	Salmet.	126	4.7	Asthmatic SABA users	91	3.9	NA	NA	5.6	9.1
							Non Asthmatic	115	1.9	NA	NA	22	7.4
Case Control Studies													
					Cases		Controls		NE Pop. type				
					Exp.	NE	Exp	NE					
Shao Lin et al. 2008 (33)	Case Control	National birth defects prevention study(clinics)+tel.intervews+prescription database 1997-2002	1st trimester	Salmet.[µ]	2	379	11	4110	Non user[µ] (asthmatic/non asthmatic)	cOR 1.97	NA	14	6.8
Tata et al. 2008 (35)	Matched Case Control 1:6	Health improvement Database 1988-2004	Any time	Any L.A.	25	4420	131	26235	Asthmatic non users	aOR 1.12	P (0.614) CI (0.72,1.75)	8.6	48.6
			1st trimester		NA	NA	NA	NA		aOR 1.09	P (0.77) CI (0.62,1.9)	—	—

Non specified (Both SABA and LABA)													
Study	Design	Data collection	Exposure Time	ß2 agonist users			Control			Effect		Power (%) for study's effect size	Power (%) for RR =1.5
				ß2 agonist	No.*	Outcome (% or mean)	Type of exposure	No*	Outcome (% or mean	OR or RR	(95% CI) or (P Value)		
Outcomes													
All Malformations													
Clark et al. 2007 (32)	Prospective Cohort	Clinics (Questionnaire/database)+neonatal details 2001-2003	Any time	Any	178	2.2	Non Asthmatic	717	2.2	cRR 1.0 [ĴĴ]	NA	__	__
							Asthamtic ICS users [£]	370	0.8	cRR 2.8 [ĴĴ]	NA	__	__
							ß2 agonist + ICS	170	3.5	cRR 0.63 [ĴĴ]	NA	__	__
Alexander et al. 1998 (29)	Retrospective Cohort	Perinatal database and hospital records 1991-1993	Not determined	Any	303	8.5	Non Asthmatic	13709	7.7	aOR 1	(0.6,1.6)	9.2	58
							Asthmatic No Med.	375	6.9	aOR 0.9	(0.6,1.4)	12.5	31
							Asthmatic ICS [µ]	139	6.2	aOR 0.8	(0.4,1.7)	12	15.5
Lao et al. 1990 (37)	Retrospective Cohort	Hospital and clinical database 1984-1987	Any time	Any [§ǂ]	54	3.8	Non Asthmatic	54	0	NA	NA	__	__

SHORT ACTING (SABA)													
Study	Design	Data collection	Exposure Time	ß2 agonist users			Control			Effect		Power (%) for study's effect size	Power (%) for RR=1.5
				ß2 agonist	No.*	Outcome (% or mean)	Type of exposure	No*	Outcome (% or mean	OR or RR	(95% CI) or (P Value)		
Outcomes													
All Malformations													
Kallen et al. 2007 (26)	Retrospective Cohort	Swedish Medical birth Register 1995-2004	1st trimester	Salbut.	271	NA	General pop.(asthm./non asthm.)	NA	NA	aOR 1.09	(0.97,1.75)	__	__
				Terbut	857	NA		NA	NA	aOR 1.11	(1.04,1.19)	__	__
Case Control Studies													
					Cases		Controls		NE Pop. type				
					Exp.	NE	Exp	NE					
Tamasi et al. 2006 (36)	Matched Case control 1:3	Hungarian congenital abnormality registry (self-reported questionnaire) 1980-1996	Any time	Salbut.	45	466	77	680	Non user (asthmatic)	pOR 0.9	(0.6, 1.3)	8	68
				Terbut.	179	332	241	516		pOR 1.2	(0.9, 1.5)	35.6	94.5
				Metaproterenol	3	508	6	751		pOR 0.7	(0.2, 3.0)	6.3	13.1
				Fenoterol	328	183	403	354		pOR 1.6	(1.3, 2.0)	98.9	95.7
Kallen et al. 2003 (27)	Case control	Swedish Medical birth Register(questionnaire by midwives+medical records) 1995-2001	Early pregnancy	Salbut.	29	4986	3446	574284	Non user (asthm./non asthm.)	cOR 0.97 aOR 0.93	(0.64, 1.36)	3.7	77
				Terbut.	104	4911	10613	567117		cOR 1.13 aOR 1.14	(0.93, 1.38)	24	99

LONG ACTING (LABA)													
Study	Design	Data collection	Exposure Time	ß2 agonist users			Control			Effect		Power (%) for study's effect size	Power (%) for RR=1.5
				ß2 agonist	No.*	Outcome (% or mean)	Type of exposure	No*	Outcome (% or mean	OR or RR	(95% CI) or (P Value)		
Outcomes													
All Malformations													
Kallen et al. 2007 (26)	Retrospective Cohort	Swedish Medical birth Registry	1st trimester	Salmet.	97	NA	NA	NA	NA	aOR 1.02	(0.83,1.25)	__	__
				Formot.	52	NA	NA	NA	NA	aOR 1.06	(0.80,1.40)	__	__
Wilton et al. 2002 (84)	Observational cohort	Prescription-event monitoring(prescription data+questionnaire to practicioners) 1996-1998	1st trimester	Formot.	31 Preg. (25 births)	2 Cases	NA	NA	NA	NA	NA	__	__
Wilton et al. 1998 (85)	Observational cohort	Prescription-event monitoring (priscriptions data+questionnaire to practitioners)	1st trimester	Salmet.	47 (births)	1 Case (2.13%)	NA	NA	NA	NA	NA	__	__
Mann et al. 1996 (86)	Observational cohort	Prescription-event monitoring (priscriptions data+questionnaire to practitioners)	Any time	Salmet.	65	1 Case (1.53%)	NA	NA	NA	NA	NA	__	__
Case Control Studies													
					Cases		Controls		NE Pop. type				
					Exp.	NE	Exp	NE					
Tamasi et al. 2006 (36)	Matched case control 1:3	Hungarian congenital abnormality registry (self-reported questionnaire) 1980-1996	Any time	Clenbuterol	28	483	56	701	Non user (asthmatic)	pOR 0.7	(0.5, 1.2)	33.3	56.7
Kallen et al. 2003 (27)	case control	Swedish Medical birth Register(questionnaire by midwives+medical records) 1995-2001	Early pregnancy	Salmet.	15	5000	1137	576593	Non user (asthm./non asthm.)	cOR 1.52 aOR 1.5	(0.90, 2.53)	36.7	34.5

Women participating in the different studies were asthmatic unless stated otherwise.

ICS: inhaled corticosteroids; Vent : Ventolin; Albut.: Albuterol; Terbut.: Terbutalin; Salmet.: Salmeterol; Formot.: Formoterol; S.A.: Short acting $beta_2$-agonist; L.A.; Long acting $beta_2$-agonist; RCT: randomized controlled trial; org. of teratology inf. services: The Organization of Teratology Information Services (OTIS); Med.: medications; aOR: adjusted odds ratio; cOR: crude odds ratio; cRR: crude risk ratio; cMD: crude mean difference; aMD: adjusted mean difference; pOR :crude prevalence odds ratio; Exp.: exposed; NE : non exposed; NE pop. type: non exposed population type; NA: data unavailable; – : power or effect size impossible to calculate.

***** Number of pregnancies unless stated otherwise.
§ Women may have concurrently received inhaled corticosteroids.
# Women may have concurrently received asthma controller medications (cromolyn).
¢ Women may have concurrently received asthma controller medications (theophylline).
£ Women may have concurrently received short-acting $beta_2$-agonists (inhaled or systemic).
µ Women may have concurrently received any other type of asthma medication.
‡ Women may have received inhaled, oral or injectable $beta_2$-agonists.
∫∫ Matching was performed and not considered in crude calculations.

2.6 Risk Factors for Congenital Malformations

2.6.1 Etiology

Congenital malformations' etiology has been the object of medical research for many years. It is believed now that the causes of birth defects could be genetic, environmental, or unknown.[87-90] However, the etiology of most human malformations is still unknown.[89] The genetic causes represent 15-25%, including chromosomal abnormalities and new mutations.[89;90] On the other hand, the environmental causes includes maternal diseases, infectious agents, teratogenic drugs, alcohol, smoking and radiations, all together representing about 10-15% of congenital malformations.[91] Finally, with about 65-75 % of unknown causes, multifactorial gene-environment interactions is one of its most significant proportions composing about 20-25% of the unknown malformations.[87-90] In the following sections we will discuss some of the important risk factors of congenital malformations that are closely related to our research objectives.

2.6.2 Maternal characteristics

Maternal age is considered one of the major factors that could affect pregnancy outcomes including malformations.[92-94] It is believed nowadays, based on several studies, that women at the extremes of the age distribution (< 20 years or ≥ 35 years) have an increased risk for congenital malformations compared to women in the mid-age (21-29 years).[92;94] While it is extensively proven that infants of older mothers have a higher risk of chromosomal anomalies, such as Down syndrome, the true risk of non-chromosomal anomalies is still equivocal.[92-94] The area of residence, urban or rural, has been shown to be associated with differences in perinatal outcomes and congenital malformations. The urban/rural status can greatly affect associations with certain birth defects, reaching more than two folds increase in relative risk of certain birth defects among rural residents.[95-97] Social position-presented by maternal education level and socioeconomic status-has been associated with different perinatal and fetal health outcomes including congenital malformations.[98-101] An increased prevalence of congenital malformations has been reported for women with lower social position, as compared with better-off women.[98;99;102] In a recent study, Women with less than 10 years of schooling had an almost three-fold increased risk of giving birth to a baby with a congenital anomaly as compared with women who had more than 4 years of higher education[102], and these results were consistent with other studies in literature.[98;100;101;103]

2.6.3 Medication use during pregnancy

Prescription and over the counter drugs are considered part of the environmental causes of congenital malformations with contribution of less than 1%, however congenital anomalies caused by environmental factors are of special importance as they are potentially preventable.[89;104]

The maternal exposure to certain environmental cause of malformation lies under the umbrella of teratology, with term “teratogen” being used to denote an agent that can produce structural or functional abnormalities in an exposed embryo or fetus.[89;104] Moreover, the dose, route of exposure, stage of pregnancy when the exposure to teratogen occurred plays the major role in identifying and labelling teratogens, so the list of teratogens only indicates teratogenic potential.[88;89;104] One of the important principles in studying teratogens is that an exposure to one is said to be following a toxicologic dose-response curve, where there is a threshold below which no effect will be observed. [88;89;104] Also as the dose of the teratogen increase, both severity and frequency of the adverse fetal effect increase.[89] Another potential principal to consider is determining the length of the exposure and the embryonic stage, since some teratogenic effects have broad period of sensitivity while others have very narrow periods.[88;89;104]

During pregnancy, many exposures may raise the concern of potential teratogenicity. Complete information on hundreds of exposures is present in clinical teratology knowledge bases such as TERIS and in reference text books.[13;77;79]

More than 80% of pregnant women take prescription or over-the-counter (OTC) drugs during pregnancy.[105] Many prescription drugs, such as anticonvulsants, angiotensin converting enzyme inhibitors, antineoplastic agents, and hormonal agents have been proven to be teratogenic.[77;88;89] On the other hand, most of over-the-counter medications have undetermined risk ratings, [106-109] while others like Aspirin showed increased fetal risk of malformation.[107;109] Pregnant women use a variety of OTC medications, including analgesics, antihistaminics, antacids, a range of herbal preparations and more.[108;109] Yet, the important issue to consider is that prescription and OTC medications risks represent less than 1% of the congenital malformations in human, and they are potentially preventable.[88;89]

2.6.4 Maternal conditions and lifestyles

The maternal disease states and different maternal conditions represent together the prime environmental cause of malformations (about 4%) [89], including different diseases like diabetes (gestational and chronic) [89;110], epilepsy [111;112], iodine deficiency [89], and intrauterine complications.[89] A wide range of malformations are caused by the previously mentioned maternal conditions, including major and minor types.[88]

Maternal diabetes is a known risk factor for congenital malformations.[113] It has also been known for many years that good metabolic control in the preconceptional period decreases the risk of congenital malformations.[113] Maternal hyperglycemia is a non-specific teratogen imposing the same risk of malformations to pregnant women with both type-1 and type-2 diabetes.[114] According to recent estimates, pregnancies complicated by pre-existing maternal type-1 and type-2 diabetes have an approximately twofold to fourfold increased risk of major malformations.[115-117]

It has been known for several decades that the risk of major and minor malformations in infants of epileptic mothers is twice higher than in the general population.[111;118] This is partly attributable to the teratogenicity of the drugs used to treat epilepsy, but the disease in itself most probably increases the risk, while no epidemiological technique is ideal to separate the effects of the disease and the drugs on the fetus.[119;120] Whereas maternal epilepsy induces a two to three-fold increase in the risk of any kind of major malformations, four main types of defects are overrepresented in infants of epileptic mothers : orofacial clefts, cardiovascular defects, spina bifida and hypospadias.[120]

Maternal overweight and obesity are also proven to be associated with an increased risk of a range of congenital malformations.[121-124] Obese women were more likely to have an infant with spina bifida, omphalocele, heart defects and multiple anomalies. [121-125] Overweight women were more likely to have infants with heart defects and multiple anomalies.[121-125] Maternal obesity often leads to diabetes which is itself associated with increased risk of birth defects.[121-125]

Lifestyles and maternal habits like smoking and alcoholism should also be cautiously considered.[89] The maternal alcohol consumption, or binge drinking, can produce wide spectrum of birth defects, which range in frequency and severity from fetal alcohol effects to typical fetal alcohol syndrome.[13;89;104;106] Smoking during pregnancy has been associated with low birth weight, stillbirth, and intrauterine growth retardation.[13;88;89;104;106] Although there are many occasional reports of malformations in women who smoke during pregnancy, there is no consistent evidence that there is a significant increase in risk of malformation due to maternal smoking during pregnancy.[13;104;106] Furthermore, the occurrence of congenital malformations due to maternal exposure to tobacco or alcohol is believed to be a dose related association.[104;106]

2.6.5 Fetal conditions and infections

The presence of embryonic and fetal infections accrues for about 3% of the malformations in humans.[88;89] The list of proven fetal and embryonic infections with teratogenic effects includes Cytomegalovirus, herpes simplex virus, lymphocytic choriomeningitis virus, rubella virus, toxoplasmosis, syphilis, and varicella-zoster virus.[89;104] Since the early 1970s, these organisms and the resulting clinical syndromes have been categorized as TORCH infections, a useful acronym referring to Toxoplasrna gondii, Other microorganisms, rubella virus, Cytomegalovirus (CMV) and herpes

viruses.[126;127] Authors often added syphilis under “other microorganisms”.[127] Most of the TORCH infections cause mild maternal morbidity, however, they often present serious fetal consequences, and treatment of maternal infection frequently has no beneficial effect for the fetus.[126-128]Infants with congenital infection due to one of the TORCH agents may result in cardiac defects, occular lesions, hearing defects, central nervous system defects, neonatal purpuras, and hepatosplenomegaly.[126;127]

2.6.6 Pregnancy related characteristics

Multiplicity is considered a known risk factor for congenital malformations. Many epidemiological studies have observed that multiple births have a higher risk of congenital malformations compared to singletons.[129-131] Central nervous defects, cardiovascular defects, alimentary tract defects, ear defects, respiratory defects have all been observed more often among multiple births.[129;130] Among the specific malformations detected frequently with multiple births are macrocephaly, encephalocele, hydrocephaly, cleft lip and palate, anomalies of the diaphragm, cardiac septal defects, atresia or stenosis of the large intestine or anus, tracheoesophageal fistula,malformations of the alimentary tract, inguinal and umbilical hernias, and cystic kidney.[129-131]

There is considerable evidence that late birth order (parity order) is associated with certain congenital malformations, such as congenital heart diseases, neural tube defects, spina bifida, and orofacial clefts.[132-134]

2.6.7 Asthma related variables

The most important asthma related factors are the asthma severity/control (i.e. being mild, moderate or severe and controlled or uncontrolled), and the medications used to control the symptoms. The use of high doses of inhaled corticosteroids (ICS) and oral corticosteroids (OCS) are considered risk factors for congenital malformations.[61;135-

137] Also the use of other asthma controller medications (leukotriene-receptor antagonists, Ipratropium, and Nedocromil), and intra-nasal corticosteroids (INCS) during pregnancy should be considered due to limited human data available for these medications.[13;61;135-138] Severe and uncontrolled asthma are potential risk factors for congenital malformations and should be adjusted for properly.[3;30;52;55] One of the credible measures to assess asthma severity and control which we used in our study is the validated indexes developed according to the Canadian Asthma Consensus Guidelines, where severity is classified into mild, moderate or severe and control into controlled or uncontrolled.[139] Moreover, the emergency department (ED) visits for asthma, hospital admission for asthma, and the use of oral corticosteroids could act as a supporting mean for the measurement of asthma severity and control. [11;139]

2.7 Potential confounders

After evaluating the different risk factors of congenital malformations, we find that the evaluation of the fetal safety of $beta_2$-agonists through examining their association with congenital malformations may be challenging due to the emergence of several potential confounders. In the analysis of the true risk of $beta_2$-agonists on fetal adverse effects, we should take into consideration the risk factors discussed above, also other confounding variables that could be retrieved from the literature on asthma during pregnancy. A summary of the confounders will include: **socio-demographic variables** such as maternal age, receipt of social assistance during pregnancy, area of residence at delivery, and education level at delivery; 2) **maternal and fetal conditions** including chronic hypertension, pregnancy induced hypertension, diabetes mellitus, gestational diabetes, epilepsy, uterine complications during pregnancy, maternal exposure to teratogenic drugs in the 1^{st} trimester, parity, multiplicity, and fetal infections; and 3) **asthma-related variables** including the use of inhaled corticosteroids, use of other asthma controller medications, use of intranasal and oral corticosteroids, and emergency department (ED)

visit or hospitalization for asthma in the 1st trimester. In addition, asthma severity level and asthma control measured prior to pregnancy and during the first trimester are considered important potential confounders.

CHAPTER 3: OBJECTIVES

Objectives of our study

3.1 General objective

To investigate the association between maternal exposure to inhaled $beta_2$-agonists during the first trimester of pregnancy and the risk of congenital malformations in newborns of asthmatic women.

3.2 Primary objectives

1. To evaluate the association between maternal exposure to SABAs and LABAs during the first trimester of pregnancy and major congenital malformations.
2. To evaluate the association between maternal exposure to SABAs and LABAs during the first trimester of pregnancy and any congenital malformations.

3.3 Secondary objectives

1. To examine the association between maternal exposure to SABAs and LABAs during the first trimester of pregnancy and the risk of different specific congenital malformations.
2. To explore whether or not there is a dose-response relationship between SABA use during the first trimester and the risk of congenital malformations.

CHAPTER 4: METHODS

This chapter encompasses the methods presented in the manuscript more comprehensively.

4.1 Source of data

This study used data from asthmatic women through the linkage of three administrative health databases from the province of Quebec; Régie de l'assurance maladie du Québec (RAMQ), MED-ECHO, and the "Fichier des événements démographiques du Québec" (birth and death registries) administered by the Institut de la Statistique du Québec (ISQ). The RAMQ's databases provide information on outpatient medical services dispensed to all Quebec residents and prescribed medications dispensed in community pharmacies. RAMQ's Public Drug Insurance Plan for residents cover about 43% of the residents of Quebec [140] including the elderly, recipients of social assistance since 1980, and 1.7 new adherents since January 1997, who are mainly consisting of workers and their families not covered by a private drug insurance plan.

MED-ECHO provides information on all acute care hospitalizations occurring in Quebec, including birth weight and gestational age for delivery hospitalizations. The Fichier des événements démographiques du Québec (ISQ) database provides demographic variables on the mother, father and baby as well as birth weight and gestational age.

Data recorded in the RAMQ public drug insurance plan database and the medical diagnosis for asthma recorded in the RAMQ Medical Services database have been formally evaluated and found to be valid and precise.[141;142] The RAMQ and MED-ECHO databases have often been used for research on asthma and pregnancy with many articles published in renowned medical journals.[11;135;138;143;144]

4.2 Study design

To achieve our goal, a population-based retrospective cohort design was used. A cohort comprising pregnancies from asthmatic women insured by the RAMQ Public Drug Insurance Plan who gave birth between January 1, 1990 and December 31, 2002 was formed. Using the gestational age and date of birth of the newborns recorded in the MED-ECHO and ISQ databases, we identified the date of the first day of the last menstrual period and the date of delivery for each pregnancy. The inclusion criteria were: 1) having at least one pregnancy ending in a delivery (live or still birth) between 1990 and 2002; 2) being 12-50 years old at the beginning of the pregnancy; 3) having at least one diagnosis of asthma (ICD-9 code 493 except 493.2) and at least one prescription for an asthma medication at any point in time two years before or during pregnancy itself; and 4) being covered by the RAMQ Public Drug Insurance Plan for at least one year before and throughout the pregnancy. Pregnancies of women taking oral $beta_2$-agonists during the first trimester were excluded in order not to affect our exposure assessment (the use of the inhaled form of $beta_2$-agonists), and those taking oral corticosteroids chronically in the year before conception were excluded, due to the previously proven increased risk of congenital malformations among women exposed to oral corticosteroids during pregnancy.[145-147] We also excluded pregnancies of women who were rheumatic cases, or suffering from Cushing disease, iodine deficiency, adrenal tumors, and folic acid deficiency, which are all rare diseases that can affect fetal development and may cause congenital malformations.[148]

For each pregnancy in the cohort, we obtained from the RAMQ data on all prescriptions dispensed (name, date of filling, dose, quantity, dosage form, duration of the prescription, encrypted identification, and speciality of prescribing physician) and data on inpatient, emergency and hospital medical services; nature of medical act, date of service, site of practice [outpatient clinic, ED, and hospital], diagnosis code, encrypted identification, and speciality of the treating physician. RAMQ also provided

socioeconomic data; date of birth of mothers and children, receipt of social assistance, and area of residence of the mother during pregnancy. These data were obtained in the year preceding and during pregnancy for the mother and during the first year of life for the newborns.

From MED-ECHO, data were obtained on all hospitalizations, including principal diagnosis, up to 15 secondary diagnoses, date of entry, and duration of hospitalization for the year before, during, and one year after pregnancy for the mothers. For delivery hospitalizations, gestational age and birth weight of the baby data were obtained in addition to other aforementioned data. Moreover, hospitalization data for the children during their first year of life were obtained.

The *Fichier des événements démographiques du Québec* (ISQ) contained data about the level of education of the mother and the parity of the ongoing pregnancy.

An authorization was obtained from the *Commission d'accès à l'information du Québec* before requesting and linking the information from RAMQ, MED-ECHO, and ISQ databases.

4.3 Outcome definition

The presence of a congenital malformation was identified within the cohort using diagnosis codes specific to congenital malformations (International Classification of Diseases-9th revision codes, ICD-9: 740-759 and 778.6) (see table 6) obtained from the RAMQ and MED-ECHO databases, either from the mother's or the infant's records. Our list of congenital malformations was compared with the list provided by the Collaborative Perinatal Group[149] and verified by a geneticist from the CHU Saint-Justine for exactness and completeness. An infant was identified as a case if he or she had at least one diagnosis of a congenital malformation at birth or during the first year

of life recorded in the RAMQ or MED-ECHO databases. Classification of congenital malformations into major or minor was performed by the geneticist. A congenital malformation was classified as major if it could be life-threatening or cause major cosmetic defects. If a malformation could be classified as either minor or major, it was considered as major if there was at least one hospitalization related to the malformation during the first year of life.

The primary outcomes were major and any congenital malformations and the secondary outcomes were different specific congenital malformations, which were anencephalus, spina bifida, other malformations of the nervous system, (eye, ear, face, and neck) group, cardiac, circulatory system, respiratory system, cleft palate & cleft lip, digestive system, genital organs, urinary system, limbs, other musculoskeletal, integument, chromosomal, congenital hydrocele, and other and unspecified congenital malformations (details in table 6).

Table 6. Congenital Malformations Codes

Congenital Malformation	ICD-9 Code
Any malformation	740-759, 778.6
Anencephalus	740
Spina bifida	741
Other malformations of the nervous system	742
Eye, ear, face and neck	743, 744
Cardiac malformations	745.0-746.9
Circulatory system	747
Respiratory system	748
Cleft palate and cleft lip	749
Digestive system	750-751

Genital organs	752
Urinary system	753
Limbs	754.4, 754.5, 754.6, 754.7, 755
Other musculoskeletal malformations	754.0, 754.1, 754.2, 754.3, 754.8, 754.9, 756
Integument	757
Chromosomal	758
Congenital hydrocele	778.6
Other and Unspecified Congenital Anomalies	759

4.4 Maternal exposure to beta$_2$-agonists

The primary exposure was the use of SABA (salbutamol, epinephrine, orciprenaline, terbutaline, fenoterol, and pirbuterol) and LABA (salmeterol and formoterol) during the first trimester of pregnancy, measured separately by the filling of at least one prescription during the 1st trimester or just before it, with the likelihood of its use during the 1st trimester. The secondary exposure studied was defined as the average number of doses per week of SABA taken during the first trimester, obtained with an algorithm that we developed and used in previous studies. [11;55;61] The average number of doses per week were divided into four categories based upon the Canadian Asthma Consensus Guidelines: non-use (0 dose, reference category), > 0 to 3 doses, > 3 to 10 doses, and > 10 doses per week.[150]

4.5 Confounding variables

The covariables that we considered were identified from previous studies in the literature on asthma during pregnancy, or being known risk factors for congenital malformations, hence they were adjusted for as potential confounders. Three classes of

variables were considered as potential confounders. Three classes of variables were chosen from the literature on asthma during pregnancy or were known risk factors for congenital malformations, hence they were considered as potential confounders. Maternal s**ocio-demographic variables** such as maternal age at the start of pregnancy (<18, 18-34, and >34 years), receipt of social assistance during pregnancy or one year before (yes/no), area of residence at delivery (rural/urban), and education level in years ($\leq$12, $\geq$13, missing). **Maternal & fetal conditions** include maternal hypertension (chronic and pregnancy induced), diabetes (mellitus and gestational) and epilepsy that were identified from either diagnoses or filled prescriptions of related medications one year before or during pregnancy using algorithms developed for each condition.[11;135;138;143;144] We also considered other maternal diseases such as uterine defects, placental embolism, and amniotic bands, measured each separately (yes/no) using ICD-9 codes (see table 7). [148;151;152] This class also includes maternal exposure to proven human teratogenic drugs during the first trimester of pregnancy (yes/no), listed in Table 8. Fetal conditions include embryonic and fetal infections (yes/no), identified using ICD-9 codes (see table 7).[148;151;152] Pregnancy related variables in this class are parity (nullipara versus primipara or multipara) and multiple pregnancies (singleton versus twins or more). **Asthma-related variables** include the use of ICS in the first trimester categorized into (0 mcg, >0-500 mcg, >500 mcg of beclomethasone chlorofluorocarbon (CFC) equivalent doses per day) [135], use of other asthma controller medications (leukotriene-receptor antagonists, theophyllines, ipratropium, cromoglycate, and nedocromil) in the first trimester of pregnancy (yes/no), and intra-nasal corticosteroids (INCS) use during the first trimester (yes/no). Severity and control of asthma prior to pregnancy were measured with validated indexes developed according to the Canadian Asthma Consensus Guidelines, where severity is classified into mild, moderate or severe and control into controlled or uncontrolled.[139] During the first trimester of pregnancy, asthma severity and control were measured using the administered daily doses of ICS,

the use of other asthma medications (INCS and asthma controller medications), emergency department (ED) visit for asthma, hospital admission for asthma, and the use of oral corticosteroids.

Table 7. Maternal and Fetal Conditions

Embryonic and Fetal Infections	**ICD-9 Code**
Cytomegalovirus Infection	771.1
Rubella	771.0
Herpes Simplex	771.2
Syphilis	090.0, 090.1, 090.2, 090.3, 090.4, .5, .6, .7, .9
Toxoplasmosis	771.2
Varicella-Zoster	052.0, .1, .7, .8, .9
Venezuelan Equine Encephalitis	66.2
Maternal Disease States	**ICD-9 Code**
Uterine complications during pregnancy	
Uterine defects	218.0, 218.1, 218.2, 218 .9, 654.1.
Placental embolism	656.9
Amniotic bands	658.8, 762.8
Rheumatic cases	710.0, 710.2
Maternal Epilepsy	345, 780.39
Maternal Diabetes (gestational and diabetes mellitus)	Algorithm based upon filled prescriptions of medications and diagnosis
Maternal Hypertension (pregnancy induced and chronic hypertension)	Algorithm based upon filled prescriptions of medications and diagnosis

Table 8. Proven Teratogenic Drugs [153-156]

acarbose	diethylstilboestrol
acetylsalicylic acid	doxepine
administered hydrochloride	doxorubicin
amethopterine	enalapril
amitriptyline	epirubicin
amoxapine	estramustine
amsacrine	ethopropazine
benazepril	ethosuximide
benztropine	ethylestrenol
biperidene	etoposide
bleomycin	etretinate
bupropion	fludarabine
busereline	fluorouracil
busulfan	fluoxymesterone
butorphanol	flupenthixol
capecitabine	fluphenazine
captopril	fluspirilene
carbamazepine	fluvoxamine
carboplatine	formestane
carmustine	fosinopril
chlorambucil	gliclazide
chlorpromazine	glimepiride
chlorpropamide	glyburide
cilazapril	haloperidol
cilazapril/hydrochlorothiazide	hydroxy-urea
cisplatine	imipramine

citalopram	interferon alfa - 2A
cladribine	interferon alfa - 2A (without human albumin)
clobazam	interferon alfa - 2B
clomipramine	interferon alfa - 2B (without human albumin)
clozapine	interferon alfacon-1
cyclophosphamide	interferon alfa-n1
cytarabine	isotretinoine
dacarbazine	lamotrigine
dactinomycin	l-asparaginase
danazol	levetiracetam
daunorubicine	lisinopril
desipramine	lisinopril/hydrochlorothiazide
lithium	pipotiazine
lomustine	primidone
loxapine	procarbazine
maprotiline	prochlorperazine
mechlorethamine	procyclidine
melphalan	promazine
mephenytoine	propylthiouracil
mephobarbital	protriptyline
mercaptopurine	quetiapine
mesoridazine	quinapril
mesuximide	ramipril
metformin	repaglinide
methimazole	risperidone
methotrimeprazine	rosiglitazone

methyltestosterone	sertraline
mirtazapine	sodium divalproex
misoprostol	sodium valproate
mitomycin	stanozolol
mitotane	temozolomide
mitoxantrone	testosterone
moclobemide	thioguanine
nandrolone	thioproperazine
nateglinide	thioridazine
nefazodone	thiotepa
nortriptyline	thiothixene
olanzapine	tolbutamide
orphenadrine	topiramate
oxcarbazepine	trandolapril
oxymetholone	tranylcypromine
paroxetine	trifluoperazine
penicillamine	trihexyphenidyl
pericyazine	trimipramine
perindopril	valproic acid
perindopril/indapamide	venlafaxine
perphenazine	vigabatrin
phenelzine	vinblastine
phenobarbitone	vincristine
phensuximide	vindesine
phenytoine	warfarin
pimozide	zuclopenthixol
pioglitazone	

4.6 Statistical analyses

We calculated descriptive statistics for the characteristics of the pregnancies and we estimated the prevalence of all, major, and specific congenital malformations according to the use of SABA and LABA during the 1st trimester. We also calculated descriptive statistics for the characteristics of the pregnancies in relation to the secondary exposure, namely the four categories on the average number of doses per week of SABA used during the 1st trimester.

Generalized estimating equation (GEE) models were used to estimate the association between the risk of congenital malformation and maternal exposure to SABA and LABA during the 1st trimester of pregnancy. Two GEE models were used, one for the outcome "major malformations", the other for the outcome "all malformations". For both, we estimated the crude and adjusted odds ratio (cOR, aOR) of congenital malformations, and unstructured correlation matrix was chosen for the analysis. Another two GEE models were used to estimate the association between the number of weekly doses of SABA and the primary outcomes. GEE models were used as they can take into account the fact that a proportion of women contributed two pregnancies or more to the analysis by estimating the correlation between consecutive pregnancies and estimate the effects of all confounders.[157] A backward selection strategy was used to find the most accurate models, retaining in the final models only variables that act as confounders (i.e. if the OR associated with SABA or LABA changed by 10% or more) and those significantly associated with the outcome (*P* value < .05).[158] Additional GEE models were performed to explore the association between the maternal exposure to SABAs and LABAs during the first trimester and specific malformations. For these models, a forward selection strategy was used to obtain the best models through adding the variables one by one in descending order of significance, then keeping only the variables that act as confounders.[159-161] A forward selection strategy was preferred for these models due to the relative small sample

sizes and in order to include the least number of variables to maintain the models' stability. All analyses were performed using SAS version 9.1.2.[162]

4.7 Sample Size and Statistical Power

We planned to have 13307 pregnancies from asthmatic women in the cohort. We expected that 55% of women used SABA and 1.3% used LABA during the first trimester.

Assuming an alpha error of 5%, and considering the prevalence for any malformations to be 9.5%, we assumed to have a power of 95% to detect an odds ratio of 1.2 for the SABA users against non users, and 83% power to detect an odds ratio of 1.6, or 70% power to detect an odds ratio of 1.5 for LABA users against non users.

For major malformations, we expected a prevalence of 5.9%. Assuming an alpha error of 5%, the study would have a power of 80% to detect an odds ratio of 1.2, (or 97% to detect an odds ratio of 1.3) comparing SABA users and non users. The study would also have a power of 82% to detect an odds ratio of 1.8 for LABA users against non users.

CHAPTER 5: MANUSCRIPT

Beta$_2$-agonists Use during Pregnancy and the Risk of Congenital Malformations

Sherif Eltonsy, BPharm[1,2], Amélie Forget,MSc[1,2], and Lucie Blais, PhD[1,2]

From [1]the Faculty of Pharmacy, Université de Montréal and [2]Hopital du Sacré-Cœur de Montréal. Montréal, Québec, Canada.

Reprint requests: Lucie Blais, PhD, Université de Montréal, Faculté de pharmacie, C.P. 6128, succursale Centre-ville, Montréal, Québec H3C 3J7, Canada. Fax: 1-514-343-6120, Phone: 1-514-343-6111 extension 3786.

L. Blais is the recipient of a Salary Award from the *Fonds de la recherché en santé du Québec* (FRSQ) and is the Endowment Pharmaceutical Chair AstraZeneca in Respiratory Health. This study was funded through grants received from the *Fonds de la recherche en santé du Québec* (FRSQ), and the Canadian Institutes of Health Research (CIHR).

Disclosure of potential conflict of interest: L. Blais has received research support from AstraZeneca, Amgen, and GlaxoSmithKline. S. Eltonsy has declared that he has no conflict of interest. A. Forget has declared that she has no conflict of interest.

Running title: Beta$_2$-agonists and Congenital Malformations

Word count: 3353

At a glance commentary: the study helps clinical practitioners to assess the safety of beta$_2$-agonists during pregnancy in order to optimize their therapeutic strategies in the management of asthma. Health practitioners should encourage their pregnant patients to adhere to their beta$_2$-agonists therapy; in the meanwhile, long-acting beta$_2$-agonists should be the objective of future research.

Abstract

Background: Short-acting inhaled beta$_2$-agonists (SABA) are frequently used as rescue medications and long-acting inhaled beta$_2$-agonists (LABA) are used as an add-on controller therapy for asthma during pregnancy. **Objective**: To investigate the association between exposure to SABA and LABA in the first trimester of pregnancy and the risk of congenital malformations among asthmatic women. **Methods**: A cohort of pregnancies from asthmatic women was formed through linkage of three administrative databases from Québec (Canada). The primary outcomes were major and any congenital malformations. The primary exposure was the separate exposure to SABA and LABA during the first trimester while secondary exposure was the weekly SABA doses during the first trimester. Using generalized estimating equation models, the association between congenital malformations and maternal exposure to SABA and LABA was assessed. Moreover, the association between different specific congenital malformations and maternal exposure to SABA and LABA was also examined. **Results**: From a cohort of 13, 117 pregnancies, we identified 1,242 infants with a congenital malformation (9.5%), of which 762 had a major malformation (5.8%). The adjusted odds ratios (95% CI) for any malformations associated with the use of SABA and LABA were 1.0 (0.9-1.2) and 1.3 (0.9-2.1), respectively. The corresponding figures were 0.9 (0.8-1.1) and 1.3 (0.8-2.4) for major malformations. Significant increased risks of cardiac, genital organs and other congenital malformations were observed with LABA use in 1st trimester. **Conclusion**: Our study supports the evidence that the use of SABA during pregnancy is safe, but more research is required to validate the safety of LABA.

Words: 250

Key words: birth defects, cohort studies, database, first trimester, salbutamol.

Introduction

Asthma has been recognized as one of the most common chronic pulmonary diseases and a serious medical complication in pregnancy, [1-3] affecting about 3.7% to 8.4% of pregnant women.[1;2] Uncontrolled maternal asthma has been associated with intrauterine growth restriction (IUGR), prematurity, and congenital malformations that may lead to compromised fetal growth,[1;4-7] with two main hypothesized mechanisms: 1) oxygen deprivation due to poor asthma control; and 2) asthma medications.[8] According to the US National Asthma Education and Prevention Program guidelines for managing asthma during pregnancy, short-acting beta$_2$-agonists (SABAs) are the drug of choice as a quick relief medication and in the management of acute exacerbations or emergency hospitalizations, while long-acting beta$_2$-agonists (LABAs) are used in combination with inhaled corticosteroids as a controller medication for patients with a moderate to severe persistent asthma that is not fully controlled with inhaled corticosteroids alone.[9]

Despite their recommended use in asthma management,[9] the beta$_2$-agonists contribution to congenital malformations is still unclear. Congenital malformations are present in approximately 4% of live births and are considered as the leading cause of infant mortality in the US and Canada.[10;11]

In the literature, we identified 15 different studies examining the association between SABA and LABA and congenital malformations,[12-26] but only seven studies compared beta$_2$-agonists users against a reference group of asthmatic pregnant women[14;16-18;21;23;26]. Among these studies, only one had uncovered a positive association between fenoterol exposure any time during a pregnancy (SABA) and the risk of congenital malformation (pOR=1.6, 95% CI=1.3-2.0),[23] but the OR was not adjusted for the level of asthma severity. The main limitations that prevent us from drawing valuable and explicit conclusions about the safety of SABA and LABA in pregnancy from these 15 studies are: 1) the choice of the control group, often made up of non-asthmatic women; 2) the timing of

the exposure during pregnancy; 3) low statistical power; and 4) incomplete adjustment for asthma severity/control and other important confounders.

In order to further investigate the impact of $beta_2$-agonists use during pregnancy, we performed a large population-based retrospective cohort study estimating the risk of congenital malformations among newborns of mothers who have been exposed to SABA and/or LABA during the first trimester of pregnancy.

Methods

Source of Data

A cohort of pregnancies from asthmatic women was formed through the linkage of three administrative health databases from the province of Quebec; Régie de l'assurance maladie du Québec (RAMQ), MED-ECHO, and the "*Fichier des événements démographiques du Québec*" (birth and death registries) administered by the *Institut de la Statistique du Québec* (ISQ).

Study Design

To achieve our goal, a population-based retrospective cohort design was used. The cohort has been used before to answer other research questions and details can be found in Blais et al.[27]. Briefly, a cohort comprising pregnant asthmatic women insured by the RAMQ Public Drug Insurance Plan who gave birth between January 1, 1990 and December 31, 2002 was formed. The inclusion criteria were: 1) having at least one pregnancy ending in a delivery (live or still birth) between 1990 and 2002; 2) being 12-50 years old at the beginning of the pregnancy; 3) having at least one diagnosis of asthma (ICD-9 code 493 except 493.2) and at least one prescription for an asthma medication at any point of time in the prior two years or during pregnancy; and 4) being covered by the RAMQ Public Drug Insurance Plan for at least one year before and throughout the pregnancy. Pregnancies of

women taking oral beta$_2$-agonists during the first trimester and those taking oral corticosteroids chronically in the year before conception were excluded, due to the previously proven increased risk of congenital malformations among women exposed to oral corticosteroids during pregnancy.[28-30] We also excluded pregnancies of women who were rheumatic cases, or suffering from Cushing disease, iodine deficiency, adrenal tumors, and folic acid deficiency, which are all rare diseases that can affect fetal development.[31]

Using the gestational age and date of birth of the newborns recorded in the MED-ECHO and ISQ databases, we identified the date of the first day of the last menstrual period and the date of delivery for each pregnancy. Pregnancy variables recorded in the RAMQ, MED-ECHO and ISQ databases have been found to be highly valid among asthmatic women.[32] A woman in the cohort may have contributed more than one pregnancy, the "pregnancy" is thus taken as the unit of analysis, with a maximum number of three pregnancies per woman, specifically the most recent pregnancies. This research project has been approved by the Ethics Committee of the Hôpital du Sacré-Cœur de Montreal.

Congenital Malformations

The presence of a congenital malformation was identified within the cohort using International Classification of Diseases-9th revision (ICD-9) diagnosis codes specific to congenital malformations recorded in the RAMQ or MED-ECHO databases at birth or during the first year of life. The primary outcomes were major and any congenital malformations while the secondary outcomes were specific congenital malformations.

Maternal Exposure to Beta$_2$-agonists

The primary exposure was the use of SABA (salbutamol, epinephrine, orciprenaline, terbutaline, fenoterol, and pirbuterol) and LABA (salmeterol and formoterol) during the first trimester of pregnancy, measured separately by the filling of at least one prescription

during the 1st trimester or just before it, with the likelihood of its use during the 1st trimester. The secondary exposure studied was defined as the average number of doses per week of SABA taken during the first trimester, obtained with an algorithm that we developed and used in previous studies. [7;27;33;34] The average number of doses per week were divided into four categories based upon the Canadian Asthma Consensus Guidelines[35]: non-use (0 dose, reference category), > 0 to 3 doses, > 3 to 10 doses, and > 10 doses per week.

Potential Confounders

Three classes of variables were chosen from the literature on asthma during pregnancy or were known risk factors for congenital malformations, hence they were considered as potential confounders: 1) maternal **socio-demographic variables** include age in years, receipt of social assistance during pregnancy or one year before, area of residence at delivery, and education level at delivery in years; 2) **maternal and fetal conditions** include chronic hypertension, pregnancy induced hypertension, diabetes mellitus, gestational diabetes, epilepsy, uterine complications during pregnancy, maternal exposure to teratogenic drugs in the 1st trimester, parity, multiple pregnancies, and embryonic and fetal infections; and 3) **asthma-related variables** include the use of inhaled corticosteroids, use of other controller medications (i.e. Leukotriene receptor-antagonist [zafirlukast and montelukast], Ipratropium, Theophylline, or anti-allergics [nedocromil and cromoglycate]), use of intranasal and oral corticosteroids, and emergency department (ED) visit or hospitalization for asthma in the 1st trimester. In addition, asthma severity and asthma control were measured with validated index in the year prior to the pregnancy.[36]

Statistical Analysis

We calculated descriptive statistics for the characteristics of the pregnancies and we estimated the prevalence of all, major, and specific congenital malformations according to the use of SABA and LABA during the 1st trimester. Generalized estimating equation

(GEE) models were then used to estimate the association between the risk of congenital malformation and maternal exposure to SABA and LABA during the 1st trimester of pregnancy.

Results

The cohort was formed of 13,117 pregnancies. Among these pregnancies, 7,182 (54.8%) used SABA during the first trimester of pregnancy while 165 (1.3%) used LABA. Regarding the SABA users, 3,420 (26.1%) pregnancies used $\leq$ 3 doses per week, 2102 (16.0%) >3 to 10 doses per week whereas 1,660 (12.7%) used >10 doses per week.

The characteristics of the pregnancies as a function of SABA and LABA use are presented in Table I. Most of the women were between 18 and 34 years old, received social assistance, had 11 years or less of education, were living in urban areas, and were not nulliparas. Less than 3% had a uterine complication or a fetal infection during pregnancy, used a teratogenic drug in the 1st trimester, or had a multiple pregnancy. LABA users were more likely to suffer from diabetes (gestational and chronic), epilepsy, or fetal infections compared to non users. In addition, LABA users were more likely to have exacerbations for asthma requiring an ED visit or hospitalization for asthma, to use higher doses of inhaled corticosteroids (e.g. ICS>500), intranasal corticosteroids, oral corticosteroids, and other asthma controller medications in the 1st trimester, as well as being more likely to have severe and uncontrolled asthma in the year prior to pregnancy than non users. Regarding the characteristics of the pregnancies in relation to the number of doses of SABA taken per week in the 1st trimester (see Table E.1), women taking >10 doses per week were more likely to use a teratogenic drug in the 1st trimester as well as higher doses of inhaled and oral corticosteroids. They were also more likely to visit an ED or being hospitalized for asthma in the 1st trimester and to suffer from severe and uncontrolled asthma during the year before pregnancy.

As presented in Table II, we identified 1,613 congenital malformations in 1,242 infants (prevalence; 9.5%) and 955 major malformations in 762 infants (prevalence; 5.8%). Cardiac and musculoskeletal malformations were the most prevalent (16.3% each), followed by limb malformations (9.7%).

In Table III, we present the adjusted odds ratios of any and major malformations associated with SABA and LABA use. We found that SABA use in the 1st trimester was not associated with an increased risk of any (aOR, 1.0; 95% CI, 0.9-1.2) and major malformations (aOR, 0.9; 95% CI, 0.8-1.1). However, LABA users were found to be more likely to have a congenital malformation, but the ORs were not statistically significant (aOR, 1.3 for any and major malformations). From the GEE models, we also observed that pregnancy induced hypertension, diabetes mellitus, and multiple pregnancy were significantly associated with an increased risk of any malformations, while pregnancy induced hypertension, maternal epilepsy, and multiple pregnancy were significantly associated with an increased risk of major malformations.

Table IV presents the analysis of the doses of SABA taken per week, which revealed no association with any or major malformations.

In Table V, we present the association between specific malformations and SABA and LABA use in the 1st trimester. We observed no significant association between SABA use and any of the specific malformations. On the other hand, significant increased risks of cardiac malformations (aOR, 2.4; 95% CI, 1.1-5.1), genital organ malformations (aOR, 6.8; 95% CI, 2.6-18.1), and other congenital malformations (aOR, 3.4; 95% CI, 1.4-8.5) were observed with LABA use in the 1st trimester.

Discussion

In this study, we found no increased risk of congenital malformations with SABA exposure during the 1st trimester even among women taking >10 doses per week. We also found no

statistically significant increased risk of any and major congenital malformations with the use of LABA in the 1st trimester, but this exposure was significantly associated with a higher risk of certain malformations; namely cardiac, genital organs, and other and unspecified congenital malformations.

This study is the first to uncover a statistically significant association between maternal exposure to LABA in the 1st trimester and congenital malformations. The previous studies found no association with any congenital malformations.[12;13;20;21;23;26;37-39] In a study which investigated the adverse maternal and fetal risks due to salmeterol exposure[26], salmeterol users were compared to women using only SABA and non asthmatics. No statistically significant differences were observed in the prevalence of major congenital malformations between the three groups, but the study had only a power of 9.1% to detect an OR of 1.5. In a retrospective cohort study using the Swedish Birth Registry[12], no association between salmeterol and formoterol exposure during the 1st trimester and congenital malformations were found. Moreover, in a case-control study using the same registry[13], a non significant increased risk of cardiovascular defects was found with salmeterol maternal exposure in early pregnancy (aOR, 1.5; 95% CI, 0.90-2.53), but the non-exposed group was formed by a mix of asthmatic women not using salmeterol and non-asthmatic women, and the study had only a statistical power of 34% to detect the observed OR. A recent matched case-control study by Tata et al.[21]with The Health Improvement Network database in the UK found no association between LABA use anytime during pregnancy (aOR, 1.12; 95% CI, 0.72-1.75) and in the 1st trimester (aOR, 1.09; 95% CI, 0.62-1.90) with major malformations, but the statistical power of the study to detect an OR of 1.5 was only 48%.

Among the seven studies that investigated SABA use during pregnancy and congenital malformations[12-14;20-23], only three studies used a control group of asthmatic women, [14;21;23] with only one of them reporting a significant increased risk of congenital malformation [23]. Tamasi et al found a positive association between fenoterol exposure

and all malformations (pOR, 1.6 95% CI, 1.30-2.0), [23] but this OR was not adjusted for asthma severity, maternal diseases, and medication use.

Our study results are consistent with the other two studies which used asthmatic pregnant women as the control group. Schatz et al. in a large prospective cohort study[14] found no increased risk of major malformations among women exposed to SABA anytime during pregnancy (cOR, 0.65) or in the 1st trimester (cOR 0.73). In a recent matched case-control study, Tata et al. [21] also found no significant increased risk of congenital malformations with SABA use anytime during pregnancy (aOR, 1.06; 95% CI, 0.94-1.19) and during the 1st trimester (aOR, 1.01; 95% CI, 0.86-1.18).

Three studies using non-asthmatic women or the general population as the control group found a positive association between SABA and congenital malformations. Kallen et al.[12] found a positive association between terbutaline and all malformations (aOR, 1.11; 95% CI, 1.04-1.19), and between salbutamol and any cardiac defect (aOR, 1.38; 95% CI, 1.12-1.70), but these ORs were not adjusted for important covariables such as asthma severity use of teratogenic medications, multiple pregnancies, and maternal and fetal diseases. In a case-control study, Shao Lin et al.[20] reported an increased risk of gastroschisis, a major para-umbilical wall defect, with maternal use of salbutamol and pirbuterol in the 1st trimester of pregnancy (cOR, 1.62), but the ORs were neither adjusted for asthma severity nor asthma control. Shao Lin et al. in another matched case-control study[22] reported an increased risk of congenital heart defects with maternal use of salbutamol in the 1st trimester (aOR, 2.37; 95% CI, 0.90-6.23). However, the study suffered from limitations such as inadequate control for asthma severity and the possibility of selection bias since the response rate was below 60% and recall bias as the study subjects were contacted up to two years after the birth of the child.

The most important question that should be considered when interpreting our results is what are the possible explanations behind the association found between LABA use and

specific congenital malformations? We suggest three explanations that could have contributed to the observed associations. First, the possibility of residual confounding by severity – LABA users appear to have more severe and uncontrolled asthma – and LABA are indicated in cases of moderate to severe asthma[3;40] while exacerbations (a marker of severe asthma) have been shown to significantly increase the risk of malformations[7]. However, we tried to reduce residual confounding through our adjustment for several markers of asthma severity and control in the analyses.[41;42] It is also worth noting that despite the fact that women using high doses of SABA per week (>10) appeared, like LABA users, to have more severe and uncontrolled asthma and were less likely to have a baby with a major malformation (aOR, 0.70; 95% CI, 0.50-1.00) than women not using SABA. This result implies that confounding by severity is not likely to be present, or not strong enough to confound the association to the point that SABA use would be associated with an increased risk of congenital malformations.

The second explanation is a true causal association between LABA use during the 1st trimester and an increased risk of certain congenital malformations by unknown mechanisms that need to be explored on the molecular basis in animal and human studies.
The third explanation is an increased risk of congenital malformations resulting from the potential effect of LABA on the steroid function.

Two different interactions of LABA on steroids have been identified, through which LABA could induce the gene transcription effect of steroids and subsequently their effects. First, LABA induce protein kinase A (PKA) activation which, in return, induces CAMP response element binding protein (CREB) binding protein (CBP). CBP activation is considered a rate limiting transcription factor for the steroids' action.[43] Second, LABA can directly induce ligand-independent nuclear translocation and activation of glucocorticoid receptors (GR) (i.e. induce migration of GR into the nucleus).[43;44] The theory postulates that by inducing the steroid-induced gene transactivation, LABA might

also enhance the steroid-induced side effects[43] and among the proven side effects of oral corticosteroids is the risk of congenital malformations.[28-30]

This study has several strengths, namely the use of three rich databases which allowed for adequate statistical power for the SABA analysis (80% power to detect an aOR of 1.2 for any and major malformations) and for adjustment for the most important potential confounders, while having a control group of asthmatic women not exposed to SABA or LABA during the 1st trimester. Furthermore, data on filled prescriptions and medical services were prospectively collected, avoiding a recall bias.

The SABA doses-per-week analysis that we performed helped to explore if there was a dose-response relationship between SABA and the risk of congenital malformations. Moreover, our large cohort of pregnancies allowed us to investigate congenital malformations in three aspects; 1) major malformations; 2) any malformations; and 3) specific malformations. The observed significant associations between pregnancy induced hypertension, diabetes mellitus, and multiple pregnancy with an increased risk of any malformations, also pregnancy induced hypertension, maternal epilepsy, and multiple pregnancy with an increased risk of major malformations are in concordance with the data in the literature, which emphasize the validity of our final models.[17;27;31;33] Regarding the external validity of our study, the prevalence of major and any congenital malformations among our cohort was similar to the average population figures.[45]

However, the results of this study should be interpreted with the following limitations in mind. The use of medications was measured by medication claims, which might not reflect their actual intake. The medications dispensed in hospitals were not recorded in the RAMQ database, which may include oral corticosteroids, and this could have underestimated their use during pregnancy. The cases of congenital malformations were identified using diagnoses recorded in the RAMQ and MED-ECHO databases and were not specifically

validated for this study. There is also a possibility of residual confounding due to our incapacity to adjust for known risk factors, like maternal obesity, over the counter medications (OTC), alcohol consumption, family history of congenital malformations, and some other environmental teratogens.[31] We only had a statistical power of 30% and 20% to detect a 30% increased risk of any malformations and major malformations, respectively, among LABA users. Moreover, in our study we did not adjust the P-values for multiple comparisons in the analyses of specific malformations, but the association of LABA exposure with genital organs malformations and other and unspecified malformations had very small P-values (P=0.0001, and P=0.008 respectively). Finally, the cohort under represents women with a higher socioeconomic status, which may limit the study generalizability, but this would be unlikely since the association between $beta_2$-agonists and congenital malformations is believed to be physiological in nature.

In conclusion, our study adds evidence, in concordance with asthma management guidelines, to the safety of SABA use during pregnancy even at doses as high as ten per week, but puts doubts on the use of LABA during pregnancy since they were found to be associated with an increased risk of certain congenital malformations. However, the observed associations cannot be entirely attributed to LABA since there is a possibility of residual confounding by asthma severity and further research is required to understand the aetiology behind these relationships. We also propose the substantial need to examine the results we reported in this study using in-vivo and in-vitro techniques. Due to the proven risks of severe and uncontrolled asthma on the mother and her fetus, risk-benefit considerations should still favour LABA use in asthma management during pregnancy until further results are reported.

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Table I. Characteristics of Pregnancies According to SABA and LABA Use during the First Trimester

	SABA Users	SABA Non Users	LABA Users	LABA Non Users
	No. of Pregnancies (%)			
	7,182 (54.8)	5,935 (45.2)	165 (1.3)	12,952 (98.7)
Socio-demographic variables				
Maternal age (years)				
<18	535 (7.4)	320 (5.4)	7 (4.2)	848 (6.6)
18-34	6,182 (86.1)	5,261 (88.6)	134 (81.2)	11,309 (87.3)
≥35	465 (6.5)	354 (6.0)	24 (14.6)	795 (6.1)
Receipt of social assistance during pregnancy or one year before	5,873 (81.8)	4,537 (76.4)	102 (61.8)	10,308 (79.6)
Urban area of residence at delivery	5,796 (80.7)	4,816 (81.2)	130 (78.8)	10,482 (80.9)
Level of education at delivery (years)				
≤11	4,313 (60.1)	3,465 (58.4)	76 (46.1)	7,702 (59.5)
12-15	2,026 (28.2)	1,665 (28.1)	64 (38.8)	3,627 (28.0)
≥16	323 (4.5)	347 (5.8)	14 (8.5)	656 (5.1)
missing	520 (7.2)	458 (7.7)	11 (6.7)	967 (7.5)
Maternal & fetal conditions				
Chronic hypertension	183 (2.6)	131 (2.2)	9 (5.5)	305 (2.4)
Pregnancy induced hypertension	323 (4.5)	265 (4.5)	8 (4.9)	580 (4.5)
Diabetes mellitus	181 (2.5)	123 (2.1)	12 (7.3)	292 (2.3)
Gestational diabetes	574 (8.0)	441 (7.4)	28 (17.0)	987 (7.6)
Epilepsy	80 (1.1)	59 (1.0)	4 (2.4)	135 (1.0)
Use of teratogenic drugs in 1st trimester	112 (1.6)	57 (1.0)	5 (3.0)	164 (1.3)
Uterine complications during pregnancy	140 (2.0)	113 (1.9)	4 (2.4)	249 (1.9)
Fetal infections during pregnancy	56 (0.8)	33 (0.6)	4 (2.4)	85 (0.7)
Nullipara	2,546 (35.7)	1,616 (27.3)	67 (40.6)	4,095 (31.8)
Multiple pregnancy	100 (1.4)	90 (1.5)	2 (1.2)	188 (1.5)
Asthma related variables				
Daily dose of inhaled corticosteroids in 1st trimester* (µg)				
0	3,178 (44.3)	5,459 (92.0)	8 (4.9)	8,629 (66.6)
>0-500	3,489 (48.6)	446 (7.5)	80 (48.5)	3,855 (29.8)
>500	515 (7.2)	30 (0.5)	77 (46.7)	468 (3.6)
Use of other controller medications in 1st trimester†	360 (5.0)	36 (0.6)	22 (13.3)	374 (2.9)
Use of intranasal corticosteroids in 1st trimester	375 (5.2)	144 (2.4)	25 (15.2)	494 (3.8)
Use of oral corticosteroids in 1st trimester	408 (5.7)	44 (0.7)	31 (18.8)	421 (3.3)

Emergency department visit or hospitalization for asthma in 1st trimester	579 (8.1)	76 (1.3)	22 (13.3)	633 (4.9)
Exacerbations for asthma in 1st trimester‡	717 (10.0)	98 (1.7)	31 (18.8)	784 (6.1)
Asthma severity in the year before pregnancy				
Mild	5,011 (69.8)	5,760 (97.1)	48 (29.1)	10,723 (82.8)
Moderate	1,447 (20.2)	163 (2.7)	47 (28.5)	1,563 (12.1)
Severe	724 (10.1)	12 (0.2)	70 (42.4)	666 (5.1)
Asthma control in the year before pregnancy				
Controlled	3,093 (43.1)	4,900 (82.6)	35 (21.2)	7,958 (61.4)
Un-controlled	4,089 (56.9)	1,035 (17.4)	130 (78.8)	4,994 (38.6)

SABA: short-acting inhaled β_2-agonist, LABA: long-acting inhaled β_2-agonist,
*ICSs in beclomethasone dipropionate-chloroflurocarbon equivalent.
†Leukotriene receptor-antagonist (zafirlukast and montelukast), Ipratropium, Theophylline, or Anti-allergics (nedocromil and cromoglycate).
‡A filled prescription for oral corticosteroids, an emergency department visit for asthma, or a hospitalization for asthma.

Table II. Distribution of Congenital Malformations

Congenital Malformation	All Malformations		Major Malformations	
	No.	***%***	***No.***	***%***
At least one malformation*	1,242	9.5	762	5.8
Specific malformations				
Anencephalus	2	0.1	2	0.2
Spina bifida	10	0.6	10	1.1
Other malformations of the nervous system	94	5.8	94	9.9
Eye, ear, face and neck	106	6.6	63	6.6
Cardiac malformations	262	16.3	262	27.5
Circulatory system	103	6.4	71	7.4
Respiratory system	56	3.5	38	4.0
Cleft palate and cleft lip	31	1.9	31	3.3
Digestive system	134	8.3	121	12.7
Genital organs	101	6.3	22	2.3
Urinary system	62	3.9	62	6.5
Limbs	156	9.7	22	2.3
Other musculoskeletal malformations	263	16.3	79	8.3
Integument	41	2.5	25	2.6
Chromosomal	20	1.2	20	2.1
Congenital Hydrocele	45	2.8	2	0.2
Other congenital anomalies	125	7.8	29	3.0
Total†	1613	100	955	100

*At least one malformation from total number of pregnancies (13,117).

†The number and percentage represents the total number of malformations in all cases. The total exceeds the number of cases (1,242 for all malformations and 762 for major malformations), because a newborn may have had more than one malformation.

Table III. Crude and Adjusted Odds Ratios of Any and Major Malformations in Association with SABA and LABA Use during the First Trimester of Pregnancy

		Any Malformations			Major Malformations		
	No. of pregn-ancies	***No. of Cases (%)***	***Crude OR (95% CI)***	***Adjusted OR (95%CI)***	***No. of Cases (%)***	***Crude OR (95% CI)***	***Adjusted OR (95%CI)***
SABA use in 1st trimester							
Yes	7,182	691 (9.6)	1.0 (0.9-1.2)	1.0 (0.9-1.2)	410 (5.7)	1.0 (0.8-1.1)	0.9 (0.8-1.1)
No	5,935	551 (9.3)	reference	reference	352 (5.9)	reference	reference
LABA use in 1st trimester							
Yes	165	21 (12.7)	1.4 (0.9-2.2)	1.3 (0.9-2.1)	13 (7.9)	1.4 (0.8-2.4)	1.3 (0.8-2.4)
No	12,952	1,221 (9.4)	reference	reference	749 (5.8)	reference	reference
Receipt of social assistance during pregnancy or 1 year before							
Yes	10,410	999 (9.6)	reference	N/R	626 (6.0)	reference	reference
No	2,707	243 (9.0)	0.9 (0.8-1.1)	N/R	136 (5.0)	0.8 (0.7-1.0)	1.2 (1.0-1.5)
Pregnancy induced hypertension							
Yes	588	73 (12.4)	1.4 (1.1-1.8)	1.4 (1.1-1.7)	48 (8.2)	1.5 (1.1-2.0)	1.5 (1.1-2.0)
No	12,529	1,169 (9.3)	reference	reference	714 (5.7)	reference	reference
Diabetes mellitus							
Yes	304	42 (13.8)	1.5 (1.1-2.1)	1.5 (1.1-2.1)	25 (8.2)	1.5 (1.0-2.2)	1.4 (0.9-2.1)
No	12,813	1,200 (9.4)	reference	reference	737 (5.8)	reference	reference
Epilepsy							
Yes	139	20 (14.4)	1.6 (1.0-2.6)	N/R	16 (11.5)	2.1 (1.3-3.6)	2.1 (1.2-3.5)
No	12,978	1,222 (9.4)	reference	N/R	746 (5.8)	reference	reference
Multiple pregnancy							
Yes	190	43 (22.6)	2.9 (2.0-4.1)	2.9 (2.0-4.0)	29 (15.3)	3.0 (2.0-4.5)	3.0 (2.0-4.5)
No	12,927	1,199 (9.3)	reference	reference	733 (5.7)	reference	reference
Use of intranasal corticosteroids in 1st trimester							
Yes	519	54 (10.4)	1.1 (0.8-1.5)	N/R	39 (7.5)	1.3 (0.9-1.9)	1.4 (1.0-1.9)
No	12,598	1,188 (9.43)	reference	N/R	723 (5.7)	reference	reference
Emergency department visit or hospitalization for asthma in 1st trimester							
Yes	655	72 (11.0)	1.2 (0.9-1.5)	N/R	47 (7.2)	1.3 (0.9-1.7)	1.3 (0.9-1.7)
No	12,462	1,170 (9.4)	reference	N/R	715 (5.7)	reference	reference

SABA: short-acting inhaled β_2-agonist, LABA: long-acting inhaled β_2-agonist, N/R: not retained

Table IV. Adjusted Odds Ratios of Any and Major Malformations in Association with the Number of Doses of SABA Taken per Week and LABA Use during the First Trimester of Pregnancy

		Any Malformations*		**Major Malformations†**	
	No. of Pregnancies	***No. of Cases (%)***	***Adjusted OR (95% CI)***	***No. of Cases (%)***	***Adjusted OR (95% CI)***
SABAs doses per week in 1st trimester					
0	5935	551 (9.3)	reference	352 (5.9)	reference
>0-3	3420	342 (10.0)	1.1 (0.9-1.3)	209 (6.1)	1.0 (0.8-1.2)
>3-10	2102	208 (9.9)	1.1 (0.9-1.3)	115 (5.5)	0.8 (0.7-1.1)
>10	1660	141 (8.5)	0.9 (0.7-1.1)	86 (5.2)	0.7 (0.5-1.0)
LABA use in 1st trimester					
Yes	165	21 (12.7)	1.4 (0.9-2.2)	13 (7.9)	1.2 (0.7-2.2)
No	12952	1221 (9.4)	reference	749 (5.8)	reference

SABA: short-acting inhaled β_2-agonist, LABA: long-acting inhaled β_2-agonist, N/R: not retained

* OR adjusted for pregnancy induced hypertension, diabetes mellitus, and multiple pregnancy.

†OR adjusted for pregnancy induced hypertension, diabetes mellitus, epilepsy, use of teratogenic drugs in 1st trimester, multiple pregnancy, use of intranasal corticosteroids in 1st trimester, emergency department visit or hospitalization for asthma in 1st trimester, and asthma severity in the year before pregnancy.

Table V. Adjusted OR and 95% CI of Different Specific Malformations in Association with SABA and LABA Use during the First Trimester of Pregnancy

Congenital Malformation	SABA			LABA		
	Users n (%)	*Non users n (%)*	*OR (95 % CI)*	*Users n (%)*	*Non users n (%)*	*OR (95 % CI)*
Anencephalus*	1 (0.0)	1 (0.0)	0.8 (0.1-13.2)	0 (0.0)	2 (0.0)	N/A
Spina bifida†	7 (0.1)	3 (0.1)	1.4 (0.3-6.5)	0 (0.0)	10 (0.1)	N/A
Other malformations of the nervous system‡	60 (0.8)	34 (0.6)	1.4 (0.9-2.2)	3 (1.8)	91 (0.7)	2.3 (0.7-7.7)
Eye, ear, face and neck§	59 (0.8)	47 (0.8)	1.2 (0.8-1.8)	2 (1.2)	104 (0.8)	1.2 (0.3-5.0)
Cardiac malformations¶	132 (1.8)	130 (2.2)	0.8 (0.6-1.1)	7 (4.2)	255 (2.0)	2.4 (1.1-5.1)
Circulatory system**	60 (0.8)	43 (0.7)	1.0 (0.6-1.6)	4 (2.4)	99 (0.8)	2.7 (0.9-8.0)
Respiratory system††	32 (0.5)	24 (0.4)	1.0 (0.5-1.8)	1 (0.6)	55 (0.4)	0.7 (0.1-4.9)
Cleft palate and cleft lip*	20 (0.3)	11 (0.2)	1.5 (0.7-3.1)	0 (0.0)	31 (0.2)	N/A
Digestive system‡	75 (1.0)	59 (1.0)	1.1 (0.8-1.5)	0 (0.0)	134 (1.0)	N/A
Genital organs‡‡	58 (0.8)	43 (0.7)	1.3 (0.8-1.9)	5 (3.0)	96 (0.7)	6.8 (2.6-18.1)
Urinary system§§	36 (0.5)	26 (0.4)	1.2 (0.7-2.1)	1 (0.6)	61 (0.5)	0.9 (0.1-6.0)
Limbs¶¶	89 (1.2)	67 (1.1)	1.3 (0.9-1.8)	1 (0.6)	155 (1.2)	0.6 (0.1-4.5)
Other musculoskeletal malformations‡	149 (2.1)	114 (1.9)	1.1 (0.9-1.4)	3 (1.8)	260 (2.0)	0.9 (0.3-2.8)
Integument***	25 (0.4)	16 (0.3)	1.0 (0.5-1.8)	0 (0.0)	41 (0.3)	N/A
Chromosomal†††	11 (0.2)	9 (0.2)	0.6 (0.3-1.3)	1 (0.6)	19 (0.2)	1.8 (0.3-12.9)
Congenital Hydrocele‡‡‡	28 (0.4)	17 (0.3)	1.1 (0.6-2.1)	1 (0.6)	44 (0.3)	1.4 (0.2-10.4)
Other congenital malformations§§§	79 (1.1)	46 (0.8)	1.4 (1.0-2.1)	5 (3.0)	120 (0.9)	3.4 (1.4-8.5)

N/A: not applicable

Forward selection strategy used for adjusted OR models

* OR adjusted for all confounding variables (no variables retained in the final model)

† OR adjusted for asthma control in the year before pregnancy

‡ OR adjusted for all confounding variables

§ OR adjusted for daily dose of inhaled corticosteroids in 1st trimester

¶ OR adjusted for multiple pregnancy

** OR adjusted for daily dose of inhaled corticosteroids in 1st trimester

†† OR adjusted for daily dose of inhaled corticosteroids in 1st trimester

‡‡ OR adjusted for daily dose of inhaled corticosteroids in 1st trimester and multiple pregnancy

§§OR adjusted for daily dose of inhaled corticosteroids in 1st trimester and asthma severity in the year before pregnancy

¶¶ OR adjusted for asthma control in the year before pregnancy and asthma severity in the year before pregnancy

*** OR adjusted for asthma severity in the year before pregnancy

††† OR adjusted for daily dose of inhaled corticosteroids in 1st trimester and asthma severity in the year before pregnancy

‡‡‡ OR adjusted for asthma control in the year before pregnancy

§§§ OR adjusted for multiple pregnancy and use of oral corticosteroids in 1st trimester

Table E 1. Characteristics of Pregnancies According to the Number of Doses of SABA Taken per Week during the First Trimester

	Number of doses of SABA per week			
	0	**>0-3**	**>3-10**	**>10**
	No. of pregnancies (%)			
	5,935 (45.2)	3,420 (26.1)	2,102 (16.0)	1,660 (12.7)
Socio-demographic variables				
Maternal age (years)				
<18	320 (5.4)	275 (8.0)	176 (8.4)	84 (5.0)
18-34	5,261 (88.6)	2,948 (86.2)	1,787 (85.0)	1,447 (87.2)
≥35	354 (6.0)	197 (5.8)	139 (6.6)	129 (7.8)
Receipt of social assistance during pregnancy or one year before	4,537 (76.4)	2,820 (82.5)	1,718 (81.7)	1,335 (80.4)
Urban area of residence at delivery	4,816 (81.2)	2,781 (81.3)	1,703 (81.0)	1,312 (79.0)
Level of education at delivery (years)				
≤11	3,465 (58.4)	2,102 (61.5)	1,283 (61.0)	928 (55.9)
12-15	1,665 (28.0)	915 (26.7)	581 (27.6)	530 (31.9)
≥16	347 (5.9)	149 (4.4)	96 (4.6)	78 (4.7)
missing	458 (7.7)	254 (7.4)	142 (6.8)	124 (7.5)
Maternal & fetal conditions				
Chronic hypertension	131 (2.2)	82 (2.4)	53 (2.5)	48 (2.9)
Pregnancy induced hypertension	265 (4.5)	144 (4.2)	113 (5.4)	66 (4.0)
Diabetes mellitus	123 (2.1)	89 (2.6)	53 (2.5)	39 (2.4)
Gestational diabetes	441 (7.4)	272 (8.0)	169 (8.0)	133 (8.0)
Epilepsy	59 (1.0)	35 (1.0)	19 (0.9)	26 (1.6)
Use of teratogenic drugs in 1st trimester	57 (1.0)	49 (1.4)	26 (1.2)	37 (2.2)
Uterine complications during pregnancy	113 (1.9)	71 (2.1)	40 (1.9)	29 (1.8)
Fetal infections during pregnancy	33 (0.6)	25 (0.7)	19 (0.9)	12 (0.7)
Nullipara	1,616 (27.3)	1,163 (34.2)	766 (36.7)	617 (37.4)
Multiple pregnancy	90 (1.5)	40 (1.2)	29 (1.4)	31 (1.9)
Asthma related variables				
Daily dose of inhaled corticosteroids in 1st trimester* (μg)				
0	5,459 (92.0)	1,855 (54.2)	903 (43.0)	420 (25.3)
>0-500	446 (7.5)	1,517 (44.4)	1,097 (52.2)	875 (52.7)
>500	30 (0.5)	48 (1.4)	102 (4.9)	365 (22.0)
Use of other controller medications in 1st trimester†	36 (0.6)	79 (2.3)	79 (3.8)	202 (12.2)
Use of intranasal corticosteroids in 1st trimester	144 (2.4)	128 (3.7)	117 (5.6)	130 (7.8)

Use of oral corticosteroids in 1st trimester	44 (0.7)	79 (2.3)	108 (5.1)	221 (13.3)
Emergency department visit or hospitalization for asthma in 1st trimester	76 (1.3)	152 (4.4)	189 (9.0)	238 (14.3)
Exacerbations for asthma in 1st trimester‡	98 (1.7)	178 (5.2)	235 (11.2)	304 (18.3)
Asthma severity in the year before pregnancy				
Mild	5,760 (97.1)	3,142 (91.9)	1,537 (73.1)	332 (20.0)
Moderate	163 (2.8)	251 (7.3)	426 (20.3)	770 (46.4)
Severe	12 (0.2)	27 (0.8)	139 (6.6)	558 (33.6)
Asthma control in the year before pregnancy				
Controlled	4,900 (82.6)	2,184 (63.9)	785 (37.4)	124 (7.5)
Un-controlled	1,035 (17.4)	1,236 (36.1)	1,317 (62.7)	1,536 (92.5)

SABA: short-acting inhaled β_2-agonist, LABA: long-acting inhaled β_2-agonist.

*ICSs in beclomethasone dipropionate-chloroflurocarbon equivalent.

†Leukotriene receptor-antagonist (zafirlukast and montelukast), Ipratropium, Theophylline, or Anti-allergics (nedocromil and cromoglycate).

‡A filled prescription for oral corticosteroids, an emergency department visit for asthma, or a hospitalization for asthma.

CHAPTER 6: DISCUSSION

Discussion

6.1 General discussion

Asthma is recognized as one of the most common chronic pulmonary diseases and a serious medical complication in pregnancy. [1-3] Most studies suggest that more severe asthma during pregnancy is associated with increased fetal and maternal risks, while better-controlled asthma is associated with decreased risks. [1;4] Treatment and control of asthma could be achieved by many drugs, but none of them has been classified as completely safe for use during pregnancy. SABA have been widely used for years to control asthma symptoms during pregnancy, which is not the case for LABA. More data on the safety of SABA, especially Salbutamol, are available due to greater pregnancy experience.[3]

Among the studies that examined the association between SABA and LABA exposure during pregnancy and congenital malformations, two studies found a positive association between SABA use and congenital malformations.[26;36], while LABA use wasn't found associated with congenital malformations in any study. Moreover, concerns about the methodologies and conduct of the previous studies have been raised. Our study tried to investigate the association between maternal exposure to SABA and LABA during the first trimester of pregnancy and the risk of major, all, and specific congenital malformations, while avoiding the weaknesses of other studies in the literature.

In our study, we found no increased risk of congenital malformations with SABA exposure during the 1st trimester even among women taking >10 doses per week on average during the first trimester. We also found no significant increased risk of any and major congenital malformations with the use of LABA in the 1st trimester. On the other hand, significant increased risks of cardiac malformations (aOR, 2.4; 95% CI, 1.1-5.1), genital organ

malformations (aOR, 6.8; 95% CI, 2.6-18.1), and other congenital malformations (aOR, 3.4; 95% CI, 1.4-8.5) were observed with LABA use in the 1st trimester.

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

Looking into the literature, SABA use during pregnancy has been found to be associated with congenital malformations in only two studies,[26;36] from which only one had a control group of unexposed asthmatic women.[36] However, SABA use hasn't been found to be associated with congenital malformations in other studies.[14;27;28;30-32;35] All previous studies examining SABA suffered from some methodological limitations which could alter their results. Our results came in concordance with studies that investigated SABA use during pregnancy and found no association with congenital malformations. To our knowledge, none of the previous studies examined SABA thoroughly in the form of SABA doses per week analysis. So, analysing SABA use in doses per week gave us more certainty about their safety in pregnancy at higher doses. The high statistical power of the SABA analyses increases our confidence about the safety of these medications.

LABA use during pregnancy is considered safe and recommended in most asthma management guidelines.[3;163] Previous studies suggested their safe use during pregnancy, and no association has been reported between their use in the management of asthma during pregnancy and an increased risk of congenital malformations.[26;27;33;35;36;39] These studies provide some evidence on the safety of LABA; however a final conclusion on their safety can't be drawn due to limitations in these studies.

Although we didn't find a significant increased risk of major or any malformations with LABA use in the 1st trimester, we found a significant association between LABA use in the 1st trimester and a higher risk of certain malformations; namely cardiac, genital organs, and other and unspecified congenital malformations. We suggested three explanations that could have contributed to the observed associations; the possibility of residual confounding by severity, a true causal association between LABA use during the 1st trimester and an increased risk of certain congenital malformations by unknown mechanisms, or an increased risk of congenital malformations resulting from the potential effect of LABA on the steroid function.

6.3 Strengths of the study

6.3.1 Databases

One of the strengths in our study is the use of prospectively gathered data from administrative databases. Using the interlinked three large Quebec's databases to identify the exposures and outcomes provided many advantages over other methods of data collection such as self-reported questionnaire or a personal interview. [164-166]

First, data on filled prescriptions and medical services were prospectively collected, avoiding a recall bias. *Second*, using administrative computerized databases helped to find the history of the medication use over long periods (one year before and during pregnancy), and for huge number of subjects. *Third*, it has been reported that patients mostly have difficulties in reporting the details of their medication use, such as time, doses, and quantity.[167-170]

Fourth, using administrative databases, we had the ability to study a large number of pregnant women in a reasonable budget and time-frame. *Fifth*, data recorded in the RAMQ

Medication Prescription database and the medical diagnosis for asthma recorded in the RAMQ Medical Services database have been formally evaluated and found to be valid and precise.[141;142] The RAMQ and MED-ECHO databases have often been used for research on asthma and pregnancy with many articles published in renowned medical journals.[11;135;138;143;144] *Sixth*, the use of three rich databases allowed for adequate statistical power for the SABA analysis (80% power to detect an aOR of 1.2 for any and major malformations) and for adjustment for most important potential confounders, while having a control group of asthmatic women not exposed to SABA or LABA during the 1st trimester.

Pregnancy variables recorded in the RAMQ, MED-ECHO and ISQ databases have been formally evaluated and found to be highly valid.[171] From the variables that have been validated and were used to perform our analyses are maternal age, length of gestation, date of delivery, and date of last menstruation. The validity of the variables was assessed by calculating Pearson correlation coefficient between the values obtained from the databases and patents' medical charts, and the correlations were found to be high for all variables ranging from 0.920 to 0.999.

6.3.2 Study methodology

An important principle in studying medication teratogenic safety profile is that an exposure to the medication (teratogen) is said to be following a toxicologic dose-response curve, where there is a threshold below which no effect will be observed. [88;89;104] Also as the dose of the teratogen increase, both severity and frequency of the adverse fetal effect increase.[89]The SABA doses-per-week analysis that we performed helped to explore if there was a dose-response relationship between SABA and the risk of congenital malformations. To our knowledge, this is the first study to investigate SABA in such manner. An analysis of medication's toxicological effects (e.g. teratogenicity) in such way

is the ideal choice, in order to reveal if there is a threshold below which no effects are observed.[88;89]

Our large cohort of pregnancies (13,117 asthmatic pregnant women) allowed us to investigate risk of congenital malformations with SABA and LABA use in three aspects; 1) major malformations; 2) any malformations; and 3) specific malformations. The assessment of specific malformations risk, which is uncommon in previous studies, could help investigators in the future to focus on the reported results in this study and try to uncover the reasons behind the association.

6.4 Limits of the study

6.4.1 Error and bias in the study

Two types of error could alter study results; random error and systematic error (bias).[164-166]

Random error

Random error (chance effect) is defined as the variability in the data and it represent the precision of the estimate. Random error usually diminishes as sample size gets larger. A small P-value and a narrow confidence interval are reassuring signs against chance effect.[164-166] As mentioned earlier, we had a large cohort of pregnancies allowing for adequate statistical power for the SABA analysis (80% power to detect an aOR of 1.2 for any and major malformations). However, we only had a statistical power of 30% and 20% to detect a 30% increased risk of any malformations and major malformations, respectively, among LABA users. This may imply that there might be a real association between LABA and any and major congenital malformations but we didn't have enough power to detect it. We also had small sample sizes with some specific malformations, but with other groups we had larger sample sizes and higher ORs allowing

to report highly significant results (cardiac malformations aOR, 2.4; 95% CI, 1.1-5.1, genital organ malformations aOR, 6.8; 95% CI, 2.6-18.1, and other congenital malformations aOR, 3.4; 95% CI, 1.4-8.5 with LABA use).

Systematic error

Systematic error (systematic bias) is a result of an error in the method the study was conducted. It could result due to errors in the way the subjects were selected, errors in the measurement of variables, or any confounding factor that is not completely controlled for. Systematic error mainly influences the internal validity of the study. Systematic bias can be classified into selection bias, information bias, and confounding bias .[164-166] Selection bias (selection effect) refers to any error that arises in the process of identifying the study populations, and in a cohort it is usually related to losses to follow-up.[164-166] In our study we don't believe that we faced a situation in which this kind of bias could have altered our results.

Information bias

Information bias occurs as a result of systematic differences in the way data on exposure, outcome, or confounders are obtained from the various study groups.[164-166] Misclassification is the reason behind information bias, which can be differential or non-differential misclassification.[164-166]

In retrospective cohort studies, in which information is obtained from past records, differential misclassification could be present if the quality and accuracy of information obtained is different among exposed and non-exposed persons.[166] In our study, the assessment of the outcome (cases of congenital malformations) was identified using diagnoses codes recorded in the RAMQ and MED-ECHO databases (administrative

databases) and were not specifically validated for this study, but the assessment of the outcome was made independently of the exposure status of the mother. Consequently, if there was any inaccuracy in outcome measurement, it will not be related to exposure status and only non-differential misclassification may have resulted. Non-differential misclassification generally dilutes the effect (towards null effect) and produces underestimation of the OR, in other words the real associations could be larger than those that we observed in our study.[164] Regarding the non-significant results in our study, non-differential misclassification might have also played a role (together with the small sample size issue) to prevent unveiling an increased risk of malformations in some groups.

Regarding the exposure assessment, the use of medications was measured by medication claims, which might not reflect their actual intake; therefore a non-differential misclassification of exposure might have been introduced, and that might have led to an underestimation of the associations. However, an article showed that only 6% of drugs dispensed for pregnant women were not used.[172]

Another limitation in our study concerning the use of the RAMQ database is that it doesn't record medications dispensed in hospitals, which may include oral corticosteroids, and this could have underestimated their use during pregnancy. Oral corticosteroids, as mentioned before, have been associated with an increased risk of congenital malformations.[145-147] Since women using high doses of SABA and women using LABA usually suffer from moderate or severe asthma, and were more likely to be hospitalized and have OCS, a differential misclassification might have been introduced. However, we do not believe this could have strongly impacted our findings on the SABA and LABA safety as the percentages of hospitalized patients were small. In both cases, in the case of differential misclassification, an overestimation of the effect of SABA or LABA on congenital malformations might have occurred.

Confounding bias

Confounding is mixing of the effect of the exposure under study on the disease (outcome) with that of a third factor that is associated with the exposure ,an independent risk factor for the disease, and not in the causal pathway between exposure and disease (even among individuals non-exposed to the exposure factor under study). The consequence of confounding is that the estimated association is not the same as the true effect and an extraneous risk factor could be the alternative reason behind the association (or part of the association) observed between the exposure and the outcome.[164-166] In order to reduce the impact of confounding in our study, we used multivariate regression models to adjust the ORs 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 of congenital malformations in our models, however, due to our incapacity to adjust for a few known risk factors, like maternal obesity, over the counter medications (OTC), alcohol consumption, family history of congenital malformations, and some other environmental teratogens,[148] there is a possibility of residual confounding in our models.

Another confounding issue in the study is a possible residual confounding by severity present in the association between LABA use in the first trimester and the risk of congenital malformations. As mentioned earlier, LABA users are likely to have more severe and uncontrolled asthma since the percentages of moderate and severe asthma in the year before pregnancy among LABA users were 28.5% and 42.4% respectively against 12.1% and 5.1% among non-users, and the percentage of uncontrolled asthma among LABA users was 78.8% against 38.6% among non-users. Also, ED visits or hospitalizations for asthma and exacerbations for asthma during the first trimester were higher among LABA users against LABA non-users (13.3% and 18.8% against 4.9% and

6.1%), and exacerbations have been shown to significantly increase the risk of malformations.[11] However, we tried to reduce residual confounding through our adjustment for several markers of asthma severity and control in the analyses, as the use of OCS, the daily dose of ICS, use of other asthma controller medications and intranasal corticosteroids, ED visit or hospitalization for asthma, and exacerbations for asthma in the 1st trimester, as well as asthma severity and control in the year before pregnancy.[173;174] It is also worth noting that despite the fact that women using high doses of SABA per week (>10) appeared, like LABA users, to have more severe and uncontrolled asthma (based upon our findings, percentage of severe asthmatic patients who used SABA >10 doses per week was 33.6% against 0.2% among non-users and percentage of uncontrolled asthma was 92.5% against 17.5% among non-users) , women using high doses of SABA per week (>10) were less likely to have a baby with a major malformation (aOR, 0.70; 95% CI, 0.50-1.00) than women not using SABA. This result tends to reveal that confounding by severity, if present, is not likely to be strong enough to have meaningfully overestimate the association between LABA use and congenital malformations.

Considering the nature of data used and the different types of bias our study suffered from, a sensitivity analysis approach might be appealing which is multiple-bias modelling. Multiple-bias models constitutes the modification of the Monte-Carlo sensitivity analysis (MCSA) procedure in a way that improves the Bayesian interpretability of MCSA methods.[175] Multiple-bias models depend on identifying priors for different bias distribution parameters and computing the odds ratios adjusted for these biases through sequential procedure of expressions.[175;176] The problem of applying multiple-bias modelling in our study is that the priors on bias parameters could be inaccurate, and biases might actually operate in a much more complicated way (correlation between biases).Using multiple-bias modelling, it has been shown that the less information about biases and the higher the uncertainty about applying results from the literature or

assumptions on bias parameters, the more uncertainty emerges in the resulting model-based estimates.[175;176]

6.4.2 Other limitations

All studies using repeated statistical analysis simultaneously in one population to assess several drug exposures are subject to multiple comparisons problems and inference error, resulting in statistically significant P-values by chance alone.[177] As usual in studies of drug safety, we used P-value <0.05 as the level for statistical significance, even if several comparisons were performed. We didn't adjust for multiple comparisons in our study since the largest numbers of comparisons were made for the analysis of specific congenital malformations, which were considered as secondary outcomes.

6.5 External validity

External validity refers generally to which extent a study's findings could be applied to other non-study populations (generalizability).[164-166;178] Our cohort under represents women with a higher socioeconomic status. This is because our database included women covered by the public drug insurance of the RAMQ which includes women receiving social assistance and middle class working women. However, this under representation might limit the study generalizability only if socio-economic status is believed to be an effect modifier for the association between the exposure in our study and congenital malformations, but this would be unlikely since the association between $beta_2$-agonists and congenital malformations is believed to be physiological in nature. Moreover, one of the reassuring points on the appropriateness of our study findings regarding the external validity is that the prevalence of major and any congenital malformations among our cohort was similar to the average population figures.[179]

6.6 Clinical implications of the results

The findings in our study can be directly transferred to physicians and specialists for management of asthma during pregnancy. Our results could be very useful in adding to the physicians' trust in SABA as a quick relief medication and solves some benefit-risk fears. An additional benefit from our results is the assurance in the safe use of SABA during the first trimester of pregnancy even at high doses (>10 doses per week).

While our results suggests that the use of LABA during pregnancy might carry a significant risk on the fetal health, we still can't define a clear-cut for that issue until further research on these medications are made on larger scale and avoiding the limitations we encountered in our study. Therefore, what we can propose is that physicians can optimize their strategy of management of asthma during pregnancy and the use of LABA through continuous reassessment of the patients' classification of asthma, trying to minimize the medication used to achieve control of asthma through using the step down approach in the guidelines in order to avoid unnecessary use of these medications until other findings.

6.7 Further research

In the field of asthma medication use during pregnancy, there are still many questions that need to be answered in proper means. We still have numerous questions regarding the safety of many asthma medications during pregnancy, and what should be the best regimen to control asthma during pregnancy, while reducing the maternal and fetal risks due to asthma disease and medications themselves.

Regarding $beta_2$-agonists use during pregnancy, none of them is considered absolutely safe during pregnancy, and they will remain an open field for further research until we obtain a complete safety profile for each drug in the group.

The findings in our study could have an impact for future research. The associations reported between LABA use and specific congenital malformations could encourage researchers from pharmaceutical and pharmacology fields to further investigate LABA in animal models and on the molecular basis to disentangle any relationship with congenital malformations, taking into account the suggested synergistic relationship between LABA and corticosteroids, and the previously reported risks of corticosteroids on fetal development.

From our part, we could further study the risk associated with LABA use using a larger cohort of pregnancies from asthmatic women. A larger cohort could help us obtain higher statistical power and adjust for multiple comparisons. Another interesting question that could be the objective of further research is the association between maternal exposure to SABA and LABA and other maternal and fetal outcomes, such as low birth weight, prematurity and small for gestational age baby, and how this could add to the safety profile of these medications. There is considerable lack of knowledge on the safety of SABA and LABA during pregnancy, and any future work exploring their use during pregnancy would be of great value.

Conclusion

Consistent with the literature, our study adds evidence to the safety of SABA use during pregnancy, and that comes in concordance with asthma management guidelines. Also we didn't find any dose-response relationship between SABA and congenital malformations. These results could be very useful in adding to the physicians' trust in SABA and solves some benefit-risk fears. On the other hand, LABA use during the first trimester was associated with cardiac, genital organs, and other congenital malformations.

The observed associations found with LABA exposure can't be attributed entirely to the drug effect since there is a possibility of residual confounding by asthma severity. Since there is a possibility of residual confounding by asthma severity and further research is required to understand the aetiology behind these relationships, due to the proven risks of severe and uncontrolled asthma on the mother and her fetus, risk-benefit considerations should still favour LABA use in asthma management during pregnancy until further results are reported.

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