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Asthma Control in Pregnancy and Selected Drug Therapy in Relation to Perinatal Outcomes.

A Dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Public Health (Epidemiology)

by

Ludmila N. Bakhireva

Committee in charge:

University of California, San Diego

Professor Hillary Klonoff-Cohen, Chair
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Professor Kenneth Lyons Jones
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San Diego State University

Professor Louise Gresham
Professor Donald Slymen

2007

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The Dissertation of Ludmila N. Bakhireva is approved, and it is acceptable in quality and form for publication on microfilm:

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University of California, San Diego

San Diego State University

2007

DEDICATION

To my parents, Nickolay and Natalia Kosykh, whose example, values, and support shaped up my interest in science and helped me to complete graduate studies.

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I am grateful to many people whose continuous support has helped me to achieve this milestone. Throughout my graduate training, I was very lucky to have the best mentors and a strong family support.

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Bakhireva LN, Jones KL, Schatz M, Klonoff-Cohen H, Johnson D, Slymen D, Chambers CD, The Organization Of Teratology Information Services Research Group. Safety of Leukotriene Receptor Antagonists in Pregnancy. *J Allergy Clin Immunol*. 2007:199(3):618-25.

The dissertation author was the primary researcher and author, while the co-authors listed in these publications directed and supervised research (Chambers, Jones, Klonoff-Cohen, Schatz, Slymen, OTIS Collaborative Research Group) or acted as junior collaborators (Johnson). Chapter 5 of this dissertation is being prepared for publication.

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ABSTRACT OF THE DISSERTATION

Asthma Control in Pregnancy and Selected Drug Therapy

in Relation to Perinatal Outcomes

by

Ludmila N. Bakhireva

Doctor of Philosophy in Public Health (Epidemiology)

University of California, San Diego, 2007
San Diego State University, 2007

Professor Hillary Klonoff-Cohen, Chair
Professor Christina Chambers, Co-Chair

Background: Asthma is a serious chronic condition which affects up to 8% of pregnant women in the United States. While severe or poorly controlled asthma might significantly complicate pregnancy and harm both mother and fetus, adequate asthma therapy in pregnancy is challenging to accomplish due to safety concerns for the fetus.

Objective: This dissertation aimed to evaluate: 1) the effect of maternal asthma control on adverse perinatal outcomes; 2) the effect of fetal sex on maternal asthma control in pregnancy; and 3) the safety of asthma controller mediations, leukotriene receptor antagonists (LTRA), in pregnancy.

Methods: Subjects were participants of the Organization of Teratology Information Specialists Asthma Medications in Pregnancy Study. Information about maternal medication use, asthma control, demographic and lifestyle characteristics, pregnancy

complications, and perinatal outcomes was prospectively collected from 1,165 pregnant women.

Results: The incidence of preterm delivery was significantly higher among women with inadequate asthma symptom control (OR=1.93; 95% CI: 1.10; 3.40) and women requiring hospitalization(s) for asthma exacerbations during pregnancy (OR=2.29; 95% CI: 1.06; 4.94) independent of other risk factors.

Asthmatic pregnant women carrying a girl had more hospitalizations for asthma during pregnancy and a tendency of having more unscheduled asthma clinic visits compared with women carrying a boy. Fetal sex did not influence the association between maternal asthma control and fetal growth.

The birth prevalence of major structural anomalies in children born to LTRA users was significantly higher compared with non-asthmatic controls (p=0.007), but not different from the asthmatic comparison group (p=0.524). Furthermore, the birth defects in the LTRA group did not represent a consistent pattern. Use of LTRAs was not associated with large risks of other adverse perinatal outcomes.

Conclusions: This study demonstrates a substantial risk posed by poorly controlled maternal asthma on preterm delivery. Pregnant asthmatic women carrying a girl might be more susceptible to asthma exacerbations, particularly early in pregnancy; however, all women with asthma should be carefully monitored for pregnancy-associated changes in asthma symptoms. LTRAs do not appear to be a major human teratogen; however, results should be interpreted with caution due to the relatively small number of women taking LTRAs.

CHAPTER 1:

BACKGROUND AND SIGNIFICANCE

ASTHMA EPIDEMIOLOGY

Asthma is a serious chronic condition which is clinically defined as the presence of variable airflow obstruction that reverses either spontaneously or with treatment [1]. According to the National Health Interview Survey conducted in 2003 by the Center of Disease Control (CDC) National Center for Health Statistics (NCHS), almost 30 million people in the United States have been diagnosed with asthma sometime in their life and 19.8 million people have current asthma. Self-reported U.S. average prevalence of current asthma in 2003 was 7.7% among adults and 8.8% among children based on estimates obtained through the CDC Behavioral Risk Factor Surveillance System (BRFSS). Even though some decrease in asthma hospitalization and death rates were observed in the late 1990s, rates of outpatient and emergency department visits for asthma have been increasing since 1995 [1].

Asthma is one of the key focuses of the Healthy People 2010 program [1]. The following eight Healthy People 2010 objectives involving asthma have been established: 1) reduce asthma deaths; 2) reduce hospitalizations for asthma; 3) reduce hospital emergency department visits for asthma, 4) reduce activity limitations among persons with asthma; 5) reduce the number of school or work days missed by persons with asthma because of their asthma; 6) increase the proportion of persons with asthma who receive formal patient education; 7) increase the proportion of persons with asthma who receive appropriate asthma care according to the National Heart Lung and Blood Institute's National Asthma Education and Prevention Program (NAEPP); and 8) establish a surveillance system for tracking asthma deaths, illnesses,

disabilities, impact of occupational and environmental factors on asthma, access to medical care, and asthma management in ≥ 25 states.

ASTHMA SEVERITY CLASSIFICATION AND STEPWISE MANAGEMENT APPROACH

The Global Initiative for Asthma (GINA) established a classification of asthma severity and guidelines for a stepwise approach in asthma management [2]. GINA classifies asthma as intermittent, mild persistent, moderate persistent, or severe persistent based on frequency of daytime and night-time symptoms, the effect of exacerbations on daily activities, and lung function (Table 1). According to GINA, the presence of one of the features of severity is sufficient to place a patient in a corresponding severity category. Patients in all severity groups may have severe asthma attacks and exacerbations.

Table 1. GINA Classification of Asthma Severity

Severity	Symptoms/Day	Symptoms/Night	PEF or FEV1* PEF variability
STEP1 Intermittent	< 1 time a week Asymptomatic and normal PEF between attacks	≤ 2 times a month	≥ 80% < 20%
STEP2 Mild Persistent	> 1 time a week but < 1 time a day Attacks may affect activity	> 2 times a month	≥ 80% 20-30%
STEP3 Moderate Persistent	Daily Attacks affect activity	> 1 time a week	60-80% > 30%
STEP4 Severe Persistent	Continuous Limited physical activity	Frequent	≤ 60% > 30%

*PEF, peak expiratory flow; FEV1, forced expiratory volume in 1 second.
Source: Global Initiative for Asthma, *Pocket guide for asthma management and prevention. A pocket guide for physicians and nurses (updated 2004).* in *NIH Publication No. 02-3659*. 2004.

GINA guidelines for stepwise management of asthma are based on the level of asthma severity assessed prior to initiation of therapy (Table 2).

Table 2. GINA Recommended Medications by Level of Severity.

Level of Severity	Daily Controller Medications	Other Treatment Options
STEP1 Intermittent	• None necessary	
STEP2 Mild Persistent	• Low-dosed inhaled glucocorticosteroid	• Sustained-release theophylline *or* • Cromone • Leukotriene modifier
STEP3 Moderate Persistent	• Low-to medium-dose glucocorticosteroid *plus* long-acting inhaled β_2-agonists	• Medium-dose inhaled glucocorticosteroid *plus* stastained-release theophylline, *o*r • Medium-dose inhaled glucocorticosteroid *plus* long-acting oral β_2-agonist, *o*r • Medium-dose inhaled glucocorticosteroid *plus* leukotriene modifier
STEP4 Severe Persistent	• High-dose inhaled glucocorticosteroid plus long-acting inhaled β_2-agonist, *plus* • one or more of the following if needed: • Sustained-release theophylline • Leukotriene modifier • Long-acting oral β_2-agonist • Oral glucocorticosteroid	

Source: Global Initiative for Asthma, *Pocket guide for asthma management and prevention. A pocket guide for physicians and nurses (updated 2004).* in *NIH Publication No. 02-3659*. 2004.

Intermittent asthma does not require a daily use of controller medications and can be managed only with reliever medications, such as short-acting β_2-agonists (e.g., salbutamol, albuterol, pirbuterol, terbutaline) or anticholinergics (e.g., ipratropium

bromide). The effect of β_2-agonists is attributed to their β_2-adrenergic stimulation, which results in bronchial dilation and vasodilation, enhancement of mucociliary clearance, and inhibition of cholinergic neurotransmission.

Inhaled glucocorticosteroids are used for long-term treatment of mild persistent and moderate persistent asthma due to their strong anti-inflammatory effects. Glucocorticosteroids have an inhibitory effect on many cells involved in airway inflammation resulting in reduced airway hyperresponsiveness in asthmatic patients. Long-acting β_2-agonists (e.g., formoterol, salmeterol) provide prolonged bronchodilation effect and are used as controller medications. The combination of long-acting β_2-agonists with inhaled corticosteroids has been shown to be more effective in asthma management than increasing the dose of inhaled corticosteroids.

Mast cell stabilizers (e.g., cromolyn sodium, nedocromil sodium) are inhaled anti-inflammatory agents used in preventive therapy of mild persistent asthma. They inhibit inflammatory cells and the release of mediators associated with asthma. Sustained-release theophylline directly relaxes bronchial smooth muscles. Despite strong bronchodilation effects, use of theophylline has been declining due side effects (especially on the central nervous system and gastro-intestinal tract) and need for serum monitoring.

Management of severe persistent asthma involves a combination therapy. The most potent controller medications for management of severe persistent asthma are oral corticosteroids due to their strong anti-inflammatory effect. However, prolonged use of oral corticosteroids might lead to osteoporosis, hypertension, diabetes, cataracts, adrenal suppression, obesity, skin thinning or muscle weakness [2]. Thus,

oral corticosteroids are used as a last resort for treatment of severe persistent asthma or acute exacerbations and often given in short taper courses.

ASTHMA IN PREGNANCY

Asthma is estimated to affect 3.7% to 8.4% of pregnant women in the United States [3] making it one of the most common complications of pregnancy. The number of childbearing-aged women (i.e., 18 to 44 years of age) in the United States who ever received a diagnosis of asthma from a health care professional ranges between 6.8-7.4 million based on the 2001-2003 NHIS and the 2000-2003 BRFSS estimates [4]. Among pregnant women of childbearing age, 233,607 to 300,151 women have received a diagnosis of asthma during these years. The prevalence of current asthma among pregnant women 18 to 44 years of age is estimated to be 8.4%-8.8%, and the prevalence among women 18 to 24 years of age is as high as 12.2%-12.3% according to the 2000-2003 BRFSS and 2001-2003 NHIS estimates. The prevalence of ever having a diagnosis of asthma among pregnant women more than doubled between 1988 (6.6%) and 2002 (14.7%). More than a third (38.5%) of pregnant women with asthma experienced at least one asthma attack in the previous year indicating significant asthma-related morbidity. Pregnant women who are young, unmarried, have a lower family income, of Puerto Rican or non-Hispanic black ethnicity, or live in the northeastern United States are more likely to experience asthma attacks or asthma-related emergency visits [4].

Severe and/or poorly controlled asthma have been associated with numerous adverse maternal and fetal outcomes (reviewed Tan and Thomson [5]), including preeclampsia/pregnancy-induced hypertension, uterine hemorrhage, premature birth,

congenital anomalies, fetal growth restriction, and low birth weight [6-9]. Thus adequate treatment of asthma during pregnancy is of great importance but may be challenging to accomplish.

ASTHMA MEDICATIONS AND PREGNANCY

While uncontrolled asthma jeopardizes the health of the mother and baby, some asthma medications might also pose a risk. Oral corticosteroids, used for treatment of severe asthma and acute asthma exacerbations, have been associated with an increased risk of preeclampsia [10], preterm delivery [10-12], reduced fetal growth [11, 13, 14], and major congenital anomalies [14, 15]. Limited or no adequate studies evaluated the safety of relatively new asthma medications, e.g., leukotriene receptor antagonists and long-acting β_2-agonists, in human pregnancy. The U.S. Food and Drug Administration (FDA) requires drug labeling into one of five letter categories (i.e., A, B, C, D, and X) based on available data on safety of those medications in pregnancy. A summary of FDA letter categories and sources of data used in each category are summarized in Table 3 [16]. All asthma medications fall into pregnancy categories B or C, providing limited aid to clinicians in choosing a particular treatment regimen and little information about specific adverse perinatal outcomes.

Table 3. FDA Categories for Drug Use in Pregnancy.

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women. **or** Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. **or** No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

Concerns regarding the safety of gestational drug therapy and potential harmful effect of asthma medications on the fetus often result in inadequate treatment of asthma in pregnant women presumably contributing to prolonged exacerbations of asthma in pregnant compared with non-pregnant women [17], while risks associated with severe asthma for adverse perinatal outcomes might be underestimated. It has been reported that only half of women who experience daily asthma symptoms during pregnancy take any controller medications and only half of women who took controller medications before pregnancy continue using them while pregnant [4]. A recent study demonstrated that women on Medicaid substantially decrease or discontinue use of asthma medications upon recognition of pregnancy despite national

guidelines recommending continuous use [18]. These women decreased use of inhaled corticosteroids by 23%, systemic corticosteroids by 54%, and short-acting β_2-agonists by 13% during the first trimester. These findings indicate that existing reports do not provide compelling enough evidence for health care providers and pregnant women to feel confident that optimal treatment of asthma in pregnancy benefits the mother and the baby.

To assist health care providers with evaluation of the risks and benefits associated with asthma medications in pregnancy and to achieve optimal management of gestational asthma, the NAEPP expert panel published a 2004 update of their guidelines for pharmacologic management of asthma during pregnancy [19]. These guidelines utilize GINA stepwise approach for managing asthma in pregnant women and are based on systematic review of the evidence from medication effectiveness and safety.

As much as asthma affects pregnancy and perinatal outcomes, physiological changes during the pregnancy may influence asthma severity and control. However, there is a great variability in reported change in asthma course during the pregnancy with some women experiencing improvement, some increased symptoms, and some no change at all. More consistent are findings which suggest that women who had severe asthma prior to becoming pregnant are more likely to have their asthma worsen during the pregnancy [20]. While multiple physiological factors that might ameliorate or exacerbate the course of asthma during pregnancy have been proposed [20], biological mechanisms which alter asthma severity and control during pregnancy remain unknown.

CLASSIFICATIONS OF ASTHMA SEVERITY AND CONTROL

Asthma severity and control are two closely-related but conceptually distinct terms, which are often confused in the literature. Asthma severity is the inherent intensity of the disease process, while asthma control is the degree to which the manifestations of the disease process are mitigated. Frequently used classifications proposed by GINA [2] (Table 1) and the National Asthma Education and Prevention Program (NAEP) [21] deal with asthma severity prior to initiation of treatment and might be of limited use for assessment of clinical measures in pregnant patients already receiving medications. Some studies classify subjects into one of four GINA severity categories based on subjects' current medication regiment [12], what might introduce some misclassification bias if patients are not treated according to the guidelines or are not compliant. Other studies categorize subjects into steroid-dependent versus non-steroid dependent groups as a measure of asthma severity, what might make difficult to disentangle the effect of severe asthma from the effect of corticosteroids on perinatal outcomes [22].

Asthma control refers to current asthma status and is a function of underlying asthma severity, medical management, and patient adherence [23]. In pregnant asthmatic women, inadequate asthma control rather than underlying severity might be most related to hypoxia and adverse perinatal outcomes. In fact, one study demonstrated that women who had daily symptoms with frequent exacerbations and night symptoms more than seven nights per month were at an increased risk of preeclampsia, while a history of physician-diagnosed asthma or overall asthma severity were not associated with preeclampsia [24].

While assessment of pulmonary function is the most objective method of asthma control in relation to perinatal outcomes [25], it is often unavailable non-hospital-based studies. Thus several questionnaires have been recently developed to assess asthma control and the adequacy of disease management. Frequency of symptoms and symptom interference with sleep and activity are the major components of several published validated asthma control assessment tools [23, 26, 27]. Use of "rescue" medications (i.e., short-acting bronchodilators) is also a common component of these questionnaires [23, 26, 27].

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Bakhireva LN, Schatz M, Chambers CD. Effect of Maternal Asthma and Gestational Asthma Therapy on Fetal Growth. Review Article. *Journal of Asthma*. 2007; 44(2): 71-76.

Bakhireva LN, Jones KL, Schatz M, Klonoff-Cohen H, Johnson D, Slymen D, Chambers CD, The Organization Of Teratology Information Services Research Group. Safety of Leukotriene Receptor Antagonists in Pregnancy. *J Allergy Clin Immunol*. 2007:199(3):618-25.

The dissertation author was the primary researcher and author, while the co-authors listed in these publications directed and supervised research or acted as junior collaborators.

CHAPTER 2:

SPECIFIC AIMS OF THE DISSERTATION

SPECIFIC AIM /STUDY I

To determine the effect of maternal asthma control on adverse perinatal maternal and fetal outcomes.

The following hypotheses were tested (not stated in the null for ease of interpretation):

1. Pregnant women who report poor or fair control of their asthma in pregnancy, as measured by symptoms, will have a higher incidence of selected adverse maternal outcomes (i.e., poor weight gain during pregnancy, higher rates of preeclampsia, gestational diabetes) compared with women who report adequate control of their asthma during pregnancy.
2. Pregnant women who report poor or fair control of their asthma in pregnancy, as measured by symptoms, will have a higher incidence of selected adverse fetal outcomes (i.e., spontaneous abortion or stillbirth, preterm birth, major structural anomalies, intrauterine growth restriction, reduced mean birth weight, and lower Apgar scores) compared with women who have a adequate control of their asthma during pregnancy.
3. Pregnant women who experience one or more severe asthma exacerbations in pregnancy (hospitalization for asthma, unscheduled physician visit for asthma, non-regular use of systemic corticosteroids) will have a higher incidence of adverse perinatal outcomes listed above.
4. Possible interaction of fetal sex and maternal asthma control will result in reduced fetal growth (i.e., mean birth weight, small for gestational age) among male neonates but not in female neonates.

SPECIFIC AIM / STUDY II

To determine the effect of fetal sex on maternal asthma control during the pregnancy.

The following hypotheses were tested (not stated in the null for ease of interpretation):

1. Pregnant women carrying a female fetus will have more poorly controlled asthma (assessed by maternally reported asthma symptoms' interference with activity and/or sleep at enrollment, 26, and 32 gestational weeks) compared with pregnant asthmatic women carrying a male fetus.
2. Pregnant women carrying a female fetus will have a higher incidence of asthma exacerbations (i.e., hospitalizations for asthma, unscheduled asthma clinic visits, burst use of systemic corticosteroids, or a combination of these measures) during pregnancy compared with pregnant asthmatic women carrying a male fetus.
3. Self-reported asthma control (assessed by maternally reported asthma symptoms' interference with activity and/or sleep) will worsen during the course of pregnancy in pregnant women carrying a female fetus compared with pregnant asthmatic women carrying a male fetus.

SPECIFIC AIM / STUDY III

To determine the safety of leukotriene receptor antagonists (i.e., montelukast sodium, zafirlukast), taken during pregnancy for treatment of maternal asthma, for the mother and fetus/newborn.

The following hypotheses were tested (not stated in the null for ease of interpretation):

1. Women with asthma who use leukotriene receptor antagonists (LTRAs) anytime in pregnancy with or without other asthma medications will have an increased incidence of adverse maternal outcomes (i.e., poor weight gain during pregnancy, higher rates of preeclampsia, gestational diabetes) compared with women with asthma who use short-acting β_2–agonists exclusively throughout the pregnancy and to non-asthmatic controls.
2. Women with asthma who use LTRAs anytime in pregnancy with or without other asthma medications will have an increased incidence of adverse fetal outcomes (i.e., spontaneous abortion or stillbirth, preterm birth, major structural anomalies, intrauterine growth restriction, reduced mean birth weight, low ponderal index, and lower Apgar scores) compared with women with asthma who used short-acting β_2–agonists exclusively throughout the pregnancy and to non-asthmatic controls.
3. Hypothesis generating exploratory aim:

   To explore whether offspring of women who used LTRAs in pregnancy have a consistent pattern of specific major structural defects (e.g., limb defects, vascular defects) suggesting possible biological plausibility.

CHAPTER 3:

RESEARCH DESIGN AND METHODS

1. OVERVIEW

The proposed study utilized archived data from the multi-center study of Asthma Medication Use in Pregnancy conducted between 1998-2003 by the Organization of Teratology Information Specialists (OTIS). OTIS is a non-profit organization of teratology information services located across North America. OTIS receives calls from approximately 100,000 women a year with questions about various exposure factors in pregnancy. The majority of calls (58%) are related to the safety of medications in pregnancy. The OTIS asthma study recruited 819 women with a current diagnosis of asthma, regardless of medications used or frequency of treatment, during their first part of pregnancy (≤ 20 gestational weeks). Pregnant women who were not asthmatic and who contacted OTIS member services with questions about pregnancy exposures not thought to adversely affect pregnancy outcome were recruited as a non-diseased comparison group (n=346). Women were followed with structured telephone interviews until the completion of pregnancy and in postpartum period through a central coordinating center located at the University of California, San Diego (UCSD). Information about medication use, asthma control and exacerbations, demographic and lifestyle characteristics, medical and pregnancy history, pregnancy complications and outcomes, as well as information about newborn children was collected and validated by review of maternal and pediatric medical records.

The conceptual framework for the present study and interrelation between specific aims are presented in Figure 1. The main focus of the study is maternal asthma control assessed by self-reported symptom control and severe asthma

exacerbations during pregnancy. Maternal asthma control is known to be influenced by internal and external factors, such as a presence of the fetus and gestational asthma therapy. Some recent studies suggested that fetal sex might affect maternal asthma control in pregnancy and modify the effect of asthma on perinatal outcomes. Poor control of maternal asthma is a known risk factor for adverse maternal and fetal outcomes, while gestational asthma therapy might also pose an independent risk on perinatal outcomes. The effect of LTRAs on perinatal outcomes was evaluated in the current study to fill a gap in medical knowledge since the safety of these medications in pregnancy has not been previously examined in controlled epidemiological studies.

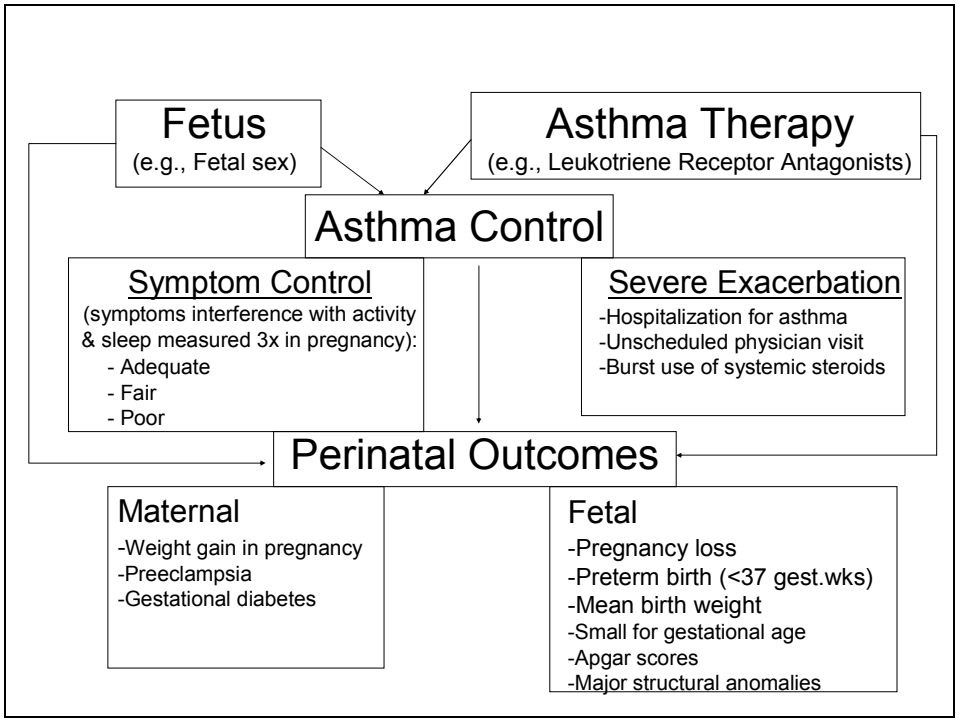

Figure 1. Conceptual Framework for the Study.

2. STUDY DESIGN

The data for this study was collected between 1998 and 2003, utilizing a prospective study design. All participating women were recruited during the first part of pregnancy (≤ 20 gestational weeks) and prior to any prenatal diagnostic test indicating an abnormal pregnancy, and followed-up until completion of pregnancy. Medication exposure, asthma control level, and relevant covariates were ascertained prior to evaluated perinatal outcomes, thus limiting recall and misclassification bias.

3. SUBJECT SOURCES AND RECRUITMENT

The majority of subjects (87.5%) were recruited through the OTIS network, which provides individualized over-the-phone counseling for pregnant women across North America regarding safety and risks associated with pregnancy exposures. The following members of the OTIS Collaborative Research group referred subjects to the study: Arizona Teratogen Information Program; California Teratogen Information Services; Connecticut Pregnancy Exposure Information Service; Nebraska Teratogen Project; Illinois Teratogen Information Service; Michigan Teratogen Information Service; Missouri Teratogen Information Service; Pregnancy Risk Network, University of Buffalo; Motherisk Program, Hospital for Sick Children, Toronto, Canada; Texas Teratogen Information Service; Pregnancy RiskLine Project, Utah Department of Health; and CARE Northwest, University of Washington, Seattle. The majority of subjects were referred to the study coordinating center by the Motherisk Program, Canada (n=493) and California Teratogen Information Services (n=205). The rest of the services each contributed under 100 subjects, with Utah referring 96,

Texas referring 73, and New York referring 48. The remaining services contributed less than 30 referrals each.

Subjects were also recruited directly through physician referrals (6.1%), the OTIS website (4.1%), or from multiple referral sources (2.3%). Maternal characteristics (i.e., age, BMI, gravidity, parity, and socioeconomic status) of women recruited through these referral sources were similar to women recruited via OTIS network (all p-values > 0.2; data not shown). Among women referred to the study by physicians 28% were of non-white ethnicity, while much smaller proportion of non-white women (5-13%) were recruited through other referral sources (p=0.004; data not shown). The overall sample consisted of 1,165 pregnant women. The rate of loss-to-follow-up in the study was 5.1%.

The University of California, San Diego Institutional Review Board approved the study. All study participants provided oral informed consent prior to enrollment, and also provided written consent for release of medical records.

4. ELIGIBILITY

Inclusion criteria.

1. Pregnant women with physician-diagnosed asthma at the time of enrollment (women with asthma).
2. Pregnant women who did not have asthma and had no pregnancy exposures thought to adversely affect any pregnancy outcomes (controls).
3. Willingness to be followed-up during the pregnancy and postpartum period by telephone interviews (all groups).

4. ≥ 18 years of age and able to understand and give informed consent in English or Spanish (all groups).
5. ≤ 20 weeks gestation at the time of enrollment (all groups).

Exclusion criteria.

1. Women who had any prenatal diagnostic test indicating an abnormal pregnancy prior to enrollment (all groups).

5. STUDY PROTOCOL

Women who met the inclusion and exclusion criteria were offered participation in the study and interviewed by a study coordinator over the telephone. A structured baseline questionnaire was used during the interview that assessed participant demographic information, medical and reproductive history, information about current pregnancy, some lifestyle characteristics, asthma symptoms, and detailed information about current use of asthma medications (**Appendix A**). Follow-up maternal telephone interviews were conducted at 26 and 32 weeks gestation, when current asthma symptoms and any change in use of asthma medications were queried (**Appendix B**). An outcome call was conducted within 4-6 weeks after delivery when maternal and fetal perinatal outcome information was collected (**Appendix C**). Information collected from maternal interviews was supplemented and validated by review of maternal and infant medical records.

6. DATA COLLECTION

Demographic and lifestyle variables.

All women were asked to report their age, race/ethnicity, use of tobacco, exposure to passive smoking, alcohol and illicit drug use. Socioeconomic status (SES)

was assessed using a Hollingshead four-factor index which incorporates both education and occupation of the mother, father or other family support person [28].

Medical and reproductive health variables.

Women were asked to report their gravidity (number of pregnancies) and parity (number of live-born children). Multi-gravid women were asked about outcomes and complications of their previous pregnancies, i.e., preterm delivery, full-term birth, spontaneous or voluntary abortion, gestational diabetes, preeclampsia, pregnancy induced hypertension (PIH).

Questions about current pregnancy included: date of the last menstrual period (LMP), menstrual cycle length, expected date of delivery (EDC), onset of fetal movement and fetal activity, and any complications during the pregnancy (e.g., preeclampsia, gestational diabetes, etc.). Results of the perinatal tests (e.g., amniocentesis, ultrasound, glucose screening, AFP screening) were also ascertained. Self-reported dates of LMP, EDC, and gestational age were subsequently confirmed by review of ultrasound reports and obstetrician records.

Women were also asked to report their pre-pregnancy weight and height, history of major chronic disorders (i.e., heart disease, psychiatric conditions, diabetes, kidney disorders, hypertension, seizure disorders, or other), and list any surgeries they had. Both maternal and paternal family history of any genetic illnesses, birth defects, or mental retardation were queried.

Exposure information.

At each interview, participants were asked about actual use, frequency, and dosage of all prescription and non-prescription medications, which has been

previously shown to be a better method to estimate actual exposure during pregnancy compared with pharmacy records [29, 30]. Women were also asked to report any occupational exposures, diagnostic x-rays, use of herbs and holistic products, prenatal and other vitamins, and caffeine.

Assessment of maternal asthma.

Subjects were considered to be asthmatic based on a diagnosis made by physicians, which has been shown to be a valid definition of asthma in epidemiological studies [31]. Age of asthma diagnosis was queried. Women were asked whether they had ever been hospitalized for asthma and ever used systemic corticosteroids. To assess asthma exacerbations during pregnancy women were asked to report a number of unscheduled asthma visits and hospitalization for asthma since the last menstrual period.

Asthmatic women were asked at each interview to categorize their symptoms during the previous two-week period using a five-point scale, developed by Dr. Schatz prior to initiation of the study in 1997 (**Appendix I**). The scale is based on asthma symptoms and their interference with daily activities and sleep. A score of zero indicated no symptoms; a score of one, some symptoms which did not interfere with activity or sleep; a score of two, occasional interference; a score of three, frequent interference; and a score of four, constant interference. Asthma control was categorized as "adequate" if women reported no symptoms or some symptoms which did not interfere with sleep or activity (score 0-1), "fair" if symptoms occasionally interfered with sleep or activity (score 2), and "poor" if symptoms frequently or constantly interfered with sleep or activity (score 3-4). At the time of initiation of the

study, no validated asthma control tools had been published. The scale used in the study had not been validated in pregnant women with asthma; however, frequency of symptoms and their interference with sleep and activity are the major components of three subsequently published validated asthma control tools [23, 26, 27]. A two-week window to ascertain asthma symptoms was chosen since this timeframe is the most commonly used in asthma-specific scales (e.g., asthma-specific quality of life tool developed by Juniper [32]) and allows capturing sufficient and representative information while recall bias is minimized.

Severe asthma exacerbation during current pregnancy (any vs. none) was defined as one or more of the following: hospitalization for asthma during pregnancy, unscheduled physician visit for asthma, or use of systemic corticosteroids in patients who do not regularly take them. This definition has been previously developed and used in gestational human studies [33, 34]. Patients who took systemic corticosteroids (i.e., prednisone, dexamethasone, methylprednisolone) for less than six weeks at any trimester were considered to be "burst" users and were included in the definition of severe asthma exacerbation. Contrary, other systemic corticosteroid users were considered using these medications chronically for severe persistent asthma rather than for asthma exacerbations and were not included in the group of patients with severe asthma exacerbations. In patients who chronically used systemic corticosteroids, significant asthma exacerbations were captured by unscheduled visits and hospitalizations for their asthma during pregnancy.

Outcome variables.

Data collected from the pregnancy outcome interview included information about pregnancy outcome (i.e., live-birth, stillbirth, terminated pregnancy, spontaneous abortion), date of birth or termination, gestational age at delivery, maternal weight gain during the pregnancy, and maternal complications (gestational diabetes, preeclampsia or pregnancy-induced hypertension (PIH)). Information about the newborn included: birth weight, length, head circumference, and birth complications (i.e., major structural anomalies, placement in the neonatal intensive care unit (NICU)). Percentiles for each measure of fetal growth were determined for full-term infants based on the National Center for Health Statistics 2000 standard U.S. growth curves [35] and for preterm infants based on growth charts adjusted for gestational age [36].

7. DATA MODIFICATIONS

Body mass index (BMI) was calculated as pre-pregnancy weight (kg)/height $(m)^2$. Since many adverse perinatal outcomes are associated with low or high BMI, it was assessed as a categorical variable with standard cut-off points: <24, 24-28, and >28 kg/m^2. Maternal age is traditionally analyzed as a categorical variable in studies involving perinatal outcomes. In fact a term "elderly parturient" was established by the Council of International Federations of Obstetrics and refers to women aged 35 years of more at the first delivery. Advanced maternal age has been associated with numerous adverse perinatal outcomes, including higher incidence of low birth weight, preterm delivery, intrauterine growth restriction, and chromosomal abnormalities [37-39]. On the other hand, young maternal age (<25 years) is also a known risk factor for low birth weight, premature birth, and some malformations (e.g., gastroschisis) [40,

41]. The relationship between maternal age and many perinatal outcomes can not be described in linear or other non-linear terms (e.g., quadratic, log-linear), thus maternal age was categorized into <25, 25-34, and ≥ 35 years.

Ponderal index was calculated as birth weight (grams)/birth length $(cm)^3$ and was dichotomized as normal (≥ 2.2) or low (< 2.2). Ponderal index was evaluated as a measure of asymmetrical intrauterine growth restriction [42]. Hollingshead SES was dichotomized into "above average" (score 1-2) and "at or below average" (score 3-5). Preterm delivery was defined as <37 completed weeks gestation. Gestational age- and sex-specific percentiles for birth weight, length, and head circumference were categorized as small for gestational age (SGA) if they were equal or below 10^{th} centile.

8. QUALITY CONTROL AND DATA MANAGEMENT

All data were collected by the coordinating center located at the Department of Pediatrics, University of California, San Diego (UCSD) and entered into the File Maker Pro database. The data was validated against medical records and checked for accuracy and completeness. Any discrepancies were reviewed and corrected by data coordinators and a data manager. The electronic data are stored on the Pediatrics server, and back-ups are conducted daily.

9. PROTECTION OF HUMAN SUBJECTS

This original data have been collected through the project entitled "Asthma Medication Use and Pregnancy Outcome: A Clinical Observational Study" and approved by the Human Research Protection Program of the University of California, San Diego (P.I. Dr. Kenneth Lyons Jones, protocol # 030101). The study and its

procedures were explained to the participants prior to obtaining any information. After a thorough explanation of the procedures, the voluntary nature of participation, and possible risk and benefits, all questions were answered and informed consents were obtained by the interviewers. The accrual of subjects was closed on 2/9/2004.

The dissertation project involved analysis of the data collected through the above mentioned project. Subjects were not re-contacted. All data obtained from this project were only used for research purposes. The study has been approved by the Human Research Protection Programs of the University of California, San Diego (P.I. Ludmila Bakhireva, protocol #060695X) and the San Diego State University (P.I. Ludmila Bakhireva, protocol # 2506).

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CHAPTER 4: STUDY I

EFFECT OF MATERNAL ASTHMA ON

ADVERSE PERINATAL MATERNAL AND FETAL OUTCOMES

1. STUDY I: LITERATURE REVIEW

Overview.

Multiple studies demonstrated that women with asthma have a higher rate of adverse perinatal maternal and fetal outcomes compared with women whose pregnancies are not complicated by asthma. Maternal asthma has been associated with preeclampsia, gestational diabetes, pregnancy-induced hypertension, chorioamnionitis, cesarean delivery, antepartum and postpartum hemorrhage, infant hypoglycemia, preterm and post-term births, increased neonatal mortality, lower mean birth weight, and an increased rate of low birth weight newborns and infants who are small for gestational age [8, 24, 43-45]. However, in many of these studies it is difficult to separate the effect of severe or uncontrolled asthma from the effects of asthma medications or even other factors not related to asthma control or treatment [46].

Several studies have shown that more severe or uncontrolled asthma is particularly likely to be associated with adverse fetal outcomes, e.g., infants born to women who required hospitalization for asthma during pregnancy had lower birth weight compared with infants born to women who did not require emergency care for asthma during pregnancy [33, 47, 48]. Forced expiratory volume in 1 second (FEV_1) (an objective assessment of maternal airflow obstruction) has been shown to significantly correlate with birth weight of children born to asthmatic women [25, 49], while lower maternal pulmonary function was associated with an increased incidence of low birth weight [49] and asymmetric intra-uterine growth restriction (IUGR) [25]. Additionally, a step-wise increase in IUGR risk was noted with increase in maternal asthma severity [12], while reduced “intensity” of asthma therapy (assumed to reflect

undertreatment) was reported to be associated with reduced birth weight and length [50].

Fetal Outcomes.

Fetal growth:

Fetal growth is often evaluated in epidemiological studies as low birth weight (<2500 grams), very low birth weight (<1500 grams), mean birth weight, and being small for gestational age (SGA). These measures of growth retardation reflect potentially different underlying mechanisms, since low birth weight and mean birth weight do not account for gestational age at birth, while SGA refers to a weight $\leq 10^{th}$ percentile for that gestational age [51]. SGA reflects the intrauterine growth retardation (IUGR) and is classified as symmetrical and asymmetrical. Symmetrical IUGR refers to reduction in all morphometric measurements (i.e., birth weight, height, and head circumference), while asymmetrical retardation refers to reduced weight with normal length and head circumference [52]. A reduced birth weight/length ratio and a ponderal index (birth weight (grams)/birth length $(cm)^3$ *100) < 2.2 have been shown to be good indicators of asymmetrical growth retardation [42].

Intrauterine growth restriction and reduced birth weight are common pregnancy complications and leading causes of perinatal morbidity and mortality. Long-term health consequences of disturbances in fetal growth include increased risk for insulin resistance, metabolic syndrome, dyslipidemia, and cardiovascular complications in later life [53].

Maternal asthma has been frequently associated with an increased risk of low birth weight [9, 22, 43, 44], reduced mean birth weight [44, 54], or small for

gestational age [9, 12, 45, 55] (reviewed by Bakhireva [51]). However, in many of these studies it is difficult to disentangle the effect of severe or uncontrolled asthma from the effects of gestational asthma therapy or even other factors not related to asthma control or treatment [46]. The existing body of literature demonstrates that, among all asthma medications, only oral corticosteroids pose some documented increased risk for impaired fetal growth; however, assessment of the independent effect of oral steroids on perinatal outcomes is problematic since the use of systemic steroids is associated with more severe and/or poorly controlled asthma [51].

Major structural anomalies:

Structural defects are classified into two major groups: those that can be explained by "a single problem in morphogenesis that leads to a cascade of subsequent defects" and those that "appear to be the consequence of multiple defects in one or more tissues" [56]. The former pattern of structural defects refers to *sequences* and thought to have a multi-factorial etiology, while the latter refers to *malformation syndromes* which are commonly thought to result from a single cause. From pathophysiological prospective, major structural anomalies are classified into *malformation* (poor formation of tissue), *deformation* (mechanical forces result in altered morphogenesis), *disruption* (breakdown of normal tissue), and *dysplasia* (abnormal organization of cells into tissue) [56]. Major structural anomalies can be caused by chromosomal abnormalities, mutant gene disorders, and environmental exposures; however, etiology of many birth defects is unknown. Among sequences, deformation is less likely to due to environmental exposures, while other types of defects can be caused by teratogens or an interaction between genetic and

environmental factors. Background birth prevalence of major structural anomalies in the Unites States is estimated to be 3-4% [57-60].

Offspring of women with asthma have been reported to have an increased risk of congenital anomalies (OR=1.37; 95% CI: 1.12-1.68) [9]. Another study reported a trend towards increased risk of total malformations (OR=1.2; 95% CI: 1.0-1.3), cardiovascular malformations (OR=1.4; 95% CI: 1.0-1.8), club foot (OR=1.5; 95% CI:1.1-2.2), and multiple malformations (OR=1.6; 95% CI: 1.0-2.6) among offspring of women with bronchial asthma [61]. The hypoxic effect on organogenesis was proposed as a possible biological mechanism for the observed effect [9]. However, it is difficult to separate the effect of maternal asthma from possible teratogenic effect of some asthma medications. In fact, oral corticosteroids have been repeatedly reported to be associated with a specific major birth defect - oral clefts [14, 15, 62-64].

Preterm delivery:

Preterm delivery refers to a delivery prior to 37 gestational weeks. Previous data suggest that women with asthma have a higher rate of preterm delivery compared with non-asthmatic women [43]. Moreover, women whose asthma was severe enough to require a hospitalization have even a greater risk of preterm delivery compared with other asthmatic women [43]. Preterm labor has also been reported to occur more often in corticosteroid-dependent patients [11, 12, 22]. On the other hand, mild asthma does not seem to influence preterm delivery [47, 65, 66].

The Apgar score:

The Apgar score is a five-point scale designed by Dr. Virginia Apgar in 1952 for evaluation of newborns at one and five minutes after birth [67]. The Apgar score is

based on assessment of five vital signs: heart rate, respiratory effort, color, muscle tone, and responsiveness to stimuli. Each sign can get a rank from 0 to 2 with a total score ranging from 0 (no signs of life) to 10 (the best possible condition). Scores below 3 are generally considered as critically low, from 4 to 7 as fairly low, and greater than 7 as normal. Even though use of Apgar scoring system for evaluation of extremely preterm infants is controversial in the light of modern perinatal and neonatal care, it remains to be a single standard tool for evaluation of all babies born in the United States [68, 69]. Previous studies found no difference between asthmatic and non-asthmatic subjects with regard to incidence of low Apgar scores in their offspring [7, 70, 71].

Maternal Outcomes.

Preeclampsia:

Preeclampsia is a disorder of unknown etiology that occurs only during pregnancy. Preeclamsia has been estimated to occur in approximately 12% of all pregnancies [72, 73]; however, differences in definitions and inaccuracy of diagnosis might substantially affect estimated prevalence rates. Preeclampsia is defined by the new onset of elevated blood pressure and proteinuria after 20 weeks of gestation.

Clinical studies examining the association between preeclampsia and asthma and/or asthma medications provided conflicting results. While some studies did not observe an increased risk of preeclampsia among women with asthma [22, 66, 74], others implicated asthma as a risk factor for preeclampsia [7, 9, 43, 45]. A recent large cohort study found that women with moderate to severe asthma symptoms (i.e., GINA symptom step 3/4) have an increased risk of preeclampsia compared with women with

no symptoms [24]. Neither a history of physician-diagnosed asthma nor GINA treatment steps were associated with preeclampsia in that study, suggesting that active asthma symptoms rather than treatment effects might influence the development of preeclampsia. However, other well-controlled studies found that use of oral corticosteroids was independently associated with the occurrence of preeclampsia (Adjusted OR=2.0, 95% CI: 1.1-3.6) [10].

Gestational diabetes:

Gestational diabetes mellitus (GDM) refers to carbohydrate intolerance first recognized or developed in pregnancy [75]. The estimated prevalence of GDM varies from 1 to 16% depending on the diagnostic criteria and study population [76]. The diagnosis relies on two or more positive 75-g oral glucose tolerance tests (OGTT). American Diabetes Association defines positive OGTT as plasma glucose $\geq$ 10 mmol/l one hour after the administration of OGTT and plasma glucose $\geq$ 8.6 mmol/l two hours after the administration of the test [76]. Women with GDM are at high risk of developing Type 2 diabetes after delivery and have complications in pregnancy, including higher rates of Cesarean sections and birth of a child with macrosomia (i.e., birth weight $\geq$ 4000g). An increased risk of gestational diabetes was observed among women with asthma in the Swedish health register [43], but not in other studies [8, 70, 77].

Maternal weight gain in pregnancy:

Maternal weight gain during pregnancy is a function of women nutritional status before and during pregnancy and is an important predictor of infant size and health [78]. Weight gain in pregnancy can be described as optimal, inadequate, and

excessive. Some studies defined low weight gain as gain less than 8 kg, optimal as 8-16 kg gain, and excessive as gain more than 16 kg [79]. However, recommended weight gain during pregnancy depends on pre-pregnancy maternal BMI. Table 4 summarizes the Institute of Medicine (IOM) recommendations for weight gain as a function of pre-pregnancy BMI [80]. Even though optimal weight gain is inversely related to pre-pregnancy BMI [81], other factors such as parity, smoking, level of education, hypertension, and nausea during pregnancy might also significantly influence weight gain [82].

Table 4. Recommendations for Total Weight Gain during Pregnancy by pre-pregnancy BMI.

BMI Level	Recommended weight gain (kg)	Recommended weight gain (lb)
> 19.8	12.5-18	28-40
19.8 - 26	11.5-16	25-35
26 - 29	7-11.5	15-25
> 29	> 7	>15

Source: Institute of Medicine, 1990

Low maternal weight gain in pregnancy is a strong and potentially preventable risk factor for low birth weight (LBW) in the offspring [78, 83]. Moreover, inadequate gestational weight gain has been linked to an increased risk of preterm delivery with indications that weight gain during the third trimester might be particularly important [84]. Maternal weight gain was reported to be lower among women with asthma who experience a severe asthma exacerbation in pregnancy compared with women whose asthma is well-controlled [85].

Spontaneous abortion:

Spontaneous abortion (miscarriage) is defined as the loss of the fetus without outside intervention within the first 20 weeks of gestation. Spontaneous abortion is estimated to occur in at least 15% of clinically recognized pregnancies [86]. The incidence is likely to be underestimated because many cases of early spontaneous abortion might be clinically unrecognized and mistaken for late menstrual period if women are unaware of their pregnancy. True incidence of spontaneous abortion has been estimated to be as high as 50-78% of all conceptions if unrecognized pregnancy loss is accounted for [86]. In the Kaiser-Permanente Prospective Study of Asthma During Pregnancy, a higher incidence of spontaneous abortion was observed in subjects with asthma versus controls [10]. However, the significance of these findings was uncertain because subjects with asthma on average entered the study earlier in pregnancy, thus a detection bias could be introduced.

Stillbirth:

Stillbirth is defined as fetal death at or after 20 weeks gestation. The average stillbirth rate in the developed countries has been estimated to be 5.3 per 1000 deliveries, while in south Asia and sub-Saharan African the average rate might be as high as 32 per 1000 [87]. In the United States stillbirth occurs in almost 1% of all deliveries (7 per 1000) [88, 89]. Stillbirth are classified into three categories based on when they occur: early preterm (before 28 gestational weeks), later preterm (28-36 gestational weeks), and term (≥ 37 gestational weeks). They are also classified into antenatal (i.e., occur before labor) and intrapartum (i.e., occur during the labor) [90]. Several studies evaluated the effect of asthma medications relative to stillbirth, e.g., the Swedish Medical Birth Registry Study examined the effect of budesonide on

stillbirths [91] and a secondary analysis from the Collaborative Perinatal Project evaluated stillbirths in relation to theophylline exposure [92]. However, we are not aware of any published studies examining the effect of maternal asthma independent from asthma medications on stillbirth.

Assessment of Interaction between Fetal Sex and Asthma in Relation to Fetal Growth.

Murphy et al. reported that "in women with asthma who did not use inhaled steroids and were pregnant with a female fetus, we observed significantly reduced birth weights" [93]. No reduction of birth weight was noted in that study among male infants born to asthmatic women. Upregulation of maternal inflammatory pathways in late pregnancy was claimed to be responsible for the observed effect, while use of inhaled corticosteroids supposedly had a protective effect. Presence of a female fetus was associated with increased maternal circulating monocytes, which release numerous cytokines and contribute to worsening of asthma symptoms. Murphy et al. proposed that changes in maternal asthma contributed to the observed changes in the placental function: reduced placental 11β-HSD2 activity (a placental enzyme which converts cortisol into inactive cortisone) and a trend towards increased cord blood cortisol in female neonates. These changes in placental cortisol metabolism and altered fetal adrenal function could have resulted in reduced growth in the female fetuses.

The later study by Murphy and colleagues linked severe maternal asthma exacerbation during pregnancy with an increased rate of low birth weight among male neonates [85]. Male infants born to women who had asthma exacerbations in pregnancy had also lower mean birth weights (approximately 300 g) compared with male infants born to women who did not have exacerbations. No such effect was observed among female neonates. These results contradict the earlier study by Murphy where maternal asthma was linked to reduced female growth [93]. However, the first

study found an association among subjects who did not use inhaled corticosteroids, that might be a marker for less severe asthma and would not necessarily identify the same patients as the marker of exacerbations used in the second study. A retrospective study conducted in Italy found similar sex-specific effect of maternal asthma on fetal growth. Maternal asthma was strongly associated with an increased risk of low birth weight (OR=4.13; 95% CI 1.01-12.53) in male but not female (OR=2.19; 95% CI: 0.41-7.51) children [94]. However, a recent study utilizing the linkage of two administrative clinical databases in Canada found no association between the presence of female fetus and delivery of a low birth weight baby (OR=1.47; 95% CI: 0.74-2.91) in patients who had at least one emergency department visit for asthma during pregnancy [95].

2. STUDY I: METHODS

Power Analysis.

The PASS 2002 (Kaysville, UT) was used to conduct power analyses. Since this study involves analysis of the previously collected data with a given sample size, power analysis was performed to determine the magnitude of association (effect size) which the current study is able to detect for selected outcomes at the given sample size and 80% power. Background rates and means used in power calculations were obtained from the earlier study by Bakhireva et al, which was based on the same study population [13].

The purpose of this study was to estimate the effect of asthma control (poor/fair vs. adequate) on perinatal outcomes. Based on earlier findings, among 819 asthmatic women in the OTIS Asthma in Pregnancy Study, 56% (n=459) were estimated to have adequately controlled asthma and 44% (n=360) to have fairly or poorly controlled asthma [13]. Power analysis for selected outcomes is presented in Table 5.

Table 5. Power Analysis for Study I.

Selected Outcomes	Given sample size in group 1 (adequate control)	Given sample size in group 2 (poor/fair control)	Mean1 or P1*	Effect size which study is powered to detect	Power
Mean birth weight	459	360	3530g	89 gram difference	80%
Mean maternal weight gain in pregnancy	459	360	15.5 kg	1.1 kg	80%
Preterm delivery	459	360	7.6%	OR=1.96	80%
Small for gestational age	459	360	5%	OR=2.2	80%

* Assumed mean value or incidence of the outcome among subjects in group 1 (women with adequately controlled asthma)

The study had 80% power to detect a 1.1 kg difference in maternal weight gain among women with adequately controlled asthma versus poorly/fairly controlled asthma. The study had 80% power to detect a two-fold increased risk of preterm delivery and SGA and to detect 89 gram difference in mean birth weight among infants born to women with adequately controlled asthma as compared with infants born to women with inadequately controlled asthma.

Statistical Analyses.

All statistical analyses were performed in SAS (Release 9.0, SAS Institute, Inc., Cary NC, 2002).

Description of the study population:

For all analyses conducted for this Specific Aim, only women with asthma were considered. Distribution of demographic, lifestyle, and reproductive health variables (i.e., maternal age, BMI, gravidity, parity, race/ethnicity, tobacco and alcohol use during pregnancy, and family SES) was compared among women with adequately controlled asthma relative to women with inadequately controlled asthma. Analysis of variance (ANOVA) was used for continuous variables and χ^2 tests for categorical variables.

Description of the sample:

For evaluation of maternal outcomes the sample size was restricted to 731 pregnancies which resulted in live births since the underlying mechanisms leading to adverse perinatal outcomes could be different among pregnancies which resulted in live births and pregnancies which resulted in spontaneous abortion or stillbirth. Additionally, for evaluation of preterm delivery, SGA, and Apgar scores the sample

size was restricted to 719 live-born singletons since twinning is a very strong risk factor for those outcomes and could confound evaluated associations [96]. When mean birth weight was analyzed, the sample size was further restricted to 659 live-born full-term singletons. Evaluation of mean birth weight in both full-term and preterm infants could introduce biases since decreased birth weight that occurs in a preterm infant whose size is appropriate for gestational age may have different antecedent causes than decreased birth weight occurring in a full-term infant whose size is small for gestational age [97]. Growth deficiency among both full-term and preterm infants was evaluated by gestational age-specific percentiles (i.e., SGA).

Univariate analysis:

The incidence or means of selected maternal (i.e., gestational diabetes, preclampsia/PIH, mean maternal weight gain in pregnancy) and fetal outcomes (i.e., pregnancy loss, preterm birth, SGA, mean birth weight, major structural anomalies, low Apgar scores at 1 and 5 minutes after birth) were compared among women with adequately controlled asthma relative to women with fair/poor control of their asthma as measured at each maternal interview (intake, 26 gestational weeks, 32 gestational weeks). Distribution of selected maternal and fetal outcomes was also compared among subjects who reported any measures of asthma exacerbation in pregnancy and specific measures of asthma exacerbations (i.e., hospitalizations for asthma, unscheduled asthma visits, burst use of systemic corticosteroids) versus subjects who did not have these measures of poor asthma control. Due to small cell sizes the incidence of some fetal outcomes, i.e., Apgar score (5 min) ≤ 7, birth height $\leq 10^{th}$ %, Ponderal index < 2.2, major structural anomalies, could not be compared among

subjects who experienced specific measures of asthma exacerbation versus those who did not. For example, a mother of only one malformed child had been hospitalized for asthma during pregnancy.

Assessment of confounders:

Given numerous perinatal outcomes evaluated in the study, covariates were selected *a priori* based on review of the literature. Common risk factors associated with asthma and perinatal outcomes include maternal age, obesity, smoking, gravidity, parity, race/ethnicity, and socio-economic status.

Multivariate analyses:

Multiple logistic regression was used to assess the effect of asthma control and specific measures of asthma exacerbation on perinatal outcomes after adjustment for covariates mentioned above. Since use of systemic corticosteroids during pregnancy has been associated with an increased risk of perinatal outcomes, effect of maternal asthma on perinatal outcomes was determined before and after adjustment for use of corticosteroids in addition to other covariates.

Assessment of Interaction between Fetal Sex and Asthma in Relation to Fetal Growth:

To assess a possible interaction between fetal sex and maternal asthma with respect to fetal growth (mean birth weight, SGA), the following four models were constructed:

1. Linear regressions:

   a) Y (mean birth weight) = β_0 + β_1(fetal sex) + β_2(asthma control) + β_3(fetal sex*asthma control)

b) Y (mean birth weight) = $\beta_0 + \beta_1$(fetal sex) + β_2(asthma exacerbations) + β_3(fetal sex*asthma exacerbations)

2. Logistic regressions:

a) Y (birth weight $\leq 10^{th}$ percentile) = $\beta_0 + \beta_1$(fetal sex) + β_2(asthma control) + β_3(fetal sex*asthma control)

b) Y (birth weight $\leq 10^{th}$ percentile) = $\beta_0 + \beta_1$(fetal sex) + β_2(asthma exacerbations) + β_3(fetal sex* asthma exacerbations)

3. STUDY I: RESULTS

Among 819 women with asthma in the OTIS study, 443 (55.4%) reported to have adequate control of asthma at their first maternal interview, while 356 (44.6%) reported to have fair or poor control of asthma, and 20 women had missing values for this variable (Table 6). At subsequent maternal interviews (at 26 and 32 gestational weeks), a slightly smaller proportion of subjects reported poor/fair control of their asthma (36.3% and 30.5%, respectively). During pregnancy 8.2% of subjects had been hospitalized for asthma, 19.5% had unscheduled asthma visits, 13.7% used systemic corticosteroids in a burst fashion, and 30.9% had one or more symptoms of severe asthma exacerbations (Table 6).

Table 6. Distribution of Asthma Symptom Control and Exacerbation Measures among Women with Asthma in the OTIS study.

Measures of maternal asthma control	N* (%)
Asthma symptom control at ≤ 20 gestational weeks:	
Adequate	443 (55.4)
Poor/fair	356 (44.6)
Asthma symptom control at 26 gestational weeks:	
Adequate	419 (63.7)
Poor/fair	239 (36.3)
Asthma symptom control at 32 gestational weeks:	
Adequate	455 (69.5)
Poor/fair	200 (30.5)
Hospitalization(s) for asthma during pregnancy	67 (8.2)
Unscheduled asthma visits during pregnancy	160 (19.5)
Burst use of systemic corticosteroids during pregnancy	110 (13.7)
Asthma exacerbations**	253 (30.9)

* Sample size varies due to missing values

** Defined as occurrence of one or more of the following: hospitalization for asthma during pregnancy, unscheduled physician visit for asthma during pregnancy, burst use of systemic corticosteroids.

Some differences were observed in demographic, reproductive health, and lifestyle characteristics of women who reported adequate control of their asthma during the first part of pregnancy (n=443) versus women who had poor or fair control of their asthma symptoms (n=356). A greater proportion of women with inadequately controlled asthma were younger (p=0.037), had been pregnant before the index pregnancy (p<0.001), had children (p<0.001), were of non-white race/ethnicity (p=0.026), and reported household socio-economic status below average (p<0.001) compared with women with adequately controlled asthma (Table 7).

Table 7. Maternal Characteristics by Asthma Symptom Control at the Time of Enrollment.

Maternal characteristics	**Women with adequately controlled asthma** (N=443)	**Women with poorly/fairly controlled asthma** (N=356)	**Overall p-value**
	N (%)	*N (%)*	
Maternal age:			0.037
<25 years	35 (7.9)	48 (13.5)	
25-34 years	267 (60.3)	201 (56.5)	
35+ years	141 (31.8)	107 (30.1)	
BMI (kg/m^2):			0.109
<24	231 (52.1)	159 (44.7)	
24-28	103 (23.3)	97 (27.3)	
>28	109 (24.6)	100 (28.1)	
Gravidity >1	256 (57.8)	250 (70.2)	<0.001
Parity >0	177 (40.0)	196 (55.1)	<0.001
White non-Hispanic	399 (90.5)	303 (85.4)	0.026
Any tobacco use in pregnancy	43 (9.7)	47 (13.2)	0.120
Any alcohol use in pregnancy	206 (49.8)	156 (46.9)	0.429
SES status above average[†]	336 (77.1)	221 (63.0)	<0.001

[†] Hollingshead four factor socio-economic status category 1 or 2 on a scale of 1-5 with 1 being the highest.

The incidence of gestational diabetes and preeclampsia/PIH were similar among subjects with adequately controlled asthma compared with subjects with fairly/poorly controlled asthma (Table 8). Mean maternal weight gain in pregnancy also did not vary among subjects with adequate and inadequate asthma control anytime in pregnancy.

Table 8. Effect of Asthma Symptom Control at Each Maternal Interview on Maternal Outcomes.

Maternal Outcomes*	Asthma Symptom Control ≤ 20 gest.wks		26 gest.wks		32 gest.wks	
	Adequate N(%)	F/P N(%)	Adequate N(%)	F/P N(%)	Adequate N(%)	F/P N(%)
Gestational Diabetes	21 (5.3)	13 (2.3)	23 (5.7)	7 (3.1)	26 (6.0)	6 (3.1)
	p=0.544		p=0.150		p=0.141	
Preeclampsia/ PIH	14 (3.5)	13 (4.3)	14 (3.5)	8 (3.6)	15 (3.4)	8 (4.2)
	p=0.615		p=0.944		p=0.653	
Maternal weight gain in pregnancy (kg)	*Mean± ±s.d* 16.2±7.4	*Mean± ±s.d* 15.8±7.4	*Mean± ±s.d* 15.8±6.4	*Mean± ±s.d* 16.1±6.8	*Mean± ±s.d* 16.1±6.3	*Mean± ±s.d* 15.7±7.4
	p=0.507		p=0.605		p=0.516	

* Sample size was restricted to pregnancies which resulted in live births
F/P, fair/poor asthma symptom control

Distribution of maternal outcomes (gestational diabetes, preeclampsia/PIH, maternal weight gain in pregnancy) was also compared among subjects who reported severe asthma exacerbations during pregnancy, hospitalizations for asthma, and unscheduled asthma visits versus subjects who did not have these measures of poor asthma control (Table 9). No difference in the distribution of gestational diabetes and mean maternal weight gain in pregnancy was observed among subjects who

experienced different manifestations of asthma exacerbation during pregnancy compared with those who did not (p>0.05). No subjects with preeclampsia/PIH were hospitalized for asthma during pregnancy probably due to a low prevalence of both conditions; thus incidence of preeclampsia could not be compared among subjects who were hospitalized for asthma versus those who were not. In this sample the incidence of preeclampsia/PIH was lower among subjects who experienced severe asthma exacerbations (1.3%) compared with asthmatic subjects who did not (5.0%; p=0.014). The incidence of preeclampsia/PIH was also lower among subjects who reported unscheduled asthma visits during pregnancy (1.3%) compared with those who did not (4.5%), but the difference was of a borderline statistical significance (p=0.068). It should be noted that both estimates were based on very small numbers, e.g., only two subjects with preeclampsia/PIH had unscheduled asthma visits and only three subjects experienced severe asthma exacerbations. Thus estimates could be unstable.

Table 9. Incidence of Maternal Perinatal Outcomes among Subject Who Experienced Asthma Exacerbations in Pregnancy versus Those Who Did Not.

Maternal Outcomes*	Specific measures of asthma exacerbations:					
	Hospitalization(s) for asthma		Unscheduled asthma visits		Asthma exacerbations**	
	Yes N(%)	No N(%)	Yes N(%)	No N(%)	Yes N(%)	No N(%)
Gestational Diabetes	2 (3.2)	33 (5.1)	8 (5.3)	27 (4.8)	11 (4.7)	24 (5.0)
	p=0.518		p=0.827		p=0.848	
Preeclampsia/ PIH	0 (0.0)	27 (4.1)	2 (1.3)	25 (4.5)	3 (1.3)	24 (5.0)
	---		p=0.068		0.014	

Table 9 continued

Maternal Outcomes*	Specific measures of asthma exacerbations:					
	Hospitalization(s) for asthma		Unscheduled asthma visits		Asthma exacerbations**	
	Yes N(%)	No N(%)	Yes N(%)	No N(%)	Yes N(%)	No N(%)
Maternal weight gain in pregnancy (kg)	*Mean*± ±*s.d* 16.5±7.2	*Mean*± ±*s.d* 16.0±7.4	*Mean*± ±*s.d* 15.4±6.7	*Mean*± ±*s.d* 16.2±7.5	*Mean*± ±*s.d* 15.9±6.7	*Mean*± ±*s.d* 16.1±7.6
	p=0.597		p=0.247		p=0.734	

* Sample size was restricted to pregnancies which resulted in live births
** Defined as occurrence of one or more of the following: hospitalization for asthma during pregnancy, unscheduled physician visit for asthma during pregnancy, burst use of systemic corticosteroids.

The effect of asthma symptom control on selected fetal perinatal outcomes is presented in Table 10. Incidence of preterm delivery was significantly higher among subjects who reported poor or fair asthma symptom control during the first part of pregnancy (11.4%) compared with subjects with adequately controlled asthma (6.3%; p=0.017). However, no association was observed between preterm delivery and asthma symptom control during the second and third trimesters (p=0.477 and p=0.324, respectively). No statistically significant differences in the distribution of other fetal outcomes were observed among subjects with adequately and inadequately controlled asthma (p>0.05).

Table 10. Effect of Asthma Symptom Control at Each Maternal Interview on Selected Fetal Perinatal Outcomes.

Fetal Outcomes	Asthma Symptom Control					
	≤ 20 gest.wks		26 gest.wks		32 gest.wks	
	Adequate N(%)	F/P N(%)	Adequate N(%)	F/P N(%)	Adequate N(%)	F/P N(%)
Pregnancy loss[1]	22 (5.2)	18 (5.4)	1 (0.2)	0 (0)	1 (0.2)	0 (0)
	p=0.873		--		--	
Preterm delivery[2]	25 (6.3)	35 (11.4)	34 (8.3)	15 (6.7)	35 (7.9)	11 (5.7)
	p=0.017		p=0.477		p=0.324	
SGA[2] (birth **weight** ≤ 10th %)	23 (5.9)	17 (5.5)	21 (5.2)	13 (5.8)	28 (6.3)	9 (4.7)
	p=0.852		p=0.732		p=0.412	
SGA[2] (birth **OFC** ≤ 10th %)	35 (10.8)	27 (11.2)	27 (7.9)	22 (12.2)	37 (10.1)	16 (10.2)
	p=0.880		p=0.110		p=0.962	
Apgar score (1 min)≤ 7[2]	52 (15.6)	36 (14.1)	57 (16.1)	26 (13.9)	57 (14.9)	25 (15.5)
	p=0.625		p=0.500		p=0.857	
Apgar score (5 min)≤ 7[2]	12 (3.6)	7 (2.7)	10 (2.8)	9 (4.8)	12 (3.1)	4 (2.5)
	p=0.563		p=0.242		p=0.675	
Major structural anomalies[3]	13 (3.2)	13 (4.2)	13 (3.1)	13 (5.6)	17 (3.8)	9 (4.5)
	p=0.511		p=0.126		p=0.660	
Birth weight (g)[4]	*Mean*± ±*s.d*	*Mean*± ±*s.d*	*Mean*± ±*s.d*	*Mean*± ±*s.d*	*Mean*± ±*s.d*	*Mean*± ±*s.d*
	3506± ±510	3528± ±511	3553± ±502	3500± ±506	3527± ±511	3510± ±491
	p=0.600		p=0.226		p=0.708	

[1] Spontaneous abortion/ ectopic pregnancy/ stillbirth
[2] Sample size was restricted to live-born singletons
[3] Sample size was restricted to live-born children
[4] Sample size was restricted to live-born, full-term singletons

Similarly to the asthma symptom control, a history of hospitalization(s) for asthma during pregnancy was a risk factor for preterm delivery (Table 11). Namely, the incidence of preterm delivery was 16.4% among subjects who experienced

hospitalizations for asthma compared with only 7.6% among asthmatic subjects who were not hospitalized for asthma during pregnancy (p=0.018). No associations with other fetal outcomes were detected (Table 11). The low incidence of spontaneous abortion/ectopic pregnancy/stillbirth, low Apgar score at 5 minutes, and major structural anomalies did not allow to evaluate their association with specific measures of asthma exacerbations.

Table 11. Distribution of Selected Fetal Outcomes among Subject Who Experienced Asthma Exacerbations in Pregnancy versus Those Who Did Not.

Fetal Outcomes	Specific measures of asthma exacerbations:					
	Hospitalization(s) for asthma		Unscheduled asthma visits		Asthma exacerbations***	
	Yes N(%)	No N(%)	Yes. N(%)	No N(%)	Yes N(%)	No N(%)
Preterm delivery*	10 (16.4)	50 (7.6)	11 (7.2)	49 (8.7)	24 (10.3)	36 (7.4)
	0.018		p=0.560		p=0.198	
SGA* (birth **weight** ≤10th %)	4 (6.6)	37 (5.7)	10 (6.5)	31 (5.5)	15 (6.4)	26 (5.4)
	p=0.775		p=0.634		p=0.578	
SGA* (OFC ≤ 10th %)	5 (11.6)	59 (11.1)	16 (13.2)	48 (10.5)	20 (10.9)	44 (11.2)
	p=0.907		p=0.907		p=0.907	
Apgar score (1 min) ≤ 7*	8 (17.4)	81 (14.6)	18 (14.4)	71 (15.0)	30 (15.8)	59 (14.4)
	p=0.612		p=0.878		p=0.654	
Birth weight (g)**	*Mean± ±s.d*	*Mean± ±s.d*	*Mean± ±s.d*	*Mean± ±s.d*	*Mean± ±s.d*	*Mean± ±s.d*
	3,430± ±444	3,522± ±514	3,527± ±539	3,511± ±501	3,487± ±514	3,528± ±507
	p=0.214		p=0.749		p=0.335	

* Sample size was restricted to live-born singletons

** Sample size was restricted to live-born, full-term singletons

** Defined as occurrence of one or more of the following: hospitalization for asthma during pregnancy, unscheduled physician visit for asthma during pregnancy, burst use of systemic corticosteroids.

Preterm delivery remained significantly associated with asthma symptom control during the first part of pregnancy (OR=1.93; 95% CI: 1.10; 3.40) and hospitalizations for asthma (OR=2.29; 95% CI: 1.06; 4.94) after adjustment for maternal age, body mass index, gravidity, parity, family socioeconomic status, smoking, and ethnicity (Table 12). The risk of preterm delivery was almost twice as high among subjects with inadequate asthma control (OR=1.83; 95% CI: 1.04; 3.25) compared with subjects with adequate asthma control independent from systemic steroid use and other risk factors (Table 12). Even though an association between hospitalizations for asthma and preterm delivery became of borderline statistical significance (p=0.080) after adjustment for systemic corticosteroid use in addition to other covariates, the magnitude of association did not change considerably (OR=2.02; 95% CI: 0.92; 4.42).

Table 12. Multivariate Analysis for Preterm Delivery.

Asthma control measures:	OR	95% CI	Overall p-value
Asthma symptom control – 1st part of pregnancy:		Unadjusted:	
Poor/Fair vs. Adequate	1.90	1.11; 3.25	0.019
		Model 1*:	
	1.93	1.10; 3.40	0.023
		Model 2**:	
	1.83	1.04; 3.25	0.038
Hospitalization(s) for asthma during pregnancy:		Unadjusted:	
Yes vs. No	2.39	1.14; 4.98	0.021
		Model 1*:	
	2.29	1.06; 4.94	0.034
		Model 2**:	
	2.02	0.92; 4.42	0.080

* Adjusted for maternal age, BMI, gravidity, parity, SES, smoking in pregnancy, ethnicity.
** Adjusted for maternal age, BMI, gravidity, parity, SES, smoking in pregnancy, ethnicity, and use of systemic corticosteroids in pregnancy.

Assessment of Interaction between Fetal Sex and Asthma in Relation to Fetal Growth.

Linear regression models fitted to evaluate the interaction between fetal sex and asthma symptom control and between fetal sex and asthma exacerbations in relation to mean birth weight yielded non-significant results (p=0.810 and p=0.323 for interaction terms, respectively). Two logistic regression models fitted to evaluate the interaction between fetal sex and asthma control and fetal sex and asthma exacerbations in relation to SGA (i.e., birth weight $\leq 10^{th}$ percentile) also yielded non-significant results (p=0.237 and p=0.453 for interaction terms, respectively). Thus, in this study population, fetal sex did not have a differential effect on the association between asthma control and fetal growth measures.

4. STUDY I: SUMMARY OF RESULTS

1. Incidence of preterm delivery was almost doubled among women who had inadequately controlled asthma during the first part of pregnancy compared with women who had adequately controlled asthma independent from maternal age, BMI, gravidity, parity, socioeconomic status, ethnicity, and use of systemic corticosteroids.
2. Incidence of preterm delivery was even higher among women whose asthma exacerbations during pregnancy were severe enough to require hospitalization compared with asthmatic women who did not require hospitalizations for their asthma. However, results were of borderline statistical significance in the final multivariate model possibly due to relatively small number of women in the study who required hospitalizations for asthma.
3. Contrary to expected, the incidence of preeclampsia/PIH was lower among subjects who experienced severe asthma exacerbations during pregnancy compared with subjects without exacerbations, even though estimates were based on very small numbers.
4. This study was not able to demonstrate the effect of inadequate asthma control on other maternal and fetal perinatal outcomes. Due to low incidence of some adverse perinatal outcomes it was difficult to fully evaluate the effect of asthma control and asthma exacerbations on these outcomes. Additionally, measures of asthma control used in this study might not capture the entire range of asthma severity and symptoms.

5. This study did not support the hypothesis that fetal sex might have a differential effect on the association between maternal asthma and fetal growth measures.

5. STUDY I: DISCUSSION

This study demonstrated that the risk posed by disease on some perinatal outcomes might be substantial. Thus accurate and repeated assessment of disease control is crucial when medications are evaluated for their safety in pregnancy.

In this study, poor maternal asthma symptom control and a history of hospitalizations for asthma during pregnancy each doubled the risk of preterm delivery (i.e., $\leq$ 37 gestational weeks) independent of other risk factors. Increased risk of preterm delivery in this group of patients might be attributed to hypoxia caused by severe and uncontrolled asthma or to an effect of gestational asthma therapy – two factors which are often difficult to disentangle. Systemic corticosteroids are a class of asthma medications which presents a particular concern for safety in pregnancy. They have been found to increase the risk of preterm delivery independent of other factors in three large cohort studies [11-13]. In our study, maternal asthma symptom control remained significantly associated with preterm delivery after adjustment for use of systemic corticosteroids in addition to other risk factors. Association between hospitalizations for asthma and preterm delivery became of borderline statistical significance after adjustment for use of systemic steroids possibly indicating a statistical power issue, while the magnitude of association was not dramatically affected. Thus, the effect of maternal asthma on preterm delivery seems to be independent from the effect of systemic corticosteroids and other risk factors.

Even though previous reports examining an association between maternal asthma and preterm delivery are inconsistent, at least five previous studies reported a positive association [9, 43, 45, 74, 98]. In these studies risk of preterm delivery ranged from 1.15 to 2.2, which is similar to our findings. Several studies reported that an association between maternal asthma and preterm delivery was only limited to subjects with severe asthma [74] or was stronger in those subjects [43] suggesting a dose-response trend.

In our study two measures of maternal asthma control (i.e., asthma symptom control during the first part of pregnancy and hospitalizations for asthma anytime in pregnancy) increased the risk of preterm delivery. Interestingly, asthma symptom control later in pregnancy (i.e., at 26 and 32 gestational weeks) was not associated with preterm delivery. The majority of previous studies, which reported a positive association between maternal asthma and preterm delivery in asthmatic women versus non-asthmatic controls, utilized an electronic record linkage study design and could not assess any change in asthma severity and control during the course of pregnancy [9, 43, 45, 98]. In the MFMU study, an increased risk of preterm delivery was observed in subjects with severe asthma and the classification of asthma severity was determined upon enrollment [74]. Since the average timing of enrollment in the MFMU study was 18 gestational weeks, it seems likely that the increased risk of preterm delivery in that study was influenced by severe asthma during the first part of pregnancy.

While poor asthma control was associated with preterm delivery in our study, no increased risk of other adverse perinatal outcomes was observed. Several factors

could account for these results. First, self-reported measures of asthma control utilized in this study may not be adequately sensitive or specific to identify severe asthma or asthma that is sufficiently uncontrolled to substantially increase the risk of some perinatal outcomes. In some earlier reports, e.g., the MFMU study, lower pulmonary function but not increased asthma symptoms was associated with adverse perinatal outcomes [49]. Second, factors that determine gestational length and preterm birth may be more sensitive to uncontrolled asthma than factors that influence other adverse perinatal outcomes. Similarly to our results, in the MFMU study, lower pulmonary function affected prematurity but not IUGR [49]. Third, an association between maternal asthma and fetal growth reported in some previous studied could be confounded by the effect of maternal asthma on gestational length. The incidence of low birth weight (less than 2500 grams) or mean birth weight are frequently used as outcomes in studies evaluating effect of maternal asthma on fetal growth. However, without attention to gestational age of the infant, low birth weight as an outcome measure inappropriately combines distinct outcomes with potentially different causes and very different clinical consequences. For example, low birth weight that occurs in a preterm infant whose size is appropriate for gestational age may have different antecedent causes than low birth weight occurring in a full-term infant whose size is small for gestational age [97]. Thus infants categorized as low birth weight can constitute a mixture of growth restricted preterm infants, growth restricted full-term infants, and normal growth preterm infants.

In this study, subjects who experienced severe asthma exacerbation(s) during pregnancy had significantly lower incidence of preeclampsia/PIH compared with

asthmatic subjects without asthma exacerbations during pregnancy. This finding seems to contradict previous reports which either found an increased risk of preeclampsia in asthmatic women [9, 43, 45] or did not find any association [22, 66, 74]. However, the majority of previous studies compared the prevalence or incidence of preeclampsia in pregnant women with asthma versus non-asthmatic controls, while in our study the incidence of preeclampsia was evaluated among asthmatic subjects. Some previous studies reported that an association between preeclampsia and oral corticosteroids could represent a drug effect [10], although a possible biological mechanism for this association is unclear.

In our study several factors could influence the observed reduced risk of preeclampsia/PIH among subjects with severe asthma exacerbations. First, higher prevalence of smoking among women with inadequate asthma control could confound the association since smoking during pregnancy has consistently been shown to reduce the risk of preeclampsia (reviewed by Conde-Agudelo, 1999 [99]). The biological mechanism by which smoking reduces the risk of preeclampsia is uncertain, even though several hypotheses have been proposed including nicotine-induced inhibition of thromboxane A2 synthesis which plays an important role in endothelial dysfunction, inhibition of cytokine production, and antioxidant activity of nicotine [99]. Second, higher proportion of nulliparous women among those with adequately controlled asthma could result in a higher incidence of preeclampsia/PIH in these subjects since nulliparity is a strong risk factor for preeclampsia (reviewed by Duckitt, 2005 [100]). Finally, increased use of short-acting β_2-agonists as rescue medications among subjects with poorly controlled asthma may also serve as a confounder of the

inverse relationship between asthma exacerbations and preeclampsia/PIH. A recent study found that use of short-acting β_2-agonists during pregnancy is associated with a reduced risk of pregnancy-induced hypertension (but not preeclampsia) in asthmatic subjects [101]. The authors proposed that the observed association could be due to vasodilating effects of β_2-agonists (which could be more profound in hypoxic women with asthma than in general population) or the presence of residual confounding (e.g., inability to adjust for cigarette smoking in the study).

Unfortunately, a limited number of subjects with asthma exacerbations and preeclampsia in our study (e.g., among subjects with severe asthma exacerbations only three developed preeclampsia) did not allow us to control for these potential confounders in multivariate analysis.

A number of possible biological mechanisms have been proposed to account for the increased risk of adverse perinatal outcomes in women with asthma and include: 1) a common pathological pathway in asthmatic patients leading to hyperactivity of both uterine and bronchial smooth muscles; 2) maternal and fetal hypoxia due to severe and/or uncontrolled asthma; 3) release of bioactive mediators, such as inflammatory products, from the mother; 4) altered placental function, including placental blood flow and enzyme activity; 5) maternal smoking; and 6) use of asthma medications in pregnancy [9, 49, 102]. Some authors suggest that an increased risk of adverse perinatal outcomes associated with severe and/or poorly control asthma is a result of a complex interaction of factors noted above [102].

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Bakhireva LN, Schatz M, Chambers CD. Effect of Maternal Asthma and Gestational Asthma Therapy on Fetal Growth. Review Article. *Journal of Asthma*. 2007; 44(2) (in press).

Bakhireva LN, Jones KL, Schatz M, Klonoff-Cohen H, Johnson D, Slymen D, Chambers CD, The Organization Of Teratology Information Services Research Group. Safety of Leukotriene Receptor Antagonists in Pregnancy. *J Allergy Clin Immunol*. 2007:199(3):618-25.

The dissertation author was the primary researcher and author, while the co-authors listed in these publications directed and supervised research or acted as junior collaborators.

CHAPTER 5: STUDY II

EFFECT OF FETAL SEX ON

MATERNAL ASTHMA COURSE IN PREGNANCY

1. STUDY II: LITERATURE REVIEW

Fetal sex has been implicated as one of the factors which might influence the course of asthma during the pregnancy. Dodds et al. reported that 14% of women carrying a male fetus require corticosteroids for treatment of their asthma compared with 20% of women carrying a female fetus [103]. Authors of that study proposed that higher use of corticosteroids among pregnant women carrying a girl might indicate that the women had more severe asthma.

Furthermore, Beecroft et al. reported that a greater proportion of pregnant women carrying a girl tended to report an increase in asthma symptoms during pregnancy (i.e., cough, shortness of breath, nocturnal waking, general state of asthma, and visits to doctors) compared with women carrying a boy [104]. Even though sample size in that study was limited to only 34 women and self-reported change in asthma symptom control was evaluated only up to the second trimester of pregnancy, a broad spectrum of asthma symptoms was evaluated.

In a recent cohort study, which examined an effect of fetal sex on peak expiratory flow (PEF) lability (an objective measure of asthma severity/control in pregnancy), pregnant asthmatic women carrying a female fetus had increased peak expiratory flow lability, indicating increased asthma severity [105]. Women carrying a male fetus had an improvement in airway lability by almost 10% throughout the pregnancy compared with women carrying a female fetus [105]. The longitudinal analysis conducted in that study provided the opportunity to evaluate the effect of fetal sex on the objective measure of asthma severity/control evaluated repeatedly over the

course of pregnancy; however, the study had limited ability to measure the effect of fetal sex during the first trimester.

Contrary, other studies found no effect of fetal sex on maternal asthma [95, 106]. Results of the Kaiser-Permanente Prospective Study of Asthma During Pregnancy did not find fetal sex to be a significant predictor of asthma course during pregnancy [106]. In the Canadian database linkage study, having an ED visit for asthma was not associated with fetal sex (OR 1.01; 95% CI: 0.85-1.19).

Biological mechanisms which might explain the effect of fetal sex on asthma severity/control during pregnancy remain uncertain. The presence of a female fetus was hypothesized to upregulate maternal inflammatory pathways, thus worsening asthma symptoms. It has been reported that the presence of a female fetus is associated with increased maternal circulating monocytes, which release numerous cytokines and contribute to worsening of asthma symptoms [93].

It has been hypothesized that a protective effect observed among women carrying a male fetus might be more notable during the second trimester of pregnancy, when production of testosterone by the male fetus peaks [105]. Some reports suggest that testosterone might influence β-adrenergic-mediated relaxation of bronchial tissue and inhibit response to histamine [105, 107]. In fact, the protective effect of the male fetus on maternal asthma severity observed in the study by Beecroft et al. was noted in the second trimester of pregnancy. However, Kwon et al. were not able to support their hypothesis that fetal effect on PEF lability would peak in the second trimester [105].

Based on previous studies one might hypothesize that asthmatic women carrying a girl might have more severe asthma, but effects of maternal asthma and hypoxia could have a greater effect on the male fetus. However, as described above, results of the previous studies are contradictory. The majority of previous studies examined the effect of fetal sex in a post-hoc analysis using proxy measures of asthma severity/control. Heterogeneity of results from previous reports presents a strong need to test this hypothesis in other studies.

2. STUDY II: METHODS

Power Analysis.

The purpose of this study was to estimate the effect of fetal sex (male vs. female) on maternal asthma control. On average, 50% of newborns are males and 50% are females. Among 819 women with asthma in the sample, 410 were expected to be pregnant with boys and 409 with girls. Power analysis for this specific aim is presented in Table 13.

Table 13. Power Analysis for Study II.

Outcome	Given sample size in group 1 (male fetus)	Given sample size in group 2 (female fetus)	P1*	Effect size which study is powered to detect	Power
Poor asthma control	410	409	10%	OR=1.8	80%
Poor/fair asthma control	410	409	43%	OR=1.5	80%

*Assumed prevalence of inadequate asthma control among women carrying male fetuses.

The study had 80% power to detect a 1.8-fold increased risk of having poorly controlled asthma and 1.5-fold increased risk of having poorly or fairly controlled asthma among women carrying a female fetus compared with women carrying a male fetus.

Statistical Analyses.

Description of the study population:

For all analyses conducted for this specific aim, only women with asthma were considered. Distribution of demographic, lifestyle, and reproductive health variables were compared among asthmatic women who gave birth to male children versus

women who gave birth to female children. ANOVA was used for continuous variables and $\chi 2$ tests for categorical variables.

Description of the sample:

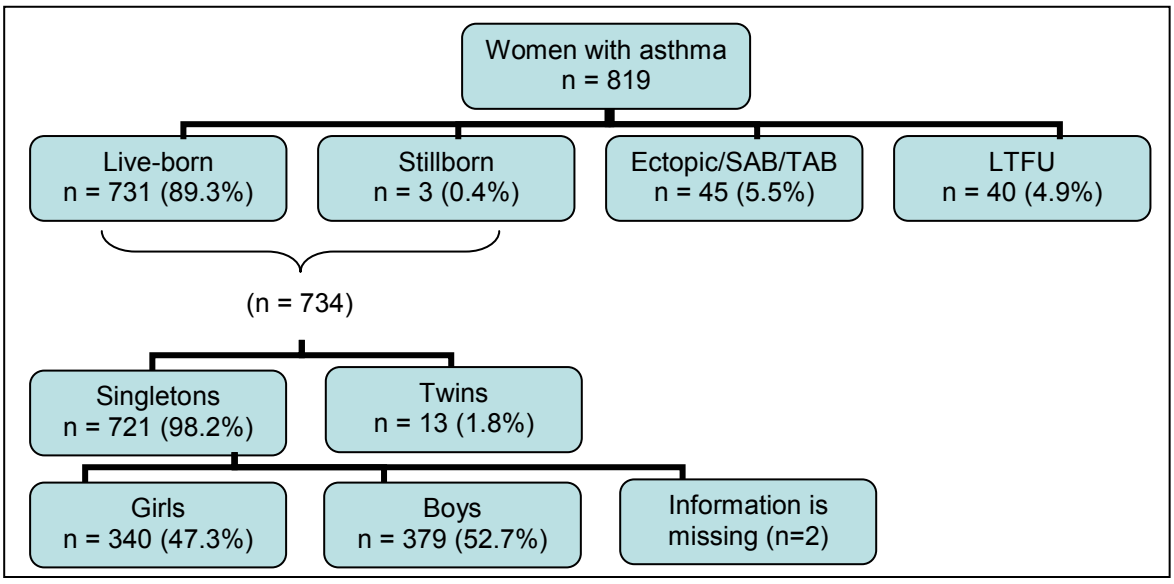

Figure 2. Selection of the Study Sample for Study II.

Among 819 women with asthma in the OTIS Asthma Medications in Pregnancy Study, 731 (89.3%) of pregnancies results in live-born children, 3 (0.4%) in stillbirths, 45 (5.5%) in a pregnancy loss due to ectopic pregnancy, spontaneous abortion (SAB) or terminated abortion (TAB), and 40 (4.9%) were lost to follow up (LTFU). For purposes of the present study, subjects who had a pregnancy loss (ectopic pregnancy/SAB/TAB) or were lost to follow up were excluded from the analysis since fetal sex was unknown for majority of them. Among 734 pregnancies which resulted in live-born or stillborn children, 721 (98.2%) gave birth to singletons and 13 (1.8%) gave birth to twins. Twin pregnancies were excluded from this analysis since the effect of fetal sex in opposite- and same-sex twin pairs might have different effect on maternal asthma compared with effect of singletons and could introduce bias. Among

721 singleton pregnancies, 340 (47.3%) resulted in a birth of a girl, 379 (52.7%) in a birth of a boy, and two subjects had missing values for this variable.

Univariate analyses:

Proportion of subjects at each level of asthma control (adequate, fair, poor) was compared among women who gave birth to male children versus women who gave birth to female children using $\chi 2$ test. This analysis was conducted for each time point when asthma control was assessed (enrollment, 26, and 32 gestational weeks). In addition to asthma symptom control, the incidence of asthma exacerbation manifestations (i.e., hospitalizations for asthma during pregnancy, unscheduled asthma visits, use of systemic corticosteroids, or a combination of these measures) was compared between women carrying a girl versus women carrying a boy using $\chi 2$ tests.

Longitudinal analysis of the effect of fetal sex on maternal asthma control over the course of pregnancy was conducted using the generalized estimating equations (GEE) approach for repeated measures. A GEE model was fitted using the REPEATED statement in the GENMOD procedure of SAS to account for repeated measures of asthma symptom control. Since the outcome variable (asthma control) is ordinal (adequate/fair/poor), a cumulative logit link function was used (i.e., dist=multinomial link=cumlogit). The independent working correlation structure was chosen (type=ind) for this analysis. Fetal sex by time interaction term was tested in the GEE model in addition to the main effects.

Since subjects were eligible to enroll up to 20 gestational weeks of pregnancy, some enrolled at the beginning of the second trimester of pregnancy. A longitudinal analysis was repeated on a subset of subjects who enrolled during their first trimester

(≤ 13 gestational weeks) in order to capture potential changes in asthma severity between the first and subsequent trimesters in relation to fetal sex.

Multivariate analyses:

Multivariate logistic regression was used to assess associations between fetal sex and different measures of asthma control and exacerbation in pregnancy. However, none of the evaluated covariates changed crude point estimates for more than 5%, thus limiting the value of multivariate analysis for this specific aim.

3. STUDY II: RESULTS

The distribution of selected maternal demographic, lifestyle, and reproductive health characteristics by fetal sex is presented in Table 14. No differences in maternal age, BMI, gravidity, parity, ethnicity, socioeconomic status, use of tobacco or alcohol anytime in pregnancy were observed among asthmatic women pregnant with a boy compared with asthmatic women pregnant with a girl (all p-values >0.1).

Table 14. Maternal Characteristics by Fetal Sex.

Maternal Characteristics	**Pregnancy with a girl** (N=340)	**Pregnancy with a boy** (N=379)	**Overall p-value**
	N (%)	N (%)	
Maternal Age:			0.539
<25 years	31 (9.1)	41 (10.8)	
25-34 years	200 (58.8)	229 (60.4)	
35+ years	109 (32.1)	109 (28.8)	
BMI (kg/m^2):			0.416
<24	166 (48.8)	191 (50.4)	
24-28	92 (27.1)	87 (22.9)	
>28	82 (24.1)	101 (26.7)	
Gravidity >1	216 (63.5)	230 (60.7)	0.433
Parity >0	156 (45.9)	173 (45.7)	0.950
White Non-Hispanic	306 (90.5)	334 (88.1)	0.299
Any Tobacco Use	32 (9.5)	43 (11.4)	0.414
Any Alcohol Use	164 (50.8)	164 (46.1)	0.220
SES status above average[†]	243 (72.8)	261 (69.8)	0.384

[†] Hollingshead four factor socio-economic status category 1 or 2 on a scale of 1-5 with 1 being the highest.

When the level of asthma symptom control (adequate/fair/poor) was compared among women carrying a girl versus women carrying a boy no difference between the groups (p>0.1) was observed during the second part of pregnancy (Table 15). However, some differences in the asthma control by fetal sex were observed during the first part of pregnancy (i.e., less than or equal to 20 gestational weeks). Namely, a higher proportion of asthmatic women carrying a girl had poor asthma symptom

control during the first part of pregnancy (13.5%) compared with asthmatic women carrying a boy (9.7%). Even though these differences in asthma control were statistically significant (p=0.037), there was no obvious dose-response relationship between the level of asthma symptom control and fetal sex. In fact, a higher proportion of women carrying a boy had fair asthma control (36.2% vs. 27.8%) and slightly higher proportion of women carrying a girl had adequate control of their asthma symptoms (58.7% vs. 54.1%).

Table 15. Effect of Fetal Sex on Maternal Asthma Symptom Control in Pregnancy.

Asthma Control	Pregnancy with a girl	Pregnancy with a boy	p-value
	N (%)*	N (%)*	
Asthma control – 1st interview (≤20 gest. wks)			0.037
Adequate	196 (58.7)	200 (54.1)	
Fair	93 (27.8)	134 (36.2)	
Poor	45 (13.5)	36 (9.7)	
Asthma control – 26 gest. wks			0.415
Adequate	190 (63.3)	221 (66.0)	
Fair	84 (28.0)	94 (28.1)	
Poor	26 (8.7)	20 (6.0)	
Asthma control – 32 gest. wks			0.405
Adequate	202 (67.1)	243 (71.9)	
Fair	69 (22.9)	68 (20.1)	
Poor	30 (10.0)	27 (8.0)	

* Sample size varies due to missing data

Among asthmatic women selected for this study, 61 (8.5%) had been hospitalized for asthma sometime during pregnancy and 153 (21.3%) had unscheduled clinic visits for asthma. Among 112 women who used systemic corticosteroids sometime during pregnancy, 11 (9.8%) used them regularly (i.e., more than 6 weeks at any trimester), while remaining 101 subjects were considered to be “burst users”.

Severe asthma exacerbations, defined as occurrence of one or more asthma exacerbation measures described above, occurred in 234 (32.6%) women in this study.

Table 16. Effect of Fetal Sex on Maternal Asthma Exacerbations in Pregnancy.

Measures of asthma exacerbation(s)	Pregnancy with a girl	Pregnancy with a boy	p-value
	N (%)*	N (%)*	
Hospitalization(s) for asthma	38 (11.2)	23 (6.1)	0.014
Unscheduled asthma visits – anytime in pregnancy	75 (22.1)	78 (20.6)	0.629
Unscheduled asthma visits: 1st interview	38 (12.8)	27 (8.2)	0.060
Unscheduled asthma visits: 26 gest. wks	28 (8.5)	35 (9.7)	0.580
Unscheduled asthma visits: 32 gest. wks	19 (5.8)	29 (8.0)	0.252
Any use of systemic corticosteroids	47 (13.8)	65 (17.2)	0.219
Burst use of systemic corticosteroids	42 (12.5)	59 (15.8)	0.213
Asthma exacerbation*	116 (34.1)	118 (31.1)	0.394

* Occurrence of one or more of the following: hospitalizations for asthma, unscheduled asthma visits, burst use of systemic corticosteroids.

As shown in Table 16, a higher proportion of asthmatic pregnant women carrying a girl had been hospitalized for asthma during pregnancy (11.2%) compared with pregnant women carrying a boy (6.1%; p=0.014). While no difference in unscheduled asthma visits anytime during pregnancy was observed among two groups (p=0.629), a trend of borderline statistical significance was observed for unscheduled asthma visits during the first part of pregnancy. Namely, 12.8% of asthmatic pregnant women carrying a girl had unscheduled asthma visits during the first part of pregnancy compared with only 8.2% of women carrying a boy (p=0.060).

No difference in the use of systemic corticosteroids (either "any" or "burst") was observed among study groups (p>0.05). Additionally, use of systemic corticosteroids during the first part of pregnancy also did not vary among study groups

(p=0.906; data not shown). Despite some differences in hospitalizations for asthma and unscheduled asthma visits during the first part of pregnancy, no difference in the overall incidence of severe asthma exacerbations has been observed among study groups (p=0.394).

Fetal sex by time interaction, evaluated in longitudinal analysis by GEE for repeated measures of asthma symptom control, yielded non-significant results (p=0.206). Thus, results of the GEE analysis suggests that fetal sex was not significantly associated with a change in asthma symptom control over the course of pregnancy in this population. When the analysis was repeated for a subset of 352 asthmatic subjects who enrolled in the study during the first trimester of pregnancy (≤ 13 gestational weeks), results remained non-significant (p=0.102; data not shown).

An additional analysis was conducted to evaluate whether women who did not demonstrate an early effect of fetal sex on asthma control (i.e., were adequately controlled during the first part of pregnancy) get a differential fetal effect later. In this sub-group, 2.8% of women carrying a girl reported poor asthma control at the second maternal interview compared with 2.7% of women carrying a boy (p=0.952), and 5.0% of women carrying a girl reported poor asthma control at the third interview compared with 3.7% of women carrying a boy (p=0.803). The proportion of women with “fair” symptom control also did not vary by fetal sex.

4. STUDY II: SUMMARY OF RESULTS

1. Fetal sex appeared to be weakly associated with asthma symptom control during the first part of pregnancy, even though no obvious dose-response trend could be detected.
2. Results of longitudinal analysis did not support the hypothesis that fetal sex was associated with an overall change in asthma symptom control during the course of pregnancy.
3. Women who did not get any effect of fetal sex on asthma control early in pregnancy (i.e., were adequately controlled during the first part of pregnancy) did not get a fetal effect later.
4. However, some differences in the specific measures of asthma exacerbation by fetal sex were observed. Namely, asthmatic pregnant women carrying a girl had significantly more hospitalizations for asthma during pregnancy compared with women carrying a boy. Additionally, there was a tendency for women carrying a girl to have more unscheduled asthma clinic visits during the first part of pregnancy.
5. Use of systemic corticosteroids and the incidence of severe asthma exacerbations were similar among two study groups.

5. STUDY II: DISCUSSION

Even though no overall effect of fetal sex on a change in maternal asthma symptom control during pregnancy was observed in the longitudinal analysis, the presence of female fetus was associated with significantly higher rate of hospitalizations for asthma and a tendency for increased number of clinic visits for asthma exacerbations. Self-reported measures of asthma symptom control utilized in this study might not be adequately sensitive or specific enough to capture the effect of fetal sex, while health care utilization measures (i.e., hospitalizations and clinic visits) might be more objective measures of maternal asthma control.

Similarly to some earlier reports, this study suggests that an effect of fetal sex on maternal asthma might be more evident during the first part of pregnancy and then appears to be lost as pregnancy progresses. Such an early effect might be due to some physiological factors or a change in gestational asthma therapy during the course of pregnancy. It has been hypothesized that the sex differences would peak in the second trimester due to surge of testosterone in male fetuses between 12 and 16 weeks. While Beecroft and colleagues reported a greater prevalence of asthma symptoms during the second trimester in female-bearing pregnancies [104], Kwon and co-authors failed to demonstrate that the difference in PEF lability between male- and female-bearing pregnancies peaks during the second trimester [105]. A fetal sex-specific effect on the maternal immune system was also proposed as a possible biological mechanism; however, timing of this effect during pregnancy was not determined [93]. In our study population with good access to health care, lack of a fetal sex-specific effect later in pregnancy could occur if asthma therapy was increased in women carrying a female

fetus as the pregnancy progressed to mitigate poor asthma control and prevent severe exacerbations.

A number of studies have tried to establish an association between fetal sex and serum steroid level in maternal serum, umbilical cord blood, and amniotic fluid. In singleton pregnancies, some studies found higher androgen levels in maternal blood in male-bearing pregnancies [108], while others failed to detect any difference by fetal sex [109-112].

The association seems to be more consistent in studies examining hormone levels in amniotic fluid or cord blood. Several earlier studies presented convincing evidence that testosterone levels are higher in amniotic fluid [111, 113] and umbilical cord blood [114] in the presence of a male fetus compared with a female fetus. Contrary, others failed to detect any significant differences in the levels of estrogen, progesterone, testosterone, growth hormone, prolactin, and dehydro-epiandrosteron-sulfate (DHEAS) measured in umbilical cord blood between male- and female-bearing pregnancies [109].

Female-bearing pregnancies were reported to be associated with significantly higher human chorionic gonadotropin (hCG) measured in maternal blood, amniotic fluid, and cord blood [109, 115, 116]; however the reason for this difference is unclear.

The few studies conducted in opposite-sex twin pregnancies found some evidence of masculinization in female fetuses [117, 118] presumably due to increased prenatal testosterone exposure through direct or indirect hormone transfer from their twin brothers. However, a recent study in twin pregnancies found no difference in

maternal serum steroid levels (i.e., testosterone, progesterone, DHEAS, sex hormone-binding globulin, estradiol, and androstenedione) among mothers carrying male-male, female-female, and opposite-sex twin pairs [119].

Lack of hormonal differences in maternal blood among male- and female-bearing pregnancies observed in the majority of studies argues against the indirect (a.k.a., maternal-fetal) route of hormonal transfer [119]. It seems that the evidence of masculinization of female fetuses in opposite-sex twin pairs and increased level of androgens in amniotic fluid and umbilical cord blood in male-bearing pregnancies result from the feto-fetal hormonal transfer route. Thus, fetal sex and fetal hormones might have a limited effect on maternal hormonal status questioning the role of fetal testosterone in maternal asthma.

Given heterogeneity of previous reports, modest effect observed in the current study, limited support in the literature for the maternal-fetal route of hormonal transfer, and other risk factors which strongly influence the course of asthma during pregnancy (e.g., baseline asthma severity, viral or bacterial respiratory infections, adherence to treatment, smoking, gastroesophageal reflux, stress, maternal body weight [5, 102]), fetal sex as a predictor of maternal asthma control might be of limited clinical use. Nevertheless, its effect might help to better understand changes in maternal immune system that occur in pregnancy and ultimately affect the course of asthma.

CHAPTER 6: STUDY III

SAFETY OF LEUKOTRIENE RECEPTOR ANTAGONISTS IN PREGNANCY

1. STUDY III: LITERATURE REVIEW

Leukotriene receptor antagonists (montelukast and zafirlukast) are newer controller medications for treatment of asthma which antagonize the contractile activity of leukotrienes C4, D4, and E4 in airway smooth muscles. Leukotrienes are biologically active fatty acids derived from arachidonic acid. They cause pathophysiological reactions in patients with asthma which lead to increased bronchial hyperresponsiveness and severe bronchospasm. Leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. Thus, leukotriene antagonists improve asthma symptoms by attenuating these pathological effects.

Zafirlukast is marketed as Accolate® by Zeneca Pharmaceuticals. Pretreatment with zafirlukast has been shown to inhibit bronchoconstriction caused by sulfur dioxide and cold air in patients with asthma. Pretreatment also attenuates reactions caused by grass, cat dander, ragweed, and mixed antigens. Montelukast, marketed by Merck as Singulair®, is a selective leukotriene receptor antagonist that inhibits the cysteinyl leukotriene (CysLT1) receptor.

Both montelukast and zafirlukast have been assigned an FDA pregnancy category “B”. The rationale is that animal studies have not demonstrated a risk to the fetus, but there are no adequate studies in pregnant women [120]. Merck Pharmaceuticals preclinical studies demonstrated that Singulair® crosses the placenta in rats and rabbits and appears in milk. Reduction in fertility in female rats has been noted at the dose 200mg/kg/d that is 160 times higher the maximum human dose. No increased incidence of malformations in pregnant rats at the dose 499 mg/kg/d (320

times higher than the maximum human dose) and rabbits at the dose 300 mg/kg/d (490 times higher the maximum human dose) have been observed.

Merck Pharmaceuticals maintains the Pregnancy Registry Program for Singulair® (montelukast) [121]. As of July 2006, information from 203 complete prospective records has been collected, and eight major congenital anomalies have been identified [122]. These include absent left hand allegedly secondary to amniotic bands; two cases of hypospadias; chordee; calcaneous valgus; triploidy 69XXY which resulted in termination at 12 gestational weeks; polydactyly; and one case with cystic kidney disease, bilateral hydroceles, and cleft tongue. The birth prevalence of major structural anomalies in the Merck Registry was 3.5% (7 out of 200 prospective live births), which is similar to the 3-4% rate in the general U.S. population. Merck also reported that among pregnant women exposed to montelukast, there was no increased risk of spontaneous abortions, low birth weight infants, or preterm deliveries noted relative to expected numbers in the general population.

From prospective and retrospective reports collected internationally, in addition to the absent left hand and polydactyly cases mentioned above, Merck has identified four additional cases of possible congenital limb reduction defects and has considered this information as a signal of a potential increased risk for this category of birth defects in association with exposure to Singulair®. However, a plausible biological mechanism by which montelukast can cause limb defects is unknown. To investigate a potential signal further Merck conducted a health insurance claims study with medical record review; no limb reduction defects were identified in offspring of 1535 women who used montelukast during pregnancy [122].

Data reported by the Merck Pregnancy Registry Program should be interpreted with caution due to numerous methodological limitations. The registry lacks an internal comparison group and the rates reported from the Registry were compared with the U.S. background rates which might not reflect the same source population. Some selection biases are likely to influence results since no systematic reporting system has been used, retrospective reports can involve biased ascertainment, and 37% of prospective cases were lost to follow-up. Additionally, the effect of asthma severity and/or control was not taken into account, and no information about maternal risk factors and other medications taken in pregnancy is available.

Preclinical studies conducted by the Zeneca Pharmaceutical to evaluate safety of zafirlukast (Accolate®) in pregnancy demonstrated no teratogenicity in mice at a dose 160 times higher than the maximum human dose, in rats at a dose 419 times higher than the maximum human dose, and in monkeys at a dose 120 times higher than the maximum human dose. In rats, at a dose 419 times higher than the maximum human dose, maternal toxicity and death were observed. In monkeys, at the dose 120 times higher than the maximum human dose, spontaneous abortions have been reported. No adequate and well-controlled trials have been conducted in pregnant women.

The safety of LTRAs in pregnancy has been previously evaluated in only one clinical study. No statistically significant associations with IUGR or preterm delivery were noted; however, only 9 subjects were exposed [12]. In the absence of controlled clinical studies with adequate power, it is premature to draw any conclusions about safety of LTRAs in pregnancy. A position statement from the American College of

Obstetricians and Gynecologists (ACOG) and the American College of Allergy, Asthma and Immunology (ACAAI) recommends use of zafirlukast and montelukast only “in patients with recalcitrant asthma who have shown a uniquely favorable response prior to becoming pregnant” [123]. The NAEPP exert panel report released in 2005 recommends LTRAs as an alternative (not preferred) therapy in patients with mild persistent asthma with a prior good response or as an add-on therapy to inhaled steroids in patients with moderate persistent asthma [19].

2. STUDY III: METHODS

Power Analysis.

The purpose of this study was to estimate the effect of LTRAs on perinatal outcomes. Power analysis for comparison of LTRAs (n=96) to a primary comparison group - non-asthmatic controls (n=346), relative to selected perinatal outcomes is presented in Table 17.

Table 17. Power Analysis for Study III.

Selected Outcomes	Given sample size in group 1 (non-asthmatic controls)	Given sample size in group 2 (LTRAs)	Mean1 or P1*	Effect size which study is powered to detect	Power
Mean birth weight	346	96	3530g	146 gram difference	80%
Mean maternal weight gain in pregnancy	346	96	15.5 kg	1.8 kg	80%
Major structural anomalies	346	96	3.2%	OR=3.99	80%
Small for gestational age	346	96	5%	OR=3.26	80%

* Mean value or incidence of the outcome among subjects in group1 (control group)

The study had 80% power to detect a 4-fold increased risk of major structural anomalies among LTRA users compared with non-asthmatic controls and a 3.26-fold increased risk for SGA. For continuous outcomes, the study was powered to detect smaller differences between groups as summarized in Table 17.

Statistical Analyses.

Description of the study population:

Women who used either montelukast or zafirlukast anytime in pregnancy with or without other medications were classified into the LTRA group (n = 96). In addition to the non-asthmatic comparison group (n = 346), 122 women who exclusively used short-acting β_2-agonists throughout pregnancy served as the asthma comparison group. This group represents women with a physician-diagnosed asthma that was mild enough to require treatment with only rescue medications. Moreover, short-acting β_2-agonists are considered generally safe for use in pregnancy [124] and should not adversely affect perinatal outcomes. Distribution of demographic, lifestyle, reproductive health variables, and measures of asthma control was compared among the three study groups in univariate analyses using ANOVA for continuous variables and $\chi 2$ tests for categorical variables.

Description of the sample:

Spontaneous abortion, stillbirth, and ectopic pregnancy were evaluated as one outcome, while all other maternal and fetal outcomes were evaluated among 497 pregnancies that resulted in a live birth. Additionally, the sample size was restricted to 490 live-born singletons when the incidence rates of preterm delivery, low Apgar scores, small for gestational age (SGA), and ponderal index were estimated, and to 447 full-term live born singletons when mean birth weight, height, and head circumference were analyzed. Prevalence of major structural anomalies was evaluated among live-born children and then separately among stillborn children and pregnancy terminations.

Univariate analyses:

Distribution of maternal and fetal perinatal outcomes was compared among the three study groups by ANOVA for continuous variables and $\chi 2$ tests for categorical variables.

Multivariate analyses:

Analysis of covariance (ANCOVA) was used to compare mean birth weight among the three study groups after adjustment for maternal age, BMI, weight gain in pregnancy, smoking, alcohol, SES, ethnicity, and parity. Moreover, mean birth weight was compared between the two asthmatic groups after adjustment for maternal asthma symptom control in addition to other covariates. Birth prevalence of major structural anomalies was compared among two asthmatic groups after adjustment for maternal asthma control by logistic regression.

3. STUDY III: RESULTS

In the OTIS Asthma Medications in Pregnancy Study, 96 women took LTRAs (72 - montelukast, 22 – zafirlukast, and 2- both) sometime during pregnancy. The majority of subjects had a first trimester exposure (89.6%) and 50% of women used LTRAs throughout the pregnancy. Over 85% of subjects took the recommended adult doses: 10mg daily for montelukast and 20mg twice a day for zafirlukast. Since LTRAs are often taken in combination with other controller and/or rescue medications, 99% of subjects in the LTRA group used short-acting β_2-agonists, 40% used oral corticosteroids, and 39% used inhaled corticosteroids sometime in pregnancy. The majority of subjects in the LTRA group who reported concurrent use of oral corticosteroids used them in a burst rather than continuous fashion.

Among 564 subjects in the three study groups, 497 (88.1%) had live-born children, 19 (3.4%) experienced a spontaneous abortion, three (0.5%) had stillborn children, one pregnancy (0.2%) was terminated, one subject (0.2%) had an ectopic pregnancy, and 43 (7.6%) subjects were lost to follow-up. There was no difference in the distribution of these birth outcomes among study groups ($p=0.362$; data not shown). Among 96 subjects in the LTRA group, 6 (6.3%) subjects were lost to follow up. Among remaining 90 subjects, 84 (93.3%) had live-born children, five (5.6%) reported spontaneous abortion, and one (1.1%) had a stillborn child.

Distribution of maternal characteristics in the LTRA group relative to non-asthmatic controls and exclusive short-acting β_2-agonist users is presented in Table 18. Significant differences among study groups were observed for BMI and SES ($p<0.05$). A higher proportion of asthmatic subjects were overweight ($p<0.001$), while women in

the non-diseased comparison group had a higher socioeconomic category (p=0.003). Interestingly, almost 15% of exclusive β_2-agonists users were smokers compared with only 8.3% of non-asthmatic controls and 7.4% of LTRA users (p=0.076).

Table 18. Maternal Characteristics by Treatment Group (n=564).

Risk Factors	LTRAs	ß$_2$-agonists only	Non-asthmatic	Overall p-value
	N (%)	N (%)	N (%)	
Maternal Age				
<25 years	9 (9.4)	20 (16.4)	42 (12.1)	0.101
25-34 years	54 (56.3)	66 (54.1)	222 (64.2)	
35+ years	33 (34.4)	36 (29.5)	82 (23.7)	
BMI (kg/m^2)				
<24	41 (42.7)	58 (47.5)	221 (63.9)	<0.001
24-28	23 (24.0)	29 (23.8)	79 (22.8)	
>28	32 (33.3)	35 (28.7)	46 (13.3)	
Gravidity >1	60 (62.5)	75 (61.5)	240 (69.4)	0.188
Parity >0	45 (46.9)	60 (49.2)	190 (54.9)	0.279
White non-Hispanic	83 (86.5)	111 (90.9)	293 (84.7)	0.219
Any tobacco use in pregnancy	7 (7.4)	18 (14.9)	28 (8.3)	0.076
Any alcohol use in pregnancy	43 (46.7)	60 (51.7)	156 (45.6)	0.521
SES status above average[†]	67 (71.3)	77 (64.7)	271 (79.7)	0.003

[†] Hollingshead four factor socio-economic status category 1 or 2 on a scale of 1-5 with 1 being the highest.

When the level of asthma control in pregnancy was compared among the two asthmatic groups, a much greater proportion of LTRA users had poor asthma symptom control, unscheduled clinic visits, and hospitalization for asthma during pregnancy compared with exclusive β_2-agonist users (Table 19). The observed pattern possibly reflects a greater underlying asthma severity in the LTRA group. Poor asthma control in the LTRA group could also be influenced by suboptimal use of other controller medications, e.g., only 39% concurrently used inhaled corticosteroids.

Table 19. Level of Asthma Control During Pregnancy.

Asthma Control Measures	LTRAs	ß$_2$-agonists only	p-value
	N (%)	N (%)	
1st part of pregnancy(≤ 20 gest. wks)**:**			
Control: Adequate	49 (51.6)	69 (58.5)	0.015
Fair	27 (28.4)	41 (34.8)	
Poor	19 (20.0)	8 (6.8)	
Unscheduled clinic visits	14 (17.3)	3 (2.9)	0.001
3rd trimester (32 gest. wks):			
Control: Adequate	43 (58.1)	66 (69.5)	0.063
Fair	18 (24.3)	23 (24.2)	
Poor	13 (17.6)	6 (6.3)	
Unscheduled clinic visits	11 (12.9)	3 (2.7)	0.006
Entire pregnancy:			
Unscheduled clinic visits	29 (30.2)	8 (6.6)	<0.001
Hospital admissions	16 (16.7)	4 (3.3)	<0.001

Use of LTRAs was not associated with a large risk of evaluated adverse maternal outcomes (Table 20). Incidence rates of preeclampsia/PIH, pregnancy loss, and mean maternal weight gain were similar among study groups (p>0.05). Differences of borderline statistical significance in the incidence of gestational diabetes were observed among study groups (p=0.069), with the highest rate observed among exclusive β_2-agonists users (7.1%).

Table 20. Selected Maternal Complications by Treatment Group.

Outcomes	LTRAs	ß$_2$-agonists only	Non-asthmatics	Overall p-value
	N (%)	N (%)	N (%)	
Pregnancy loss*:	6 (6.7)	6 (5.6)	11 (3.4)	0.338
SAB	5 (5.6)	6 (5.6)	8 (2.5)	
Ectopic pregnancy	0 (0.0)	0 (0.0)	1 (0.3)	
Stillbirth	1 (1.1)	0 (0.0)	2 (0.6)	
Gestational diabetes*	3 (3.7)	7 (7.1)	7 (2.3)	0.069
Preeclampsia/PIH*	3 (3.6)	5 (5.1)	6 (1.9)	0.241
	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	
Maternal weight gain (kg)**	16.7 (11.8)	14.8 (6.2)	15.6 (5.8)	0.194

SAB, spontaneous abortion; PIH, pregnancy induced hypertension.
* Subjects lost to follow up and terminated pregnancies were not included in denominator when rates were estimated.
** Sample size was limited to 497 pregnancies which ended up with a live birth.

The distribution of selected fetal/newborn outcomes among study groups is presented in Table 21.

Table 21. Selected Fetal/Newborn Outcomes by Treatment Group[1].

Outcomes	LTRAs	ß$_2$-agonists only	Non-asthmatics	Overall p-value
	Univariate Analyses:			
	N (%)	N (%)	N (%)	
Preterm delivery (< 37 wks)	8 (9.8)	12 (11.8)	23 (7.5)	0.398
Major structural anomalies	5 (5.95)†	4 (3.9)	1 (0.3)	0.002
Apgar score (1 min) ≤ 7	15 (20.3)	12 (15.0)	41 (15.8)	0.608
Apgar score (5 min) ≤ 7	1 (1.4)	2 (2.5)	9 (3.5)	0.613
Birth weight ≤ 10th %	5 (6.1)	4 (3.9)	15 (4.9)	0.794
Birth height ≤ 10th %	1 (1.2)	2 (2.0)	11 (3.8)	0.413
Birth OFC ≤ 10th %	8 (11.6)	6 (8.3)	23 (9.5)	0.801
Ponderal index < 2.2[2]	10 (12.2)	8 (7.8)	42 (13.7)	0.292
	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	
Mean birth length (cm)	51.1 (2.3)	51.5 (2.7)	51.5 (2.7)	0.616
Mean OFC (cm)	34.6 (1.4)	34.6 (1.2)	34.7 (1.4)	0.815
Mean birth weight (g)	3447 (450)	3544 (446)	3529 (482)	0.341
	Multivariate Analyses:			
	Mean (s.e.)	Mean (s.e.)	Mean (s.e.)	
Adjusted mean birth weight[3]	3384 (72)†	3533 (68)	3529 (54)	0.063
Adjusted mean birth weight[4]	3449 (96)	3576 (99)	--	0.094

OFC, occipital-frontal circumference.

[1] For preterm delivery, Apgar scores, birth weight ≤10th %, birth length ≤10th %, birth OFC ≤10th %, and ponderal index, the sample size was restricted to 490 live-born singletons. For major structural anomalies, the sample size was limited to 497 pregnancies ended up in livebirths. For mean birth weight, length, and OFC, sample size was restricted to 447 live-born full-term singletons.

[2] Ponderal index = (birth weight (grams)/birth length (cm)^3)*100.

[3] Adjusted for maternal age, BMI, weight gain in pregnancy, smoking, alcohol use, SES, ethnicity, parity.

[4] Adjusted for maternal age, BMI, weight gain in pregnancy, smoking, alcohol use, SES, ethnicity, parity, and asthma control

† p<0.05 for comparison between LTRAs and non-asthmatic controls.

The use of LTRAs was not associated with preterm delivery, low Apgar scores, or any measures of fetal growth in unadjusted analyses (p>0.05). Some

differences in mean birth weight were found among study groups after adjustment for maternal age, BMI, weight gain in pregnancy, smoking, alcohol use, socioeconomic status, ethnicity, and parity (p=0.063). Full-term children born to LTRA users had lower adjusted mean birth weight (3384±72g) compared with non-asthmatic controls (3529±54g; p=0.024) and to exclusive β_2-agonists users (3533±68g; p=0.051). However, when the two asthmatic groups were compared with each other after adjustment for maternal asthma control in addition to other covariates differences in mean birth weight of their offspring became non-significant (p=0.094).

Subgroup analysis conducted among 48 subjects who used LTRAs continuously throughout the pregnancy yielded similar results (data not shown), except for preterm birth. Among subjects who used LTRAs continuously in pregnancy, 13% of offspring were born premature (< 37 gestational weeks) compared with 9.8% in the entire LTRA group. However, the proportion of premature births among LTRA continuous users (13%) was not statistically different from that in the β_2-agonist (11.8%) and non-asthmatic control (7.5%) groups (p=0.261).

Major structural defects observed in the LTRA group included one sequence: Sturge-Weber; one syndrome with an autosomal dominant inheritance pattern: neurofibromatosis, type I; one isolated major malformation: imperforate anus; and two deformations: congenital hip dislocation and bilateral club foot (Table 22). All five malformed subjects were exposed to LTRAs during the first trimester, and two subjects took medications throughout the pregnancy. All five cases also took β_2-agonists and inhaled corticosteroids throughout the pregnancy, and two subjects used

prednisone sometime in pregnancy (Table 22). No particular pattern in major structural anomalies was observed in the LTRA group.

Table 22. Major Structural Anomalies in the LTRA Group.

Major Structural Anomaly	LTRAs	Timing of exposure (T*)	Concurrent use of oral corticosteroids
Sturge Weber sequence	zafirlukast	T1, T2, T3	Yes (T2, T3)
Congenital hip dislocation	zafirlukast	T1, T2, T3	No
Bilateral club foot	montelukast	T1	No
Neurofibromatosis, type I	montelukast	T1	No
Imperforate anus	montelukast	T1	Yes (T1)

* T, trimester

4. STUDY III: SUMMARY OF RESULTS

1. Use of LTRAs was not associated with a large risk of evaluated maternal complications, including pregnancy loss, gestational diabetes, preeclampsia/PIH, or low maternal weight gain. In addition, no association was found with preterm delivery, low Apgar scores, reduced measures of birth length or head circumference in the newborns.
2. Even though the incidence of preterm delivery seemed higher in subjects who used LTRAs continuously in pregnancy than in the subjects who used LTRA anytime in pregnancy (majority of them had a first trimester exposure), no statistically significant difference in the incidence of preterm delivery was observed between continuous LTRA users and asthmatic comparison group.
3. The birth prevalence of major structural anomalies observed in live-born infants of LTRA users was 5.95% that is higher than the expected prevalence of 3-4% in the general U.S. population; however, the estimate was based on a relatively small sample size.
4. The prevalence in the LTRA group was significantly higher compared with non-asthmatic controls, but this difference was influenced by a very low birth prevalence of major structural anomalies (0.3%) among infants born to women in the non-asthmatic comparison group.
5. No statistically significant difference in the prevalence of major birth defects was observed between LTRA and exclusive β_2-agonist users.
6. No particular pattern of major structural anomalies was observed in the LTRA group what might be more reassuring than non-significant differences in birth

prevalence of major structural anomalies between LTRA and exclusive β_2-agonist users.

5. STUDY III: DISCUSSION

This is the first controlled epidemiological study evaluating the safety of montelukast and zafirlukast in pregnant women. Even though this study could not rule out mild effects of LTRAs on perinatal outcomes, this report provides some reassuring information to clinicians and pregnant women that LTRAs are not human teratogens on the scale of a major teratogenic compound. However, results should be interpreted with caution until safety of these medications is studied in larger samples.

In this study, use of LTRAs was not associated with large risks of any evaluated maternal complications, including pregnancy loss, gestational diabetes, preeclampsia/PIH, or low maternal weight gain. In addition, no association was found with preterm delivery, low Apgar scores, reduced measures of birth length or head circumference in the newborns. The only previously published study, which we are aware of, evaluated the effect of LTRAs on intrauterine growth restriction and preterm delivery [12]. However, only nine subjects were included in the analysis since LTRAs were not a primary focus of that study, and no conclusions about LTRAs safety could be made due to limited power [12].

Slightly decreased birth weight in infants born to women who used LTRAs in our study is most likely attributable to more severe and/or poorly controlled maternal asthma in that group. Maternal asthma has been associated with an increased risk of low birth weight [9, 22, 43, 44], reduced mean birth weight [44, 54], and intrauterine growth restriction [9, 12, 45, 55] (reviewed by Bakhireva [51]). Moreover, relationships have been reported between reduced intrauterine growth and more severe or poorly controlled asthma, as defined by lower pulmonary function [49], increased

symptoms [12], or exacerbations [33]. In the LTRA group, 20% reported poor asthma symptom control in the first part of pregnancy compared with only 6.8% among exclusive β_2-agonists users. After adjustment for asthma symptom control, the difference in birth weight between the two asthmatic groups became non-significant.

The birth prevalence of major structural anomalies observed in live-born infants of the LTRA users was 5.95%, which seems higher than the expected prevalence of 3-4% in the general U.S. population [57-60]. The prevalence in the LTRA group was significantly higher compared with non-asthmatic controls, but this difference was influenced by a very low birth prevalence of major structural anomalies (0.3%) among infants born to women in the non-asthmatic comparison group. To be qualified for the comparison group in this study, subjects had to have no pregnancy exposures which might adversely affect perinatal outcomes, which might help to explain the low prevalence of birth defects observed in that group compared with the general U.S. population. No statistically significant difference in the prevalence of major birth defects was observed between LTRA and exclusive β_2-agonist users, even though this could result from a limited statistical power. More reassuring is the absence of a particular pattern of major structural anomalies in the LTRA group. Additionally, among malformations observed in the LTRA group, neurofibromatosis is a disorder with an autosomal dominant inheritance pattern; therefore, not thought to be due to teratogenic exposure. The etiology of other birth defects observed in the LTRA group is unknown or multi-factorial; however, the plausible mechanism by which LTRAs may cause these defects is unknown.

We are not aware of any previously published peer-reviewed articles which evaluated teratogenicity of LTRAs. Given a signal for potential limb reduction defects identified by the Merck Pregnancy Registry Program for Singulair®, close attention was given to this category of birth defects in our study. In the current study, two major congenital anomalies involved a limb or a joint, but both defects (i.e., congenital hip dislocation and bilateral club foot) involve deformation, while limb defects observed in the Merck Registry are likely to represent disruptive defects. Deformation refers to the mechanical forces which result in altered morphogenesis, while disruption is a breakdown of normal tissue [56]; thus pathophysiological mechanisms which cause these defects are different. Preliminary data from the Motherisk Program, a teratology information service located in Toronto, Canada, presented in an abstract form reported two heart defects among infants born to 64 women exposed to montelukast, while no limb defects were identified in that population [125].

The heterogeneity of major congenital anomalies observed in a few previous reports and our study as well as the overall birth prevalence suggests that LTRAs are unlikely to be a major human teratogen; however, our results should be interpreted with caution. This study had adequate power to detect only a four-fold increased risk in all major structural anomalies combined in the LTRA group; thus absence of a risk of this magnitude or greater can be assumed. Due to a limited number of major anomalies attainable in a prospective study the primary purpose of this study was not to detect a statistically significant difference between study groups but rather detect a pattern of major malformations and other adverse outcomes.

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The dissertation author was the primary researcher and author, while the co-authors listed in these publications directed and supervised research or acted as junior collaborators.

CHAPTER 7:

OVERALL CONCLUSIONS, STRENGTHS AND LIMITATIONS OF RESEARCH DESIGN AND METHODS, FUTURE RESEARCH DIRECTIONS

OVERALL CONCLUSIONS

1. This study demonstrated that the risk of preterm delivery is doubled in women with inadequate asthma control during pregnancy compared with pregnant women whose asthma is well controlled.
2. Asthmatic pregnant women carrying a girl had more hospitalizations for asthma and a tendency of having more unscheduled asthma clinic visits during pregnancy compared with women carrying a boy. However, all women with asthma should be carefully monitored for pregnancy-associated changes in asthma symptoms.
3. This study did not support the hypothesis that fetal sex might have a differential effect on the association between maternal asthma and fetal growth measures.
4. Use of LTRAs in pregnancy was not associated with a specific pattern of major structural anomalies in offspring or large risks of other adverse perinatal outcomes. This study suggests that LTRAs do not appear to be a major human teratogen; however, results should be interpreted with caution due to limited sample size.

STRENGTHS OF RESEARCH DESIGN AND METHODS

Strengths Common to All Three Studies.

1. The prospective study design is one of the major strengths of the study. Recall bias and differential recall were minimized since the exposure information was collected through a series of prenatal interviews before adverse outcomes occurred. Recruitment prior to 20 gestational weeks and minimal proportion of women lost to follow-up (5%) minimized possible participation and selection bias.
2. Multiple maternal interviews during pregnancy allowed capturing information on any change in asthma severity/control, use of medications, and other risk factors.
3. Information on multiple potential confounding factors was collected during the course of study.
4. The study examined numerous maternal and fetal outcomes in the same cohort that allowed making conclusions about the effect of certain asthma medications and asthma severity/control on overall well-being of the mother and fetus.
5. Information collected through maternal interviews was validated against maternal and children medical records.

Strengths Specific to Study I.

1. The study utilized multiple measures of asthma control (i.e., asthma symptom control measures three times during the pregnancy, hospitalizations for asthma,

unscheduled clinic visits for asthma, burst use of systemic corticosteroids, and a combined measure of severe asthma exacerbations).

2. The effect of maternal asthma was evaluated relative to multiple maternal and fetal adverse perinatal outcomes.
3. The analyses were based on a large sample size (i.e., 819 women with asthma).
4. An interaction between maternal asthma and fetal sex in relation to fetal growth was evaluated.

Strengths Specific to Study II.

1. The effect of fetal sex was evaluated relative to multiple measures of asthma control.
2. The analyses were based on a large sample size (i.e., 819 women with asthma).
3. Longitudinal analysis allowed evaluating the effect of fetal sex on change in asthma control over the course of pregnancy.

Strengths Specific to Study III.

1. This is the first controlled epidemiological study evaluating the safety of montelukast and zafirlukast in pregnant women.
2. Prospective study design and repeated maternal interviews during pregnancy combined with information from medical records allowed to verify whether prescribed medications were actually taken or taken at the frequency and dose prescribed. Additionally, this allowed for capture of information on asthma medications administered during hospital admissions and emergency room visits, asthma symptom control, and numerous covariates.

3. This study evaluated the safety of both montelukast and zafirlukast and captured the information on timing and dosage of exposure, as well as concurrent use of other asthma medications.
4. This study accounted for the effect of maternal asthma symptom control on perinatal outcomes.
5. Two internal comparison groups, concurrently enrolled using the same recruitment sources and methods, were utilized in the study.

LIMITATIONS OF RESEARCH DESIGN AND METHODS

Limitations Common to All Three Studies.

1. A potential limitation of this study is that majority of subjects were recruited among women who chose to contact OTIS with questions about prenatal exposures. Selection bias could be potentially introduced if women with a history of adverse outcomes in previous pregnancies or women who have better access to Internet recourses (e.g., women of higher socioeconomic class) were more likely to contact OTIS or enroll in the study. However, an earlier study demonstrated that women who enroll in OTIS studies do not substantially differ from non-participants with respect to numerous pregnancy and lifestyle risk factors [126]. Moreover, participating OTIS sites which recruited subjects for the present study were located throughout North America and study subjects were drawn from a wide and diverse geographic area.
2. Some differences in ethnicity of recruited subjects were observed by referral source, e.g., among women referred to the study by physicians 28% were of non-white ethnicity, while only 5% of non-white women were recruited through Internet and 13% through OTIS network. However, no differences in other maternal characteristics (i.e., age, BMI, gravidity, parity, socioeconomic status) were observed by referral source.
3. Results of the study might not be generalizable to all pregnant women with asthma. Majority of the subjects in the OTIS study were white/non-Hispanic women and more than a half of participants reported household socioeconomic status above average. Moreover, results cannot be generalized to twin

pregnancies, since these pregnancies were not included in the analysis due to strong risk posed by twinning on perinatal outcomes. However, among 819 women with asthma in the OTIS sample only 13 (1.6%) had twin pregnancies.

4. Another limitation of this study design is lack of data on maternal pulmonary function as an objective measure of asthma severity/control. However, asthma symptom control and severe asthma exacerbations were evaluated in the study.
5. Subjects were considered to be asthmatic based on a diagnosis made by physicians. However, some women might have symptoms of asthma but do not have a diagnosis of asthma, thus introducing potential misclassification bias. Nevertheless, a physician-diagnosed asthma has been shown to be a valid definition for epidemiological studies [31].
6. Among 819 asthmatic subjects in the OTIS study, 799 had complete information about asthma symptom control at enrollment, while only 658 and 655 subjects had this information at the follow-up interviews (at 26 and 32 gestational weeks, respectively) since not all women could be reached during these two weeks. In addition to reduced sample size, potential bias could be introduced if data were not missing at random.
7. While a prospective study design has numerous advantages, power to detect an increased risk of some rare perinatal outcomes (e.g., major structural anomalies) was limited.
8. Even though women were recruited during their first part of pregnancy, incidence of some early outcomes (e.g., spontaneous abortion, termination of pregnancy) could be underestimated. Additionally, a rate of some other

outcomes (e.g., certain malformations) could be underestimated due their prenatal diagnosis in early pregnancy thus preventing subjects from enrollment. Thus bias towards the null could be introduced.

Limitations Specific to Study I.

1. Self-reported measures of asthma control utilized in this study may not be adequately sensitive or specific to identify severe asthma or asthma that is sufficiently uncontrolled to substantially increase the risk of some perinatal outcomes.
2. When incidence of some relatively rare perinatal outcomes (e.g., preeclampsia) was estimated among subjects with certain symptoms of poor asthma control (e.g., hospitalizations for asthma), limited number of people who had both events could result in unstable estimates.
3. Limited number of subjects with asthma exacerbations and preeclampsia in our study did not allow controlling for potential confounders (e.g., smoking, parity, use of short-acting β_2–agonists) in multivariate analysis.

Limitations Specific to Study II.

1. While a change in asthma control during the course of pregnancy was evaluated in this study, no information about asthma severity and/or control prior to pregnancy was available. Thus, effect of fetal sex on maternal asthma very early in pregnancy could not be evaluated.

Limitations Specific to Study III.

1. In this study LTRAs were evaluated by class, while there could be some differences in clinical safety between montelukast and zafirlukast. A small

number of zafirlukast exposed subjects did not allow examining them separately; however, when montelukast exposed subjects were evaluated separately conclusions remained the same. Moreover, both montelukast and zafirlukast have the same mechanism of action (i.e., antagonize the CysLT1 receptor) and demonstrated a similar safety profile in placebo-controlled clinical trials [127].

2. The asthmatic comparison group was selected to account for underlying effect of maternal asthma on perinatal outcomes and to represent milder asthma. However, this group could include some subjects who were under-treated during pregnancy, but the asthma symptom control and exacerbation data do not suggest that in general. This group of women on average had better symptom control than LTRA group and less than 10% of them have poor control on any measure of maternal asthma. Unfortunately, study design did not allow collecting information on maternal pulmonary function as an objective measure of asthma severity. However, asthma symptom control and asthma exacerbations were evaluated in the study.
3. Non-asthmatic comparison group in the OTIS study could be too restrictive and might not represent general population since subjects with prenatal exposures known to affect any perinatal outcomes could not serve as controls.

FUTURE RESEARCH DIRECTIONS

1. Examine the effect of underlying asthma severity, measured prior to initiation of therapy and/or before pregnancy, on perinatal outcomes.
2. Further examine biological mechanisms responsible for an increased risk of adverse perinatal adverse outcomes among pregnant women with severe and/or uncontrolled asthma.
3. Examine biological mechanisms involved in a possible differential effect of fetal sex on maternal asthma control during pregnancy.
4. Given the ability of case-control studies to attain considerably larger sample size compared with prospective studies, the former design should be used to examine teratogenicity of LTRAs and their potential association with specific birth defects.

APPENDICES

APPENDIX 1. ENROLLMENT QUESTIONNAIRES

1. ENROLLMENT DEMOGRAPHICS

Name

Address

Telephone
home:
work:

Nearest relative/friend not living in same household
Name:

Phone:

Date of birth

Occupation
Education

Current pregnancy
LMP
Cycle Length
Conception
EDC

Determined by

Previous pregnancies
Full term:
Preterm:
Spontaneous abortion:
Voluntary abortion:

Prepregnancy weight:
Prepregnancy height:

Race/Ethnicity	MOM	DAD
White		
Black		
Asian		
Hispanic		
Native American		
Other:		

Other information on Dad
Date of birth
Occupation
Education
Same father of any previous children

Family History	MOM	DAD
Genetic illness		
Birth defects		
Mental retardation		

Details:

Health care provider for the pregnancy
Name
Address
Telephone

Delivery
Name of facility
Address
Telephone

Pediatrician
Name
Address
Telephone

Primary language spoken at home

English Spanish French
Other:

Medical History

Asthma	Diabetes	Hypertension
Heart	Kidney	Seizure
disorder		
Psychiatric	Surgery	Other

Details:

ASTHMA INFORMATION
Age at diagnosis:

2a. EXPOSURES AT ENROLLMENT					
Exposure	**Explanation**	**Dose**	**Date started**	**Date stopped**	**Wks postconception**
Prenatal vitamins					
Other vitamins					
Oral contraceptives					
Spermicides					
Caffeine products					
Tobacco					
Passive smoke					
Alcohol					
Illicit drugs					
Illness					
Fever					

2b. EXPOSURES AT ENROLLMENT					
Exposure	**Explanation**	**Dose**	**Date started**	**Date stopped**	**Wks postconception**
Asthma meds - Rx:					
a) inhaled:					
b) oral:					
Asthma meds - OTC:					
a) herbal or natural remedies					
Prescription meds:					
Over the counter meds:					
Occupational exposures:					
X ray					
Tests:					
Amniocentesis/ CVS					
Ultrasound					
Glucose screening					

Assessment of Asthma Severity/Control at Intake

INTAKE CALL

When were you diagnosed with asthma?

Have you ever been hospitalized for asthma?
If yes, were you ever intubated?

Have you ever been treated with systemic steroids?

Do you use a spacer?

SINCE PREGNANCY:

unscheduled asthma visits

hospitalizations
If yes, # intubations

immunotherapy visits

If yes, any systemic reactions to shots?

Are peak flow velocities recorded daily?
Levels for past 2 wks:

Taking theophylline?
If yes, are blood levels measured?

By which physician?

IN LAST 2 WEEKS:

nights awakened by asthma symptoms

mornings woke up with asthma symptoms

days asthma caused significant phlegm production

days needed any asthma med more than 4x

days daily activities limited because of asthma

SEVERITY RATING IN LAST 2 WEEKS:

0 = no sx

1 = sx present, but don't interfere with activity/sleep

2 = sx occasionally interfere with activity/sleep

3 = sx frequently interfere with activities/sleep

4 = sx constantly interfere with activities/sleep

APPENDIX 2. FOLLOW-UP QUESTIONNAIRES

INTERIM PREGNANCY CALLS

SEVERITY/CONTROL QUESTIONNAIRE

SINCE PRIOR CALL:

unscheduled asthma visits

hospitalizations

If yes, # intubations

immunotherapy visits

If yes, any systemic reactions to shots?

Are peak flow velocities recorded daily?

Levels for past 2 wk.:

Taking theophylline?

If yes, are blood levels measured?

By which physician?

IN LAST 2 WEEKS:

nights awakened by asthma symptoms

mornings woke up with asthma symptoms

days asthma caused significant phlegm production

days needed any asthma med more than 4x

days daily activities limited because of asthma

SEVERITY RATING IN LAST 2 WEEKS:

0 = no sx

1 = sx present, but don't interfere with activity/sleep

2 = sx occasionally interfere with activity/sleep

3 = sx frequently interfere with activities/sleep

4 = sx constantly interfere with activities/sleep

NOTES:

EXPOSURES:

Prenatal vitamins	Asthma meds
Other vitamins	
Herbs/holistic	Rx
Caffeine	OTC
Cigarettes/Passive Smoke	Occupational
Alcohol	X-ray
Street drugs	CVS, AFP, amino, glucose tolerance
Illness	Ultrasound
Fever	EDC Has EDC changed?

Depression Scale Sent Yes ☐ No ☐

Onset Fetal Movement _____

Fetal Activity Active Not Active Very Active

APPENDIX 3. OUTCOME QUESTIONNAIRE

OUTCOME CALL:

EDC:

DOB or termination: _____
Liveborn Stillborn SAB
TAB Multiple

Delivery: Vaginal C-Sec
Forceps/Vaccuum Vertex Breech

Preeclampsia: Yes No
PIH: Yes NO
Maternal Complications:

Maternal Weight Gain: _____

Child's Name: _____
Male Female

Weight:_____ Length:_____

OFC:_____ Apgars:_____

Cord Gases: Yes No
Resuscitated: Yes No
NICU Admit: Yes No

Hospitalization after neonatal discharge:

Abnormalities diagnosed at birth or later:

Neonatal illness:

Breastfeeding: Yes No
How long?
Supplementing: Yes No
Start date?
Between last call and delivery:
unscheduled asthma visits:
hospitalizations due to asthma:
uses of systemic steroids:
immunotherapy visits:
Systemic rxns to allergy shots?

EXPOSURES:
Prenatal vitamins:
Other vitamins:
Herbs/Holistics:
Caffeine:
Cigarettes/Passive Smoke:
Alcohol:
Street Drugs:

Illness and/or Fever:

Asthma Meds:

Rx:

OTC:

Occupational, X-ray:
Tests, Ultrasounds:

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