RISK OF CONGENITAL MALFORMATIONS FOLLOWING IN UTERO EXPOSURE TO INHALED CORTICOSTEROIDS IN EARLY PREGNANCY IN CONTROLLED VERSUS UNCONTROLLED ASTHMATICS

A Thesis

Presented to the Faculty of the Weill Cornell Graduate School of Medical Sciences

Cornell University

in Partial Fulfillment of the Requirements for the Degree of

Master of Science in Health Science

by

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May 2017

ABSTRACT

Problem: Asthma requiring daily medication is a major medical condition in nearly 3-8% of pregnancies. Currently, there are no medications deemed safe by the US Food and Drug Administration (FDA) for pregnancy. The effects of many medications are still unknown. **Purpose**: To identify the effects on normal fetal development of inhaled corticosteroid use during pregnancy. To identify the role asthma control has on fetal development. **Research Questions:** Does inhaled corticosteroid use during pregnancy cause more congenital anomalies in infants of uncontrolled asthmatics than those of controlled asthmatics? **Methods:** A prospective cohort study will follow women from their first prenatal visit through the end of the neonatal period. They will be asked to complete surveys regarding asthma symptoms and treatment. Neonates will be assessed on days 1 and 28 of postnatal life to assess for any congenital malformations. **Outcomes:** A literature review was performed and a total of thirteen articles were chosen. These articles highlighted the various effects of in utero exposure to corticosteroids when taken for maternal asthma. **Benefit:** This prospective cohort study will help clinicians better understand the effects of treating asthma during pregnancy by giving a better understanding of the potential dangers of uncontrolled asthma on fetal development.

BIOGRAPHICAL SKETCH

Betsy Distelburger is a candidate for a Master of Science in Health Science degree at the Weill Cornell Graduate School. She received her bachelor's degree in communication with a minor in applied economics and management from Cornell University in May 2011. She subsequently completed the post-baccalaureate premedical program at Columbia University. She grew up in Goshen, New York, where she lived with her parents and older brother.

I dedicate this thesis to my family, friends, and boyfriend, without whom I would not be where I am today.

ACKNOWLEDGMENTS

I would like to thank Dr. Katherine Hajjar for being my mentor and helping prepare my thesis.

I would also like to acknowledge the faculty of the Weill Cornell Graduate School Physician Assistant program for teaching me and supporting me during the past two years.

Lastly, I would like to thank my family and friends, especially Emily Brasco, who has been my “study buddy” and emotional support during the past two years.

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CHAPTER I

INTRODUCTION

Asthma is a common medical condition affecting both children and adults. It is classically described as reversible airway disease, because asthmatics' lung function typically improves in response to bronchodilators. Asthmatics typically develop a variety of symptoms in response to certain triggers. Treatment involves a stepwise approach beginning with short-acting beta agonists as a "rescue" treatment then escalating to inhaled corticosteroids for daily symptoms. During pregnancy, physiologic changes can affect an asthmatic's lung function. For example, as the fetus develops it may cause diaphragmatic elevation, which leads to a decrease in both residual volume (RV) and functional residual capacity (FRC).

The treatment of asthma in pregnancy is a complex issue centered around stabilizing the mother without compromising the health of the fetus. Research studies have been divided over the effects of asthma medications on a developing fetus. Many articles have found higher rates of preterm labor, low birth weight and congenital malformation.

1.1 Pathophysiology of Asthma

By definition, asthma is airway inflammation leading to reversible airway obstruction.[1] Inflammation typically occurs in response to specific triggers, which vary and may include but are not limited to exercise, allergens or air pollution.[1] However, when exposed to various triggers, asthmatics develop inflammation leading to

bronchospasm or bronchoconstriction, which may occur immediately or develop over 4-6 hours, which is known as a late asthmatic response.[1] From a pathophysiologic standpoint, bronchoconstriction leads to decreased lung function as measured by pulmonary function tests or a peak flow meter.[1] Asthmatics typically experience decreased forced expiratory volume (FEV1), peak expiratory flow (PEF), and FEV1/FVC (forced vital capacity).[1] The airway inflammation leads to a smaller airway diameter, which results in increased airway resistance.[1] These reductions in lung function typically improve with administration of a bronchodilator, such as albuterol.[2] Additionally, many asthmatics have normal lung function between exacerbations.[2] Symptomatically, asthmatic patients tend to experience wheezing, chronic cough, dyspnea and/or chest tightness in response to various triggers.[2] Some asthmatics with chronic disease will experience symptoms on a more daily basis, rather than simply when exposed to triggers.[2]

1.2 Prevalence of Asthma

Over the past several decades, the incidence of asthma has increased significantly and now affects approximately 10% of the population. Additionally, asthma tends to affect female adults more than male adults.[2] Furthermore, a strong genetic predisposition has been identified with asthma, allergies and dermatitis; a triad called "atopy."[1] More specifically, the term "atopy" refers to the presence of antigen-directed IgE antibodies.[3] Obesity has also been linked to the development of asthma.[1]

During pregnancy, asthma is one of the most common medical problems encountered, occurring in 3-8% of pregnancies.[4]

1.3 Diagnosis of Asthma

Diagnosis of asthma is made using the medical history, physical exam and lung function assessment.[2] Historically, patients will present with complaints of episodic wheezing, dyspnea and cough.[2] Typically, patients may be able to identify specific triggers for these symptoms.[1] The physical exam may be completely normal at times when the patient is asymptomatic.[1] Alternatively, the patient may be experiencing wheezing if examined during an exacerbation or even a silent chest during a severe exacerbation.[1] Patients with allergic asthma might exhibit more allergic symptoms such as increased swelling and secretions of the nasal mucosa or even nasal polyps. Patients with atopy are likely to have eczema or dermatitis.[1] Pulmonary function tests including spirometry are also utilized in the diagnosis of asthma. When evaluating for asthma, spirometry is obtained both before and after the administration of bronchodilators.[2] An improvement in lung function by 12% or greater strongly suggests the presence of asthma.[2]

1.4 Treatment of Asthma

Treatment of asthma is very complex and depends on the severity and chronicity of the disease. When developing a treatment plan for asthmatics, clinicians must take into account the types of symptoms, frequency of symptoms and lung function as

measured by pulmonary function testing. This information is used to classify patients as either intermittent, mild persistent, moderate persistent or severe persistent. Patients are then started on an appropriate management plan based on their categorization.

Asthma medication can be categorized as either long-term control medications or quick relief medications. Long-term control medications include anti-inflammatories, long-term bronchodilators, leukotriene modifiers, desensitization, omalizumab, vaccination and oral sustained-release beta-2 agonists. Quick relief medications include beta adrenergic agonists, anticholinergics, corticosteroids, antimicrobials and phosphodiesterase inhibitors.[2]

Some patients, specifically those in the "intermittent" category, may require only a beta agonist to be used as a "rescue inhaler" when symptomatic whereas other patients with "persistent" asthma may require daily medication to control symptoms interfering with daily activities. Patients with mild persistent asthma typically begin with inhaled corticosteroids and may be titrated up using a "stepwise" approach, which can later include combination therapy with inhaled corticosteroids and long acting beta agonists. During exacerbations, oral corticosteroids may be utilized.[5]

1.5 Treatment of Asthma in Pregnancy

As mentioned above, asthma can be treated in a variety of ways but when treated appropriately using the stepwise approach, treatment has been shown to reduce symptoms and improve quality of life.[5] However, pregnancy complicates the matter as it can both affect the underlying asthma and be affected by asthma. Treating a

pregnant asthmatic requires clinicians to take into account the needs of the mother while maintaining safety of the fetus, leaving the clinician faced with a balancing act.[4] Finding the balance between adequately treating the mother without harmful effects on the fetus is extremely complex. Additionally, uncontrolled asthma in the mother may lead to harmful effects on the fetus including hypoxia.[5]

As with any medication, inhaled corticosteroids may have potential maternal side effects.[2] Local side effects including cough, hoarseness and oral thrush are much more common than systemic side effects, as seen with oral corticosteroids.[2] However, at high doses easy bruising, bone density changes and adrenal suppression may occur.[2]

Complicating the issue even further is the US Food and Drug Administration (FDA) categories of asthma medication. The FDA classifies all medication into five categories based on the presumed safety of the medication on the fetus based on animal studies. Category "A" is any drug which has been proven to be safe in pregnant women. However, no asthma medication belongs to category "A." In fact, most asthma medications are category "C" meaning that risk has neither been proven or disproven, leaving clinicians with a difficult choice to make between the health of mother and the health of fetus.[4]

CHAPTER II

REVIEW OF THE LITERATURE

2.1 Method

This thesis began with research using the search engine Google Scholar, which resulted in many scholarly works. The initial search term used was “asthma in pregnancy.” As expected, this returned a search of tens of thousands of articles. The search was further narrowed by searching the terms “asthma treatment in pregnancy.” Furthermore, some articles used were articles listed as “related articles” to ones found through Google Scholar. Lastly, to broaden the scope and not be limited by the use of only one search engine, the same search terms “asthma treatment in pregnancy” were entered into the PubMed database.

2.2 Results

The search term “asthma treatment in pregnancy” through the use of Google Scholar yielded approximately 180,000 results in 0.8 seconds. The same search using the PubMed database yielded 1809 articles. These results were then narrowed down using a variety of inclusion and exclusion criteria. Firstly, the inclusion criteria included only studies that took place within the past twenty years with special attention being placed on articles within the past five years. While some might argue that research from nearly twenty years ago holds little value today, with this particular issue this seems not to be the case as the pendulum has swung back and forth regarding treatment of asthma in pregnancy. Additionally, specific medications may have changed slightly during that time, but overall asthma management has stayed

relatively the same with an emphasis on inhaled corticosteroids for mild and moderate persistent asthma, and beta agonists and oral corticosteroids for acute exacerbations. Another important inclusion criterion was that articles had to follow patients over a period of time, rather than just during a single exacerbation. This was important as asthma tends to wax and wane, particularly during pregnancy. Therefore, treatment of a single exacerbation may not provide adequate data on the severity of the mother's asthma nor on the effect on the fetus. Additional criteria included articles written in English, which did not require translation services, as information may be skewed in translation.

Literature reviews which did not include any original research were initially excluded because these articles do not provide any additional data. However, after more research it became apparent that literature reviews contribute a wealth of information and a better understanding of the topic, and the exclusion criteria were subsequently revised. While initially the search was limited to articles with a large sample size, the search became difficult and the criteria limited articles with good data and important conclusions, despite a small sample size. Therefore, articles were not excluded based on sample size. However, the smaller sample size has been taken into account when looking at the validity of various articles. An additional exclusion criterion was that the articles had to focus exclusively on asthma, rather than asthma and other comorbidities including allergic rhinitis. Articles were not excluded based on geographic location as asthma affects all populations and has similar treatment approaches globally.

2.3 Discussion

After accounting for the aforementioned inclusion and exclusion criteria 11 articles were selected, which shed light on the treatment of asthma in pregnancy. This section of the paper discusses each article and how it contributes to the current understanding of both the effects of asthma and pregnancy, and the role of treatment in asthma in pregnancy.

The first study by Cydulka et al corroborates data obtained during two prospective cohort studies and examines how pregnant asthmatics presented differently than a non-pregnant cohort during an acute exacerbation requiring an emergency room visit. In the emergency department, historical data was collected including demographics, chronic asthma history and information related to the current exacerbation. Objective data included the PEFR (Peak Expiratory Flow Rate), which was utilized to categorize the exacerbation as mild, moderate or severe. This work interestingly points out that, while both pregnant and non-pregnant asthmatics had similar presentations, their treatment plans vastly varied leaving the pregnant asthmatics with worse outcomes.[6] While each woman was equally likely to receive nebulized albuterol initially, non-pregnant women were much more likely to receive oral corticosteroids than their counterparts with 66% of non-pregnant women receiving oral corticosteroids as compared to 44% of pregnant asthmatics (p=0.002).[6] Additionally, Cydulka et al compared outcomes two weeks after discharge and found that pregnant asthmatics were more likely to still be symptomatic at that time (p=0.09).[6] Of note, this study is limited by its small population with only 51 asthmatics participating, compared to 500 non-pregnant women.[6] Despite being

written in 1999, this articles provides useful data that sheds light on the management of pregnant asthmatics in the emergency department. Furthermore, no data was obtained to suggest that this management has drastically changed since the article was written in 1999.

While Cydulka et al provide key background information regarding maternal presentation and outcomes of emergency department visits for asthma exacerbations, the remainder of the articles focus more on the specific treatments and their effects on the mother, the fetus or both. Some of these articles focused on specific treatments and looked for specific side effects, while others were much broader and examined outcomes in general. One article that focuses on a very specific outcome is by Tegethoff et al, which is a prospective cohort study examining the use of inhaled corticosteroids in pregnancy and more specifically whether this treatment leads to an increased risk of childhood diabetes. Any pregnant asthmatic with a singleton birth was eligible to join the study and was followed from early pregnancy through childhood. Tegethoff et al did find an increased incidence of metabolic and endocrine disorders in children born to asthmatic mothers treated with inhaled corticosteroids with 43.94% versus 29.2%, p=0.012.[7] However, they did not find a significant difference in intrapartum complications or birth defects.[7] Separating this article from many others was the exceptionally large population, with an n = 65,085. Some of the pitfalls of this article include that the source of the information regarding the children's health was from the mothers rather than physicians, and this study did not account for the amount and type of exposure to inhaled corticosteroids.

A similar article that also examined the effect of inhaled corticosteroids on the fetus was an article entitled *Fetal Glucocorticoid-Regulated Pathways Are Not Affected by Inhaled Corticosteroid Use for Asthma During Pregnancy* by Hodyl et al, which is a prospective study that examined the effects of inhaled corticosteroids on pregnancy and fetal development by measuring maternal plasma levels of four hormones involved in the glucocorticoid pathway including cortisol, estriol, osteocalcin and corticotropin releasing hormone. Unlike the previous Tegethoff et al study, Hodyl et al accounted for the amount of inhaled corticosteroid exposure by measuring the dose and usage of the inhaler. The Hodyl study did not find any significant difference in plasma levels of the estriol in pregnant versus non-pregnant women.[8] From this finding, the authors concluded that inhaled corticosteroid use does not affect fetal glucocorticoid pathways.[8] Interestingly, mothers carrying female fetuses were more likely to experience hypothalamus-pituitary-axis suppression than both their non-pregnant counterparts and pregnant mothers carrying male fetuses.[8] One major limitation to this study is that women were asked whether or not they used inhaled corticosteroids during pregnancy, but some women may have remembered incorrectly or confused albuterol for an inhaled steroid.

Unlike the previous two articles, which focused specifically on inhaled corticosteroids and the effects on glucocorticoids, many articles focused more broadly on the effects of asthma on congenital malformations. Interestingly, among the various articles different results were obtained. The Blais et al study is a follow-up to an earlier study by the same researchers, who previously identified increased congenital birth defects in fetuses born to mothers with asthma. However, this retrospective

cohort study comprising 36,587 pregnant women found that only severe exacerbations had a statistically higher rate of birth defects with 19.1% of babies born to mothers with severe asthma exacerbations suffering from congenital malformations.[9] Furthermore, if this exacerbation occurred during the first trimester, the researchers found a significant odds ratio of 1.64 with a 95% confidence interval of 1.02 to 2.64.[9] The criteria included by Blais et al, but was not limited to delivering between January 1998 and March 2009, which allowed the sample size to be much larger than many similar studies. Additionally, inclusion criteria controlled for other potential causes of birth defects including gestation age and maternal age. However, acceptable gestational age was between 20 and 45 weeks, which is not very limiting and includes fetuses who are not yet considered viable. Furthermore, the maternal age range was between 15 and 45, which is inconsistent given the significantly increased risk of birth defects with increasing maternal age. This study also classified the types of congenital malformation based on their severity, but while severe asthma exacerbations were associated with increased risk for congenital malformations, there was no correlation between mild, moderate and severe asthma with mild, moderate and severe congenital malformations.

Similarly to the Blais et al study, a study by Murphy et al entitled *The Risk of Congenital Malformations, Perinatal Mortality and Neonatal Hospitalisation Among Pregnant Women with Asthma: A Systematic Review and Meta-Analysis* also found higher rates of congenital malformations in babies born to asthmatic mothers. Murphy et al is a meta-analysis of four prospective cohort studies and eight retrospective cohort studies, which sought to identify a relationship between maternal asthma and

congenital malformations and overall neonatal outcomes. Women were classified based on medication use, exacerbations requiring medical intervention and asthma severity. Data was collected using a standardized form that was reviewed by a second interviewer to ensure accuracy. Murphy et al found a significantly higher risk of congenital defects in asthmatics than in their counterparts with a relative risk of 1.11, 95% CI 1.02-1.21, $p<0.1$. Additionally, there was an increased odds ratio of 1.18 (CI 1.03-1.35).[10]

Interestingly, all pregnant asthmatics had the same increased risk for congenital defects regardless of which medications they received or how many exacerbations they suffered. The various studies differed in the types of congenital malformations that they found to occur most commonly. For example, Kallen et al found cardiac defects to occur more commonly, but Blais et al found nervous system defects to occur more commonly, though all studies found there to be an increased risk of congenital malformations in babies born to mothers with asthma.[10] The researchers also studied the relationship between asthma and stillbirths and did not find a significantly increased risk for stillbirth in asthmatic mothers with a RR = 1.06 CI 0.90-1.25, $p>0.1$.[10] However, the researchers did find an increased risk of neonatal death (RR = 1.49 95% CI 1.11-2.00) and increased perinatal mortality (RR = 1.25% 95% CI 1.05-1.50).[10] This article utilized observational data from thousands of pregnant women creating a large sample size. However, the observational nature of the study makes the data less reliable as it was self-reported and therefore could be inaccurate. Overall, this study builds from the previous Blais study and was very

informative. The Murphy et al article provides clinicians with a better understanding of what specific risks pregnant asthmatics may face.

Risk of Congenital Anomalies After Exposure to Asthma Medication in the First Trimester of Pregnancy – a Cohort Linkage Study by Garne et al also focuses on the potential congenital anomalies that may result secondary to asthma medication. Garne et al is a meta-analysis of data obtained during three different cohort studies, which collectively examined 519,242 fetuses and infants in Norway, Wales and Denmark between the years of 2000 and 2010. Garne et al included all live births, stillbirths and spontaneous abortions occurring after 20 weeks. Additionally, they included any fetus who was electively terminated due to fetal anomaly, regardless of gestational age. Of these 519,242 the researchers focused on the 19,513 fetuses whose mothers were treated with at least one asthma medication beginning 91 days before pregnancy through 91 days after pregnancy. Statistical analysis then included odds ratios, which were combined using Mantel-Haenszel methods. Furthermore, 99% confidence intervals were combined using Cornfield approximation. Lastly, individual odds ratios (ORs) were calculated for each medication separately, providing individual data specific to that medication rather than based on exposure in general. Garne et al found that 650 of the 19,513 fetuses exposed to any medication had a major congenital malformation with an adjusted OR of 1.21 (99% CI 1.09-1.34).[11] Additionally, 512 fetuses exposed to inhaled beta-2 agonists, 492 fetuses exposed to short-acting beta-2 agonists, 42 fetuses exposed to long-acting beta-2 agonists, 202 fetuses exposed to inhaled corticosteroids, 202 fetuses exposed to combination treatments and 47 fetuses exposed to systemic corticosteroids were all noted to have congenital anomalies with a

99% confidence interval.[11] Of significance, the article points out that the only anomaly noted to be significant at the 1% level was the increased risk of anal atresia or stenosis in fetuses exposed to inhaled steroids with an OR = 3.40, 99% CI 1.15-10.04.[11] However, this anomaly only occurred in 6 of 202 fetuses exposed to inhaled corticosteroids, illustrating that, despite being statistically significant, the incidence rate is still quite low. In fact, Garne et al conclude that most of these congenital defects occurred in anywhere from 1 in 1000 to 1 in 10,000 births depending on which medications the fetus is exposed to. This article provides a comprehensive breakdown of specific congenital anomalies and which medications they are associated with, providing clinicians with excellent data regarding risk of exposure. However, the data is somewhat confusing as many of these medications were used in conjunction with other medications, making it difficult to attribute the teratogenic effects to just one medication.

A study that focused on a more specific outcome was Van Zutphen et al which was a multi-center, population-based case control study which sought to determine if there is a correlation between asthma medication and 37 different congenital heart defects (CHD). The study spanned 10 states within the continental United States and studied infants born with congenital heart defects between October 1, 1997 and December 31, 2007. Infants with known genetic syndromes or defects were then excluded from the study. Additionally, stillbirths with confirmed CHD on autopsy were included in the "case" group. For all other infants included in the "case" category, diagnosis was made by echocardiogram, catheterization or surgery. The control group was a randomly selected set of infants born in the same locations with

birth certificates or hospital records. The mothers of both case and control group patients were then contacted within two years of their expected due date for a structured telephone interview, which collected demographic information as well as information regarding maternal health. Specifically, mothers were asked about past medical history, their medication use, as well as potential behavioral and environmental influences in the perinatal period. Mothers were asked to recall the specific prescription and over the counter medications taken from three months prior to pregnancy throughout the pregnancy itself. Additionally, they were asked to recall the timing of when they took each specific medication. Women were then categorized based on which type of medications they used, bronchodilators, anti-inflammatories or a combination of the two. They further categorized the women based on when the exposure occurred. Women who were exposed from one month prior to conception through the end of the first trimester were categorized as being exposed during "the critical period of cardiac development." However, those who had been exposed prior to one month before conception or after the first trimester were considered to have been exposed after cardiac development. Exclusion criteria included multiple gestations and diabetic mothers. An odds ratio was then calculated which attempted to take into account confounding factors such as body mass index (BMI) and tobacco use. Of the 37 congenital heart defects studied, only three were found to have statistically significant increased risks in asthmatic mothers.[12] Specifically, mothers who used only bronchodilators, 85% of whom used albuterol, were found to have an increased risk of delivering an infant with anomalous pulmonary venous return with an OR = 2.3 (95% CI = 1.1, 4.8).[12] Conversely, mothers who only used anti-

inflammatory medications, (46.1% used fluticasone and 15.6% used prednisone) were found to be at increased risk of delivering infants with transposition of the great arteries, OR = 2.0 (95% CI = 1.0, 4.3).[12] Lastly, mothers who used both categories of medications, bronchodilators and anti-inflammatory medications, were found to be at increased risk of coarctation of the aorta, OR = 2.1 (95% CI 0.9, 5.0).[12] However, none of the other congenital heart defects were found in statistically significant higher rates among asthmatic mothers.[12]

While this study clearly shows an increased risk of only three of 37 studied congenital heart defects, it is not specific to inhaled corticosteroids. In fact, all medications that are considered "anti-inflammatory" were studied together. However, this group included both inhaled and oral corticosteroids. Additionally, this study interviewed mothers up to 24 months after their expected delivery date and then asked them to recall medications taken. Therefore, it is unclear how accurately these mothers may have remembered. Another limitation of this study is that it did not take into account how well controlled the asthma was during pregnancy.

Another study by Garne et al utilized a population-based case-control study in Europe to determine if there is an increased risk of congenital malformations in neonates born to mothers being treated for asthma during the first trimester. Garne used data collected through a European database entitled EUROCAT, which is a national database of birth defects which includes information on live births, fetal demise after 20 weeks gestational age and any "termination of pregnancy for fetal anomaly (TOPFAs)." The researchers used information obtained from thirteen different registries in twelve European countries to identify a population of 76,249

congenital malformations between the years 1995 and 2010 in the selected countries. Anyone with a congenital malformation that previous literature deemed to be associated with asthma was placed in the "case" group. Those anomalies that were not previously found to be associated with asthma were then divided into two groups based on whether or not chromosomal abnormalities were present. Both the chromosomal and nonchromosomal group made up the "control" group. Data was then collected from various medical providers and prescription databases regarding the exposure of the fetus to any asthma medication during the first trimester. Those who were exposed were then further categorized into three groups based on type of exposure, beta-2 agonists, inhaled corticosteroids or "all asthma medication." The case and control groups were then compared for each congenital malformation including spina bifida, cleft lip, cleft palate only, cleft lip with cleft palate, major cardiac, severe congenital heart disease, tetralogy of fallot, esophageal atresia, anorectal atresia, gastroschisis, omphalacele and hydrospadias. Interestingly, this study did not find increased risk for any of the birth defects in fetuses exposed to inhaled corticosteroids during the first trimester.[13] However, increased rates of cleft palate and gastroschisis were found to be associated with beta-2 agonist exposure with OR = 1.63 (95% CI 1.05-2.52) and OR = 1.89 (95% CI 1.12-3.20) respectively.[13] Additionally, the cases who were categorized "all asthma medication" were also found to have higher rates of anal atresia with OR = 1.64 (95% CI 1.18 -3.44).[13]

While this article seems to contradict the previous two articles in that it did not find significant differences following exposure to inhaled corticosteroids, its methodology varied significantly. First of all, this study only measured exposure as

being exposure during the first trimester, whereas the previous two articles looked at exposure from 1 month prior to conception through the end of pregnancy. Additionally, this study looked at inhaled corticosteroid use separately rather than looking at all corticosteroid use together, regardless of route of administration.

Similarly to the above article, a study by Skuladottir et al also did not find statistically significant differences between asthmatics and non-asthmatics. They chose a study design using data from the National Birth Defects Prevention Study (NBDPS), which was a "population-based, multi-center case-control" study that collected data on all births between October 1997 and December 2009, which occurred at any of the chosen study centers across ten different states. The study was comprised of data from all living infants and stillbirths, with diagnosis of orafacial clefts, such as cleft lip with palate (CLP) or cleft palate only (CPO), being made either clinically, surgically or on autopsy. Any deliveries resulting in either of these defects were then classified as "case" infants, with the "control" group consisting of those infants born without orofacial defects. Any "case" infant, who was believed to have an alternative cause of the defect was subsequently excluded from the study. Data was then collected in the same fashion as in the above article examining CHD, in that mothers were interviewed by telephone anywhere from six weeks to two years after estimated date of delivery (EDD). During these interviews they were asked to answer questions regarding preexisting medical conditions, any medications taken beginning three months prior to conception through delivery --- and the duration of such medications, and any other medical complications arising during pregnancy.

Researchers then used logistic regression models to compare rates of orofacial defects in infants born to mothers with exposure to corticosteroids as compared to those who were not exposed to corticosteroids. The data collected was then further examined according to when in pregnancy the exposure occurred and the route of administration to see if there were any specific correlations with orofacial defects. A total of 8924 mothers were enrolled with 66.4% (5922) delivering neonates without orofacial defects, classified as the "control" group. Of the 3002 infants with malformations, 52.5% (1577) had both cleft lip and cleft palate (CLP), with the remainder of the mothers enrolled (795) delivering infants with cleft palate only (CPO).[14] Of the control group, 2.4% of mothers were noted to have corticosteroid exposure from one month before conception through the end of the first trimester. During that same time period, 2.3% of infants with CLP had mothers who reported corticosteroid exposure, OR = 1.0 (95% CI 0.7-1.4), and 1.7% of infants with CPO had mothers who reported corticosteroid exposure, OR = 0.7 (95% CI 0.4-1.2).[14] Interestingly, researchers did not find any statistically significant differences based on mode of delivery or the specific compound of medication. Based on these results, Skuladottir concluded that there was no statistically significant difference between mothers exposed to corticosteroids and those without exposure.[14] The researchers also point out that this data directly contradicts earlier research performed using the NBDPS data collected from 1997-2002, which stated that exposure to corticosteroids was associated with an increased risk of CLP, OR = 2.7 (95% CI 1.1 – 6.7).[14] However, Skuladottir also points out that the earlier data was specific to prednisone, not all corticosteroids, and was only administered orally and therefore had systemic absorption, whereas the more

recent data incorporated all modes of administration and compounds of corticosteroids. Similarly to the article above, which also used data collected by the NBDPS, this study design has a major flaw as it relies on self-reported information, which dates back as far as two years prior. Additionally, this study is very broad as it includes all modalities of corticosteroids used for a variety of medical conditions and is not specific to asthma.

Unlike the previous studies, which compared congenital malformations in pregnant women with asthma as compared to women without asthma, the Eltonsy article *Risk of Congenital Malformations for Asthmatic Pregnant Women Using a Long-Acting β2-Agonist and Inhaled Corticosteroid Combination Versus Higher-Dose Inhaled Corticosteroid Monotherapy* is a cohort study, which sought to compare the risk of serious congenital malformations seen in women with asthma after exposure to long-acting B2- agonist (LABA) and inhaled corticosteroids and those on monotherapy of inhaled corticosteroids at higher doses during the first trimester. The question at hand is whether the combination of LABA and ICS is safe during pregnancy. A population-based retrospective cohort study design was used. Patients were selected from the Quebec Asthma and Pregnancy database, from a period of 1990-2010. A total of 6632 patients were involved in the study, which was a sufficiently large sample size for this purpose. The instance of major malformation was recorded at birth during the first two years of life in the child. The sample population was separated into users of LABA in addition to ICS and users of LABA plus medium dose ICS combinations. What the results showed were that prevalence of major malformations was similar in both sub-categories with a prevalence of 6.9%

among women treated with LABA plus low-dose ICS as compared to a prevalence of 7.2% among women treated with LABA plus either medium-dose or high-dose ICS.[15] When evaluating the risk of ICS alone, some prior studies have stated that there is no increase of risk of congenital malformations with ICS use, while others have found that there was a 63% increase of malformations when using high doses of ICS compared with low-to-moderate doses of ICS during the first trimester.[15]

Another study that looked more broadly at the effect of asthma on pregnancy was by Grzeskowiak et al entitled *Patterns, Predictors and Outcomes of Asthma Control and Exacerbations During Pregnancy: A Prospective Cohort Study*. This study sought to determine the relationship between asthma exacerbations and perinatal outcomes. Through a non-interventional prospective cohort study, 189 women were recruited between May 2009 and May 2012. During that time, the women were assessed by a midwife at 12, 20, 28 and 36 weeks gestation; the midwife collected various data including demographic, maternal smoking, socioeconomic, asthma therapy, asthma control, asthma triggers, comorbid medical conditions, asthma hospitalizations and oral contraceptive use. An exacerbation was considered moderate or severe if a woman needed medical intervention including hospitalization, emergency room visit, emergency doctor appointment or oral corticosteroids. Interestingly, Grzeskowiak found a direct relationship between weeks of gestation and asthma exacerbations.[16] While the study did not find maternal smoking, age or weight to be predictive factors for asthma exacerbations, they did find those factors could be protective factors. Specifically, younger women, non-smokers and women with lower BMIs were all less likely to have exacerbations or uncontrolled asthma. Women who

were found to have uncontrolled asthma at two or more prenatal visits were more likely to have daughters who were small for their gestational age (SGA), occurring in 33.3% as opposed to 9.5% in their non-asthmatic or well controlled counterparts with $p = 0.018$.[16] However, uncontrolled asthma did not put women at increased risk for preterm birth, which occurred in 11.1% of births as opposed to 9.5% of births with a $p = 1.000$.[16] However, women who were found to have uncontrolled asthma at two or more prenatal visits who were carrying male fetuses, were more likely to experience preterm birth, occurring in 25% of births compared to 11.8% ($p = 0.201$), but had an equal risk for delivering a baby determined to be SGA, which occurred in 8.3% of births as compared to 11.8% ($p = 1.000$).[16]

Similarly to the Grzeskowiak study, the Dembrowski article "*Asthma During Pregnancy"* also broadly examines the risks and outcomes of maternal asthma during pregnancy. This study was a multicenter, prospective observational cohort study, which took place over 4 years and examined the role of moderate and severe asthma on the perinatal period, specifically focusing on pre-term delivery. This article sought to prove that moderate and severe asthmatics were more likely to deliver before 32 weeks, as compared to non-asthmatics. Dombrowski further stratified asthmatics by severity with categories of mild and moderate-severe based on FEV1, symptoms and medication use. Furthermore, they sought to enroll 900 patients into each of these categories, with another 900 in the control group. There were several exclusion criteria to ensure the validity of the study including known multiple gestation, intrauterine fetal demise, significant congenital defects, other comorbid pulmonary illnesses, lack of ultrasound prior to 26 weeks or enrollment in an asthma control study.

Statistical analysis was performed by the Biostatics Center of George Washington University using SAS 8.2 Statistical Software, which utilized the Kruskal-Wallis, Chi-Squared and logistic regression studies, which were reported as an odds ratio. A confidence interval of 95% was applied with $p < .05$ being considered statistically significant. Logistic regression took into account a variety of variables, which could affect the results including previous obstetrics history, tobacco use, race, insurance and level of education. When comparing gestational diabetes, they also accounted for additional measures such as BMI and steroid medications.

Interestingly, Dombrowski found that there were no significant differences between mild asthmatics and moderate-severe asthmatics in terms of pre-term delivery with a prevalence of 3% among moderate and severe asthmatics, 3.4% among mild asthmatics and 3.3% among the control group.[17] However, subsequent post-hoc testing demonstrated asthmatic mothers were more likely to develop gestational diabetes. There was also an increased risk of pre-term labor, before 37 weeks, and an increased need for cesarean sections among asthmatics, but only among those stratified into the moderate-severe category. As to be expected, women were also more likely to experience wheezing during labor with increasing severity of asthma. Additionally, neonates born to asthmatic mothers fared the same as neonates born to the control group. One result that seems to defy logic was the finding that neonatal sepsis was highest amongst babies born to mothers with mild asthma, when compared to the control group and the moderate-severe group.

2.4 Implications For Further Research

Upon review of the literature, it appears that much of the data that currently exists regarding treatment of asthma looks at the potential congenital malformations secondary to corticosteroid use. However, little research seems to exist which compares inhaled corticosteroid use in controlled and uncontrolled asthma. It is important to determine whether it is truly the corticosteroids or the level of control which dictates neonatal outcomes and risk of birth defects. Understanding this will help clinicians better understand how to treat asthma in pregnancy and will contribute to the current debate between the health of the mother and the health of the baby.

CHAPTER III

RESEARCH PROPOSAL

3.1 Aims

3.1.1 Project Overview

This thesis project explores some of the many issues that providers must take into account when treating pregnant asthmatics. Treating asthma in pregnancy is an extremely complex issue as there are at least two patients that must be cared for, as is the case with all pregnancies. However, asthma is already a complex disease with a variety of treatments. As demonstrated in the above literature review, it is well understood that corticosteroid use during pregnancy is associated with a range of congenital malformations, preterm labor and low birth weights. However, it is not well understood if there is a difference between controlled asthmatics and uncontrolled asthmatics. By using a prospective cohort study this thesis explores the effect of corticosteroids on fetal development and the neonatal period, and more specifically if this effect differs in controlled versus uncontrolled asthmatics. Corticosteroids, specifically inhaled corticosteroids, are at the cornerstone of asthma treatment. Therefore, it is imperative that one understands what role they play in fetal development, before prescribing.

3.1.2 Research Questions

While there are many questions that could be asked about this topic, this thesis focuses on one specific research question. Is there a difference in congenital malformations among controlled versus uncontrolled asthmatics being treated with inhaled corticosteroids? Asthma is treated in a stepwise approach beginning with inhaled corticosteroids, therefore understanding their impact is most important as they are most widely prescribed. A better understanding of this questions will help researchers determine if corticosteroids should be administered during pregnancy, and if so, what outcomes mothers can expect.

3.1.3 Specific Aims

AIM 1: To provide a better understanding of the effects of inhaled corticosteroids on congenital malformations among controlled and uncontrolled asthmatics.

Specifically, whether or not congenital malformations occur in equal rates when inhaled corticosteroids are prescribed for maternal asthma regardless of the status of the mother's asthma.

AIM 2: To help clinicians better understand the effects of prescribing inhaled corticosteroids during pregnancy on fetal development.

3.1.4 Hypothesis

> Null Hypothesis: There is no difference in congenital malformations among neonates born to asthmatic mothers treated with inhaled corticosteroids in controlled versus uncontrolled asthma.
> Alternative Hypothesis: There will be increased rates of congenital malformations among neonates born to mothers with uncontrolled asthma treated with inhaled corticosteroids.

3.2 Background and Significance

3.2.1 Background

Inhaled corticosteroids are at the forefront of asthma maintenance in mild and moderate asthmatics. While combination therapy with inhaled corticosteroids and long acting beta agonists (LABA) are used for severe asthmatics. Most asthmatics requiring daily medication take inhaled corticosteroids.

3.2.2 Project Significance

Much literature exists regarding the possible harmful effects of exposing a fetus to both oral and inhaled corticosteroids. However, much of this literature poses conflicting information. Additionally, these studies often examine the congenital malformations that may occur secondary to corticosteroid exposure. However, little data exists which directly compares inhaled corticosteroid use in controlled versus uncontrolled asthmatics. Understanding this is crucial as many asthmatics require treatment with inhaled corticosteroids and those women are warned about the potential harmful side effects, which includes but is not limited to congenital malformations. However, it is unclear if all women can expect the same side effects. Perhaps, controlled asthmatics have decreased risk of congenital malformations as compared with uncontrolled asthmatics despite comparable oral corticosteroid use.

Understanding this relationship is crucial both for prescribers and for patients to understand. If the alternative hypothesis proves to be true, it might act as proof that providers should prescribe inhaled corticosteroids more liberally. In fact, if the congenital malformations seem to be associated with uncontrolled asthma rather than with the inhaled corticosteroids, perhaps the management of pregnant asthmatics should be changed to reflect this data. At the present time, asthmatics who are rarely symptomatic are not prescribed inhaled corticosteroids. However, if research proves that congenital malformations are more likely to occur in uncontrolled asthmatics, regardless of daily inhaled corticosteroid use, it may be wise to treat all pregnant asthmatics with inhaled corticosteroids to prevent their asthma from becoming uncontrolled and thereby reduce the risk of congenital malformations.

3.3 Preliminary Studies

Not Applicable

3.4 Research Design and Method

3.4.1 Design

This paper is proposing a prospective cohort study, which will follow pregnant asthmatics receiving inhaled corticosteroids through the neonatal period to assess for congenital malformations. This study will be prospective as not all congenital malformations may be well documented. Additionally, some asthmatics may not accurately recall how well controlled their asthma was during pregnancy.

This prospective cohort study will enroll women at their first prenatal visit. All participating obstetricians will administer a questionnaire to all patients at their first prenatal visit asking if they have asthma, if they take medication, and if they are willing to participate in a study. Women will be then be selected based on the following inclusion and exclusion criteria. After they are selected they will be asked to fill out a daily survey online asking them what medication they took for their asthma that day and what symptoms they experienced. The questionnaire will also highlight if they needed to use a rescue inhaler such as albuterol, or if they sought medical attention for their asthma. Lastly, the questionnaire will ask about possible environmental toxins that could be worsening asthma. They will continue to fill out this questionnaire daily for the remainder of the pregnancy. They will then be asked to fill out two more questionnaires, one on day one of life for their baby and one on day 28 of life. These last two questionnaires will focus on any complications with the baby, specifically any birth defects or malformations. After mothers have delivered, the data regarding symptoms and medication usage will be used to categorize mothers as controlled or uncontrolled asthmatics.

Controlled asthma will be defined as asthma that requires albuterol no more than two times weekly, no more than two nocturnal awakenings due to asthma monthly and no need for oral steroids. Once asthmatics have been categorized as uncontrolled versus uncontrolled, researchers will extract data from the second two questionnaires to determine the number of congenital malformations occurring in each group.

3.4.2 Methods

The subjects for this study will include any asthmatic between the ages of 20 and 39 attending their first prenatal visit, who meet the following criteria. Women will be selected for the study if they are attending a first prenatal visit no more than 10 weeks from their last known menstrual period, have an official diagnosis of asthma and have taken or are taking inhaled corticosteroids for their asthma. Women will be excluded from the study if they have a history of congenital malformations with a previous pregnancy, have a known genetic mutation that puts their babies at risk for congenital malformations and are taking any medications with known teratogenic effects. Additionally, women will be excluded if they engage in any alcohol, tobacco or illicit drug use during pregnancy.

This study will use controlled and uncontrolled asthma as the independent variables with congenital malformations being the dependent variables.

3.4.3 Statistical Analysis

This research will utilize a chi-squared test of independence to compare two sets of nominal data (incidence of congenital malformation in controlled versus uncontrolled asthma).

The statistical analysis includes:
1. $p < 0.05$
2. Desired power = 0.95
3. Minimum sample size = 220

3.4.4 Limitations

As with any research project, this study has several limitations. Firstly, it is rather difficult to encourage participants to fill out daily questionnaires. However, understanding daily symptoms is crucial to understanding asthma control. Similarly, the status of one's asthma is constantly changing as someone may be controlled for the majority of pregnancy, but then develop an upper respiratory infection at 38 weeks gestational age, causing an exacerbation and shifting that participant from the "controlled" to the "uncontrolled" group. Furthermore, asthma is typically treated in a stepwise fashion; therefore, anyone whose asthma is classified as "uncontrolled" should be treated with additional medication to help control their asthma. However, the additional medication may range from oral corticosteroids to addition of a long acting beta agonist. Therefore, if there is a difference between "controlled" and "uncontrolled" asthmatics, it may be difficult to assess whether this difference is due to asthma control as opposed to whatever additional medication is being given to treat the poorly controlled asthmatics. Another confounding variable that needs to be accounted for is environmental factors that could be contributing to both poor asthma control as well as congenital malformations. For example, if someone is living in an apartment with mold, which will worsen asthma, but may also lead to fetal anomalies.

3.4.5 Timeline

The study will follow patients for approximately 9 months, but will enroll patients for a total of three years to obtain a meaningful sample size. Approval will be obtained by the Institutional Review Board (IRB) prior to enrolling patients. Patients

will be recruited at their initial prenatal visit, which is approximately 8 weeks after their last menstrual period. Patients will continue to be followed throughout pregnancy with routine prenatal visits a recommended by the American College of Obstetrics and Gynecology. Their babies will then be followed from birth until the end of the neonatal period at 28 days.

CHAPTER IV

CONCLUSION

Asthma is one of the leading medical complications occurring in pregnancy, which has become increasingly more widespread over time. Understanding how to treat asthma during pregnancy is a hotly debated topic, for which the pendulum has swung back and forth over time. As with any complication of pregnancy, at least two lives must be considered at all times. Understanding how to treat the mother without harming the fetus is often tricky and can be the source of much debate. Additionally, with so many classes of medications currently in existence to treat asthma it is often to difficult to know which ones are best for the fetus.

Asthma is currently treated with a stepwise approach with most asthmatics receiving inhaled corticosteroids for daily symptoms. However, per FDA regulations, no inhaled corticosteroid is currently deemed safe for pregnancy, considered to be category "A." In fact, most asthma medications are categorized as a "C." As evidenced by the literature above, corticosteroids have been shown to be associated with poorer outcomes in pregnancy including preterm labor, low birth weights and increased congenital malformations. Despite the evidence in this literature, there continues to be a debate between obstetricians, pulmonologists and pediatricians regarding the treatment of asthma in pregnancy. One piece of information that is currently missing, which may help guide clinicians in future practice, is whether these outcomes associated with corticosteroid use are affected by the level of control of the

asthma. By using a prospective cohort study this paper hopes to determine if there is a correlation between asthma control and congenital malformations in the setting of inhaled corticosteroid use. By understanding this relationship, we will have a better understanding of the role of corticosteroids in pregnancy.

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