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ORIGINAL ARTICLE

Antenatal Steroid Therapy for Fetal Lung Maturation: Is There an Association with Childhood Asthma?

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Purpose: This study was designed to test the hypothesis that fetal exposure to corticosteroids in the antenatal period is an independent risk factor for the development of asthma in childhood. **Methods:** A population-based cohort study was conducted of all pregnant women who resided in Nova Scotia, Canada, and gave birth to a singleton fetus between January 1989 and December 1998 and lived to discharge. After exclusions, 79,395 infants were available for analysis. Using linked health care utilization records, incident asthma cases between 36 to 72 months of age were identified. Generalized Estimating Equations were used to estimate the odds ratio of the association between exposure to corticosteroids and asthma while controlling for confounders. **Results:** Over the 10 years of the study corticosteroid therapy increased by threefold. Exposure to corticosteroids during pregnancy was associated with a risk of asthma in childhood: adjusted odds ratio of 1.23 (95% confidence interval: 1.06, 1.44). **Conclusions:** Antenatal steroid therapy appears to be an independent risk factor for the development of asthma between 36 and 72 months of age. Further research into the smallest possible steroid dose required to achieve the desired post-natal effect is needed to reduce the risk of developing childhood asthma.

Keywords asthma, Canada, cohort studies, glucocorticoids, pediatrics, perinatal care

INTRODUCTION

Research on the etiology and natural history of asthma has identified a web of predisposing factors (e.g., genetics, atopy), causal factors that may sensitize the airways (e.g., animal dander, dust mites, workplace allergens), and contributing factors (perinatal events such as mode of delivery, exposure to cigarette smoke during pregnancy, gestational age and childhood respiratory infections, air quality, socioeconomic status, and pollution)(1–6). Conclusions that can be drawn from this research outline a myriad of exposures and complex interactions in the etiology of pediatric asthma(7–10).

Given the complex nature of pediatric asthma etiology, factors in the perinatal period that would predispose individuals to asthma are of particular interest (11,12). Corticosteroid (CS) therapy, administered during labor and delivery to accelerate fetal lung maturation, has not been fully examined as a potential risk factor for the development of asthma in humans (13). CS therapy has been shown to alter the development of the fetal lung and has been linked, in animal studies, to changes in brain chemistry and subsequent hypertension later in life (14–28).

The use of CS therapy in Canada among preterm infants before 34 weeks' gestation has increased in the last 15 years from less than 25% to approximately 60% (29, 30). This increase of CS therapy follows from randomized controlled trial evidence indicating increased infant survival among preterm infants exposed to antenatal CS therapy (31).

A limited number of previous studies have investigated lung function (not asthma) in childhood among those previously exposed to CS therapy (32–35). The small sample sizes and convenience samples of these studies do not provide sufficient evidence for or against an association between CS therapy and asthma (13). Therefore, a large population-based cohort study where confounding by indication can be controlled is warranted.

This study was designed to test the hypothesis that fetal exposure to corticosteroids in the antenatal period is an independent risk factor for the development of asthma in childhood.

METHODS

A population-based cohort study of all pregnant women who resided in Nova Scotia, Canada, and gave birth to a singleton fetus between January 1989, and December 1998 and lived to discharge was conducted in 2006.

Data from The Maternal-Child Health Database (MCHD) were used. The MCHD is a longitudinal population-based database of all mothers and infants delivered while residing in Nova Scotia that is linked to health services utilization data. Four independently collected linked databases comprise the MCHD used in this study including data from the Nova Scotia Atlee Perinatal Database (NSAPD), the Nova Scotia

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physician visits Medical Services Insurance File database, the Nova Scotia Vital Statistics Database, and the Nova Scotia portion of the Canadian Institute for Health Information hospital admissions database.

Pregnancies that resulted in the birth of more than one infant (twins, triplets, quadruplets) differ from singleton pregnancies both physiologically and obstetrically and therefore were not eligible for inclusion. Mothers who had thyroid conditions (due to higher levels of hormones already present) and mothers experiencing active asthma during the gestational period (due to increased risk of obstetrical complications and the possibility of fetal exposure to steroids because of the pharmaceutical interventions used to manage the mothers' asthma) were also excluded (36–38).

Previous work in Canada has established that health service administrative records can be used to identify and describe children with asthma (39–42). The definition of asthma in this study was based on previous work determined by examining physician visits or hospitalizations where the primary diagnostic field was for asthma or asthma-like conditions (asthma - ICD-9-CM code 493, bronchitis - ICD-9-CM code 490, or bronchiolitis - ICD-9-CM code 466). Subjects who experienced at least two health care interactions in any 365-day period, between 36 and 72 months post-birth, where the diagnosis was asthma or an asthma-like condition and at least one visit was not in the winter period (December to March inclusive) or experienced one hospitalization specifically for asthma (ICD-9-CM code 493) were considered to be asthmatic (39). This definition encompasses all levels of asthma severity. The majority of childhood asthma has been shown to be diagnosed by 72 months of age (42, 43). Seventy-two months of follow-up data were available for all subjects.

A second more conservative definition of asthma was developed to examine the potential that the primary definition would be too encompassing and therefore have a high level of misclassification. The conservative definition of asthma was similar to the primary definition except that only interactions where asthma (ICD-CM code 493) was the primary diagnostic field were considered. This case definition was used as a sensitivity analysis to assess the robustness of the results from the primary asthma definition.

The primary exposure of interest is antenatal CS therapy. Maternal systemic steroid therapy is coded in the NSAPD (44). The first dose of the first course of betamethasone or dexamethasone coupled with the timing of the administration is recorded. For this study, infants were considered exposed to CS therapy if either of these drugs was administered regardless of timing.

The current Canadian standard of care for the administration of antenatal corticosteroids is one course at a standard dose (31). Although multiple courses of antenatal corticosteroids have been administered to some mothers this is not considered standard clinical practice. Information on repeat courses is not available in NSAPD. Given that repeat courses are not considered standard of care, only a few infants would have been exposed to repeat courses over the time period under study. The mixing of infants who were exposed to single and repeat courses would only serve to attenuate the risk estimates towards the null.

Numerous potential risk factors for childhood asthma have been identified in the literature. Potential confounders con-

sidered in this analysis included the infant's sex, gestational age at birth, maternal age, 1-minute Apgar score, administration of surfactant, infant's birth weight, delivery by caesarian section, maternal smoking during the gestational period, socioeconomic status (SES), hyaline membrane disease, maternal insulin dependent diabetes mellitus, gestational diabetes, number of siblings, and year of birth.

The infant's gestational age at birth, in completed weeks, was examined both continuously and as a dichotomous variable indicating full-term/pre-term, with full-term being 37 or more completed weeks of gestation. Infants born at an early gestational age are at increased risk of poor lung function, and preterm labor is often used as an indication for CS therapy (29, 45–47).

CONFOUNDING

Control for confounding by indication was achieved in this study given not all infants who are preterm or low birth weight were exposed to CS therapy and a portion of infants who are full-term or full birth weight will have been exposed. There is a portion of infants in each year of the cohort where the therapy is clinically indicated, but for various reasons not administered (e.g., where mothers presented to the hospital too late). Therefore, each year a proportion of preterm and low birth weight infants are unexposed and a portion of full-term infants are exposed to CS therapy (therapy was clinically indicated) allowing for differences in the development of childhood asthma to be examined.

Maternal age was examined continuously. Maternal age has been shown to be related to preterm birth and related to obstetrical complications leading to the administration of CS (30, 48). The infant's 1-minute Apgar score (examined in three categories, 0–3, 4–6, 7–10) has been shown to be an independent risk factor for childhood asthma (49). Delivery by cesarean section was examined as a dichotomous variable where, regardless of other obstetrical interventions during delivery (e.g., the use of forceps before surgery), if the infant was ultimately born by cesarean section it was considered a cesarean section. Delivery by cesarean section is related to CS therapy and CS therapy has been shown to be associated with poor lung function and asthma in the infant (49, 50).

Maternal smoking during pregnancy was examined as a dichotomous variable. Cigarette exposure during the gestational period has been shown to be related to the development of childhood asthma and risk of obstetrical complications (including prematurity) that are related to the administration of CS (47, 51–56). Differences in the complication rate and the potential for threatened preterm labor is increased when the mother is diagnosed with either type 1 diabetes mellitus or gestational diabetes.

Hyaline membrane disease is a respiratory condition in the infant that is often associated with pre-term delivery and subsequent morbidity. CS therapy was primarily instituted to ameliorate this disease. However, the administration of surfactant to alleviate various respiratory difficulties in the infant after birth, such as hyaline membrane disease, has been shown to be related to both long-term lung function and the use of CS therapy (57–60).

Owing to the declining incidence of asthma over the time period under study, the year of birth was used to control for birth cohort effects (temporal effects).

A greater number of older siblings in a household have been shown to be associated with reduced risk of childhood asthma and forms part of the basis for the hygiene hypothesis (61–63). Also related to the hygiene hypothesis is the socioeconomic status of the infant's family (64, 65). Mothers who are of low socioeconomic status are also more likely to have various pregnancy complications that include threatened preterm labor (66). Therefore, two socioeconomic status measures were used in this study. Marital status at the time of delivery (married or common law versus single, widowed, divorced, or separated) and quintiles of neighborhood income (based on the postal code of residence at the time of delivery).

ANALYSIS

Logistic regression models were used to estimate an odds ratio (OR) of the association between exposure to CS therapy and subsequent development of childhood asthma (using the primary asthma definition). A Generalized Estimating Equation (GEE) (67,68) with the mother as the cluster (infants who share the same mother are non-independent) and an independent correlation structure was used to generate the parameter estimates and robust 95% confidence intervals (CI). A GEE with an independent correlation structure was used since mothers provide more than one infant to the cohort and no relationship between siblings was hypothesized. Potential confounders were initially examined individually. Each potential confounder's effect on the association between the exposure variable and outcome was assessed by examining the difference in the exposure parameter estimate. Differences larger than 10% in the parameter estimate for the exposure variable were considered evidence of confounding. Potential cofounders that did not demonstrate evidence of confounding were not retained in the final model. All statistical analysis was performed using SAS version 8.12.

RESULTS

There were a total of 113,145 births to 76,782 mothers between January 1, 1989, and December 31, 1998, in Nova Scotia. Exclusions included 1,325 fetal, neonatal or infant deaths that occurred before 1 year of age, 2,408 infants who were delivered from a multiple gestation, 4,958 infants who were born to mothers experiencing active asthma during the gestational period and a further 89 infants were excluded because they were born to mothers experiencing endocrine abnormalities.

There were 104,365 infants eligible for record linkage. Birth records for 18,627 infants could not be successfully linked to the health care follow-up data. Because of deaths, migration, and other events an additional 4,619 infants did not have 12 months of accrued follow-up time with which to assess the outcome. A further 1,590 infants did not have either a birth weight or gestational age recorded, which is required for the analysis; 134 infants were greater than or less than 3 standard deviations from their mean sex-specific birth weight for gestational age and therefore were excluded. This left 79,395 infants from 56,168 mothers for analysis.

All data presented in table form are using the primary asthma case definition. Table 1 provides descriptive statistics for the study sample by asthma status. Table 1 also provides odds ratio estimates for the crude association between the covariate and asthma status. Note that the asthma incidence

among birth cohorts peaked in 1991 and has been on a decline since. The number of siblings, income, marital status, mean birth weight, and mean maternal age at birth are similar between asthmatics and non-asthmatics. Infants born preterm had an elevated incidence of asthma over the follow-up period.

Table 2 provides the rates of antenatal steroid therapy administration and perterm birth by year of birth. The use of antenatal steroid therapy increased threefold over the 10-year time period of the study, from a rate of 7.5 in 1989 to 23.2 per 1,000 births in 1998. The perterm birth rate increased approximately 30% over the same period, from a rate of 40.6 in 1989 to 52.6 per 1,000 live births in 1998.

Table 3 provides the unadjusted and adjusted odds ratio estimates for the relationship between antenatal steroid administration and the subsequent development of childhood asthma.

Only the infant's year of birth and gestational age in completed weeks were identified as confounders. The unadjusted odds ratio of 1.57 (95% confidence interval: 1.37, 1.80) was attenuated to 1.23 (95 percent confidence interval: 1.06, 1.44) when adjusted for these confounders (labeled as model 1). A second adjusted model is presented in Table 3 that controls for an additional set of covariates that changed the exposure parameter estimate by 5% or greater (labeled model 2). The adjusted odds ratio when controlling for these additional covariates is attenuated to 1.16 (95% confidence interval: 0.98, 1.36). Preterm birth, neighborhood income, marital status, bronchopulmonary dysplasia, birth weight, and maternal age were not seen to further alter the parameter estimate for antenatal corticosteroids by greater than 5%.

When considering the more conservative definition of asthma the prevalence of asthma decreased from 18.5% to 12.1%. The estimated odds ratio for the development of asthma (using the conservative definition) between 36 and 72 months of age after exposure to antenatal corticosteroid therapy was OR= 1.34 (95%CI: 1.13, 1.59) adjusted for gestational age and year of birth.

DISCUSSION

Antenatal steroid therapy appears to be an independent risk factor for the development of childhood asthma after controlling for year of birth and gestational age. The reasons for this increased risk are not obvious, but many animal studies have established latent effects of corticosteroid exposure in utero. Previous human studies were limited in their ability to draw conclusions about the risk of exposure to CS and the subsequent development of childhood asthma.

Strengths of this study are rooted in the large population cohort that were assembled and followed for extended lengths of time. The availability of potential confounders for control was extensive. Control for confounding by indication was also inherent in this study design providing considerable methodological strength.

The retrospective nature of this study design has a number of limitations. The reliability and validity of an asthma diagnosis in the Medical Services Insurance file data are unknown. Errors in the primary reason for admission in the Canadian Institute for Health Information Hospital Discharge Data may occur when several competing causes of admission are present in any one individual. Errors of this sort, with both

TABLE 1.—Descriptive characteristics of the study sample by asthma status.

	Asthma				Total		Unadjusted	
	No		Yes					
	Num	%	Num	%	Num	%*	OR	95% CI
Total	64,672	81.5	14,723	18.5	79,395	100.0		
Birth year								
1989	4,524	77.1	1,343	22.9	5,867	7.4	1.76	1.61–1.92
1990	6,709	77.3	1,969	22.7	8,678	10.9	1.74	1.60–1.89
1991	6,420	77.0	1,923	23.0	8,343	10.5	1.77	1.63–1.93
1992	6,634	80.1	1,646	19.9	8,280	10.4	1.47	1.35–1.60
1993	6,620	81.2	1,529	18.8	8,149	10.3	1.37	1.25–1.49
1994	7,001	82.7	1,469	17.3	8,470	10.7	1.24	1.14–1.35
1995	6,884	82.9	1,417	17.1	8,301	10.5	1.22	1.12–1.33
1996	7,084	85.3	1,219	14.7	8,303	10.5	1.02	0.93–1.11
1997	6,600	85.0	1,161	15.0	7,761	9.8	1.04	0.95–1.14
1998	6,196	85.5	1,047	14.5	7,243	9.1	1.00	
Antenatal steroid exposure	826	73.8	293	26.2	1,119	1.4	1.57	1.37–1.80
Number of siblings								
0	28,398	80.2	7,031	19.8	35,429	44.6	1.50	1.37–1.64
1	23,322	81.6	5,263	18.4	28,585	36.0	1.36	1.25–1.49
2	9,160	83.6	1,801	16.4	10,961	13.8	1.19	1.08–1.31
3+	3,784	85.8	626	14.2	4,410	5.6	1.00	
Preterm birth (< 37 weeks)	2,759	75.0	918	25.0	3,677	4.6	1.49	1.38–1.61
Cesarean section	11,880	79.5	3,060	20.5	14,940	18.8	1.17	1.11–1.22
Income								
Quintile 1	13,749	80.7	3,280	19.3	17,029	21.4	1.07	1.01–1.14
Quintile 2	13,656	81.5	3,106	18.5	16,762	21.1	1.02	0.96–1.09
Quintile 3	12,230	82.0	2,680	18.0	14,910	18.8	0.99	0.92–1.05
Quintile 4	13,470	81.7	3,026	18.3	16,496	20.8	1.01	0.95–1.08
Quintile 5	10,485	81.8	2,332	18.2	12,817	16.1	1.00	
Surfactant administration	149	64.2	83	35.8	232	0.3	2.46	1.88–3.21
1 Minute Apgar Score								
0–3	1,416	77.4	413	22.6	1,829	2.3	1.31	1.17–1.46
4–6	4,774	79.3	1,243	20.7	6,017	7.6	1.17	1.09–1.24
7–10	58,242	81.7	13,014	18.3	71,256	89.7	1.00	
Maternal smoking	17,840	79.6	4,560	20.4	22,400	28.2	1.19	1.14–1.24
Married/common law	46,080	81.6	10,412	18.4	56,492	71.2	0.94	0.90–0.98
Hyaline membrane disease	742	69.5	326	30.5	1,068	1.3	1.95	1.71–2.22
Bronchopulmonary dysplasia	107	60.1	71	39.9	178	0.2	2.92	2.17–3.94
Birth weight:grams (mean, SD)	3,484.1	555.9	3,440.4	601.0	3,476.0	564.8	1.00	1.00–1.00
Gestational age:weeks (mean, SD)	39.5	1.7	39.3	2.0	39.4	1.7	0.94	0.93–0.95
Maternal age:years (mean, SD)	27.5	5.3	27.1	5.2	27.4	5.3	0.99	0.98–0.99

Note. All totals do not add to grand total given missing values for some variables.

*Percent of total cohort.

databases, would have a conservative effect on the estimate of association generated in this study.

Limitations in the measure of exposure exist in that there is no measure of the CS that crosses the placenta and that is biologically available to each fetus. Information that pertains to multiple exposure to CS therapy and the actual amount of medication administered is not recorded in the NSAPD. With all data limitations outlined, bias would only result if

there was a systematic difference between those exposed to CS therapy and those not exposed. There is no indication that physician billing or hospital discharge records would be different based on exposure.

Given that this study is focussed on mothers and infants from the province of Nova Scotia, Canada, any findings from this current study would need to be replicated in other populations to strengthen external validity. Although no factors specifically related to the biological effects of CS therapy are postulated to differ between this population and others, other factors related to childhood asthma may differ. The trend in the incidence of asthma by birth year for this population appears to be different than that of other populations and therefore, replication of these findings in different populations is warranted.

The increased risk of asthma attributed to exposure to CS therapy appears to be consistent when considering the similar nature of the results between the primary and secondary case definition. As expected, any misclassification in the primary definition appears to attenuate the risk estimate towards the null.

Continued research into the perinatal factors in the etiology of childhood asthma is warranted. Information continues to surface that draws attention to the potential long-term consequences of exposures in utero and subsequent disease

TABLE 2.—Rates of antenatal steroid therapy administration and preterm birth by year of birth.

Year of birth	Total Births Num	Steroid Administration				Preterm Birth	
		Preterm		Full Term			
		Num	Rate	Num	Rate	Num	Rate
1989	5,867	26	109.24	18	3.20	238	40.57
1990	8,678	48	127.66	18	2.17	376	43.33
1991	8,343	58	165.71	28	3.50	350	41.95
1992	8,280	78	200.51	38	4.82	389	46.98
1993	8,149	67	195.34	35	4.48	343	42.09
1994	8,470	68	184.78	48	5.92	368	43.45
1995	8,301	77	186.44	34	4.31	413	49.75
1996	8,303	99	237.98	46	5.83	416	50.10
1997	7,761	106	263.03	59	8.02	403	51.93
1998	7,243	97	254.59	71	10.35	381	52.60
Total	79,395	724	196.90	395	5.22	3,677	46.31

Note. Rate is per 1,000 births.

TABLE 3.—Association between antenatal steroid therapy exposure and childhood asthma.

	Unadjusted		Adjusted-Model 1		Adjusted-Model 2	
	OR	95% CI	OR	95% CI	OR	95% CI
Total sample size	79,395		79,395		76,113	
Antenatal steroid exposure	1.57	1.37–1.80	1.23	1.06–1.44	1.16	0.98–1.36
Birth year						
1989			1.80	1.64–1.97	1.79	1.63–1.96
1990			1.77	1.63–1.92	1.75	1.61–1.90
1991			1.80	1.66–1.96	1.81	1.66–1.97
1992			1.49	1.37–1.62	1.48	1.35–1.61
1993			1.38	1.27–1.51	1.37	1.25–1.49
1994			1.25	1.15–1.36	1.24	1.13–1.35
1995			1.23	1.13–1.34	1.22	1.12–1.33
1996			1.02	0.94–1.12	1.01	0.92–1.10
1997			1.04	0.95–1.14	1.04	0.95–1.14
1998			1.00		1.00	
Gestational age (weeks)			0.94	0.93–0.95	0.96	0.94–0.97
Hyaline membrane disease					1.23	1.45–1.05
Male gender					1.31	1.36–1.26
Number of siblings						
0					1.52	1.38–1.67
1					1.40	1.28–1.54
2					1.21	1.09–1.34
3+					1.00	
1 Minute Apgar Score						
0–3					1.20	1.07–1.34
4–6					1.11	1.04–1.19
7–10					1.00	
Cesarean section					1.11	1.17–1.06
Maternal smoking					1.18	1.23–1.13

Note. Model 1 presents control for confounders noted to alter the parameter estimate for antenatal steroid exposure by 10% or greater. Model 2 presents control for co-variables noted to alter the parameter estimate for antenatal steroid exposure by 5% or greater. In Model 2 the sample size differs due to missing information on covariates.

risk. Although only a small but significant elevated risk for childhood asthma and antenatal steroid exposure was demonstrated in the current study, further research is needed into the smallest possible dose required for the steroid to achieve the desired post-natal effect, potentially limiting the long-term consequences such as childhood asthma.

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