Maternal Asthma, Preterm Birth, and Risk of Bronchopulmonary Dysplasia

Susan Gage, MD[1], Peiyi Kan, MS[1], Henry C. Lee, MD[1,2], Jeffrey B. Gould, MD[1,2,3], David K. Stevenson, MD[1], Gary M. Shaw, DrPH[1], and Hugh M. O'Brodovich, MD[1]

Objective To study the relationship between maternal asthma and the development of bronchopulmonary dysplasia (BPD).

Study design Using a large population-based California cohort, we investigated associations between maternal asthma and preterm birth subtype, as well as maternal asthma and BPD. We used data from 2007-2010 maternal delivery discharge records of 2 009 511 pregnancies and *International Classification of Diseases, Ninth Revision* codes. Preterm birth was defined as <37 weeks gestational age (GA), with subgroups of <28 weeks, 28-32 weeks, and 33-37 weeks GA, as well as preterm subtype, defined as spontaneous, medically indicated, or unknown. Linkage between the 2 California-wide datasets yielded 21 944 singleton preterm infants linked to their mother's records, allowing estimation of the risk of BPD in mothers with asthma and those without asthma.

Results Maternal asthma was associated with increased odds (OR, 1.42; 95% CI, 1.38-1.46) of preterm birth at <37 weeks GA, with the greatest risk for 28-32 GA (aOR, 1.60; 95% CI, 1.47-1.74). Among 21 944 preterm infants, we did not observe an elevated risk for BPD in infants born to mothers with asthma (aOR, 1.03; 95% CI, 0.9-1.2). Stratification by maternal treatment with antenatal steroids revealed increased odds of BPD in infants whose mothers had asthma but did not receive antenatal steroids (aOR, 1.54; 95% CI, 1.15-2.06), but not in infants whose mothers had asthma and were treated with antenatal steroids (aOR, 0.85; 95% CI, 0.67-1.07).

Conclusion Asthma in mothers who did not receive antenatal steroid treatment is associated with an increased risk of BPD in their preterm infants. *(J Pediatr 2015;167:875-80)*.

Asthma is a common, if not the most common, chronic disease to complicate pregnancy and has been associated with poor obstetric outcomes.[1] Despite medical advances in both asthma and preterm birth, mothers with asthma are at greater risk for preterm birth (defined as delivery at <37 weeks gestational age [GA]).[2,3] In the US, preterm birth occurred in 13% of all births[4] (during the study time frame), and infants born preterm are at increased risk for substantial morbidity, one of the most common being bronchopulmonary dysplasia (BPD).

Previous studies involving relatively small numbers of patients have reported that infants with BPD, or those who require prolonged supplemental oxygen in the neonatal intensive care unit (NICU), are more likely to have a family member with asthma.[5,6] This has led to speculation that maternal asthma may be casually linked to the development of BPD.[5,6] Given these findings, we endeavored to explore the potential relationship among maternal asthma, preterm birth, and BPD in a large population-based cohort.

A further motivation to explore such a relationship is the biological underpinnings that may be common to asthma and preterm birth. Of note, these include inflammatory pathways with transcription factors nuclear factor kappa light chain enhancer of activated B cells, specific chemokines and leukotrienes (interleukin-6 and tumor necrosis factor 2),[7] and beta receptors in smooth muscle.[8] For example, Bertrand et al[9] observed a relationship between the degree of bronchial reactivity and preterm birth. The authors speculated that there might be a common physiological basis for the reactivity of uterine and bronchial smooth muscle, which would suggest a common origin of underlying disease. These may be inherited conditions or innate risk factors that predispose the fetus to spontaneous preterm birth and BPD.

The objectives of the present study were: (1) to estimate preterm birth risks, by subtype (ie, GA-specific and spontaneous vs medically indicated), among mothers with asthma using California-wide data; and (2) to estimate the risk of BPD in singleton preterm infants whose mothers have asthma. We hypothesized that maternal asthma is associated with increased risk of

BMI	Body mass index
BPD	Bronchopulmonary dysplasia
BW	Birth weight
CPQCC	California Perinatal Quality Care Collaborative
GA	Gestational age
ICD-9	*International Classification of Diseases, Ninth Revision*
ID	Identification number
NICU	Neonatal intensive care unit
OSHPD	California Office of Statewide Health Planning and Development
RDS	Respiratory distress syndrome

From the [1]Department of Pediatrics, Stanford University, Stanford, CA; [2]California Perinatal Quality Care Collaborative, Stanford, CA; and [3]California Office of Statewide Health Planning and Development, Sacramento, CA

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spontaneous preterm birth and subsequent BPD owing to these conditions having an innate predisposition associated with maternal asthma.

Methods

Our analyses used 2 large California-wide datasets. The first dataset was from the California Office of Statewide Health Planning and Development (OSHPD). The OSHPD administrative database captures all hospital discharge diagnoses associated with each woman, including diagnoses antecedent to the pregnancy. We extracted data from this dataset informative of births in the period 2007-2010 and obtained information on maternal delivery discharge records of 2 009 511 pregnancies and their *International Classification of Diseases, Ninth Revision* (ICD-9) codes. This dataset served as the information for demographic and some clinical data; variables considered included maternal age, maternal body mass index (BMI), maternal education, race/ethnicity, payer type, maternal diabetes, maternal asthma, gestational diabetes, hypertension, preeclampsia, polyhydramnios, oligohydramnios, GA, birth weight (BW), and preterm birth subtype. The second dataset was from the California Perinatal Quality Care Collaborative (CPQCC; www.cpqcc.org). The CPQCC data represent >90% of NICU admissions in California. The study protocol was approved by Stanford University's Investigational Review Board.

First, we examined the frequency of maternal asthma in the OSHPD cohort of 2 009 511 singleton live births using ICD-9 code 493 at delivery discharge. Then, using OSHPD data, we examined the frequency of preterm birth by the presence of maternal asthma among singleton births.

GA was based on an obstetric estimate of gestation at delivery in weeks provided on the birth certificate. Preterm birth was defined as <37 weeks and was stratified into groups by GA at birth to <28 weeks, 28-32 weeks, and 33-37 weeks. Preterm birth was further subtyped as spontaneous, medically indicated, and unknown. The algorithm for these subtypes is shown in **Table I**. Data were analyzed by logistic regression models, with ORs adjusted for maternal BMI, maternal education, maternal race/ethnicity, and payer status at delivery.

Table I. Categorization tool for preterm type coding using OSHPD and VS data

Preterm birth group (specific)	ICD-9/VS code
Spontaneous	(Preterm premature rupture of membranes, premature labor, and/or tocolytics) 658.1 VS labor/delivery code 10 644.0-645.0 VS complications/procedure of pregnancy code 28
Indicated	(Not spontaneous, "induced," or cesarean section before 37 wk) Procedure codes 73.0, 73.1, and/or 73.4 VS labor/delivery codes 11 and/or 12; procedure codes 74.0-75.0 VS method of delivery codes 01, 11, 21, 31, 02, 12, 22, and 32
Unknown	Not spontaneous or indicated

VS, Vital Statistics.

Data linkage was performed between the OSHPD and CPQCC datasets from 2007-2010. The CPQCC-OSHPD linkage was created using a probabilistic method based on CPQCC stay identification number (ID) and NICU ID for the NICU that discharged the infant to home, infant's age at discharge (in days), infant's date of birth, infant's sex, location of birth, mother's date of birth, BW, GA at birth (days), multiple birth status, number of multiples in the set, and birth order.

The majority of matches found were based on the CPQCC stay ID and NICU ID for the NICU that discharged the infant home. For these matches, the other data elements listed must have shown a minimum level of concordance. In the absence of the CPQCC stay ID and/or NICU ID, the agreement for the other matching data elements must be very strong. The goal of the linkage is to match CPQCC records to infants registered in the OSHPD database with near 100% certainty.

We were able to link 21 944 premature infants in the CPQCC database from the 2 009 511 pregnancies in the OSHPD database. Using the linked data, we evaluated rates of BPD in preterm infants, defining the use of supplemental oxygen at 28 days after birth but room air at 36 weeks postmenstrual age as mild BPD and the requirement for supplemental oxygen at 36 weeks postmenstrual age as moderate/severe BPD.[10] The CPQCC database does not provide information on the amount of supplemental oxygen or the use of nasal positive pressure, so we were unable to differentiate between moderate and severe BPD as defined elsewhere.[10] We used the ICD-9 code from the OSHPD database to identify mothers with asthma. We compared CPQCC and OSHPD data GA, sex, and maternal age for data rigor.

Associations among maternal asthma, preterm birth, preterm birth subtype, BPD, and BPD with and without antenatal steroid use were estimated with ORs and their 95% CIs. Antenatal steroid use was defined as corticosteroids given to expectant women in anticipation of a preterm delivery. Regarding preterm birth and subtype, ORs were adjusted for maternal BMI, maternal education, maternal race/ethnicity, payer status at delivery, and maternal age. When we analyzed the data for odds of BPD, in addition to the foregoing characteristics, we adjusted for sex and BW, and then stratified separately for the use of antenatal steroids.

All analyses were performed with SAS version 9.3 (SAS institute, Cary, North Carolina).

Results

To reproduce and compare with results from previous studies and to validate our database, we present in **Table II** (available at www.jpeds.com) the characteristics of the 2 009 511 singleton live births that provided our initial basis of analysis for those with mothers with asthma (2.4%) and those with mothers without asthma. Compared with mothers without asthma, those with asthma were