Cystic Fibrosis is Associated with Adverse Neonatal Outcomes in Washington State, 1996-2013

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Objective To determine whether cystic fibrosis (CF) is associated with adverse neonatal outcomes in a recent birth cohort in the US.

Study design A retrospective matched cohort study of infants born in Washington State from 1996 to 2013 was identified through birth certificate data and linked to statewide hospital discharge data. Infants with CF were identified by hospitalization (through age 5 years) in which a CF-specific *International Classification of Diseases, Ninth Revision* code was recorded. "Unexposed" infants lacked CF-related *International Classification of Diseases, Ninth Revision* codes and were randomly selected among births, frequency-matched to "exposed" infants on birth year. Associations of CF with adverse neonatal outcomes (low birth weight [LBW], small for gestational age [SGA], preterm birth, and infant mortality) were estimated through Poisson regression. We performed extreme value imputation to address possible ascertainment bias.

Results We identified 170 infants with CF and 3400 unexposed infants. CF was associated with increased relative risk (95% CI) of 3.5 (2.5-4.9), 1.6 (1.1-2.4), 3.0 (2.2-4.0), and 6.8 (1.7-26.5) for LBW, SGA, preterm birth, and infant death, respectively. The estimated relative risks were similar among infants born from 2006 to 2013, except SGA was no longer associated with CF diagnosis. Results were robust to extreme value imputation and exclusion of infants with meconium ileus.

Conclusions Observed associations of CF with LBW, preterm birth, and infant death are unlikely to be due to ascertainment bias. Further work is needed to determine how to prevent these adverse neonatal outcomes. *(J Pediatr 2017;180:206-11).*

Cystic fibrosis (CF) is the most common early lethal genetic disease in Caucasians, occurring in approximately 1 in every 3500 live births.[1] CF is caused by autosomal recessive inheritance of a defect in the CF transmembrane regulator (*CFTR*) gene. This mutation results in reduced chloride transport across membranes and accumulation of thick, abnormal mucus in the lungs, pancreas, liver, intestine, and reproductive tract.[2] *CFTR* mutations can lead to pancreatic insufficiency and recurrent respiratory infections, among other complications. There is evidence that the *CFTR* gene also has physiologic importance in fetal development because of its activity in the fetal pituitary gland,[3] the placenta,[4-8] and the fetal pancreas.[7]

Late in development, typically developing fetuses grow rapidly, in part through absorption of nutrients transported by the placenta into amniotic fluid.[7,9-11] Impaired pancreatic exocrine function has been associated with intrauterine growth retardation in babies born small for gestational age (SGA).[12] It is plausible that the CFTR would be particularly important in the final stages of fetal development, when fetal pancreatic insufficiency or disruption of the transplacental nutrient transport system could constrain growth.[7] This hypothesis has been supported by several studies in which CF was associated with lower mean birth weight,[4,7,13,14] SGA,[14] and with preterm delivery.[14] These studies were small, several suffered methodologic limitations, and 2 were conducted in the 1950s. It is yet unknown whether CF increases neonatal mortality.

Thus, we sought to determine whether there were associations of CF with low birth weight (LBW), SGA, preterm birth, and infant mortality in a recent cohort in the US. Until 2006, CF was not diagnosed in Washington State until patients displayed clinical symptoms, often between birth and the age of 14.5 months.[15] Since 2006, newborn screening for CF has been mandated in Washington State, and nearly all infants with CF are diagnosed within weeks of delivery. Poor neonatal outcomes could be a harbinger of more severe disease in infants with CF, and when infants are diagnosed through screening, these

CF	Cystic fibrosis
CFTR	CF transmembrane regulator
ICD-9	*International Classification of Diseases, Ninth Revision*
SGA	Small for gestational age
LBW	Low birth weight
RR	Risk ratio

adverse neonatal outcomes may identify infants who need earlier and more aggressive nutritional interventions[16,17] or targeted CF therapies.[18,19]

Methods

We conducted a retrospective matched cohort study of infants born in Washington State between 1996 and 2013, with a focused analysis of the cohort born since newborn screening for CF began, from 2006 to 2013. We used birth certificate data from Washington State, linking the records to hospital discharge data from the Comprehensive Hospital Abstract Reporting System for the mother and child birth hospitalization, infant hospitalizations through the first 5 years of life, and birth and death certificate data.[20] The exposed cohort, infants with CF, was identified by the first hospitalization (through age 5 years) in which a CF-specific diagnosis code was recorded (*International Classification of Diseases, Ninth Revision* [ICD-9] codes 277.00, 277.01, 277.02, 277.03, 277.09). A CF-related complication need not have been the primary indication for hospitalization, rather, any hospitalization for which a CF-specific ICD-9 code was listed would have led to inclusion in the study. For comparison, an unexposed group of infants without CF (ie, without these ICD-9 codes) were randomly selected from among birth certificates over the same time period and frequency-matched to the exposed infants on year of birth at a ratio of 20:1.

All variables used to ascertain neonatal outcomes were derived from birth certificate data, with the exception of mortality, which was taken from infant death certificates.[20] The primary outcome of interest was LBW, birth weight <2500 g. Secondary outcomes were birth weight; SGA, defined as birth weight below the 10th percentile for gestational age and sex; preterm birth, defined as gestational age <37 weeks; and infant death during the first year of life. For SGA, the gestational age was a clinical estimate noted by the birth certificate certifier. For preterm birth, this "clinical" estimate was used if available, and, if not, a "calculated" estimate from maternal report of last menstrual period was substituted.

We identified potential confounders a priori by fitting directed acyclic graphs[21]; only maternal diagnosis of CF and maternal and paternal race met the standard definition of a confounder, which must be associated with risk of CF and the adverse neonatal outcome and not be in the causal pathway between them. Because of the high proportion of infant records lacking paternal race and because of a small number of mothers with a diagnosis of CF (n = 2; 1 in each exposure group), these covariates were not included in the adjusted analysis. We estimated the association of CF with outcomes by fitting unadjusted regression models and models adjusted for maternal race (white or nonwhite): linear regression for birthweight and Poisson regression for LBW, SGA, preterm birth, and infant death. When an outcome is binary, the exponentiated coefficient from Poisson regression yields a risk ratio (RR) instead of an incident rate ratio.[22] We used the sandwich estimator to obtain robust estimates of SEs to estimate 95% CIs.[23] It is possible the *CFTR* mutation might influence birth weight by

leading to prematurity. We performed secondary analyses to estimate the association of CF with LBW independent of prematurity by (1) additionally adjusting for gestational age as a continuous covariate or (2) limiting the analysis to term infants.

Not all children with CF are hospitalized during their first 6 years of life.[24] Thus, ascertaining the exposed cohort through hospitalization records raises the possibility of selection bias for the cohort. To address this limitation, we performed a sensitivity analysis using information provided by the Washington State Department of Health CF newborn screening program, which should identify almost every infant with CF within weeks of birth.

There were 137 infants born with CF in Washington state during the newborn screening period (2006-2013); 9 of these infants had normal newborn screening results and were diagnosed with CF after clinical symptoms occurred.[25] The overall birth prevalence of CF in Washington State can be calculated based on vital statistics data; between 2006 and 2013, there were 702 670 live births in Washington State,[17] giving an estimated birth prevalence of CF of 1 per 5128 live births. The birth prevalence in the overall period, 1996-2013, should not have differed substantially from the prevalence in the subcohort. Applying the prevalence 1 per 5128 live births to the 1 502 273 live births in 1996-2013[17] gives an expected 293 infants with CF. We used this information to estimate the under-ascertainment of CF and performed extreme value imputation for the missing exposed infants. In imputing the missing outcome information, we conservatively assumed outcomes among missed infants with CF occurred in the same proportion as in infants without CF.

Imputation of Extreme Values

For the 1996-2013 cohort, we expected 293 infants with CF but ascertained only 170. Therefore, we assumed there were 123 "missed cases" during this time, infants born in the cohort who had CF but for whom CF was not noted in the records used for ascertainment.

We conservatively assumed that missed cases would have the same adverse neonatal outcome prevalence (LBW, SGA, preterm birth, and infant death) as in infants without CF (5.9%, 8.4%, 8.5%, and 0.3%, respectively). We then calculated the additional number of cases of the adverse outcomes (LBW, SGA, preterm birth, and infant death) expected in the 123 missing infants with CF (missed cases: 7, 10, 10, and 0, respectively) to derive the total number of expected infants with CF who experienced each adverse outcome (totals: 39 LBW infants, 33 SGA infants, 51 preterm infants, and 3 neonatal deaths).

For the 2006-2013 subcohort, the infants identified after the initiation of mandatory newborn screening for CF, we expected 137 infants with CF but ascertained only 68. Therefore, there were 69 "missed cases" of CF during this time. We made the same assumption as for the overall cohort, that missed cases would have the same adverse neonatal outcome prevalence (LBW, SGA, preterm birth, and infant death) as in infants without CF (6.8%, 8.0%, 10.3%, and 0.4%, respectively).

We then calculated the additional number of cases of the adverse outcomes (LBW, SGA, preterm birth, and infant death)