OBSTETRICS

Medical and obstetric complications among pregnant women with cystic fibrosis

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OBJECTIVE: The objective of this study was to estimate the nationwide prevalence of cystic fibrosis (CF) in pregnancy and determine what medical complications exist at delivery among pregnant women with CF.

STUDY DESIGN: The Nationwide Inpatient Sample (NIS) was queried for all delivery-related discharges. Women with CF were identified by *International Classification of Diseases, 9th revision, Clinical Modifications* codes and compared with women without CF. The prevalence of selected severe medical complications was compared between the 2 groups (NIS years 2008-2010) using multivariable logistic regression and the linear change in prevalence of CF at delivery determined (NIS years 2000-2010).

RESULTS: From 2000 to 2010, there was a significant linear increase in the prevalence of CF at delivery from 3.0 to 9.8 per 100,000 deliveries, in 2000 and 2010, respectively ($R^2 = 0.92$, $P < .0001$). From 2008-2010, there were 1119 deliveries to women with CF and 12,627,627 to women without CF. Women with CF were more likely to be white ($P < .0001$) and have diabetes (odds ratio [OR], 14.0; 95% confidence interval [CI], 11.8—16.7) or asthma (OR, 5.1; 95% CI, 4.3—6.1). Multivariable logistic regression demonstrated that women with CF were more likely to die (adjusted OR [aOR], 76.0; 95% CI, 31.6—183), require mechanical ventilation (aOR, 18.3; 95% CI, 10.8—31.2), or have pneumonia (aOR, 56.5; 95% CI, 43.2—74.1), acute renal failure (aOR, 17.3; 95% CI, 9.1—32.6), preterm labor (aOR, 2.2; 95% CI, 1.9—2.6), or an adverse composite CF outcome (aOR, 28.1; 95% CI, 21.8—36.3).

CONCLUSION: Pregnant women with CF are more likely to die, require mechanical ventilation, and have infectious complications compared with women without CF, although the absolute risks are low and these events are relatively rare.

Key words: cystic fibrosis, morbidity, mortality, pregnancy

Cite this article as: Patel EM, Swamy GK, Heine RP, et al. Medical and obstetric complications among pregnant women with cystic fibrosis. Am J Obstet Gynecol 2015;212:98.e1-9.

Cystic fibrosis (CF) is an autosomal recessive disorder that affects 1 in 3500 live births in North America.[1] Nearly 2000 different gene mutations causing CF having been described with an estimated gene prevalence of 1 in 25 in whites and a less frequent carrier rate among other ethnic/racial groups.[2,3] The disease is characterized by a disorder of the cystic fibrosis transmembrane conductance regulator protein that leads to abnormalities of the transmembrane transport of chloride and sodium ions.[4] This defect can affect multiple systems and lead to viscous secretions and impaired clearance in the respiratory, gastrointestinal, and reproductive tracts. Primary manifestations of the disease in adults include respiratory failure from chronic infections and inflammation and nutritional deficiencies because of malabsorption and pancreatic insufficiency. Other manifestations of CF include cirrhosis of the biliary tract, diabetes mellitus, and male-factor infertility.[5]

There have been substantial advances in the care for individuals with CF including improved nutrition and respiratory care. Women with CF are now likely to survive into adulthood with the median predicted survival at 36.8 years in 2011.[6] Although earlier reports have reported decreased fertility associated with CF, more recent literature suggests that the reproductive tract, pituitary and ovarian hormones, and ovulatory function of women with CF is normal with the exception of possible thickened mucous in the cervical canal.[4,7,8] If women maintain appropriate weight and lung function, there is little evidence to suggest that fertility is reduced in this population, thus providing women with CF the opportunity for reproduction.[9]

With the improvement in life expectancy and more women with CF seeking pregnancy, we sought to characterize pregnancy outcomes among women with CF. To date, most reports on outcomes among pregnant women with CF have been from relatively small case reviews of fewer than 100 pregnancies obtained from CF registries or single sites.[10-22] Based on these and other studies, experts believe that women with CF who have moderate to good lung function, defined as forced expiratory

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Received March 26, 2014; revised June 8, 2014; accepted July 8, 2014.

The authors report no conflict of interest.

Presented at the 34th annual meeting of the Society for Maternal-Fetal Medicine, New Orleans, LA, Feb. 3-8, 2014.

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0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2014.07.018

volume in 1 (FEV1) second 50-70%, tolerate pregnancy well.[10,13,14,23] The aim of this study was to determine the period prevalence of maternal CF and estimate national medical and obstetric outcomes among women with CF at delivery using a nationwide administrative database.

Materials and Methods

The Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality was queried for pregnancy-related discharges from January 2008 through December 2010. The NIS contains information from approximately 8 million hospital stays from over 1000 hospitals in 45 states and is the largest all-payer inpatient care database in the United States. The sampling frame uses 5 strata including ownership, hospital size, geographic region, teaching status, and location (urban or rural). The NIS is sampled to approximate a 20% stratified sample of US community hospitals. The data are weighted to generate nationwide estimates based on probabilities proportional to the number of hospitals in each stratum. This accounts for changes in the number of states included over the years and the different hospitals sampled over time. The sampling frame comprises over 96% of the US population.

Information contained in the NIS includes discharge diagnoses and procedure codes based on the *International Classification of Diseases, 9th revision, Clinical Modifications* (ICD-9-CM). The Agency for Healthcare Research and Quality receives data from individual states and insures data values are valid and internally consistent. Further information about the NIS can be found elsewhere.[24] The information included in the NIS contains safeguards to protect the privacy of individual patients, physicians, and hospitals. Although the nature of the data is limited to discharge diagnoses and demographic information, the NIS allows for the study of relatively rare conditions. Because the NIS excludes data elements that could directly or indirectly identify individuals, the study was deemed exempt by the Duke University Health System Institutional Review Board (eIRB approval no. Pro00045222).

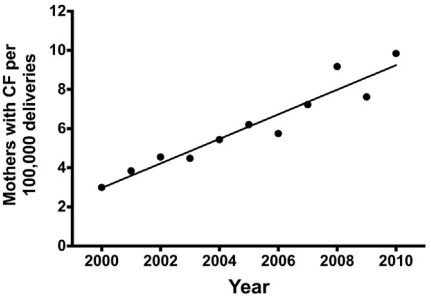
Using the NIS for each of the years 2008-2010, all delivery-related discharge records were identified. We focused only on admissions for delivery to eliminate the possibility of counting a woman more than once per pregnancy in the analysis. There is a chance that over the 3-year period, 1 woman may have had 2 pregnancies and therefore be represented twice in the study. Nonetheless, outcomes are unique for each pregnancy and therefore there is value in counting 1 woman with 2 different pregnancies during that period. An admission for delivery was defined as any discharge record that included a delivery code (ICD-9-CM codes 74.x [except 74.91] for cesarean delivery and V27, 72.x, 73.x, and 650-659 for general delivery codes). Deliveries were also identified by diagnosis-related group codes. Diagnosis-related group codes 765 and 766 were used to identify cesarean deliveries and codes 767, 768, 774, and 775 for vaginal deliveries.[25-29]

Women with CF were identified by an ICD-9-CM code of 277.0x and were compared with women without CF. For comorbidities, both the ICD-9-CM for a particular condition in pregnancy (ie, 6xx code) and the general ICD-9-CM codes for that condition were used (Appendix; Supplementary Table for ICD-9-CM codes used). A composite CF outcome variable was created that included any one of the following: death, mechanical ventilation, sepsis, pneumonia, acute respiratory failure, acute respiratory distress syndrome, or acute renal failure. Data were weighted by the sampling weights provided by the NIS. Continuous variables were compared between pregnant women with CF and pregnant women without CF using Student *t* test or Wilcoxon sign rank tests where appropriate. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for medical conditions and medical and obstetric outcomes among women with CF at delivery compared with women without CF at delivery. Next, a multivariable logistic regression model was constructed for medical and obstetric outcomes among women with CF whereas controlling for age, race/ethnicity, diabetes, gestational diabetes, hypertension, preeclampsia, multiple gestation, and mode of delivery.

To determine the change in prevalence of CF at delivery, delivery admissions were identified using the NIS from the years 2000 through 2010. A period of 11 years was chosen to allow for assessment of change over a longer time frame. For each year, the number of women with CF per 100,000 deliveries was calculated. Linear regression was then used to determine whether there was a significant linear change in the number of women with CF at delivery over the 11-year time period.

Statistical significance was assigned as a P value of $< .05$. Analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC) and GraphPad Prism version 6.0 for Macintosh (GraphPad Software, La Jolla, CA).

FIGURE
Trend in the number of pregnant women with cystic fibrosis per 100,000 deliveries



There was a significant linear increase in the number of women with cystic fibrosis at delivery from 2.99 per 100,000 deliveries in 2000 to 9.84 per 100,000 in 2010 ($P < .0001$, $R^2 = 0.91$).

Patel. Cystic fibrosis in pregnancy. Am J Obstet Gynecol 2015.

Results

Over the years 2000 to 2010, there was a significant linear increase in the number of women with CF at delivery from 2.99 per 100,000 deliveries in 2000 to 9.84 per