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Maternal medical and behavioral risk factors for congenital diaphragmatic hernia

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ABSTRACT

Purpose: Maternal factors contributing to the etiology of congenital diaphragmatic hernia (CDH) remain unclear. We hypothesized that specific maternal medical conditions (pregestational diabetes, hypertension), and behaviors (alcohol, tobacco) would be associated with CDH.

Methods: We conducted a population-based case–control study using Washington State birth certificates linked to hospital discharge records (1987–2009). We identified all infants with CDH (n = 492). Controls were randomly selected among non-CDH infants. Maternal data were extracted from the birth record. Logistic regression was used to adjust for covariates.

Results: Cases and controls were generally similar regarding demographics, although CDH infants were more likely to be male than controls (58.5% vs. 52.5%). Isolated and complex (multiple-anomaly) CDH had similar characteristics. Each of the exposures of interest was more common among case mothers than among control mothers. In univariate analysis, alcohol use, hypertension, and pregestational diabetes were each significantly associated with the outcome. After multivariate adjustment, only alcohol use (OR = 3.65, p = 0.01) and pregestational diabetes (OR = 12.53, p = 0.003) maintained significance. Results were similar for both isolated and complex CDH.

Conclusions: Maternal pregestational diabetes and alcohol use are significantly associated with occurrence of CDH in infants. These are important modifiable risk factors to consider with regard to efforts seeking to impact the incidence of CDH.

Congenital diaphragmatic hernia (CDH) is one of the most important severe congenital malformations compatible with potential long-term survival. With an incidence of 2–5 cases per 10,000 live births, the condition is a relatively common major anomaly at tertiary pediatric centers [1,2]. CDH is a significant cause of morbidity and mortality in neonatal ICU's, and management of these infants consumes significant institutional resources [3,4]. It represents the most costly non-cardiac anomaly in the United States in terms of total annual cost, with the use of extracorporeal membrane oxygenation greatly increasing these expenses [5,6].

Despite advances in the prenatal diagnosis of this condition, its etiology remains unknown. CDH has been found to be associated with a number of demographic factors, including male gender, advanced maternal age, plural births, nulliparity, and low maternal BMI, although such findings have been inconsistent [7–12]. Genetic factors have also been suggested to play a role, though the majority of cases are not hereditary [13,14]. The importance of first trimester processes in primary organogenesis, including fusion of diaphragmatic components, has led to increasing interest in the role of chronic maternal vascular and metabolic diseases as well as early environmental exposures in the etiology of certain congenital anomalies [15–17]. Pregestational diabetes, chronic hypertension, and maternal tobacco and alcohol use have all been shown to be associated with other major congenital gastrointestinal malformations [18–20]. No prior study has considered these exposures together with regard to their association with CDH.

In order to determine the association between the above maternal risk factors and the occurrence of CDH in offspring, we conducted a population-based case control study of state birth records linked to hospital discharge data. We hypothesized that mothers with any of these four medical or environmental risk factors would have an increased risk of giving birth to an infant with CDH, after adjusting for confounding factors.

1. Methods

1.1. Study design

We performed a population-based case–control study using state birth certificates linked to the Washington State Comprehensive Hospital Abstract Reporting System (CHARS), a statewide inpatient

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hospital discharge database that provides de-identified patient data regarding age, gender, payer status, diagnoses, procedures, length of stay, and discharge disposition. The database is created and maintained by the Washington State Department of Health. The study was approved by the University of Washington Institutional Review Board (IRB #43226).

1.2. Patients and controls

Using birth records from January 1, 1987 to December 31, 2009, cases were identified as any live-born infant with a diagnostic code for CDH (ICD-9 code 756.6), regardless of whether they underwent CDH repair or died of the disease. We included all infants diagnosed up to 1 year of age, as ascertained from hospital discharge records for the first year of life, in order to avoid missing less severe cases. We also performed our analyses restricting cases only to patients who were diagnosed during the birth admission. Since our risk estimates did not substantively change, we included all cases in our analysis. Patients were restricted to singleton infants. Since previous studies have suggested that the etiology of isolated and complex (multi-anomaly) CDH may be different, we elected to present our results for all cases as well as broken down according to isolated/complex status [1,10]. The anomalies used to identify complex patients are listed in Appendix A.

Controls were randomly chosen in a 10:1 ratio relative to cases from among all singleton infants without a diagnosis of CDH born during the same time frame. Controls were frequency matched to cases by year of birth in order to account for changes in prevalence of risk factors between controls and cases over time. We also performed our analyses restricting controls to only those patients without any other congenital anomalies (as listed in Appendix A). Since our results did not substantively change, we present the data obtained using our original controls.

1.3. Covariates of interest

Exposures of interest were defined by maternal characteristics coded on the birth certificate, and included maternal smoking during pregnancy (yes/no), maternal alcohol use during pregnancy (yes/no), and maternal diagnoses of chronic hypertension (diagnosed prior to pregnancy, not pregnancy-induced) and pregestational diabetes mellitus.

Potential confounders identified *a-priori* were those clinical factors previously found to be associated with CDH or presumed to be potential confounders of the associations of interest. These factors were collected from the birth record and included infant gender, maternal age (<20 years, 20–34 years, and 35+ years), maternal race (White, Black, Native American, Hispanic), maternal marital status, maternal parity, and maternal body mass index (BMI) in kg/m^2 (<19, 19–25, >25–30, >30). Maternal parity was categorized as nulliparous (no previous births by mother), primiparous (one previous birth), or multiparous (2+ previous births).

1.4. Statistical analysis

Descriptive statistics were used to compare characteristics between cases and controls. Characteristics were similarly compared between isolated and complex CDH cases. Chi-squared tests of homogeneity were used to compare distribution of variables between groups. CDH incidence was calculated as number of incident cases of CDH divided by the total number of singleton live births in Washington State over the study period, as determined from Washington State Department of Health data.

Univariate logistic regression was used to quantify the unadjusted association of each of the four maternal exposures of interest and the occurrence of CDH in the infant. A multivariate logistic regression model was used to quantify the adjusted associations. Risk estimates were adjusted for the covariates listed above. Separate models were run for all cases, isolated CDH only, and complex CDH only. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using Stata 12 (College Station, TX).

Table 1
Characteristics of cases and controls.

	Controls (n = 4920)	Congenital Diaphragmatic Hernia (n = 492)	p-value
	n (%)	n (%)	
Infant gender			
Male	2581 (52.5)	288 (58.5)	0.01
Female	2339 (47.5)	204 (41.5)	
Maternal age			
<20	548 (11.1)	46 (9.4)	0.23
20–34	3702 (75.2)	368 (74.8)	
35+	670 (13.6)	78 (15.9)	
Maternal race			
White	3584 (74.8)	367 (77.6)	0.45
Black	192 (4.0)	18 (3.8)	
Native American	125 (2.6)	10 (2.1)	
Hispanic	546 (11.4)	54 (11.4)	
Other	345 (7.2)	24 (5.1)	
Unknown	128	19	
Maternal marital status			
Married	3468 (70.6)	352 (72.0)	0.53
Single	1442 (29.4)	137 (28.0)	
Unknown	10	3	
Maternal parity			
Nulliparous	2017 (41.8)	177 (37.1)	0.12
Primiparous	1563 (32.4)	171 (35.9)	
Multiparous	1241 (25.7)	129 (27.0)	
Unknown	99	15	
Maternal BMI			
<19	192 (6.4)	11 (4.0)	0.08
19–25	1476 (49.5)	128 (46.9)	
>25–30	733 (24.6)	65 (23.8)	
>30	583 (19.5)	69 (25.3)	
Unknown	1936	219	
Maternal smoking			
Yes	691 (14.5)	71 (15.4)	0.61
No	4071 (85.5)	390 (84.6)	
Unknown	158	31	
Maternal alcohol use			
Yes	66 (2.9)	14 (6.4)	0.004
No	2243 (97.1)	204 (93.6)	
Unknown	2611	274	
Chronic hypertension			
Yes	52 (1.1)	13 (2.8)	0.002
No	4560 (98.9)	446 (97.2)	
Unknown	308	33	
Pregestational diabetes			
Yes	15 (0.3)	8 (1.7)	<0.001
No	4597 (99.7)	451 (98.3)	
Unknown	308	33	

2. Results

We identified 492 incident cases of CDH over the study period. The overall disease incidence was 2.74 CDH cases per 10,000 live births. Compared to controls, a greater proportion of cases were male (58.5% vs. 52.5%, p = 0.01) (Table 1). Cases were also more likely to be born to mothers with BMI >30 (25.3% vs. 19.5%, p = 0.08). Maternal alcohol use was more common among CDH infants than among control infants (6.4% vs. 2.9%, p = 0.004). Mothers of CDH infants also had a significantly higher prevalence of chronic hypertension and pregestational diabetes than control mothers.

Of CDH patients, a total of 174 (35.4%) had at least one other congenital anomaly characterizing them as complex CDH.