Maternal Risk Factors and Perinatal Characteristics in Congenital Diaphragmatic Hernia: A Nationwide Population-Based Study

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Keywords

Congenital diaphragmatic hernia · Risk factors · Epidemiology

Abstract

Background: The etiology of congenital diaphragmatic hernia (CDH) remains poorly understood. We hypothesize that environmental factors play an important role in the development of CDH. **Aim:** The objective of this study was to investigate associated maternal risk factors in pregnancies with CDH. **Material and Methods:** The study was a nationwide, population-based prospective case-control study consisting of a cohort of newborn children entered into the records of pregnant women receiving antenatal care in Sweden, registered in the Medical Birth Registry during the period from January 1, 1982 to December 31, 2015. The study outcome CDH and the different exposures were assessed through linkage to the Swedish National Patient Registry for both cases and mothers. **Results:** A total of 972 cases of CDH were registered into one of the national registries in Sweden between 1982 and 2015. The incidence of neonates with CDH in Sweden from 1982 to 2015 was 3/10,000 live births. The mortality rate during the study period was 31%. Maternal age, ethnicity, parity, exposure to tobacco, BMI, IVF, previous

history of spontaneous abortion or intrauterine fetal demise, and coexisting chronic diseases (urinary tract infection, chronic renal disease, pregestational diabetes, epilepsy, asthma, ulcerative colitis, inflammatory bowel disease, or systemic lupus erythematosus) were not associated with an increased risk of CDH in the fetus. There was a significant association between maternal hypertension and the risk of the child being affected by CDH (OR 3.32, 95% CI 1.41–7.79, $p = 0.01$). No association was found between preeclampsia and CDH. **Conclusions:** Pregestational hypertension is associated with an increased risk of giving birth to a baby with CDH, but no association was observed in pregnancies developing preeclampsia and the occurrence of CDH.

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Introduction

The etiology of congenital diaphragmatic hernia (CDH) remains poorly understood. The association of CDH with chromosomal abnormalities, the existence of

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familiar CDH, and the co-occurrence of CDH with additional malformations support an underlying genetic etiology [1–3]. However, environmental and endogenous factors also seem to play a critical role. Maternal exposure to tobacco [4], alcohol [5, 6], and pregestational diabetes [5], maternal underweight [7], or age [8] have been suggested as potential risk factors for the development of CDH. Most likely, the etiology is multifactorial. With an incidence of only 3/10,000 live births [9–12], research concerning the etiology of CDH remains elusive.

We hypothesize that environmental factors play an important role in the development of CDH. The aim of this study was to investigate the maternal risk factors and perinatal characteristics of CDH pregnancies in a nationwide, population-based study undertaken in Sweden.

Materials and Methods

Study Design

This was a nationwide, population-based prospective nested case-control study within a cohort of newborn children of women registered in the records of antenatal care clinics in Sweden and the Medical Birth Registry (MBR) during the observational period from January 1, 1982 to December 31, 2015. The outcome of CDH and the study exposures were assessed through linkage to the Swedish National Patient Registry (NPR) for both cases and their mothers. All Swedish residents are assigned a unique 10-digit personal identification number at the time of birth or following immigration, which enables linkage among the different national registries and a complete follow-up, which was undertaken in the present study.

Registers

The Swedish National Board of Health and Welfare started the NPR in 1964, which contains prospectively collected information on all hospital admissions in Sweden, including diagnosis and surgical procedures according to the WHO International Classification of Diseases (ICD) system. Since 1987 the register has covered 100% of the Swedish population. Reporting is good, with less than 2% of all hospitalizations missing [13].

The MBR contains prospectively collected data on pregnancies and deliveries in Sweden since 1973. Since 1982 more detailed data have been entered into the register, including information on antenatal care, deliveries, and medical examinations of the newborn. Records for only a small percentage of all infants (0.5–3.9%) are lacking. At the moment, information on prenatal testing is not available. The risk of not identifying a patient using a combination of these registers has been reported as negligible [13].

Outcome Assessment and Definition of Cases and Controls

Eligible case participants of this cohort were children who were born and diagnosed with CDH, whereas control participants without a history of CDH were randomly sampled from within the cohort and matched for birth year and sex. For each case, 5 controls

were randomly chosen. The following codes of the ICD were used to identify the diagnosis of CDH: ICD-9 756.6, ICD-10 Q79.0 and Q79.1.

Assessment of Exposures and Covariates

Maternal Risk Factors

Exposure data on maternal age, ethnicity, parity, smoking or use of chewing tobacco, BMI, IVF, previously spontaneous abortion or intrauterine fetal demise (IUID), and coexisting chronic diseases (urinary tract infection, chronic renal disease, pregestational diabetes, epilepsy, asthma, inflammatory bowel disease, systemic lupus erythematosus, and chronic hypertension) were prospectively collected in the MBR. Data concerning preeclampsia was collected from the NPR using the codes ICD codes O13, O14, 642D-642F (ICD-9), and O13, O14, O15 (ICD-10).

The maternal age was categorized into 5 groups (<20, 20–24, 25–29, 30–34, and 35+ years). Data on ethnicity were categorized into 6 groups: Nordic, European (including Russia, excluding the Nordic countries), Asian (including Oceania), African, North American, and South American. Data on maternal smoking or use of chewing tobacco was categorized into non-smokers/tobacco users, 1–9 cigarettes/day, >10 cigarettes/day both at the time of conception and in the second trimester. Parity was categorized into 3 groups: 1, 2, or 3+ children. Maternal BMI was calculated as body weight (kg) divided by the square of the body length (m²), and categorized into 5 groups: <18 (underweight), 18–24 (normal weight), 25–29 (overweight), 30–34 and 35+ (obese).

Perinatal Characteristics

Exposure data on the delivery mode, gestational age at birth (GA), birth weight (Bw), gender, Apgar scores, and placental weight (Pw) were obtained from the MBR. A Pw/Bw ratio was calculated. The delivery mode was categorized as vaginal, or elective or emergency Cesarean section (CS). Birth was categorized into small for GA (SGA) or appropriate for GA.

Statistical Analysis

Possible risk factors for CDH (maternal age, ethnicity, parity, tobacco exposure, BMI, IVF, previous spontaneous abortion or IUID, and coexisting chronic diseases) were analyzed using conditional regression models (clogit in R) stratifying over the matched pairs. The results are presented as odds ratios (OR) with 95% CI. All ORs of developing CDH were calculated using a univariate approach.

The association between CDH and perinatal characteristics was examined using the Fischer exact test for categorical variables and *t* test or Mann-Whitney U test for numerical variables. Values of *p* < 0.05 were considered to be significant. All statistics were performed in R software version 2.38 (<http://CRAN.R-project.org/package=survival>).

Results

A total of 972 cases of CDH were registered in one of the national registries in Sweden between 1982 and 2015. As reported earlier [12], the incidence of CDH in Sweden between 1982 and 2015 was 3/10,000 live births. The

Fig. 1. Number of children born with CDH during the study period in Sweden.

number of children born with CDH in Sweden decreased during the latter part of the study period (Fig. 1a, b), probably due to the increasing number of terminations following improvements in prenatal diagnosis, as we have previously reported [12]. We did not find any association between calendar time and the incidence of CDH (Fig. 2). All the cases of CDH were within the same interval of days every month with the exception of the month of December. The mortality rate during the study period was 31% (304/972). Maternal age, ethnicity, parity, exposure to tobacco, BMI, IVF, previous history of spontaneous abortion or IUFD, and coexisting chronic diseases (urinary tract infection, chronic renal disease, pregestational diabetes, epilepsy, asthma, ulcerative colitis, inflammatory bowel disease, or systemic lupus erythematosus) did not increase the risk of CDH occurring in the fetus. There was a significant association between maternal hypertension and the risk of CDH (OR 3.32, 95% CI 1.41–7.79, $p = 0.01$; Table 1). We did not find any changes of diagnosis of pregestational hypertension over time (Fig. 3). However, the observations with pregestational hypertension were low among cases and controls, with 9 versus 14, respectively. No association was observed between preeclampsia developing during pregnancy and the diagnosis of CDH in the neonate. The maternal risk factors are summarized in Table 1.

There were no differences in gender distribution, but children born with CDH were significantly more often delivered by planned and emergency CS. Increas-

Fig. 2. Calendar time effect on the incidence of CDH.

ing trends of CS deliveries in pregnancies with CDH were observed during the study period. The cases were also observed to be born at a significantly earlier GA (mean 37.6 vs. 39.1 weeks), with lower birth weights (3.01 vs. 3.52 kg), were to a larger extent SGA (11 vs. 2%), and had overall lower Apgar scores at 1, 5, and 10 min. The placental weight was also significantly lower in CDH babies compared to controls, but the Pw/Bw ratio was higher in cases of CDH (Table 2; Fig. 4). The data on perinatal characteristics are summarized in Table 2.

Table 1. Maternal risk factors

	Cases (<i>n</i> = 972)	Controls (<i>n</i> = 4,722)	<i>p</i> values	Unadjusted OR (95% CI)
Maternal age				
Mean ± SD	30.1±5.3	29.9±5.2	0.28	
<20 years	20 (2)	87 (2)	0.49	1.19 (0.72–1.92)
20–24 years	151 (16)	756 (16)	0.95	0.99 (0.8–1.23)
25–29 years	310 (32)	1,574 (34)		1
30–34 years	309 (32)	1,450 (31)	0.27	1.10 (0.93–1.32)
35+ years	182 (19)	805 (17)	0.17	1.16 (0.94–1.42)
Ethnicity			0.113	
Nordic	827 (87)	4,013 (88)	n.s.	
European	27 (3)	143 (3)	n.s.	
Asian	60 (6)	270 (6)	n.s.	
African	17 (2)	99 (2)	n.s.	
North American	5 (0.5)	16 (0.3)	n.s.	
South American	10 (1)	44 (1)	n.s.	
Parity				
1	430 (44)	1,970 (42)		1
2	333 (34)	1,703 (36)	0.13	0.89 (0.76–1.04)
3+	208 (21)	999 (21)	0.49	0.10 (0.78–1.13)
BMI				
<18	14 (2)	66 (2)	0.74	1.11 (0.59–2.08)
18–24	433 (63)	2,359 (66)	0.67	0.96 (0.78–1.18)
25–29	157 (23)	838 (23)		1
30–34	57 (8)	232 (6)	0.18	1.27 (0.9–1.8)
>35	22 (3)	80 (2)	0.16	1.45 (0.86–2.45)
Tobacco exposure at conception				
Non-smoking	334 (83)	1,775 (82)		1
Smoking 1–9 cigarettes/day	37 (9)	196 (9)	0.87	0.97 (0.67–1.41)
>10 cigarettes/day	32 (8)	186 (9)	0.47	0.86 (0.58–1.29)
Non-chewing tobacco	395 (99)	2,089 (97)		1
Chewing tobacco	6 (1)	57 (3)	0.24	0.6 (0.25–1.42)
Tobacco exposure during second trimester				
Non-smoking	732 (86)	3,756 (86)		1
Smoking 1–9 cigarettes/day	83 (9)	389 (9)	0.58	1.08 (0.83–1.39)
>10 cigarettes/day	39 (5)	236 (5)	0.18	0.78 (0.55–1.12)
Non-chewing tobacco	404 (98)	2,201 (99)		1
Chewing tobacco	7 (2)	26 (1)	0.3	1.58 (0.66–3.75)
IVF	15 (2)	51 (1)	0.25	1.47 (0.81–2.69)
Previous spontaneous abortion or IUFD	216 (22)	872 (18)	0.1	1.18 (0.97–1.43)
Maternal chronic diseases				
Urinary tract infection	13 (1)	58 (1)	0.48	1.1 (0.58–2.06)
Renal disease	0	3	0.28	1.78 (0.79–4.01)
Pregestational diabetes	6 (1)	22 (<1)	0.61	1.25 (0.49–3.15)
Epilepsy	8 (1)	26	0.37	1.67 (0.74–3.77)
Asthma	42 (4)	206 (4)	0.16	0.94 (0.66–1.33)
IBD	7 (1)	22	0.32	1.6 (0.68–3.78)
SLE	1	2	0.43	2.5 (0.23–27.57)
Hypertension	9 (1)	14 (<1)	0.01	3.32 (1.41–7.79)
Preeclampsia	24 (3)	132 (2)	0.87	0.54 (0.38–1.4)

Data are presented as *n* (%) or as indicated. Values in bold are significant. IUFD, intrauterine fetal demise; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus.

Fig. 3. Number of observations of pregestational hypertension among cases and controls.

Fig. 4. Correlation between Pw (g) and Bw (g).

Discussion

In our study we observed that maternal pregestational hypertension was associated with a higher risk of giving birth to a baby diagnosed with CDH, but no association was found when preeclampsia developed during pregnancy. Furthermore, we found that CDH patients have a lower GA at birth, and lower birth and placental weights.

To our knowledge, this is the first nationwide register-based study exploring risk factors for CDH. The well-established population-based medical registries in Sweden, with high validity and coverage, allow these kind of powerful studies, with prospectively collected data, and low risk of selection or information bias.

The completeness of the data, including all cases of CDH in the nation during the study period and follow-up through linkages among the different registries through the personalized 10-digit identification number, makes this study unique. Potential limitations of the study are the possible misclassifications of exposures or outcomes.

However, such a potential error should be similar between cases and matched controls, and thus be balanced.

The limited knowledge of the etiology of CDH hampers the possibility of selecting potential confounders, but by matching and stratification and performing multivariate adjust analysis we tried to control for most plausible biological confounders.

There have been previous studies that have tried to show a relationship between maternal hypertension and congenital malformations. A Danish nationwide study showed a correlation between maternal hypertension and male hypospadias and cryptorchidism [14]. Other studies have demonstrated contradictory results regarding the correlation between treatment with antihypertensive agents, for example beta-blockers and renin-angiotensin antagonists during pregnancy and the risk for congenital heart anomalies [15, 16], although lately a systematic review has shown an association between maternal hypertension and an increased risk of congenital heart disease in the offspring [17]. To the best of our knowledge, the

Table 2. Perinatal characteristics

	Cases (<i>n</i> = 972)	Controls (<i>n</i> = 4,722)	<i>p</i> value
Delivery mode			
Vaginal	529 (54)	3,450 (74)	<0.001
CS			
Elective	120 (12)	174 (4)	<0.001
Emergent	74 (8)	202 (4)	<0.001
GA at birth, weeks	37.67±3	39.19±2	<0.001
Bw, g	3,031±803	3,524±594	<0.001
SGA	108 (11)	103 (2.2)	<0.001
Median 1-min Apgar score (IQR)	7 (4.9)	9 (9.9)	<0.001
Median 5-min Apgar score (IQR)	8 (5.10)	10 (10.10)	<0.001
Median 10-min Apgar score (IQR)	9 (6.10)	10 (10.10)	<0.001
Pw, g	553±141	613±146	<0.001
Pw/Bw ratio	0.20±0.07	0.18±0.06	<0.001

Data are presented as *n* (%), mean ± SD, or as indicated. All of the *p* values are significant. CS, Cesarean section; GA, gestational age; Bw, birth weight; SGA, small for GA; Pw, placental weight.

observations in this study comprise the first report on the association between maternal hypertension and the risk for CDH.

However, it remains unclear if the physiological and biological changes derived by pregestational hypertension result in a plausible molecular and embryological mechanism early in gestation that causes an increased incidence of CDH, or if the association is a consequence of the medical treatment administered to the pregnant women for hypertension. Unfortunately, we are currently unable to answer this question with enough statistical power, since the National Swedish Registry for Drugs Prescription has only been available since 2005, and thus too few entries relevant for this study are currently available. The increasing trends of CS deliveries in pregnancies with CDH that were observed during the study period could probably be explained by an improved prena-

tal detection rate and national strategies of planned delivery mode in pregnancies with CDH [18].

In conclusion, pregestational hypertension but not preeclampsia is associated with an increased risk of the fetus developing CDH. CDH babies are born at an earlier GA, with lower birth and placental weights.

Statement of Ethics

The study was approved by the regional ethical committee in Stockholm, Dnr 2013/1550-31/3.

Disclosure Statement

The authors have no conflicts of interest.

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