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Predictors of congenital diaphragmatic hernia in newborns: A case control study

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***Abstract*---**Congenital diaphragmatic hernia (CDH) is a disorder that is defined by a rupture of the diaphragm, which permits an abdominal hernia to enter the chest space. This disease may be present from birth. Our objective was to identify the features of a person that placed them at a higher risk for developing CDH. A case control study design was used to collect data from the registry for 66 people who had been diagnosed with CDH. The data were acquired from the registry. CDH infants were more likely to be preterm (OR, 3.79; 95 percent CI, 2.01-7.21) and weigh lower than 2500 gr at birth (OR, 3.32; 95 percent CI, 1.65-5.89). Maternal age of 35 years or older (OR, 3.51; 95 % CI, 1.49-6.12) and being small for gestational age (OR, 3.71; 95 % CI, 1.87-6.69) were associated with increased odds of having a CDH infant. Being preterm and small for gestational age as well as low birth weight were independent risk factors for congenital diaphragmal hernia. The chance of having a child born with CDH rises with the mother's age. Detection of these newborn and maternal characteristics may prompt consideration of CDH, therefore enhancing the prognosis of these patients, particularly in developing countries.

***Keywords*---**CDH, risk factors, preterm, weight, gestational age.

1 Introduction

The disease known as a congenital diaphragmatic hernia (CDH) is characterized by a diaphragm rupture that allows abdominal organs to enter the chest. CDH is a rare anomaly that results in severe morbidity and mortality in neonates (Burgos et al., 2019; Paoletti et al., 2020). In various nations, the incidence of CDH varies from 2.0 to 7.0 per 10,000 babies. Not much is known about the pathogenesis of congenital diaphragmatic hernia; nonetheless, it is thought that genetic factors and early environmental variables during pregnancy are the key causes. Embryogenesis and fetal development between the third and sixteenth weeks of pregnancy are crucial for the occurrence of developmental abnormalities that may result in the congenital diaphragmatic hernia (CDH). This suggests that the developing embryo must be exposed to CDH risk factors at an unusually early stage (Kaya et al., 2021).

There is a rather poor survival probability, with just 61% at birth and up to 32% at one year of age (Gupta et al., 2021). Despite advancements in CDH treatment, the infant mortality rate among babies with CDH remains relatively high (Barroso & Correia-Pinto, 2018). As a consequence of pulmonary hypoplasia and persistent pulmonary hypertension (Akhmedov Yu.M, 2021; Barroso & Correia-Pinto, 2018; Gupta et al., 2021; De Bie et al., 2020), patients with CDH often battle with severe respiratory failure. This is the greatest clinical challenge these patients encounter. Previous studies on congenital diaphragmatic hernia have shown that maternal age and the male gender are the two most important risk factors (Akhmedov Yu.M, 2021; Paoletti et al., 2020; Schulz et al., 2021).

The occurrence of a congenital diaphragmatic hernia may be solitary, a component of a syndrome, or associated with other congenital abnormalities. Up to 70% of cases are isolated, with the remainder including additional abnormalities such as pulmonary hypoplasia, heart dextroposition, etc. (Russo et al., 2018).

The current gold standard for prenatal diagnosis of CDH is the use of ultrasonography, which often identifies evidence of abdominal viscera displacement of the heart (Cordier et al., 2020; Kamran et al., 2018). The aim of this study was to identify the potential risk factors of CDH.

2 Materials and Methods

We used a case control study design in this study. Data for 66 patients with CDH were obtained from the registry of Regional Children's Multidisciplinary Medical Center of Samarkand. All patients were under hospital admission between January 2004 and December 2019.

Data for the case-control study was acquired by the physicians through interviews with the mother. This data was recorded using a data collection form that included over 90 variables related to the information on maternal and neonatal characteristics.

All neonates with CDH were included in the main group while healthy newborns were matched in the control group for each of the cases, with a ratio of three controls per case. An informed consent form was signed by all study participants.

Maternal age, gender, maternal weight, gestational age, history of stillbirths or deaths, and associated malformations were among the patient-related factors. Mother BMI, young age at pregnancy, number of prenatal visits, family history of congenital abnormalities, prenatal pathologies, methods of delivery, and smoking exposure (active vs passive) were all included in the case control study.

We performed data analysis by R studio software version 3.6.2 using statistical packages “epidisplay”, “dplyr”, “ggplot2”, “tinyverse”. Two-way t-test, Pearson’s Chi-squared test and where applicable Fisher’s exact tests were utilized to compare results. This study used a statistical significance of $p<0.05$ with a corresponding 95 % confidence interval. For continuous outcomes mean values and standard deviations were calculated.

3 Results and Discussions

For this study, there were 66 CDH patients and 198 controls. Table 1 shows the demographic characteristics of the cases and controls.

Table 1. Demographic characteristics of study participants

	Cases (n=66) n(%)	Control (n=198) n(%)	Chi square test/ Fisher’s exact test p-value.
Maternal age (years)			
<20 n(%)	12 (18.2)	41 (20.7)	0.78
20-35 n(%)	35 (53.0)	132 (66.7)	
>35 n(%)	19 (28.9)	25(12.6)	<0.001*
Maternal body mass index			
<18 n(%)	6(9.1)	29(14.6)	0.36
18-25 n(%)	32 (48.5)	111 (55.5)	
>25 n(%)	28(42.4)	58 (29.3)	<0.04*
Delivery			
Vaginal n(%)	19 (28.8)	104 (52,5)	<0.001*
Cesarean n(%)	47 (71.2)	94 (47.5)	
Passive/active smoking n(%)	13(19.7)	33(16.7)	0.49
No passive/active smoking n(%)	53 (80.3)	165 (83.3)	
Sex			
Female n(%)	29 (43.9)	81 (40.9)	
Male n(%)	37 (56.1)	117(59.1)	0.57
Weight at birth (gram)			
<2500 n(%)	24 (36.7)	25(12.6)	<0.001*
>2500 n(%)	42 (63.3)	173 (87.4)	
Preterm birth n(%)	23 (34.8)	31(15.6)	<0.001*
Gestational age (weeks)			
<37 n(%)	26 (39.4)	27(13.6)	<0.001*
>37 n(%)	40 (60.6)	171 (86.4)	

In CDH cases, 28.9% of women were 35 years or older, compared to 12.6% in controls (p<0.001). In 19.7% of the instances, the postnatal diagnosis was accomplished after the first day of life. Preterm births accounted for 43.9% of the cases. In comparison to 13.6% of controls, 39.4 % of cases were undersized for gestational age (p<0.001). CDH patients had an average birth weight of 2621±532 grams, compared to 2969±482 grams for controls (p<0.001). 36.7% of the cases had low weight (<2500 grams) at birth. CDH patients had an average gestation age of 35.8±5.4 weeks at delivery, compared to 37.8±3.1 weeks for controls (p<0.001).

According to the univariate analysis, mothers aged 35 years or older had a higher risk of CDH (OR, 2.87; 95 % CI, 1.42-5.79), and preterm neonates were more likely to be affected by CDH (OR, 3.39; 95 % CI, 1.77-6.48). Also neonates with CDH tend to weigh less than 2500 grams at birth (OR, 3.95; % CI, 2.06-7.6), and be small for gestational age (OR, 4.12; 95 % CI 2.17-7.8) (see Table 2). There was no link established between CDH and cigarette smoking (active/passive), maternal age, or BMI.

Table 2. Univariate logistic regression analysis

	Unadjusted OR (95% CI)
Maternal age (years)	
>20-35	Reference
<20	0,93(0.44-1,96)
>35	2.87 (1.42-5.79)
Body mass index	
18-25	Reference
<18	0.72 (0.27-1.88)
>25	1.67 (0.92-3.05)
Type of delivery	
Vaginal	Reference
Cesarean	3.1 (1.69-5.68)
Passive/active smoking	
No	Reference
Yes	1.23 (0.6-2.5)
Sex	
Male	Reference
Female	0.88 (0.5-1.55)
Weight at birth (gr)	
>2500	Reference
<2500	3.95 (2.06-7.6)
Gestational age of neonates	
Normal 37-42 weeks	Reference
Preterm 32-36 weeks	3.39 (1.77-6.48)
Size for gestational age	
Adequate	Reference
Small	4.12 (2.17-7.8)

We discovered that the maternal age of 35 years or older was associated with a higher probability of having a CDH newborn using logistic regression (OR, 3.51;

95 % CI, 1.49-6.12). CDH-affected neonates were also more likely to be born prematurely (OR, 3.79; 95 % CI, 2.01-7.21). Multivariate analysis also found that a neonate's birth weight of less than 2500 grammes was linked to a higher risk of CDH (OR, 3.32; 95 % CI, 1.65-5.89), as well as being small for gestational age (OR, 3.71; 95 % CI, 1.87-6.69). (see table 3).

Table 3. Multivariate logistic regression analysis

Variables	Adjusted OR (95% CI)
Maternal age (years)	
>20-34	Ref.
>35	3.51 (1.49-6.12)
Weight at birth (g)	
>2500	Ref.
<2500	3.32 (1.65-5.89)
Gestational age (in weeks)	
Normal 37-42	Ref.
Preterm 32-36	3.79 (2.01-7.21)
Size for gestational age	
Adequate	Reference
Small	3.71 (1.87-6.69)

This researchers focused at risk factors for CDH and found some similar characteristics with the demographic features of women and babies who were diagnosed with CDH that were documented in the previous research. There was a statistically significant difference between the patients with CDH and the controls in that a considerable majority of the CDH patients were male. Additionally, women who were 35 or older were at an elevated chance of having a child affected by CDH. The case-control study did not discover any evidence of a connection between CDH and maternal smoking while pregnant. In the case-control research, there was shown to be no connection between CDH and maternal BMI.

We did not examine the role of ethnicity in this study as the majority of cases were Uzbek Asians. However, some studies pointed out the potential association between ethnic groups, male gender and risk of CDH. There were also potentially modifiable such as maternal age and cigarette smoking during pregnancy (Kamran et al., 2018; Paoletti et al., 2020). This study supports findings on the elevated risk of CDH and maternal age while no associations were found between smoking exposure and CDH.

According to the results, the percentage of CDH patients who had preterm infants ranged from 10 to 30 % (Burgos et al., 2019; Paoletti et al., 2020). This was similar to the rate that was discovered in this study (cases: 34.8% versus controls: 15.6%; $p<0.001$). According to Peluso et al. (2020), the overall survival rate of children was as low as 49% with a survival range of 21.2% for gestational age <26 weeks and 62.3% for 35-36 weeks, respectively (Peluso et al., 2020). Birth weight less than 2500 grams was associated with increased odds of CDH (36.7% vs 12.6%; $p<0.001$, OR, 3.32; 95% CI, 1.65-5.89). Gestational age was also an independent risk factor for CDH. According to the results, being small to gestational age is linked with elevated odds of having CDH (39.4% vs 13.6%;

p<0.001; OR, 3.71; 95% CI, 1.87-6.69). The observed rate of small gestational age in this study was three times the rate (15%) reported by Zenilman et al. (2022). The rate of traditional delivery was statistically significantly lower among cases (28.8%) when compared to the control group (52.5%, p<0.001).

4 Conclusion

Preterm delivery, small for gestational age, and low birth weight were risk factors for congenital diaphragmal hernia. As to results, the chance of having a child born with CDH rises with the mother's age. Detection of these newborn and maternal characteristics may prompt consideration of CDH as an early diagnosis, therefore enhancing the prognosis of these patients, particularly in developing countries where awareness of this condition is limited. The results of this research demonstrate the significance of enhancing prenatal diagnosis. This would lower overall mortality and morbidity among pediatric patients with CDH. Determining a clear aetiology and possibly modifiable risk variables in order to find techniques for primary prevention of this syndrome need more research and effort, particularly in low-income and developing countries.

Conflict of interest

None of the research authors have disclosed any conflicts of interest or financial ties to this submission.

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