Crossing birth and mortality data as a clue for prevalence of congenital diaphragmatic hernia in Sao Paulo State: A cross sectional study

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Summary

Background Congenital diaphragmatic hernia (CDH) is a severe embryological defect that causes pulmonary hypoplasia and hypertension. The prevalence and mortality rate of CDH varies around the world and little information is available about CDH in Latin America. Our aim was to estimate the general prevalence, mortality rate, prevalence of associated anomalies and features related to the outcomes of CDH in newborns from São Paulo state, Brazil.

Methods Population-based cross-sectional study based on data gathered from the Live Births Information System (SINASC) and the Mortality Information System (SIM) of children born in São Paulo state between January 1st, 2006, and December 31st, 2017.

Findings From 7,311,074 total survival discharges between 2006 and 2017, 1,155 were CDH-related, resulting in a prevalence rate of 1:6329 (95%CI = 1/6715 - 1/5984) and a mortality rate of 63·72% (95%CI = 60.95 - 66.50), 510 presented complex associated anomalies (44·15%). Maternal data showed higher prevalence among older mothers (older than 35 years old: 2·13 per 10,000) and, also, women with more years of schooling (higher than 12 years: 1·99 per 10,000). Presence of associated anomalies (95%CI = 5.69-11.10), 1-min Apgar (95%CI = 1.44-2.95), maternal schooling (95%CI = 1.06-2.43) and birth weight (95%CI = 1.04-2.26) were the most significant features associated with mortality.

Interpretation There was 1 CDH case for every 6329 newborns in São Paulo and the mortality rate among those cases was 63·72% - a high rate compared to other countries.

Funding This study didn't receive any specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Keywords: Congenital diaphragmatic hernia; Incidence; Epidemiology; Risk factors

Background

Congenital diaphragmatic hernia (CDH) is one of the most common embryological defects defined as a malformation of the diaphragm muscle, leaving an aperture that may cause the herniation of abdominal organs into the thorax, most commonly on the left side of the body. Consequently, the disease is often followed by pulmonary hypoplasia and persistent pulmonary hypertension of the newborn (PPHN), both leading to significant morbidity and mortality, and therefore constituting important risk factors, as well as liver herniation, size of the diaphragmatic defect and lung-to-head

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Research in context

Evidence before this study

Congenital diaphragmatic hernia (CDH) is a severe embryological defect that causes pulmonary hypoplasia and hypertension. The global frequency of CDH is uncertain; while in Europe, the frequency is 2.3 cases per 10,000 births, in Utah (USA) the frequency is 3·2 cases per 10,000 births. The frequency may also depend on access to legal abortion services. In Sweden, where abortion is legal, the total prevalence of CDH was 3·5/10,000, while the prevalence among live births was 3/10,000. The prevalence, risk factors and mortality rate of CDH varies worldwide, and little information is available about CDH in Latin America. Using free population health data to obtain information on congenital diseases can provide information that improves perinatal care. There is no data related to the populational prevalence of CDH in Sao Paulo, Brazil.

Added value of this study

This information is particularly important considering that congenital anomalies are identified as one of the 20 main causes of morbidity and mortality in the world by the WHO, with 303,000 deaths occurring in the neonatal period (2015). Data regarding the epidemiology of CDH are restricted to a cohort of hospitals in neonatal tertiary care. This study makes it possible to identify the prevalence of CDH (1/6329) and its high mortality (63−72%) related to perinatal factors such as the presence of associated anomalies, 1st min Apgar, birth weight and maternal education.

Implications of all the available evidence

Identifying the prevalence and risk factors linked to CDH in a highly populated region of Latin America can provide subsidies for government programs involving perinatal care since the densely populated areas have an economic and social similarities. The information makes it possible to outline strategies for neonatal surgical care and perhaps increase the survival of congenital defects with high mortality.

ratio (LHR).[1] One relevant hypothesis refers to lung hypoplasia being both cause (primary factor) and consequence (secondary to herniation of abdominal viscera into the thoracic cavity), and it is called the "two-hit hypothesis". However, the embryologic basis of this defect remains controversial,[1] but it appears that a signaling error may occur in the retinoic acid pathway.[2]

The global frequency of CDH is uncertain; while in Europe, the frequency is 2.3 cases per 10,000 births,[3] in Utah (USA) the frequency is 3·2 cases per 10,000 births.[4] The frequency may also depend on access to legal abortion services. In Sweden, where abortion is legal, the total prevalence of CDH was 3·5/10,000,[5] while the prevalence among live births was 3/10,000.

In 2015, 303,000 deaths occurred in the neonatal period due to congenital anomalies.[6] Congenital anomalies are identified as one of the 20 leading causes of morbidity and mortality in the world by the WHO Global burden of disease study because their significant Disability Adjusted Life Years (DALY)[7] defined as one lost year of healthy life due to premature mortality or to time lived without full health. In this context, pediatric surgery has a significant role because it improves the quality of life for an extended period. In some reviews, basic pediatric surgery procedures are seen as cost-effective as vaccination.[8]

Pediatric surgery interventions and post-operative neonatal care are an essential resource for improving children's global health.[8] In this context, the correction of congenital anomalies has been particularly neglected. These anomalies affect children disproportionately in low and middle-income countries due to the lack of structure and investment and uneven access to the health system and pediatric surgeons.[9] While data from low and middle-income countries are sparse, the available evidence suggests that the human and economic cost from congenital anomalies is underestimated,[10] being considered the second leading cause of perinatal mortality[11] in Brazil.

Data from developing countries are harder to obtain because their databases do not reach all deaths or do not include some essential information about mortality.[12] In South America, the only available published data about CDH are from Bogota, with 81 patients with CDH, the total prevalence was 2.1 per 10,000 births [CI 95 % (2.09−2.10)].[13] In Brazil, there is a lack of reliable sources for epidemiologic studies examining the prevalence of CDH. This occurs because some studies are based on referral centers, overestimating the prevalence, and others are based on birth data available at DATASUS (Informatic Department of the Brazilian Health System), which may underestimate the number of cases.[14]

This study aimed to highlight the sub-notification of CDH prevalence by analyzing data obtained from crossing birth and mortality information and recognizing demographic and clinical features related to poor outcomes. The analysis was based on the prevalence of each demographic and clinical feature and indicates which of them was related to higher mortality.

Methods

Data acquisition

A cross-sectional study based on analysis of publicly available data downloaded from DATASUS Live Births Information System (SINASC) and Mortality Information System (SIM) was designed to gather information about perinatal care and child mortality in the Brazilian state of São Paulo. This data was composed of all birth and death records related to CDH from São Paulo state. As the study is based on administrative databases, some data related to surgical approaches or radiologic findings were unavailable. For crossing mortality records

with birth records, only the years with birth declaration numbers specified (a unique identifier given to every newborn in Brazil which firstly appeared in annual records from 2006) were selected, resulting in a sample space composed of information about patients born between 2006 and 2017 (the last year available at the DATASUS platform).

The files were collected between July and September of 2019 and distributed in separate files organized according to their corresponding year. Several individual files in DBC ("Database Container") format were downloaded, converted to DBF ("dBase database file") format with the support of TabWin software version 4.1.5, and merged into two CSV ("comma-separated values") files: one for birth data and another for mortality data. The birth file contains 15 features: Number of Birth Declaration, Mother's Age, Mother Schooling, Parity, Number of Prenatal Consultations, Date of Birth, Biological Sex, 1 min Apgar, 5 min Apgar, Race, Birth Weight, Associated Anomalies, Gestational Age, Type of Delivery, and Multiplicity. The mortality file contains 8 features: Number of Birth Declaration, Date of Birth, 1 min Apgar, 5 min Apgar, Age of Death, Immediate Cause of Death, Underlying Cause of Death and Other Significant Diseases.

Categorization and sample building

The first step of the analysis was filtering the records with the ICD-10 "Q790" (10th Revision of the International Classification of Diseases) - the code of CDH - from both birth and mortality files and setting up the initial sample with all available data from every record. Then, we checked all the rows that had unique identifiers (Number of Birth Declaration Number - NUMERODN) assigned. This identifier is a unique, sequential number automatically generated by SINASC for every newborn in Brazil that was, by Brazilian laws, obligatorily registered in the Ministry of Health; therefore, every newborn in Brazil must have a record in SINASC and, consequently, will be given a unique NUMERODN.

Unfortunately, not all rows from birth and mortality files had NUMERODN assigned. Therefore, it was necessary to analyze every row on these files and assign them "alive" or "dead" tags, according to the presence or absence of NUMERODN. Thus, records with NUMERODN on both birth and mortality files were tagged as "dead" since they refer to patients born with CDH and who died. Additionally, records with NUMERODN just at the birth file were given the "alive" tag considering that all deaths must be informed and registered by the Brazilian authorities. Similarly, records with NUMERODN exclusively at the mortality file were given the "dead" tag, since it refers to patients not registered with CDH right after they were born. Finally, records that did not have any NUMERODN associated (neither in the birth file nor in the mortality file) were discarded.

Mortality rate assessment

To evaluate the mortality rate directly related to CDH (i.e., deaths mainly caused by this condition), the rows of the sample composed of death records were filtered based on two features (or "columns"): "Other Significant Diseases" and "Underlying Cause of Death". The "Other Significant Diseases" feature consists of a string that contains all the ICD-10 codes of the diseases that each patient had before death but was not the fundamental cause of death. Therefore, the "Underlying Cause of Death" feature holds the ICD-10 of the disease directly linked to each death.

In possession of this information, it was possible to evaluate the mortality rate from the samples for each year considered in the study (2006–2017). Those rates were assessed by dividing the number of deaths directly caused by CDH by the total number of CDH cases related to each year. Additionally, the whole period's mortality rate considered in this study was assessed by applying the same formula to the total number of records.

Estimated prevalence rate assessment

The 2 last characters of the feature "Date of Birth" were used to determine the year of birth, each row with the same year was summed and divided by the number of total births, obtained from the original table.

Demographic data assessment

To study the prevalence of demographic and clinical aspects of CDH, the features Birth Weight, Maternal Age, 1 min Apgar, 5 min Apgar, Maternal Age were analyzed as quantitative variables and divided into clusters.

The features Type of Delivery, Baby Sex, Maternal Schooling, Prenatal Care Consultations, Multiple Gestation, Gestational Age and Race were analyzed following the clusters determined by the DATASUS system.

The prevalence of CDH on each cluster was calculated, as well as the confidence interval, using the Wald method for binomial proportions considering a normal distribution.

Malformations data assessment

The ICD-10 codes found in "Associated Anomalies" in birth records and in "Other Significant Diseases" in death records were accounted for when they were part of the chapter of congenital malformations. The ICD-10 allows classifying the malformations according to the related system.

Outcome assessment

To study the impact of each feature (independent variables) on death or survival outcome (dependent variable), we performed a univariable logistic regression model. The objective of this step was to evaluate the possible

associations, represented by its odds ratio, of each feature (independent variable) over the response variable classification (dead or alive) and its correspondent significance. The features used were 1 min Apgar, 5 min Apgar, Maternal Age, Maternal Schooling, Prenatal Care Consultations, Type of Delivery, Multiplicity, Birth Weight, Gestational Age, Baby Sex, Race, and the presence of associated anomalies - and by "associated anomalies" we mean any anomaly that is or not inherent to CDH (e.g., pulmonary hypoplasia and eye defects, respectively). The features 1 min Apgar and 5 min Apgar were divided into three different clusters according to depression severity: severely depressed (0-3), moderately depressed (4-6), and well condition (7-10). The feature Presence of Associated Anomalies was divided into two groups: presence and absence. The Birth Weight was classified into 2 clusters < 2500g and ≥ 2500g, considering the WHO classification that defines a weight at birth less than 2500 g as low birth weight. The Maternal Schooling was divided into clusters < 8 years and ≥ 8 years, given that this cutoff corresponds to the mean time of elementary school duration in Brazil. The Multiplicity was classified into simple and others (twins and triplets). The number of Prenatal Care Consultations was divided into two different classes: less than 7 consultations and more or equal to 7 consultations. This division is due to the fact that, in Brazil, the public health system indicates at least 6 consultations during pregnancy, and it was not possible to put 6 consultations as the cutoff because rows with this number of consultations were initially clustered with 4 and 5 consultations rows. For the univariable analysis, features with p-values < 0.20 were considered possibly significant variables for death or survival outcome and, therefore, were included in the second statistical analysis, a multivariable logistic regression. For this step, features with p-values < 0.05 were considered indeed statistically significant. The dataset presented 79 rows (6.83%) containing missing values. From this, 64 rows had just one missing value and the maximum number of missing values in a row was 5. Considering each feature, the minimum and maximum numbers of missing values in a column were 3 and 31 for Birth Weight and Race, respectively. We considered that these numbers are not sufficiently relevant to disturb the analysis quality, hence, the two statistical steps were executed without any filling strategy or discard of rows containing missing values. The software used for these analyses was IBM SPSS Statistics® version 20.

The reporting of this study conforms to the STROBE statement.

Role of the funding source

This study didn't receive any specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Results

The assembly with all CDH-related records considered in this study was made by filtering original content available at the DATASUS database joining 885 rows from SINASC data and 920 rows from SIM data, both available and downloaded from the DATASUS database as DBC files. A total of 244 records from the initial sample were dismissed because they didn't have any NUMERODN information. These files were then converted to CSV format and merged into a single major sample file by Python scripts, keeping all the original features: 15 features from birth records and 8 features from death records (Figure 1). Initially, the 885 birth records with NUMERODN were compared to the 676 death records with NUMERODN. Of these, 419 birth records didn't have a corresponding NUMERODN in the death records, being identified as "alive". From the total, 466 rows presented the ICD code in both data, being identified as "dead". When comparing the death records with the birth records, 665 of 676 rows were in SINASC data too and the other 11 corresponded to the discarded sample. Of these 665 records, 270 contained the ICD code only in death records, being necessary to search in all birth records. The final sample included 1155 patients.

The first information extracted from all records composing the major sample consists of the prevalence of CDH in the period between 2006 and 2017. Those numbers may be seen in the figure below. Considering this period, the average number of CDH cases per year was 96·25 (Figure 2).

The relative mortality rate per year, calculated based on a reduced sample space of 1155 cases with unique and exact correspondence, is shown in Table 1. The average relative mortality rate calculated by dividing the total number of deaths from CDH patients by the total number of CDH cases was 63·72% (95%CI = 60.95 - 66.50) (Table 1).

Considering the birth and mortality crossed data, from 2006 to 2017, 1102 cases of CDH live births were identified from a database with 7,311,074 live births. The total prevalence in this period was 1/6,329 (95%CI = 1/6715 - 1/5984) (Table 2).

Data with unique and exact correspondence were used to analyze the prevalence of CDH in each indicator. The prevalence was higher in 35 years old or older mothers (2·13 cases per 10,000 births) and mothers with more than 12 years of formal education (1·99 cases per 10,000 births). C-section was the most common type of delivery. The CDH newborns frequently presented a weight in the cluster between 1000g and 1500g (13·15 cases per 10,000 births) determined by DATASUS, it was also observed a high number of premature children between 28 and 31 weeks (9·78 cases per 10,000 births). The sex proportion was 0·736 females for each male. Few records didn't have

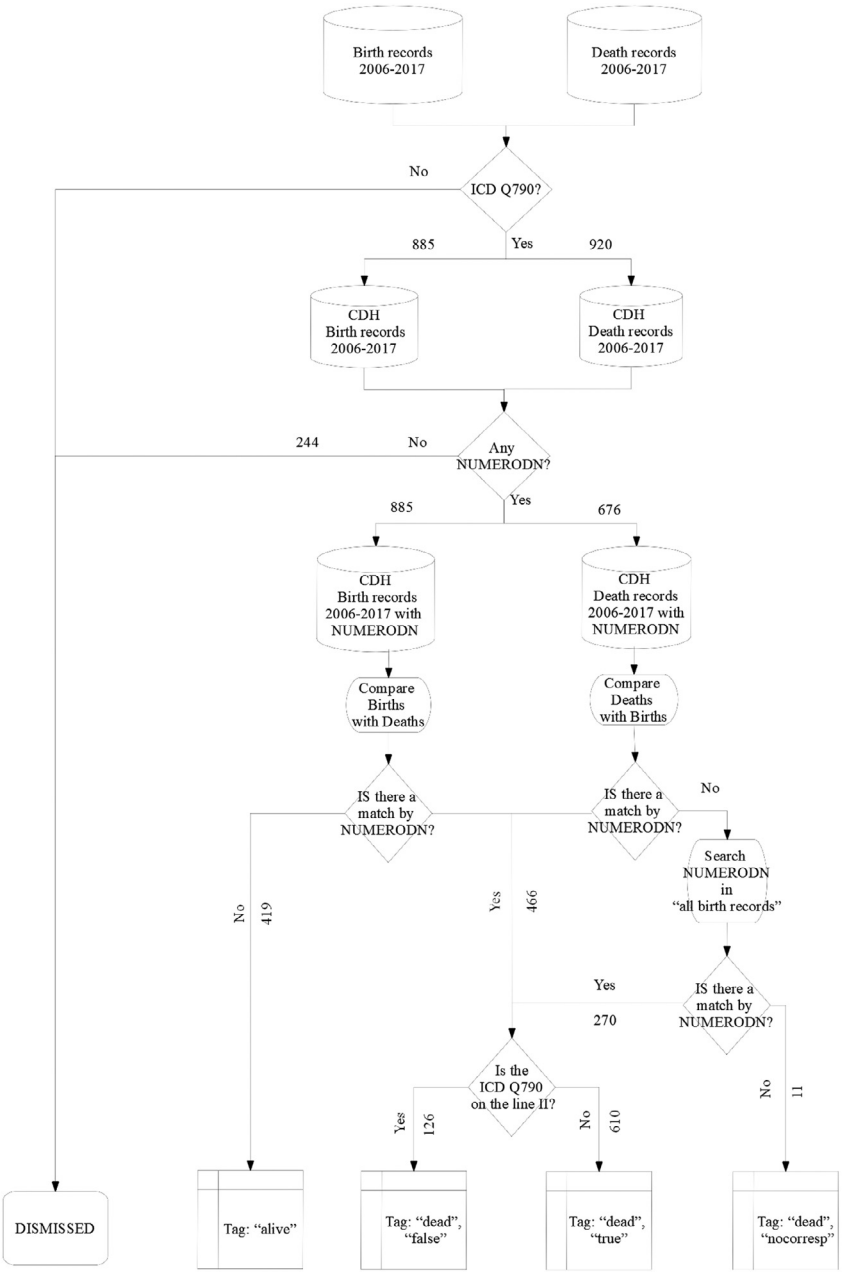

Figure 1. Diagram showing the categorization and sample building process. According to the presence or absence of NUMERODN information, the birth and death files records were classified as "alive" or "dead". The final sample was composed of 1155 records, of which 419 were tagged as "alive" and 747 were tagged as "dead".

information about some features, so they were considered "ignored" in each category of parameters (Table 3). The number of cases with associated malformations to CDH, also called complex CDH, was 510, corresponding to 44,15% of all CDH cases. The 929 malformations associated with CDH were divided into the most frequent malformation clusters in ICD-10, emphasizing the cardiac malformations, which represented 140 cases, because they are frequent and are related to a worse prognosis (Figure 3). However, the most frequent malformations were those associated with the respiratory system, represented by pulmonary hypoplasia which is directly related to CDH and occurs in the lung at the ipsilateral side of the herniation.[6] Other specific malformations that were not frequently found in the sample and that are not directly linked to the

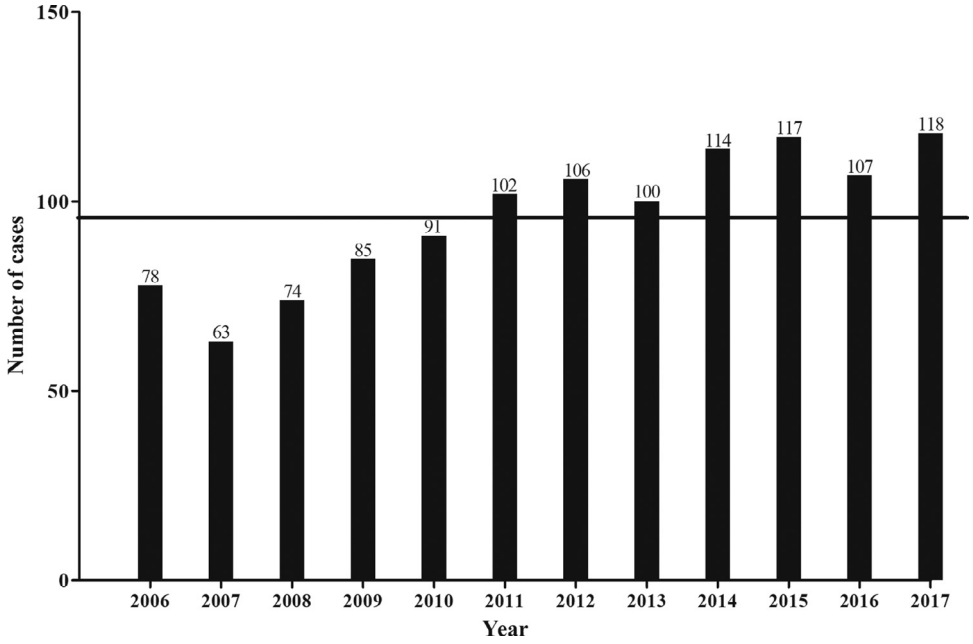

Figure 2. Average number of cases of CDH per year considering all 1102 cases collected between 2006 and 2017. The mean was 96·25 cases per year.

Year	Number of deaths related to CDH	Total number of deaths in CDH patients	Number of CDH cases	Percentage
2006	43	49	78	62·82%
2007	29	34	63	53·97%
2008	44	48	74	64·86%
2009	39	50	85	58·82%
2010	49	59	91	64·84%
2011	54	66	102	64·71%
2012	43	66	106	62·26%
2013	57	67	100	67·00%
2014	69	82	114	71·93%
2015	67	79	117	67·52%
2016	58	66	107	61·68%
2017	58	70	118	59·32%
Total	**610**	**736**	**1155**	**63·72%**

***Table 1*: Mortality rate of newborns with CDH by year.**

development of CDH were also represented, but clustered to the systems where they occur.

According to the univariable logistic regression results, 1 min Apgar, 5 min Apgar, Maternal Schooling, Prenatal Care Consultations, Birth Weight, Gestational Age, Race and Presence of Associated Anomalies were considered possibly significant with p-values < 0.2 and then, included in the multivariable analysis (Table 4).

The multivariable logistic regression has shown significance in odd's ratio for the following features: Presence of Associated Anomalies, 1 min Apgar, Maternal Schooling, and Birth Weight (Table 5).

Discussion

Congenital diseases affect 1·73 to 6·3% of the newborns,[15] varying according to genetics, due to "*de novo*" or inherited mutations; uncontrolled chronic maternal diseases; exposure to medication or pesticides; infection; radiation; alcohol; tobacco; and demographic factors. About 94% of the severe anomalies occur in low- and middle-income countries.[6]

Another study reinforces the cost-effectiveness of surgical procedures but states that some surgeries are not available in low- and medium-income countries which may cause a bias, considering only the simple

Year	Number of CDH cases	Number of births	Estimated prevalence per 10,000
2006	78	603,368	1·2927434
2007	63	595,408	1·058097977
2008	74	601,795	1·229654617
2009	85	598,473	1·420281283
2010	91	601,352	1·513256795
2011	102	610,221	1·671525562
2012	106	616,608	1·719082464
2013	100	610,896	1·636939839
2014	114	625,687	1·821997261
2015	117	634,026	1·845350191
2016	107	601,437	1·779072455
2017	118	611,803	1·928725423
Total	**1155**	**7,311,074**	**1·579795253**

***Table 2*: Prevalence of CDH by year.**

surgical procedures. For instance, CDH is a disease associated with a high cost. In a survey from North American hospitals, between 2009 and 2012, the cost of CDH was $165,964·00 in high volume centers and $104,107·00 in low volume centers, which represents an important resource mobilization.[16] The quality of the technical team and the volume of surgery centers are related to better outcomes.[16]

Among them there are clinical practices that may improve the outcome of some anomalies, the main practice is gestational monitoring. In the case of congenital anomalies, ultrasound in the second trimester is considered standard of care.[17] Prenatal imaging of CDH also allows prediction of the outcome based on the observed-to-expected lung-head ratio (strong recommendation, level of evidence B non-randomized).[18] We hypothesized that the number of cases of CDH in the birth and mortality crossed database would be larger than in the official birth data serving as an optimizer feasible to be used for other congenital conditions, depending on how easy it is to diagnose the condition at birth. The estimated prevalence between 2006 and 2017 was 1/6635. The completeness of congenital anomalies data from mortality cases has recently risen. In 2000, it was 62·9%; in 2005, it was 92%; in 2010, it was 96·5%; and in 2015, it was 97·6%.[19] For that reason, it is more reliable to estimate the prevalence through the last five years. Following this estimation, the prevalence was 1/5,796 or 1·72 per 10,000. The idea of crossing birth and mortality data provided a more complete database (1155 rows) than the birth data only, which counted 885 rows.

The mortality rate of CDH in our population was 63·72%, considered high compared to Sweden,[5] which has an overall mortality of 31%, and the State of Utah in the USA,[4] which has an overall mortality of 32·5%. When comparing our data, Iran[20] shows a similar mortality rate to Brazil. Nonetheless, their mortality data is related to the delivery, and our data are related to the overall mortality. About the mortality rate, it is also interesting to note the rate variation according to the year; between 2 and 17% of the deaths of newborns with CDH was not related to CDH itself, but with conditions such as sepsis, aspiration syndromes, chromosomal abnormalities, or others congenital conditions.

New fetal treatment strategies have emerged to increase survival from CDH. The placement of a fetal intratracheal balloon (FETO) based on the findings of the lung-head ratio (LHR) reduces lung hypoplasia and has provided strong evidence of decreased ECMO use and, therefore, decreased the cost of neonatal treatment.[21] Initial results of a randomized trial performed in Brazil have demonstrated that FETO increased neonatal survival.[22] Recent trials with FETO for severe (27−29 weeks of gestation) and mild (30−32 weeks) CDH demonstrated better outcomes among severe ones, despite the risk of prematurity, pre-labor rupture of membranes, and preterm birth for both severe and mild CDH.[23,24]

The male/female ratio was 1:0·736, a little higher than the European rate (1:0·69) shown by McGivern *et al.*[3] The maternal data showed a higher prevalence in women older than 35 years (2·13 per 10,000), as well as a higher prevalence in women with more than 12 years of formal education (1·99 per 10,000). We may hypothesize that this higher prevalence is biased by the possible greater medical access and consequently the higher number of diagnoses in the population that have more years of formal education.[25] In addition, another possible bias is that women that live in big centers tend to have access to more specialized medical care and the urban population has more years of schooling and deliveries at older ages when compared to the rural population.[26] Also, there is weak evidence supporting that older mothers have higher risks of genetic mutations[27] and the onset of CDH is associated with a series of mutations, mainly in the retinoic acid pathway.[28] The Public Health System from Brazil recommends at least four prenatal consultations, and only 6·23% of the CDH pregnancies were below this rate, but the newborns with CDH presented a higher prevalence in the cluster with 1-3 consultations (2·37 per 10,000). Cesarean section was the most frequent mode of delivery. The newborn parameters showed a higher prevalence of children with CDH in the cluster of babies with a birth weight between 1000 and 1499 grams (13·15 per 10,000). The race with the higher prevalence of CDH was Black, followed by yellow, indigenous, and white.

In a survey developed by Zaiss *et al.*[29] CDH had an associated malformation in 39.5% of the cases and the most frequent malformations were cardiovascular (mainly ventricular septal defect and atrial septal defect), gastrointestinal (mainly Meckel diverticulum and anal atresia), urogenital (mainly hydronephrosis, hypospadias and renal agenesis) and musculoskeletal

Variable		CDH	Total of Births	Birth prevalence of CDH per 10·000 births (95% CI)	Confidence Interval	
Maternal Age (years)	**<= 14**	3	39877	0·752313	0·74805	0·756576
	15-19	115	1040181	1·105577	1·105379	1·105775
	20-24	256	1782284	1·436359	1·436227	1·436491
	25-29	279	1867731	1·493791	1·493663	1·493919
	30-34	283	1554489	1·820534	1·820364	1·820704
	>= 35	219	1026478	2·133509	2·13323	2·133788
	Ignored	0	34	0	0	0
Maternal Schooling	**0**	3	19.989	1·500825	1·488814	1·512837
(complete years)	**1-3**	18	153.054	1·176056	1·174667	1·177444
	4-7	165	1.146.255	1·43947	1·439265	1·439675
	8-11	657	4.391.021	1·496235	1·496181	1·49629
	> 12	299	1.503.178	1·989119	1·988935	1·989303
	Ignored	13	97.577	1·332281	1·329963	1·3346
Prenatal Care Consultations	**0**	8	82.218	0·97302	0·97067	0·97537
	1-3	64	273.614	2·33906	2·33797	2·34016
	4-6	255	1.295.302	1·96865	1·96844	1·96887
	> 7	816	5.599.680	1·45723	1·45718	1·45727
	Ignored	12	60.260	1·99137	1·98678	1·99596
Type of Delivery	**Vaginal**	305	2.995.901	1·018058	1·017992	1·018124
	Cesarean Section	850	4.309.638	1·972323	1·97226	1·972387
	Ignored	0	5.535	0	0	0
Multiple Gestation	**Singleton**	1119	7.137.536	1·567768	1·567734	1·567802
	Twin	32	164.629	1·943764	1·942105	1·945424
	Triplets	4	5.140	7·782101	7·675767	7·888435
	Ignored	0	3.769	0	0	0
Birth weight (g)	**< 500**	0	5.762	0	0	0
	500-999	30	38.897	7·712677	7·698688	7·726666
	1000-1499	79	60.050	13·155704	13·143873	13·167534
	1500-1999	124	125.449	9·884495	9·879585	9·889405
	2000-2499	201	438.941	4·579203	4·578248	4·580158
	2500-2999	342	1.812.756	1·88663	1·886482	1·886779
	3000-3499	272	3.054.757	0·890415	0·890354	0·890475
	3500-3999	83	1.461.148	0·568046	0·567945	0·568148
	>4000	21	292.513	0·717917	0·717349	0·718485
	Ignored	3	20.801	1·442238	1·430923	1·453553
Gestational age (weeks)	**<22**	0	3.080	0	0	0
	22-27	22	35.193	6·251243	6·237323	6·265163
	28-31	66	67.497	9·778212	9·769136	9·787288
	32-36	324	619.811	5·2274	5·226677	5·228123
	37-41	719	6.423.702	1·119292	1·11926	1·119325
	> 42	12	84.836	1·414494	1·411746	1·417241
	Ignored	12	76.955	1·559353	1·556173	1·562533
Baby Gender	**Male**	661	3.745.559	1·7647566	1·7646871	1·7648261
	Female	487	3.564.451	1·3662693	1·366205	1·3663336
	Ignored	7	1064	65·7894737	64·3002521	67·2786953
Ethnicity	**White**	778	4.753.431	1·636713	1·63666	1·636765
	Black	60	255.264	2·350508	2·349331	2·351685
	Yellow	7	32.453	2·156965	2·148096	2·165834
	Pardo	277	2.019.823	1·371407	1·371294	1·371521
	Indigenous	2	9.195	2·175095	2·143661	2·206529
	Ignored	31	240.908	1·286798	1·285875	1·287721

***Table 3*: Number of CDH cases and the number of total births in each category of the parameters: maternal age, maternal schooling, prenatal care consultations, type of delivery, multiple gestations, birth weight, gestational age, baby sex, and race, as well as the prevalence in each category and the confidence interval.**
Some records did not have any information about some features, so they were considered "ignored" in each category of parameters.

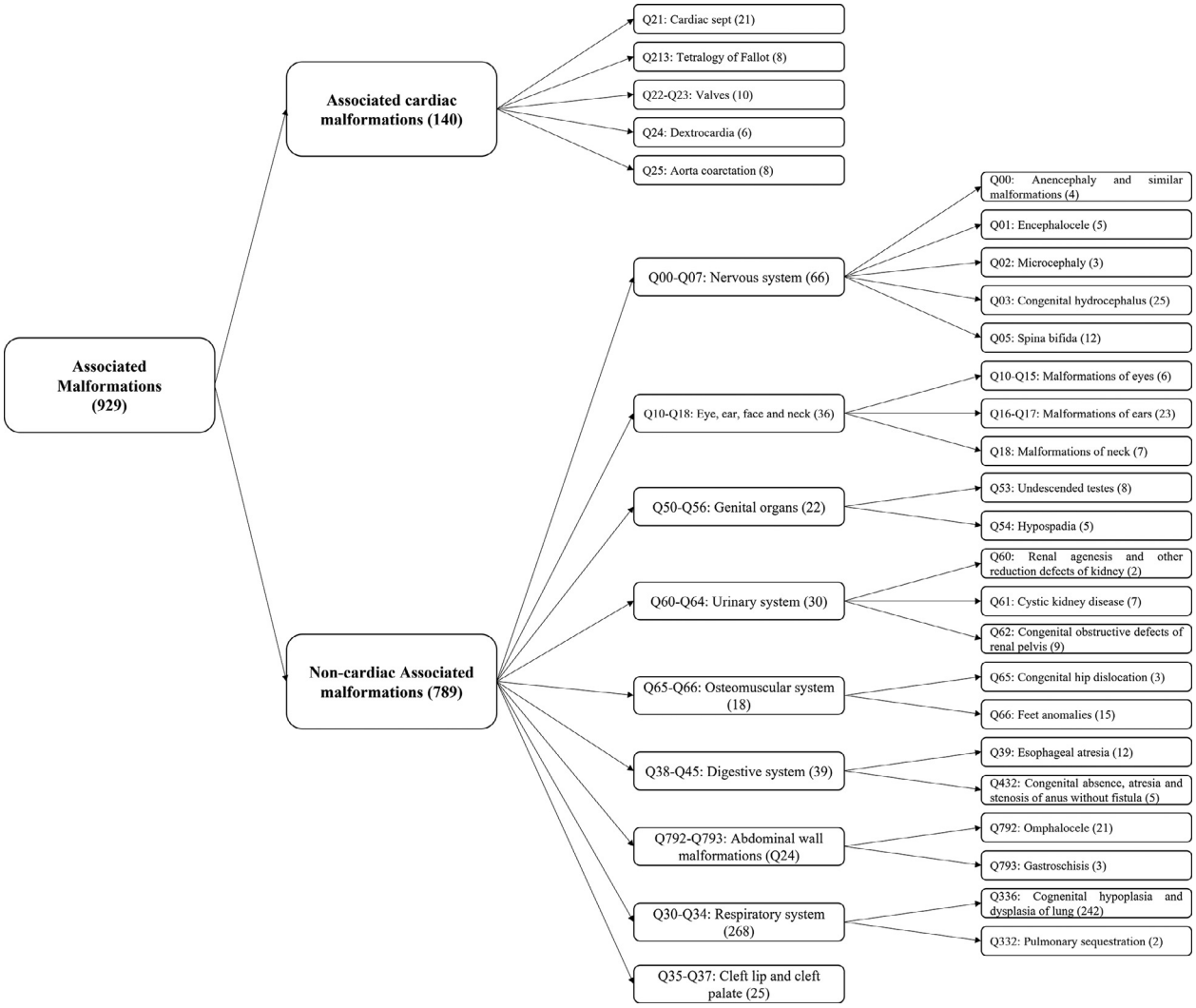

Figure 3. Number of associated malformations in cases of CDH (also called complex CDH). The malformations were divided into the most frequent malformation clusters in ICD-10, emphasizing the cardiac malformations because they are frequent and are related to a worse prognosis. The code is the ICD-10 corresponding to the malformation, and the number inside the parentheses is the number of malformations related to this cluster.

(mainly auricular dysplasia, aplasia of the radius and cleft lip and palate). CDH occurs as an isolated defect in 50% to 70% of babies, the remaining 30% to 50% are considered "complex or "non-isolated" defects and are associated with chromosomal (one plus gene) defects and major structural abnormalities. Non-isolated CDH have 10–30% of prenatal diagnosis of associated aneuploidies (trisomy 13, 18, 21 and 45, X).[30] Furthermore, in a population epidemiological study, the quantity and magnitude of malformation associations can vary greatly. The main clinical determinant of mortality is the presence of syndromes (particularly trisomy and major malformations, especially congenital heart defects.[5] We found 929 malformations, of which 140 were cardiac malformations that are related to a worse prognosis.[31] Other frequent associated anomalies were related to the respiratory system (mainly pulmonary hypoplasia and dysplasia) and genitourinary system (e.g., bilateral renal hypoplasia), confirming other studies' findings.[29] In São Paulo State, in a tertiary perinatal care center of reference, the incidence of associated structural malformations was observed in 55% of babies with CDH.[32] It is important to note that (*i*) the presence of associated anomalies (mainly heart diseases), (*ii*) the extent of lung hypoplasia and (*iii*) the position of the liver, are considered major determinants for prognosis: higher survival rates were found in cases with isolated CDH, and a meta-analysis reported only 45% of CDH patients with liver herniation survived.[1]

The factors associated with a worse prognosis in this study were the presence of associated anomalies, 1 min Apgar, Maternal Schooling, and Birth Weight. All these

Factor		OR	95%CI	*p*-Value
APGAR1	7 — 10	1	..	..
	4 — 6	2.64	1.95-3.58	$p < 0.001$
	0 — 3	4.99	3.64-6.86	$p < 0.001$
APGAR5	7 — 10	1	..	..
	4 — 6	2.33	1.71-3.17	$p < 0.001$
	0 - 3	4.24	2.71-6.62	$p < 0.001$
Maternal Age		1.00	0.98-1.02	p = 0.52
Maternal Schooling (Years)	More than or equal to 8 years	1	..	..
	Less than 8 years	1.72	1.21-2.44	$p < 0.05$
Prenatal Care Consultations	7 or more	1	..	..
	Less than 7	1.31	1.00-1.72	$p = 0.05$
Type of Delivery	Natural	1		
	Cesarean	0.88	0.67-1.16	$p = 0.35$
Multiplicity	Simple	1		
	Multiple	0.70	0.36-1.37	$p = 0.30$
Birth Weight	More than or equal to 2,500 g	1	..	..
	Less than 2,500 g	1.97	1.51-2.54	$p < 0.001$
Gestational Age (weeks)	37 - 41	1	..	..
	22 — 27	1.75	0.67-4.52	$p = 0.25$
	28 — 31	2.23	1.23-4.04	$p < 0.05$
	32 — 36	1.39	1.05-1.83	$p < 0.05$
	42 or more	1.31	0.39-4.40	$p = 0.66$
Baby Sex	Male	1		
	Female	1.12	0.88-1.42	$p = 0.36$
Race	White	1	..	..
	Black	1.26	0.72-2.20	$p = 0.41$
	Yellow	0.84	0.19-3.79	$p = 0.82$
	Brown	1.42	1.06-1.91	$p < 0.05$
	Indigenous	0.63	0.04-10.12	$p = 0.74$
Presence of Associated Anomalies	No	1	..	..
	Yes	9.41	6.90-12.85	$p < 0.001$

***Table 4*: Univariable logistic regression of factors possibly associated with the outcome of CDH.**
The presence of associated anomalies, 1 min Apgar, 5 min Apgar, Maternal Age, Maternal Schooling, Prenatal Care Consultations, Type of Delivery, Multiplicity, Birth Weight, Gestational Age, Baby Sex and Race are shown with its corresponding corrected odds ratio (OR), confidence interval (CI), and p-value.

factors, except Maternal Schooling, are consistent with the results of other studies, thus reinforcing their findings. It is the first time, however, as far as we researched, that Maternal Schooling was confirmed as a prognosis predictor for CDH patients. In this sense, further studies should evaluate its prognostic importance in other contexts.

The epidemiological studies developed using DATASUS publicly available information provided a large amount of information that may contribute to clarify some aspects of the congenital disease. Calderon et al.'s gastroschisis study has been the pioneer in epidemiologic studies about a specific anomaly developed through DATASUS information.[33] It is essential to

Factor		OR	95%CI	*p*-Value
APGAR1	7 – 10	1	..	..
	4 – 6	2.07	1.44-2.95	$p < 0.001$
	0 – 3	2.66	1.66-4.27	$p < 0.001$
APGAR5	7 – 10	1	..	..
	4 – 6	1.28	0.83-1.95	$p = 0.26$
	0 - 3	1.65	0,90-3.02	$p = 0.10$
Maternal Schooling (Years)	More than or equal to 8 years	1	..	..
	Less than 8 years	1.60	1.06-2.43	$p < 0.05$
Prenatal Care Consultations	7 or more	1	..	..
	Less than 7	0.917	0.65-1.29	$p = 0.61$
Birth Weight	More than or equal to 2,500 g	1	..	..
	Less than 2,500 g	1.53	1.04-2.26	$p < 0.05$
Gestational Age (weeks)	37-41	1	..	..
	22-27	0.72	0.21-2.47	$p = 0.60$
	28-31	0.76	0.35-1.69	$p = 0.51$
	32-36	0.90	0.60-1.33	$p = 0.59$
	42 or more	0.48	0.10-2.29	$p = 0.36$
Race	White	1	..	..
	Black	1.01	0.52-1.96	$p = 0.96$
	Yellow	0.78	0.14-4.40	$p = 0.78$
	Brown	1.36	0.96-1.93	$p = 0.09$
	Indigenous	0.13	0.01-2.25	$p = 0.16$
Presence of Associated Anomalies	No	1	..	..
	Yes	7.95	5.69-11.10	$p < 0.001$

***Table 5*: Multivariable logistic regression of possibly significant factors associated with the outcome of CDH.**
The presence of associated anomalies, 1 min Apgar, 5 min Apgar, Maternal Schooling, Prenatal Care Consultation and Birth Weight are shown with its corresponding corrected odds ratio (OR), confidence interval (CI), and *p*-value.

highlight that a limitation of this study is the absence of data from other Brazilian states. Although the diagnosis of CDH is easy for neonatologists, we did not have access to information regarding radiological confirmation that may be a bias in the final assessment of incidence. Furthermore, such demographic findings are specific to the population of the state of São Paulo, and they may not provide similar data when applied to other locations without considering their specific demographics. In conclusion, this study provides important epidemiologic information for São Paulo state, bringing a clue for CDH incidence in the population of big centers in Latin America and enabling generalizations to other countries with similar demographic data, considering that São Paulo is the most populous and wealthiest state of Brazil and corresponds to the size of some countries.

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Data sharing statement

The data obtained in this study are freely obtained from DATASUS, as they do not present any possibility of identifying patients. The Live Birth Information System was developed by DATASUS (Departamento de Informática do Sistema Único de Saúde –www.datasus.saude.gov.br), maintained by the Ministry of Health of Brazil to gather epidemiological information on births reported throughout the country to subsidize interventions related to women's and children's health for all levels of the Unified Health System (SUS – Sistema Único de Saúde), such as actions of attention to the pregnant woman and to the newborn, as well as the monitoring of the evolution of the SINASC's historical series (SINASC – Sistema de Informação sobre Nascidos Vivos), that allows the identification of intervention priorities and contribution to the effective improvement of this information system. Through the Internet, DATASUS and the Health Surveillance Service (SVS – Sistema de Vigilância em Saúde) provide the main information for tabulation on the SINASC's Databases.[33]

Declaration of interests

None to declare.

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References

1 Chandrasekharan PK, Rawat M, Madappa R, Rothstein DH, Lakshminrusimha S. Congenital diaphragmatic hernia - a review. *Matern Health, Neonatol Perinatol*. 2017;3(1):1–16. https://doi.org/10.1186/s40748-017-0045-1.
2 Donahoe PK, Longoni M, High FA. Polygenic causes of congenital diaphragmatic hernia produce common lung pathologies. *Am J Pathol*. 2016;186(10):2532–2543. https://doi.org/10.1016/j.ajpath.2016.07.006.
3 McGivern MR, Best KE, Rankin J, et al. Epidemiology of congenital diaphragmatic hernia in Europe: a register-based study. *Arch Dis Child Fetal Neonatal Ed*. 2015;100(2):F137–F144. https://doi.org/10.1136/archdischild-2014-306174.
4 Shanmugam H, Brunelli L, Botto LD, Krikov S, Feldkamp ML. Epidemiology and prognosis of congenital diaphragmatic hernia: a population-based cohort study in Utah. *Birth Defects Res*. 2017;109(18):1451–1459. https://doi.org/10.1002/bdr2.1106.
5 Burgos CM, Frenckner B. Addressing the hidden mortality in CDH: a population-based study. *J Pediatr Surg*. 2017;52(4):522–525. https://doi.org/10.1016/j.jpedsurg.2016.09.061.
6 WHO (World Health Organization). Congenital anomalies, Fact sheet N°370. 2014. http://www.who.int/mediacentre/factsheets/fs370/en/. Accessed January 2014.
7 Sitkin NA, Farmer DL. Congenital anomalies in the context of global surgery. *Semin Pediatr Surg*. 2016;25(1):15–18. https://doi.org/10.1053/j.sempedsurg.2015.09.004.
8 Smith ER, Concepcion TL, Niemeier KJ, Ademuyiwa AO. Is global pediatric surgery a good investment? *World J Surg*. 2019;43(6):1450–1455. https://doi.org/10.1007/s00268-018-4867-4.
9 de Jesus LE, Aguiar A, de Campos Mdo S, et al. Formação e demanda do cirurgião pediátrico no Brasil [Needs and specialization for pediatric surgeons in Brazil]. *Rev Col Bras Cir*. 2009;36(4):356–361. https://doi.org/10.1590/s0100-69912009000400016.
10 Sitkin NA, Ozgediz D, Donkor P, Farmer DL. Congenital anomalies in low- and middle-income countries: The unborn child of global surgery. *World J Surg*. 2015;39(1):36–40. https://doi.org/10.1007/s00268-014-2714-9.
11 Guinsburg R, Sanudo A, Kiffer CRV, et al. Annual trend of neonatal mortality and its underlying causes: population-based study – São Paulo State, Brazil, 2004–2013. *BMC Pediatr*. 2021;21:54. https://doi.org/10.1186/s12887-021-02511-8.
12 Greenberg SLM, Ng-Kamstra JS, Ameh EA, Ozgediz DE, Poenaru D, Bickler SW. An investment in knowledge: research in global pediatric surgery for the 21st century. *Semin Pediatr Surg*. 2016;25(1):51–60. https://doi.org/10.1053/j.sempedsurg.2015.09.009.
13 García AM, Machicado S, Gracia G, Zarante IM. Risk factors for congenital diaphragmatic hernia in the Bogota birth defects surveillance and follow-up program, Colombia. *Pediatr Surg Int*. 2016. https://doi.org/10.1007/s00383-015-3832-7.
14 Gallindo RM, Gonçalves FL, Figueira RL, Sbragia L. Manejo pré-natal da hérnia diafragmática congênita: presente, passado e futuro. *Rev Bras Ginecol e Obstet*. 2015;37(3):140–147. https://doi.org/10.1590/S0100-720320150005203.
15 Mekonnen AG, Hordofa AG, Kitila TT, Sav A. Modifiable risk factors of congenital malformations in bale zone hospitals, Southeast Ethiopia: an unmatched case-control study. *BMC Pregnancy Childbirth*. 2020;20(1):129. https://doi.org/10.1186/s12884-020-2827-0.
16 Sømme S, Shahi N, McLeod L, Torok M, McManus B, Ziegler MM. Neonatal surgery in low- vs. high-volume institutions: a KID inpatient database outcomes and cost study after repair of congenital diaphragmatic hernia, esophageal atresia, and gastroschisis. *Pediatr Surg Int*. 2019;35(11):1293–1300. https://doi.org/10.1007/s00383-019-04525-x.
17 Edwards L, Hui L. First and second trimester screening for fetal structural anomalies. *Semin Fetal Neonatal Med*. 2018;23(2):102–111. https://doi.org/10.1016/j.siny.2017.11.005.
18 Puligandla PS, Skarsgard ED, Offringa M, et al. Diagnosis and management of congenital diaphragmatic hernia: a clinical practice guideline. *CMAJ*. 2018. https://doi.org/10.1503/cmaj.170206.
19 Health Brazil 2017. *An Analysis of the Health Situation and Challenges to the Achievement of the Sustainable Development Goals*. Brasília: Ministério da Saúde; 2003. p. 30.
20 Dehdashtian M, Bashirnejad S, Malekian A, Aramesh MR, Aletayeb MH. Seasonality, epidemiology and outcome of congenital

diaphragmatic hernia in South West of Iran. *J Neonatal Surg*. 2017;6(2):28. https://doi.org/10.21699/jns.v6i2.506.
21 Van der Veeken L, Russo FM, De Catte L, et al. Fetoscopic endoluminal tracheal occlusion and reestablishment of fetal airways for congenital diaphragmatic hernia. *Gynecol Surg*. 2018;15(1):9. https://doi.org/10.1186/s10397-018-1041-9.
22 Ruano R, Yoshisaki CT, da Silva MM, et al. A randomized controlled trial of fetal endoscopic tracheal occlusion versus postnatal management of severe isolated congenital diaphragmatic hernia. *Ultrasound Obstet Gynecol*. 2012;39(1):20–27. https://doi.org/10.1002/uog.10142.
23 Deprest JA, Nicolaides KH, Benachi A, et al. TOTAL trial for severe hypoplasia investigators. Randomized trial of fetal surgery for severe left diaphragmatic hernia. *N Engl J Med*. 2021;385(2):107–118. https://doi.org/10.1056/NEJMoa2027030.
24 Deprest JA, Benachi A, Gratacos E, et al. Total trial for moderate hypoplasia investigators. Randomized trial of fetal surgery for moderate left diaphragmatic hernia. *N Engl J Med*. 2021;385(2):119–129. https://doi.org/10.1056/NEJMoa2026983.
25 Viellas EF, Domingues RM, Dias MA, et al. Prenatal care in Brazil. *Cad Saude Publica*. 2014;30(suppl 1):S1–S5. https://doi.org/10.1590/0102-311X00126013. PMID: 25167194.
26 Martinelli KG, Santos Neto ET, Gama SG, Oliveira AE. Access to prenatal care: inequalities in a region with high maternal mortality in southeastern Brazil. *Cien Saude Colet*. 2016;21(5):1647–1658. https://doi.org/10.1590/1413-81232015215.23222015.
27 Ahn D, Kim J, Kang J, Kim YH, Kim K. Congenital anomalies and maternal age: a systematic review and meta-analysis of observational studies. *Acta Obstet Gynecol Scand*. 2022;101(5):484–498. https://doi.org/10.1111/aogs.14339.
28 Dalmer TRA, Clugston RD. Gene ontology enrichment analysis of congenital diaphragmatic hernia-associated genes. *Pediatr Res*. 2019;85(1):13–19. https://doi.org/10.1038/s41390-018-0192-8.
29 Zaiss I, Kehl S, Link K, et al. Associated malformations in congenital diaphragmatic hernia. *Am J Perinatol*. 2011;28(3):211–217. https://doi.org/10.1055/s-0030-1268235.
30 Chatterjee D, Ing RJ, Gien J. Update on congenital diaphragmatic hernia. *Anesth Analg*. 2020;131(3):808–821. https://doi.org/10.1213/ANE.0000000000004324.
31 Hautala J, Karstunen E, Ritvanen A, et al. Congenital diaphragmatic hernia with heart defect has a high risk for hypoplastic left heart syndrome and major extra-cardiac malformations: 10-year national cohort from Finland. *Acta Obstet Gynecol Scand*. 2018. https://doi.org/10.1111/aogs.13274.
32 Ruano R, Bunduki V, Silva MM, et al. Prenatal diagnosis and perinatal outcome of 38 cases with congenital diaphragmatic hernia: 8-year experience of a tertiary Brazilian center. *Clinics (São Paulo)*. 2006;61(3):197–202. https://doi.org/10.1590/s1807-59322006000300003.
33 Calderon MG, Santos EF de S, Abreu LC de, Raimundo RD. Increasing prevalence, time trend and seasonality of gastroschisis in São Paulo state, Brazil, 2005-2016. *Sci Rep*. 2019;9(1):14491. https://doi.org/10.1038/s41598-019-50935-1.