Perinatal mortality associated with congenital defects of the central nervous system in Colombia, 2005–2014

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Abstract

In Colombia, congenital anomalies are the second leading cause of death in children aged less than 1 year, and central nervous system (CNS) anomalies are the second most common cause within this group. The aim of the study is to determine the frequency of perinatal mortality attributable to CNS anomalies in Colombia between 2005 and 2014. Using data from the Integral Information System of Social Protection (SISPRO), we determined the perinatal mortality rate associated with CNS anomalies; we also determined frequency of mortality according to age, type of abnormality, year of presentation, and georeferencing. A total of 4706 deaths were recorded to be primarily caused by CNS anomalies (anencephaly and hydrocephalus) in departments and prominent urban centers. The perinatal mortality rate associated with CNS defects has remained relatively constant over the past several years. Major referral centers in the country registered the highest mortality rates. The impact of CNS defects increased with the decrease in infant mortality rates and other health issues. Reinforcement of primary and secondary prevention strategies is warranted for reducing its incidence.

Keywords Perinatal mortality · Infant mortality · Central nervous system defects · Colombia

Introduction

Globally, congenital defects in children aged < 5 years are associated with a mortality rate of 76/100,000 individuals (World Health Organization 2017a, b). Over the last century, significant progress has been made regarding health conditions and developmental indicators across the world, particularly in Latin America, which has led to transitions in global health. The causes of infant mortality have fluctuated substantially, with congenital defects now ranked as one of the leading causes of death in children aged < 1 year. Currently,

congenital defects, the number one cause of death in children aged < 5 years, is associated with a mortality rate of 63/100,000 in the Americas region (World Health Organization 2017a, b).

In Colombia, the neonatal mortality rate has decreased from 12.0/1000 live births (LBs) (range, 10.7–13.4 LBs) in 2005 to 8.7/1000 LBs (range, 6.8–11.1 LBs) in 2015 (World Health Organization 2017a, b). Currently, congenital disorders are the second leading cause of death in children aged < 1 year (Instituto Nacional de Salud 2011); after congenital heart disease, malformations in the CNS are the most

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frequently reported congenital disorders (Misnaza et al. 2016). Congenital disorders, especially CNS disorders, have a significant association with spontaneous abortions; and multiple genetic, infectious, and environmental factors have been identified that may increase the incidence of congenital disorders (Rasmussen et al. 2016).

With the control of disease burden due to birth asphyxia, infectious etiologies, and other causes, the morbidity and mortality associated with birth defects have currently become more relevant. It is worth noting that reliable health-related statistics and comprehensive studies are scarce in most developing countries; this poses a challenge in environments with limited health resources and elevated risk factors related to many conditions. Neural tube defects (spina bifida and anencephaly) have global prevalence rates in the range of 1.2–124.1 per 10,000 births (Zaganjor et al. 2016). These data raise concerns because these defects can be prevented through periconceptional folic acid supplementation, highlighting the importance of this public health issue in low- and middle-income countries.

The objective of this study was to characterize the CNS disorder-associated mortality in Colombia based on data provided by the Integral Information System of Social Protection (SISPRO) (<http://www.sispro.gov.co/>) between 2005 and 2014 in order to analyze the dynamics of mortality attributable to CNS disorders during the last 10 years (prior to the Zika virus epidemic). This will provide a baseline reference for developing public policies that encourage essential prenatal care and psychosocial care programs for families whose members are affected by any of these pathologies.

Methodology

This study was approved by our local Ethics Committee. The study population consisted of all infants aged < 1 year who were born between 2005 and 2014 in Colombia and whose cause of death was associated with a CNS abnormality. The study data were collected from SISPRO, which consolidates the country's health data and is freely available (<http://www.sispro.gov.co/>). The data were requested through a letter addressed to the Ministry of Health and Social Protection using the following criteria: number of live births with CNS disorders differentiated according to mortality at birth, perinatal mortality, and mortality in the first year of life, for each city in Colombia from January 2005 to December 2014.

Nomenclature of the tenth revision of the International Classification of Diseases (ICD-10) was used to categorize different CNS pathologies into nine groups: hydrocephalus, holoprosencephaly, spina bifida, anencephaly, agenesis of the corpus callosum, encephalocele, microcephaly, nonspecific CNS alteration by hypoxia or prematurity (AHP), and

unspecified abnormality (AUN) of the CNS, including septo-optic dysplasia and other brain malformations. For the purpose of this study, microcephaly was considered as a malformation due to its public health importance.

We classified the subjects into six groups according to the age at death: fetal death; death before 7 days of age; death between 7 and 28 days of age; death between 28 days and 3 months of age; death between 3 and 6 months of age; and death after 6 months of age. Mortality rates were determined for each group of CNS anomalies and were stratified according to age, year, and the department in which it was reported.

Statistical analysis

The data were recorded and analyzed using Microsoft Excel® 2016. Prevalence relative to 10,000 LBs was calculated for each defect according to the ICD-10 classification, considering the number of LBs per department for each year, with 95% confidence intervals (CIs) based on Poisson distribution. Linear trend estimation was used for historical analysis of perinatal mortality rates of CNS disorders throughout the study period.

Results

A total of 4706 perinatal and infant deaths during the first year of life that were associated with CNS disorders were registered in SISPRO between 2005 and 2014 in Colombia. A high frequency of mortality was observed in the fetal period (41.1%), with a progressive decrease in mortality with increasing age.

Regarding data of CNS disorders, anencephaly was associated with a significantly high number of deaths at fetal age (51.8%) and less than 7 days of age (33%). After 7 days of age, hydrocephalus was the main cause of mortality (32.9%). Additionally, the lowest mortality rates were observed with spina bifida (0.4%) and microcephaly (1.9%) (Table 1).

We found that the perinatal mortality rate due to CNS disorders has remained relatively constant over the past several years in Colombia, with the lowest value recorded in 2014 (0.644/10,000 LBs) and the highest value reported in 2008 (0.873/10,000 LBs). Additionally, hydrocephalus was consistently associated with the highest mortality rate (2.248/10,000 LBs), followed by anencephaly (2.129/10,000 LBs). Contrastingly, spina bifida was consistently associated with the lowest mortality rate (0.032/10,000 LBs), followed by microcephaly (0.130/10,000 LBs) (Table 2).

Historical trend analysis of mortality showed increased mortality rates of agenesis of the corpus callosum, AUN of the CNS, spina bifida, and AHP of the CNS. Contrastingly, a decrease was observed in microcephaly, encephalocele, and hydrocephalus mortality rates over the years. Anencephaly

Table 1 Associated perinatal mortality due to CNS abnormalities

Abnormality (Q00-Q09)	Fetal	< 7 days	7–28 days	28–90 days	3–6 months	> 6 months	Total
Agenesis of the corpus callosum (Q04.0)	13 (13.54%)	18 (18.75%)	16 (16.66%)	20 (20.83%)	16 (16.66%)	13 (13.54%)	96 (100%)
AUS of the CNS (Q07.9)	266 (48.54%)	115 (20.98%)	83 (15.14%)	49 (8.94%)	17 (3.10%)	18 (3.28%)	548 (100%)
Anencephaly (Q00.0)	1004 (68.34%)	418 (28.45%)	39 (2.65%)	5 (0.34%)	2 (0.13%)	1 (0.06%)	1469 (100%)
Encephalocele (Q01)	79 (43.40%)	66 (36.26%)	22 (12.08%)	7 (3.84%)	5 (2.74%)	3 (1.64%)	182 (100%)
Spina bifida (Q05)	8 (36.36%)	6 (27.27%)	3 (13.63%)	0 (0%)	2 (9.09%)	3 (13.63%)	22 (100%)
Hydrocephalus (Q03)	381 (24.58%)	351 (22.64%)	258 (16.64%)	294 (18.96%)	136 (8.77%)	130 (8.38%)	1550 (100%)
Holoprosencephaly (Q04.1–04.2)	109 (40.52%)	99 (36.8%)	27 (10.03%)	15 (5.57%)	11 (4.08%)	8 (2.97%)	269 (100%)
AHP of the CNS (Q04.9)	61 (12.7%)	165 (34.37%)	107 (22.29%)	95 (19.79%)	31 (6.45%)	21 (4.37%)	480 (100%)
Microcephaly (Q02)	14 (15.55%)	27 (30%)	12 (13.33%)	9 (10%)	6 (6.66%)	22 (24.4%)	90 (100%)
Total	1935 (41.11%)	1265 (26.88%)	567 (12.04%)	494 (10.49%)	226 (4.8%)	219 (4.65%)	4706 (100%)

AUS unspecified abnormality, AHP nonspecific alteration by hypoxia or prematurity

Source SISPRO

and holoprosencephaly mortality rates remained stable during this period (Fig. 1).

On georeferencing analysis, we found that the Colombian city of Bogotá showed the highest perinatal mortality rate associated with CNS disorders in the study period (15.6%), followed by Antioquia (13.6%), and Valle del Cauca (9.2%); these cities are considered as major referral centers for the country. Other cities, including Atlántico (6.1%), Córdoba (4.6%), Santander (4.6%), Bolívar (3.6%), Nariño (3.6%), Huila (3.5%), and Magdalena (3.5%), reported significantly low frequencies (Fig. 2).

The congenital abnormality associated with the greatest number of perinatal deaths was hydrocephalus (1550 deaths) followed by anencephaly (1469 deaths). The departments with the highest number of fatal cases associated with hydrocephalus included Bogotá with 229 (14.8%), Antioquia with 171 (11%), Atlántico with 154 (9.9%), and Valle del Cauca with 109 (7%). Anencephaly as the abnormality associated with the second-highest perinatal mortality was most frequent in

Bogotá (212 cases, 14.4%), followed by Antioquia (210 cases, 14.3%), and Valle del Cauca (122 cases, 8.3%) (Fig. 2).

Discussion

Our study described and analyzed mortality due to CNS defects during the first year of life from 2005 to 2014 at various departments in Colombia. Our study is one of few retrospective longitudinal cohort studies ever conducted in the region that describes mortality patterns attributable to these defects during the last 10 years (Roncancio et al. 2018).

In Colombia, congenital defects account for 22% of the mortality in children aged < 1 year (INS 2011), similar to the 26% mortality rate reported in Argentina (Bidondo et al. 2015). Of these, CNS disorders are the second-highest contributors to the mortality rate (0.75 per 10,000 LBs); this value is similar to the values in Costa Rica (0.49 per 10,000 LBs) (Barboza-Arguello et al. 2013) and Mexico, where CNS

Table 2 Perinatal mortality rate due to CNS disorders per 10,000 live births from 2005 to 2014

Abnormality (ICD-10)	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	MEAN (SD)
Agenesis of the corpus callosum (Q04.0)	0.097	0.056	0.056	0.112	0.143	0.229	0.180	0.163	0.212	0.164	0.141 (0.06)
AUS of the CNS (Q07.9)	0.625	0.840	0.479	0.825	0.743	0.886	0.962	0.886	0.865	0.882	0.799 (0.14)
Anencephaly (Q00.0)	2.139	1.974	2.355	2.516	2.386	2.047	1.999	2.216	1.912	1.749	2.129 (0.25)
Encephalocele (Q01.9)	0.417	0.280	0.296	0.266	0.214	0.260	0.255	0.295	0.106	0.239	0.263 (0.05)
Spina bifida (Q05)	0.028	0.014	0.028	0.014	0.057	0.031	0.060	0.030	0.015	0.045	0.032 (0.01)
Hydrocephalus (Q03)	2.139	2.421	2.411	2.684	2.301	2.872	2.044	2.128	1.882	1.599	2.248 (0.39)
Holoprosencephaly (Q04.2)	0.319	0.490	0.226	0.433	0.500	0.367	0.391	0.369	0.486	0.329	0.391 (0.08)
AHP of the CNS (Q04.9)	0.458	0.420	0.691	0.881	0.757	0.917	0.646	0.857	0.622	0.747	0.700 (0.15)
Microcephaly (Q02)	0.097	0.238	0.113	0.126	0.171	0.168	0.180	0.089	0.076	0.045	0.130 (0.06)
Total	0.702	0.748	0.739	0.873	0.808	0.864	0.746	0.781	0.686	0.644	0.759 (0.07)

AUS unspecified abnormality, AHP nonspecific alteration by hypoxia or prematurity

Fig. 1 Trend analysis of perinatal mortality rate for CNS disorders per 10,000 live births throughout Colombia from 2005 to 2014. In the X axis, the numbers represent the years in ascending order, being 2005 the first year and 2014 the year number 10

disorders are the second-highest cause of mortality among congenital disorders (Fernández Cantón et al. 2013).

Contrastingly, 17–43% of infant mortality is attributed to congenital anomalies in Europe, according to the World Health Organization. However, the European Surveillance of Congenital Anomalies (EUROCAT) states that the perinatal mortality attributable to congenital anomalies is 1.27 per 1000 births (95% CI, 1.23–1.31) in these territories (Boyle et al. 2018). Of these, isolated CNS anomalies are responsible for the highest rates of stillbirth and early neonatal mortality (age less than 7 days). Neural tube defects, including anencephaly, spina bifida, and encephalocele, account for the highest mortality rates among CNS defects in Europe (Groen et al. 2017).

Anencephaly was responsible for the highest number of fetal deaths and deaths in children under 7 days of age, with a mortality rate of 2.12 per 10,000 LBs. This rate is similar to that reported by Bronberg et al. (2011) in Argentina (2.46 per 10,000 LBs). Additionally, in Colombia, the perinatal mortality rate for anencephaly was 21.34 per 100,000 LBs, whereas it was 9.5 per 100,000 LBs in Mexico (Fernández Cantón et al. 2013).

Hydrocephalus was the principal abnormality associated with mortality after 7 days of birth, with a corresponding mortality rate of 31.6%. The majority of CNS disorders are

associated with an increase in the volume of the lateral ventricles following the mechanical process of intracranial pressure regulation, which occurs during certain pathological processes such as herniation, encephalocele, and spina bifida (Schrandt-Stumpel and Fryns 1998); according to data provided by the government, the primary cause of hydrocephalus has not been specified. Therefore, specific reports made by physicians on SISPRO of each CNS abnormality are necessary to provide a comprehensive analysis of the described abnormalities.

Previous studies have compared the prevalence rates of congenital disorders in Latin America. In Chile, the prevalence rate of microcephaly was reported to be 5.5/10,000 LBs between 1995 and 2005 compared to 3.5/10,000 in the Latin-American collaborative study of congenital malformations ECLAMC study for the same period (Nazer and Cifuentes 2011). In Brazil, microcephaly was reported in 2464 live births between 2000 and 2014, corresponding to an annual average of 164 cases (standard deviation = 15) and an average rate of 5/100,000 LBs (Fatima Marinho et al. 2016). In 2016, a microcephaly prevalence rate of 11.6/10,000 LBs was recorded in Colombia, showing a net increase of 8.5/10,000 LBs from the average prevalence over the last 4 years (Hurtado et al. 2017). In this study, mortality associated with

Fig. 1 continued.

microcephaly was approximately 0.130/10,000 LBs—with a minimum of 0.045 and a maximum of 0.238—and was most frequent in subjects less than 7 days of age.

Owing to its public health relevance, it is important to consider microcephaly as a malformation, but it can also be considered as a sign of other brain anomalies. For this reason, it is necessary to characterize the diseases accompanying this malformation. Collection of this data could be fundamental for understanding the clinical presentation and primary physiopathology of these infant deaths, opening a new pathway for investigation and development of public health policies.

In Colombia, mortality was associated with spina bifida in 22 patients from 2005 to 2014; it was the least frequent cause

of mortality in children under 28 days of age (0.032/10,000 LBs). In Argentina, spina bifida was the most frequent congenital CNS abnormality from 2009 to 2013, with an associated mortality of 2.5% in the first 28 days of life (Bidondo et al. 2015); in Mexico, the mortality rate associated with spina bifida was 6.9/100,000 LBs (Fernández Cantón et al. 2013).

These differences in mortality could be due to multiple causes or risk factors for neural tube defects, such as maternal age, exposure to teratogenic substances, malnutrition, and genetic causes (Centers for Disease Control 1991). In Latin America, several countries have developed policies for the fortification of wheat flour and other cereals (Rosado et al.

Fig. 2 Average perinatal mortality rate for CNS disorders per 10,000 live births throughout Colombia from 2005 to 2014

1999); however, the development of a policy on paper does not guarantee its implementation and acceptance across the entire population. In this sense, it is recommended that all countries develop and implement public health policies for primary prevention to reduce the prevalence of neural tube defects (Bol et al. 2006). A comparative study on prevalence of neural tube defects before and after folic acid fortification reported a significant reduction in the rate of neural tube defect formation ($p < 0.02$) after folic acid fortification in Chile and Argentina, according to data provided by the ECLAMC study (Nazer and Cifuentes 2011).

Although we observed historical trends for each congenital defect, no relevant variations were observed in mortality rates throughout the years. The Colombian city of Bogotá showed the highest perinatal mortality rate associated with CNS disorders in the study period (15.6%), followed by Antioquia (13.6%), and Valle del Cauca (9.2%). These high rates are associated with the high population concentrations in these territories.

In contrast to the findings of this study, Misnaza et al. reported that there were 13.7 perinatal deaths per 10,000 LBs due to CNS disorders in Colombia from 1999 to 2008. Among these deaths, a significant percentage (51.8%) was caused by neural tube defects, of which anencephaly (76.5%), spina bifida (13.8%), and encephalocele (9.8%) were the most frequent; this corresponded to a national rate of 2.1 deaths per 10,000 LBs due to neural tube defects. Moreover, they

reported that the municipalities of Antioquia (up to 36.32/10,000 LBs) and Boyaca (up to 34.84/10,000 LBs) had the highest perinatal mortality rates due to CNS disorders.

The main limitation of this study lies in the fact that among the CNS defects that cause perinatal mortality, AUN of the CNS was reported in 548 cases. Currently, the national system of epidemiological surveillance (SIVIGILA) uses the ICD-10 classification system for processing all mandatory reporting sheets, including records of congenital anomalies (F215); at the time of birth, if it is unclear that the cause of death is an abnormality, the death is recorded as an AUN of the CNS, limiting specific diagnoses in minors.

Conclusions

Transitions in global health determine evident changes in mortality dynamics. The impact of birth defect-related deaths increases with the decrease in infant mortality rates and other health problems, demanding the development of novel approaches by health systems to cope with this new environment. The impact of CNS defects has remained relatively constant over the past several years, as these abnormalities are still causing neonatal deaths, chronic illnesses, and disabilities in Colombia.

Socioeconomic factors play an important role in the development of congenital anomalies. In Latin America, several of the greatest difficulties are barriers to health care, such as a lack of insurance, access to health services, and specialized medicine. A direct relationship has been found between the index of unsatisfied basic needs and several important outcomes, such as prematurity, low birth weight, congenital disorders, and perinatal mortality (Bidondo et al. 2015).

Reduction of the impact of birth defects warrants a multi-stage process that requires contributions from both health authorities and the communities. These strategies include basic reproductive care, nutritional interventions, adequate prenatal check-ups, prevention of infections during pregnancy, and preventive care against exposure to teratogenic and toxic agents (e.g., tobacco, alcohol, and drugs). Secondary prevention by prenatal diagnosis is also essential. Careful assessment of patients with CNS abnormalities is important for good prognosis and for providing adequate genetic counseling.

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Compliance with ethical standards

The authors declare that they have no conflict of interest. This article does not contain any studies with human or animal subjects that were performed by any of the authors.

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