Original article

Study on the prevalence and neonatal lethality in patients with selected congenital anomalies as per the data of the National Registry of Congenital Anomalies of Argentina

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ABSTRACT

Introduction. Congenital anomalies (CAs) account for 26% of infant mortality in Argentina. The lethality rate for CAs measures the risk of death among affected infants.
Objectives. To describe the prevalence at birth of a group of selected CAs, to estimate the neonatal lethality rate, and to examine its association with different variables.
Population and Methods. The study was conducted using data provided by the National Registry of Congenital Anomalies. Prevalences of encephalocele, spina bifida, gastroschisis, omphalocele, diaphragmatic hernia, esophageal atresia, intestinal atresia, or anorectal malformation were estimated (2009-2013 period). Lethality was assessed at 7 and 28 days of life in affected infants with an isolated anomaly (2013). Association with the following variables was analyzed: sex, gestational age, birth weight, antenatal ultrasound screening, percentage of unmet basic needs in the district where the mother lives, geographic region, and level of care at the hospital where the delivery took place.
Results. Gastroschisis was the most prevalent CA (8.53/10,000 births), while diaphragmatic hernia was the CA with the highest neonatal lethality rate (66.67%). Out of all selected CAs, there was a significant association between an higher gestational age and survival at 7 days –OR: 0.81 (0.70-0.95)– and survival at 28 days –OR: 0.79 (95% confidence interval [CI]: 0.68-0.91)–. A higher percentage of unmet basic needs was associated with a higher lethality for diaphragmatic hernia –OR: 1.59 (95% CI: 1.30-1.95)– and for intestinal atresia or anorectal malformation –OR: 16.00 (95% CI: 1.63-157.24)–.
Conclusions. The high prevalence of gastroschisis is consistent with the increase observed globally. Prematurity and a high percentage of unmet basic needs increased the risk of death among affected infants.
Key words. neonatal mortality, congenital anomalies, lethality, infant mortality, Argentina.

INTRODUCTION

In the past decades in Argentina, the epidemiological transition[1] has led to a reduction in infant mortality (IM) and its two components: neonatal mortality (before 28 days of life) and postneonatal mortality (between 28 days of life and one year old). As of the 1970s, the relative importance of neonatal mortality has increased and exceeded the postneonatal component. In 2012, there were 8227 infant deaths in Argentina, with an infant mortality rate of 11.1 per 1000 live births. Most deaths took place in the neonatal period, which accounted for 67% of all deaths.[2]

In this setting, the relative importance of congenital anomalies (CAs), which correspond to Chapter XVII (q00-q99) of the International Classification of Diseases, has risen. At present, CAs are the second cause of IM, but are more relevant as a cause of death than prematurity and low birth weight related disorders.

CAs account for 26% of infant mortality,[2] with deaths predominantly occurring in the neonatal period.[4] However, the relative importance of CAs in infant mortality is geographically heterogeneous and largely depends on the management of other causes of death across the different jurisdictions.[4]

The risk of death among newborn infants with CAs depends on different factors, such as the severity of each specific anomaly, the clinical characteristics of patients, and the opportunity to access medical/surgical care. This study focuses on a group of selected CAs: encephalocele, spina bifida, gastroschisis, omphalocele, diaphragmatic hernia, esophageal

atresia/stenosis with or without fistula, intestinal atresia/stenosis, and anorectal malformations. These CAs were selected based on their impact on morbidity and mortality, their prevalence, and because they can be reduced through medical/surgical interventions. To date, there are no publications on the topic of neonatal lethality rate among infants affected with CAs in Argentina.

The objectives of this study were to describe the prevalence at birth of selected CAs, to estimate the neonatal and early neonatal lethality rates among newborn infants with such isolated CAs, and to examine their association with different variables at the maternity centers participating in the National Registry of Congenital Anomalies (RENAC) so as to identify determining factors that may be the subject of future interventions.

POPULATION AND METHODS

The target population of this study was all infants born at the hospitals participating in the RENAC, whose coverage reached 65% of births in the public sector and 38% of all births in Argentina in 2013. The RENAC was started in 2009 in four hospitals and progressively included the most important maternity centers of Argentina. In 2013, there were 122 participating institutions from the public sector. The RENAC is made up of a network of neonatologists who collect data from the hospitals and a coordinating body. Neonatologists record all live births and stillbirths with a weight of >500 grams who have CAs at birth, describe anomalies present, and complete other variables as per procedures standardized in an operational manual and an atlas. In each hospital, there are at least two RENAC representatives responsible for submitting data. The coordinating body reviews the quality of descriptions made and has geneticists code CAs, then reviews and shares the information in regular reports.[5]

The RENAC's organization and operation have been previously published.[6]

This study consisted of two stages: prevalence and lethality. The first stage included all live births and stillbirths with a weight of >500g who had any of the selected CAs as detected by the RENAC between November 1st, 2009 and December 31st, 2013. Cases were classified into live births or stillbirths and into isolated CAs, multiple CAs, or syndromic cases. *Cases of isolated CAs* are defined as those with a major single CA, or two or more major CAs corresponding to a sequence or located in the same body structure. *Cases of multiple CAs* are defined as those with major CAs

affecting different, unrelated body structures and corresponding to a known (association) or unknown pattern. *Syndromic cases* are defined as those with a definite cause.

The prevalence of selected CA was estimated as per Poisson's distribution, with a 95% confidence interval. For each selected CA, estimations included the percentage of live births and stillbirths, and of cases with isolated CAs, cases with multiple CAs, and syndromic cases.

The second stage, the lethality study, included follow-up until one month old of infants born between January 1st and December 31st, 2013 who had an isolated selected CA. Lethality analysis was conducted using data only from 2013, since the number of maternity centers included by that year was considered adequate.

The early neonatal lethality rate (ENLR; death before 7 days of life) and the overall neonatal lethality rate (ONLR; death before 28 days of life) were estimated. These rates were stated as percentages and estimated as the ratio between the number of live newborn infants affected by each CA and those deceased in each period (numerator) over the total number of live newborn infants affected by each CA (denominator).

In order to investigate factors involved in ENLR and ONLR, their association with the following variables was analyzed. Sex: female/male. Gestational age (GA): analyzed as a continuous variable. Birth weight (weight): analyzed as a continuous variable. Antenatal ultrasound screening: yes/no; defined as no screening if the Division of Neonatology lacked antenatal data on CAs either because no ultrasound had been performed or because there were no pathological findings. Level of care at the hospital where the delivery took place (category IIIB versus IIIA + II as per the National Ministry of Health's classification).[7] Geographic region of the hospital where the delivery took place: Patagonia, Center, Cuyo, Northwest (NOA), and Northeast (NEA). Percentage of population with unmet basic needs (%UBNs)[8] in the district where the mother lives: analyzed as a continuous variable. Data on weight were obtained in 98.4% of cases; on gestational age, in 98.8%; on sex, in 98.8%; on antenatal diagnosis, in 100%; on the hospital level of care, in 96.6%; and on %UBNs, in 98.7%.

First of all, associations were analyzed by grouping all newborn infants with selected CAs. As a measure of association, the adjusted risk (OR) was estimated for each variable using a multivariate logistic regression analysis. Secondly,

each CA was analyzed and its association was assessed using a bivariate analysis to estimate the risk (OR). For the assessment of the association between the hospital level of care and antenatal diagnosis, an adjusted x^2 test was performed using the Mantel-Haenszel test to estimate the *p* value stratified by type of malformation and considering a statistical significance level of 0.05 (type I error= 5%). The statistical software used was Stata 11.1.

RESULTS

There were 2275 cases with selected CAs out of a total of 703,325 births assessed between November 1st, 2009 and December 31st, 2013. Of these cases, 95.64% were live births and 4.31% were stillbirths; 66.24% of cases had isolated CAs, 26.29% had multiple CAs, and 7.47% were syndromic cases. The most prevalent CA was gastroschisis (*Table 1*).

For the lethality study, there were 528 live newborn infants born between January 1st and December 31st, 2013 who had an isolated CA. Survival up to 7 days of life was reported in 471/528 (89.20%), while follow-up continued up to 28 days of life in 436/528 (82.58%). Diaphragmatic hernia was the anomaly with the highest ENLR (57.38%) and ONLR (66.67%); spina bifida was the anomaly with the lowest ONLR (2.50%) and was not associated with any death before 7 days of life; values for the remaining CAs were intermediate (*Table 2*).

In terms of studied variables, the following results were observed for the total of 528 infants affected with isolated CAs: 394/510 (77.25%) were born at hospitals with a IIIB level of care; male sex ratio was 1.10 (276/251); mean weight was 2667.10 grams (SD= 678.40); mean gestational age was 36.90 weeks (SD= 2.43); mean %UBNs was 10.71%; and 308/528 (58.33%) had an antenatal diagnosis. The percentage of antenatal screening for each anomaly was as follows: 88.89% for encephalocele, 74.02% for gastroschisis, 68.57% for spina bifida, 62.50% for omphalocele, 65.4% for diaphragmatic hernia, 25.6% for esophageal atresias, 23.33% for intestinal atresias and anorectal malformations. At hospitals with a IIIB level of care, 65.52% of cases had had an antenatal diagnosis, while at hospitals with a II or IIIA level of care, only 34.48% of cases had been diagnosed antenatally.

A statistically significant association was observed between antenatal screening and the level of care at the hospital where the delivery took place (χ^2= 26.59; $p \leq 0.001$), which was stratified into the seven CA categories.

In the review of all newborn infants with selected CAs, a statistically significant association was observed between survival of affected infants and their gestational age, both in the early neonatal period (adjusted OR: 0.81; 95% CI= 0.70-0.95) and in the overall neonatal period (adjusted OR: 0.79; 95% CI= 0.68-0.91). Likewise, the increase of the %UBNs in the district where

TABLE 1. *Prevalence at birth of selected congenital anomalies and distribution by outcome and clinical presentation. National Registry of Congenital Anomalies, Argentina, 2009-2013*

Congenital anomaly	Cases	Prevalence x 10,000 (95% CI)*	Cases by outcome					Cases by clinical presentation					
			Live births		Stillbirths		NS	Isolated		Multiple		Syndromic	
			n	%	n	%		n	%	n	%	n	%
Gastroschisis	600	8.53 (7.86-9.24)	573	95.50	27	4.50	0	546	91.00	52	8.67	2	0.33
Spina bifida	389	5.53 (4.99-6.11)	372	95.87	16	4.12	1	305	78.41	72	18.51	12	3.08
Anorectal malformation	231	3.28 (2.87-3.74)	218	94.37	13	5.63	0	116	50.22	112	48.48	3	1.30
Esophageal atresia	230	3.27 (2.86-3.72)	227	98.70	3	1.30	0	98	42.61	117	50.87	15	6.52
Diaphragmatic hernia	225	3.20 (2.79-3.65)	219	97.33	6	2.67	0	164	72.89	54	24.00	7	3.11
Intestinal atresia (jejunum-ileum)	218	3.10 (2.70-3.54)	217	99.54	1	0.46	0	110	50.46	32	14.68	76	34.86
Omphalocele	167	2.37 (2.03-2.76)	144	86.23	23	13.77	0	64	38.32	93	55.69	10	5.99
Duodenal atresia	118	1.68 (1.39-2.01)	117	99.15	1	0.85	0	53	44.92	24	20.34	41	34.75
Encephalocele	97	1.38 (1.12-1.68)	89	91.75	8	8.25	0	51	52.58	42	43.30	4	4.12
Total	2275		2176	95.64	98	4.31		1507	66.24	598	26.29	170	7.47

NS: not specified; CI: confidence interval.
* Prevalence estimated on 703,325 births out of the total number of cases (live births and stillbirths).

the mother lives showed a tendency towards increasing the risk of death in both periods, although it was not statistically significant. The antenatal screening variable was excluded because it was collinear with the hospital level of care variable (*Table 3*).

The highest percentage of deceased infants in the neonatal period was observed in the Northwest (NOA); however, differences among regions were not statistically significant (*p*= 0.147) (*Table 4*). The percentage of births covered by the public subsector in all regions was over 50%.

In the review of each separate CA, omphalocele and encephalocele were excluded because the number of cases was insufficient. It was not possible to estimate adjusted risks because of the number of deceased infants with each CA.

A statistically significant association was observed between a shorter survival and an increased %UBNs for diaphragmatic hernia and

intestinal and anorectal atresia. Likewise, a risk over 5 was observed in relation to low birth weight and preterm birth for esophageal atresia and spina bifida, although these results were not statistically significant (*Table 5*).

DISCUSSION

This was the first study conducted in Argentina with the purpose of determining the prevalence and lethality of selected CAs based on data with a high coverage from across the 24 jurisdictions in the country. Both the prevalences observed and the proportion of isolated, multiple and syndromic cases by CA category are consistent with the values expected as per the international bibliography. However, it is worth noting that the frequency of gastroschisis was high. The frequency of this congenital anomaly has been increasing worldwide.[9] This situation has been strongly associated with younger maternal ages and, to a lesser extent, with other factors such

TABLE 2. *Newborn infants with isolated selected congenital anomalies: percentage of follow-up and deceased before 7 and 28 days of life. National Registry of Congenital Anomalies, Argentina, 2013*

CA	Total number of affected infants	Follow-up until 7 days of life	Follow-up until 28 days of life	Deceased before 7 days of life (ENLR)	Deceased before 28 days of life (ONLR)
Gastroschisis	204	186/204 (91.18%)	173/204 (84.80%)	10/186 (5.38%)	18/173 (10.40%)
Spina bifida	105	92/105 (87.62%)	80/105 (76.19%)	0/92 (0.00%)	2/80 (2.50%)
Intestinal atresia and ARM	90	78/90 (86.67%)	72/90 (80.00%)	1/78 (1.28%)	3/72 (4.17%)
Diaphragmatic hernia	65	61/65 (93.85%)	60/65 (92.31%)	35/61 (57.38%)	40/60 (66.67%)
Esophageal atresia	39	32/39 (82.05%)	32/39 (82.05%)	4/32 (12.50%)	8/32 (25.0%)
Omphalocele	16	14/16 (87.50%)	13/16 (81.25%)	3/14 (21.43%)	6/13 (46.15%)
Encephalocele	9	8/9 (88.89%)	6/9 (66.67%)	1/8 (12.50%)	2/6 (33.33%)
Total	528	471/528 (89.20%)	436/528 (82.58%)	54/471 (11.46%)	79/436 (18.12%)

CA: congenital anomaly; ENLR: early neonatal lethality rate; ONLR: overall neonatal lethality rate; ARM: anorectal malformation.

TABLE 3. *Risk of death in the early neonatal and overall neonatal periods in newborn infants with selected anomalies, as per the different variables. National Registry of Congenital Anomalies, Argentina, 2013*

Variables	Death	
	Before 7 days of life OR (95% CI)	Before 28 days of life OR (95% CI)
< Birth weight*	1.00 (0.99-1.00)	1.00 (0.99-1.00)
> Gestational age*	0.81 (0.70-0.95)	0.79 (0.68-0.91)
Female sex	0.55 (0.30-1.02)	0.60 (0.35-1.01)
> %UBNs in the district where the mother lives	1.05 (1.00-1.10)	1.05 (1.00-1.10)
Low level of care at the hospital where the delivery took place	0.77 (0.36-1.68)	0.58 (0.29-1.20)

%UBNs: percentage of unmet basic needs; OR: odds ratio; CI: confidence interval.
* Variables continuously reviewed.

as: urogenital infections in the periconceptional period, low body mass index, low socioeconomic level, and tobacco, alcohol and illegal drug use.[9-11]

The antenatal ultrasound detection rate observed in the cases of encephalocele, spina bifida, gastroschisis, diaphragmatic hernia, and omphalocele was lower than that described in other studies.[12,13] Intestinal and esophageal atresias were the CAs with the lowest detection rate, quite likely because ultrasound findings are indirect.[14,15]

During the follow-up of affected infants, it was possible to recover over 80% of cases. Diaphragmatic hernia was the CA with the highest lethality rate, and most deaths occurred in the early neonatal period. This is classified as a "hardly reducible" anomaly as per the criteria of the National Ministry of Health;[16] therefore, findings observed in this study are consistent with such classification. The high lethality rate of diaphragmatic hernia may be the reason for the higher percentage of deceased infants in the NOA region.

Spina bifida was the only CA associated with no deaths before 7 days of life and with a lower ONLR, which is consistent with follow-up studies that have reported most deaths occurred after one year old.[17,18]

TABLE 4. *Number of deceased cases with isolated selected congenital anomalies and overall neonatal lethality rate (ONLR) by geographic region of the hospital where the delivery took place. National Registry of Congenital Anomalies, Argentina, 2013*

Region	Gastroschisis	Spina bifida and anorectal malformation	Diaphragmatic atresia	Intestinal hernia	Esophageal atresia	Omphalocele	Encephalocele	N deceased/ N affected	ONLR (95% CI)
Patagonia	0	0	0	2	0	0	0	2/26	7.69% (0.93-27.80)
Center	11	1	0	19	4	6	2	43/249	17.27% (12.50-23.27)
Cuyo	0	0	0	5	0	0	0	5/33	15.15% (5.00-35.36)
NOA	3	1	3	12	3	0	0	22/80	27.50% (17.23-41.64)
NEA	4	0	0	2	1	0	0	7/48	14.58% (5.86-30.05)
Total	18	2	3	40	8	6	2	79/436	18.12% (14.35-22.58)

Region: Patagonia (Chubut, La Pampa, Neuquén, Río Negro, Santa Cruz, Tierra del Fuego); Center (Autonomous City of Buenos Aires, Buenos Aires, Córdoba, Entre Ríos, Santa Fe); Cuyo (La Rioja, Mendoza, San Juan and San Luis); NOA (Catamarca, Jujuy, Salta, Santiago del Estero and Tucumán); NEA (Corrientes, Chaco, Formosa and Misiones).
CI: confidence interval.

TABLE 5. *Risk of death before 28 days of life in newborn infants with selected anomalies examined separately, as per the different variables. National Registry of Congenital Anomalies, Argentina, 2013*

Variables	Isolated anomalies OR (95% CI)				
	Diaphragmatic hernia	Esophageal atresia	Gastroschisis	Spina bifida	Intestinal atresia and anorectal malformation
< Birth weight*	1.05 (0.70-1.60)	5.44 (0.76-39.25)	1.56 (0.54-4.51)	5.58 (0.37-83.32)	0.00
> Gestational age*	0.95 (0.61-1.48)	5.44 (0.76-39.25)	1.72 (0.68-4.37)	6.18 (0.42-91.77)	0.00
Female sex	0.77 (0.51-1.17)	0.95 (0.28-3.27)	1.06 (0.44-2.54)	1.05 (0.07-16.23)	2.65 (0.25-26.87)
> %UBNs in the district where the mother lives	1.59 (1.30-1.95)	1.80 (0.50-6.51)	1.45 (0.46-4.58)	0.00	16.00 (1.63-157.24)
Low level of care at the hospital where the delivery took place	0.86 (0.53-1.38)	0.41 (0.06-2.84)	0.38 (0.05-2.72)	2.55 (0.17-38.93)	1.69 (0.16-17.43)

%UBNs: percentage of unmet basic needs; OR: odds ratio; CI: confidence interval.
* Variables continuously reviewed.

Neonatal lethality rates in the cases of intestinal atresia and anorectal atresia observed in our study are similar to those reported in other studies.[19] Neonatal lethality for gastroschisis, omphalocele and esophageal atresia observed in other investigations was generally below the rates observed in our study.[20-22] Consistent with our work, several studies have associated prematurity to a higher mortality rate among infants affected with selected CAs.[18,20,23-25] However, some investigations conducted in gastroschisis patients have demonstrated that elective preterm C-sections prevented the occurrence of intestinal inflammation and improved enteral functioning because the exposure time of bowel loops to amniotic fluid meconium was shorter.[26,27] The results of other studies are not consistent with this latter observation.[28,29]

In our study, results showed a tendency that correlated shorter survival with a lower birth weight when specifically examining esophageal atresia and myelomeningocele; however, this association was not statistically significant. As per the bibliography, low birth weight is a risk factor for the survival of newborn infants with CAs.[18,20,25,30] In the case of esophageal atresia, the patient's weight is a criterion internationally established as a mortality prognostic factor when conducting pre-surgical assessments.[31]

Regarding the review of unfavorable socioeconomic indicators and CAs, Pawluk, et al.[32] found an association between poverty (as measured by family and regional socioeconomic level indices) and the prevalence at birth of ventricular septal defect (VSD) and oral clefts. On their side, Vrijheid, et al. observed a positive association between a low maternal socioeconomic level and newborn infants with non-chromosomal septal heart defects and gastrointestinal anomalies.[33] Bronberg, et al. found no association between the mortality rate of a specific CA and the socioeconomic disadvantage of the districts where mothers live.[4,34] In our study, an increased %UBNs showed a significant association with the risk of death, specifically in cases of diaphragmatic hernia and intestinal/anorectal atresias. Such result may indicate that the most disadvantaged districts are the ones with greater difficulties in having access to perinatal care. Consistent with our findings, Smith, et al. observed a higher risk of death in newborn infants with isolated CAs whose mothers lived in financial hardship.[35]

The estimated lethality rates may serve as an indicator to assess the impact of health interventions and as an input to organize antenatal or immediate neonatal referral services for newborn infants with CAs. The Ministry of Health has recently established the Tertiary Care Perinatal Package, which is one of the priority items for the implementation of the SUMAR Program as of 2013. This set of services includes the CAs analyzed in this study and is considered important since it has been selected for its potential to have a significant impact on the reduction of the hard core of infant mortality.

A strength of this study is that it included newborn infants from the main public maternity centers across the 24 jurisdictions of Argentina, with a high birth coverage.

One of its weaknesses is the number of affected newborn infants lost to follow-up. Another limitation is that, in the analysis of each separate CA, it was not possible to estimate the adjusted risk of each CA in both periods because of the small sample size. In addition, it is not possible to rule out the effect of the so-called ecological fallacy for the %UBNs variable since there are no individual data available on maternal socioeconomic level. Finally, although the coverage of births in each region was over 50%, this coverage was heterogeneous.

CONCLUSION

Prevalences of studied CAs were consistent with expected values. Gastroschisis was the most prevalent CA, while diaphragmatic hernia was the CA with the highest lethality rate. Prematurity and socioeconomic hardship variables increased the risk of death among affected infants. ∎

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ANNEX

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    Hospital Ana Goitía, Avellaneda: Adriana Mosquera, M.D., Valeria Vera, M.D.
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    Hospital Argentina Diego, Azul: Victoria Rizzo, M.D.
    Hospital Bocalandro, Tres de Febrero: Mariana Oreglia, M.D., David Fernández, M.D.
    Hospital Carlos Gianantonio, San Isidro: Blanca Cristina Senra, M.D., María Laura Sznitowsky, M.D.
    Hospital Diego Thompson, San Martín: Alicia Fana, M.D., Lidia Santana, M.D.
    Hospital Equiza, González Catán: Rubén Goncalvez, M.D., Rodolfo Zaiat, M.D.
    Hospital Eurnekian, Ezeiza: José Vega Chancafe, M.D.
    Hospital Eva Duarte de Perón (formerly Menem), Malvinas Argentinas: Elisa Duro, M.D.
    Hospital Eva Perón, San Martín: Maricel Pontorno, M.D., Andrea Becerra, M.D.
    Hospital Evita, Lanús: Marta Noemí Raggio, M.D., Graciela Schabvlosky, M.D.
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    Hospital San José, Pergamino: Ángela Pacífico, M.D.
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    Hospital Virgen del Carmen, Zárate: Carlos Bachiochi, M.D.
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