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The path made and where to go: trends in the neonatal mortality rate. A cross-sectional study

Rita Ramos[1a], Inês Carneiro[1b], Pedro Fonseca[2c], Bruno Sanches[3d], Margarida Cabral[3e], and António Gomes[3f]*

[1]Department of Pediatrics, Hospital Garcia de Orta, Almada; [2]Institute of Economics and Management of the University of Lisbon, Lisbon; [3]Neonatal and Pediatric Intensive Care Unit, Hospital Garcia de Orta, Almada. Portugal

ORCID: [a]0000-0002-3655-5222; [b]0000-0001-8038-198X; [c]0000-0002-5708-081X; [d]0000-0002-9287-4666; [e]0000-0001-9903-2974; [f]0000-0002-2313-6205

Abstract

Introduction: Neonatal mortality is an indicator of maternal and child health, which reflects the level of pre- and post-natal care. The objective of the present study was to determine the neonatal mortality rate, its trend, and respective causes in a Neonatal Intensive Care Unit. **Methods:** Retrospective, descriptive observational study that included newborns who died between 1992 and 2020 in a differentiated perinatal support unit. **Results:** There were 390 deaths (mortality rate 5.7%). Fifty per cent of deaths occurred in the early neonatal period; 77% in premature infants. The trend in neonatal mortality decreased over the decades, mainly due to early and late neonatal mortality. Post-neonatal mortality remained stable. The main causes of death were prematurity-related organ dysfunction (39%), infections (24%), and congenital anomalies (16%). There was a decrease in the proportion of deaths from congenital anomalies and an increase in the proportion of infections. An autopsy was performed in 176 newborns (45%). **Discussion:** This study offers a long period of analysis of mortality rates with more extent data from a particular neonatal population. The decrease in neonatal mortality rates and deaths due to congenital anomalies reflect the progress achieved in prenatal diagnosis and differentiated prenatal and postnatal healthcare. On the other hand, infection remained one of the main causes of late neonatal and post-neonatal death. Analysis of neonatal mortality has the potential to enable a refined clinical practice. Focus on post-neonatal and infection-related mortality should be the next priorities in the improvement of neonatal care.

Keywords: Early-neonatal mortality. Post-neonatal mortality. Neonatal intensive care. Prematurity.

O caminho percorrido e para onde ir: evolução da taxa de mortalidade neonatal. Um estudo transversal

Resumo

Introdução: A mortalidade neonatal constitui um indicador de saúde materno-infantil, que reflete o nível de cuidados pré e pós-natais. O objetivo do presente estudo foi determinar a taxa de mortalidade neonatal, a sua tendência e as respetivas causas numa Unidade de Cuidados Intensivos Neonatais. **Métodos:** Estudo retrospetivo, observacional e descritivo. Incluídos recém-nascidos que faleceram entre 1992 e 2020 numa unidade de apoio perinatal diferenciado. **Resultados:** No período de estudo ocorreram 390 óbitos (taxa de mortalidade de 5.7%). Cinquenta por cento das mortes ocorreram no período neonatal

***Correspondence:**
Rita Ramos
E-mail: rita23ramos@gmail.com

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precoce; 77% em prematuros. A taxa de mortalidade neonatal apresentou uma tendência decrescente ao longo dos anos, maioritariamente devido à diminuição da mortalidade neonatal precoce e tardia. A mortalidade pós-neonatal manteve-se estável. As principais causas de morte foram: complicações da prematuridade (39%), infeções (24%) e anomalias congénitas (16%). Verificou-se uma diminuição da proporção de mortes por anomalias congénitas, contrariamente às infeções cuja proporção aumentou. Foi realizada autópsia em 176 recém-nascidos (45%). **Discussão:** Neste estudo apresentamos um período longo de análise da taxa de mortalidade de uma determinada população neonatal. A diminuição da taxa de mortalidade neonatal e dos óbitos por anomalias congénitas refletem os progressos alcançados a nível de diagnóstico pré-natal e de cuidados pré e pós-natais diferenciados. Por outro lado, a infeção manteve-se como uma das principais causas de morte neonatal tardia e pós-neonatal. A análise da mortalidade neonatal, tem potencial para possibilitar uma prática clínica mais apurada. O foco na mortalidade pós-neonatal e infeção devem ser as próximas prioridades para uma melhoria dos cuidados neonatais.

Palavras-chave: Mortalidade neonatal precoce. Mortalidade pós-neonatal. Cuidados intensivos neonatais. Prematuridade.

Keypoints

What is known
- Neonatal mortality results from a complex relationship between biological, social and health care variables.
- Neonatal mortality accounts for 2/3 of child mortality.
- Premature newborns and/or those with low birth weight are at greatest risk of neonatal mortality.

What is added
- There has been a decrease in the neonatal mortality rate in recent years due to advances in pre- and postnatal care.
- Infection and post-neonatal mortality are areas of possible intervention.
- Pathology examination can offer more answers and enable a better future care.

Introduction

Neonatal mortality, defined as death within the first 28 days of life, results from a complex relationship between biological, social, and health care variables[1]. It constitutes an important maternal and child health indicator, reflecting the healthcare provided to the neonatal population. Globally, in 2019, 2.4 million children died in the first month of life, which is equivalent to 6.700 deaths daily[2]. Neonatal mortality accounts for 2/3 of child mortality[3,4]. Premature newborns (NB) and/or those with low birth weight (LBW) are those at greatest risk, accounting for 85% of neonatal deaths[2,3].

Advances of technical and scientific knowledge, with an increase in the quality of perinatal and neonatal care, resulted in a reduction in neonatal mortality in recent decades. Between 1990 and 2019, there was a 52% reduction in neonatal mortality worldwide (from 37 deaths/1000 births to 17 deaths/1000 births)[2]. Portugal has followed this downward trend with a reduction from 6.9 to 1.9 deaths/1000 births in the same period[2]. In developing countries, most neonatal deaths occur from preventable causes such as infections or perinatal asphyxia[5-7]. In developed countries such as Portugal, published data are scarce, focusing mainly on the circumstances of death and end-of-life care[8,9].

The present study was conducted at a Neonatal Intensive Care Unit (NICU) with a differentiated perinatal support. The main objective was to determine the mortality rate (MR), its trend, and the respective causes of death in the last three decades. The specific objectives were to characterise data on pregnancy and delivery; analyse the causes of death according to gestational age (GA) and birth weight (BW); assess the distribution of causes of death by time of death; identify the percentage of autopsies performed; analyse the concordance between clinical and pathological diagnoses and compare the results with national and international published data.

Material and methods

Retrospective and descriptive observational study with the data obtained from the database/clinical records of the NICU. All NB who were admitted and died between January 1, 1992, and December 31, 2020, were included. All stillbirths and NBs who died in the delivery room were excluded. Data were obtained by consulting the clinical records of the NB and the mother, death certificate and autopsy reports. The information collected included data on maternal medical history, gestation, and delivery. From the NB, data were obtained from sex, GA, BW and weight at death, chronological and corrected age at death, cause of death and pathology diagnosis. When information was incomplete, subtotals were presented for each variable analysed.

The study was approved by the Ethics Committee.

The manuscript was written according to the STROBE checklist.

Definitions and classifications

In recent years, improvement in neonatal intensive care may have led to a biased definition of neonatal death due to the exclusion of patients who remained hospitalised and died after 28 days of life. Thus, the term *neonatal-related deaths*, introduced by Phibbs, et al.[10] includes all neonatal deaths and those occurring between 28 days of life and one year, if the child remained hospitalized. Therefore, neonatal deaths were categorised as follows: early neonatal death (first 6 days of life), late neonatal death (between 7 and 27 days of life) and post-neonatal death (after 28 days of life).

In this study, the causes of death were classified using an adaptation of the Wigglesworth scale[11]. Five groups were defined: group 1- infections; group 2- congenital anomalies; group 3- immaturity/conditions associated with prematurity (hyaline membrane disease, necrotizing enterocolitis, central nervous system (CNS) haemorrhage, pulmonary haemorrhage, extreme immaturity, other causes of death resulting from prematurity complications); group 4- asphyxia during labour; group 5- other causes not included in the previous groups.

The concordance between clinical and pathological diagnosis was evaluated using the modified Goldman classification (Table 1)[12].

Table 1. Concordance between clinical and pathological diagnosis according to modified Goldman classification

Class	Description
IA	Diagnosis that, if detected before death, would probably have led to change in management that might have resulted in cure or prolonged survival
IB	Diagnosis with significant implications for future genetic advice
II	Diagnosis that, if detected before death, would probably not have led to change in management or survival because: – No appropriate therapy was available at the time – Appropriate therapy was given even though the diagnosis was unknown at the time – Patient had acute cardiopulmonary arrest that was appropriately managed, but patient did not survive for definitive management – Patient had "do not resuscitate" status
III	Diagnosis that may or may not have been related to main disease process and was contributory cause of death
IV	Diagnosis unrelated to outcome and may or may not have affected the patient's prognosis
V	Complete concordance between diagnosis before death and findings at autopsy

Statistical analysis

Data were processed using Excel Windows 7®, SPSS (Statistical Package for Social Sciences)® version 24 and Rstudio version 1.4.1717. The analysis of the annual trend of neonatal mortality and respective causes of death was performed using the chi-square test for trends in proportions. A significance level of $p < 0.05$ was considered.

Results

During study period, 6816 NB were admitted, corresponding to an average of 235 admissions/year, of which 28% (n = 1884) were very low birth weight (VLBW) NB.

Of the 6816 NB admitted, 390 deaths were registered, which corresponded to a MR of 5.7%. Among the deceased NB, 204 (52%) were male. Median GA was 29 weeks (minimum 22 and maximum 42 weeks). Three hundred (77%) were premature NB, 54% (163/300) of which were extremely premature. Median birth weight (BW) was 1092g (minimum 420 and maximum 4400g) and 237 (60%) NB were VLBW.

Regarding maternal, pregnancy and delivery data: the median maternal age was 28 years (minimum 14 and maximum 47 years) and in 44 cases (14%; 44/312) a relevant medical history was recorded (Table 2). In 73 cases (23%; 73/312) there was a history of miscarriage and in 13 cases (4%; 13/312) a history of previous fetal or neonatal death. Three hundred and twenty (82%) pregnancies were monitored and 322 (83%) were single pregnancies. In 312 cases (80%) there was a history of at least one complication during pregnancy and the most frequent were: threatened preterm delivery in 183 cases (58%; 183/312), premature rupture of membranes in 65 cases (20%; 65/312), fetal growth restriction in 48 cases (15%; 48/312), clinical suspicion of chorioamnionitis in 37 cases (11%; 37/312), placental abruption in 29 cases (9%; 29/312), pre-eclampsia in 28 cases (9%; 28/312) and gestational diabetes in 16 cases (5%; 16/312). In 124 cases (44%; 124/280), a scheme of prenatal corticosteroids for pulmonar maturity stimulation was performed. This procedure increased over the years of study ($p < 0.01$).

Evolution of neonatal mortality

During the study period, 195 NB (50%) died in the early neonatal period, 153 (39%) in the late neonatal period and 42 (11%) in the post-neonatal period. MR

Table 2. Relevant maternal medical history during pregnancy

Relevant maternal medical history	n (%)
Chronic arterial hypertension	20 (45.5%)
Drug addiction	9 (20.5%)
Human immunodeficiency virus infection	3 (6.8%)
Hereditary thrombophilia	3 (6.8%)
Epilepsy	3 (6.8%)
Type 1 diabetes mellitus	2 (4.5%)
Type 2 diabetes mellitus	1 (2.2%)
Chronic alcoholism	1 (2.2%)
Systemic lupus erythematosus	1 (2.2%)
Steinert myotonic dystrophy	1 (2.2%)
	44

decreased 24% during the period of the study, which ranged from 6.3% in 1992 and 4.8% in 2020 (Fig. 1). This reduction was mainly related to a decrease in early neonatal and late neonatal mortality ($p < 0.001$ and $p = 0.003$ respectively), once post-neonatal mortality remained stable over the years ($p = 0.6$).

The most prevalent causes of death (Table 3) were complications of prematurity (154 cases; 40%), infection (93 cases; 24%), congenital anomalies (64 cases; 16%) and perinatal asphyxia (47 cases; 12%). In four cases, the cause of death was undetermined. Of the NB who died due to congenital anomalies, 50 (78%) had no prenatal diagnosis (PND), and of these, the majority (86%; n = 43) occurred in the first 15 years of the study. The most prevalent conditions associated with early neonatal death were complications of prematurity (40%; 78/195) and perinatal asphyxia (18%; 35/195). In the group of late neonatal death, the most prevalent causes of death were complications of prematurity (44%; 67/153) and infection (29%; 44/153). In the post-neonatal mortality group, infection (45%; 19/42) was the main cause of death. Congenital anomalies and complications of prematurity were the second main causes (21%; 9/42).

At a lower GA and BW, complications of prematurity and infections were more frequent. As GA and BW increased, perinatal asphyxia and congenital anomalies become the most common causes of death.

Over the years of study, there was a decrease in the proportion of congenital anomalies related deaths ($p = 0.04$), mainly due to the decrease in congenital heart disease deaths ($p = 0.03$). On the other hand, there was an increase in the proportion of deaths due to infection ($p = 0.01$). The proportion of deaths from complications of prematurity and perinatal asphyxia remained stable (Fig. 2).

Clinical and pathological concordance

Autopsy was performed in 176 NB (45%). The annual rate of autopsies ranged from 10% in 2005 to 75% in 2010. A higher rate of autopsies was performed in term NB compared to premature NB (52% and 32% respectively; $p < 0.001$) and in NB with higher BW (58% in BW > 2500g and 42% in BW ≤ 2500g; $p = 0.01$). Of the 176 autopsies performed, the pathology report was available in 118 cases. Applying the modified Goldman Classification[12], a clinical and pathological concordance was found in 91 cases (77%). Additional findings were identified in 27 (23%) autopsies (Table 4).

Discussion

In recent years, there has been a global reduction in the neonatal MR. In Europe, between 1970 and 2014, there was a reduction from 13.2 to 2.4 deaths per 1000 births[13]. A Swiz study performed between 1997 and 2006 identified a MR of 2.3% with complications of prematurity accounting for 78% of deaths (including 3499 NB)[14]. Hagen, et al.[15] conducted a study at a NICU in Norway comparing data on neonatal mortality in two different periods (1987-1988 and 1997-1998, including 1473 and 1705 NB, respectively) and found a reduction in neonatal mortality from 6.9% to 3.4%[15]. Two studies have been published in Portugal but with differences to our study as explained below[8-9]. The first study identified a 5.7% MR in a population of 1938 NB admitted between 2004-2008. The main causes of death were congenital anomalies (50%), prematurity complications (33.6%) and infections (4.5%). The second study (4026 admissions) analyses the following decade (2008-2018) and found a reduction in the MR to 3.9%.

The present study adds a longer period of analysis, during three different decades, offering more extensive data from a more representative neonatal population. The reduction in the MR shows similarities with what has been observed in other studies performed in Portugal and other European countries[8,9,13,16,17]. It reflects the progress achieved in pregnancy, childbirth and NB care. The increased use of prenatal corticosteroids, as evidenced in this study, is currently considered to be one of the interventions with greatest impact on the improvement of prognosis and survival of preterm NB[18-20].

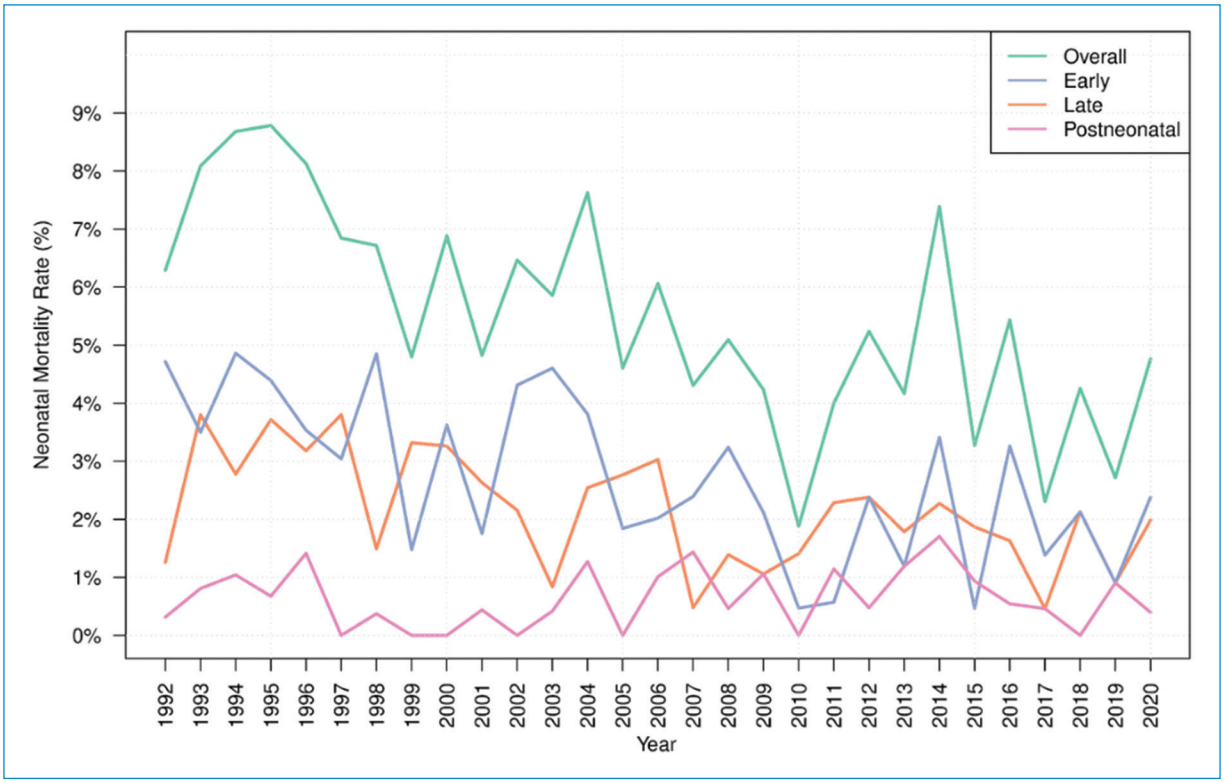

Figure 1. Evolution of the mortality rate between 1992 and 2020.

The unchanged post-neonatal MR suggests that, in some patients, death was only delayed. This highlights the need to reflect on the limitation or suspension of invasive and life-supporting measures in some cases[6,14].

As expected, most deaths occurred in NB with lower gestational age and lower BW. As regards the causes of death, there was a predominance of deaths due to complications of prematurity and infection. Comparing our results with those of the study of Costa S. et al.[8] we found a similar MR (5.6% between 2004 and 2008), but a lower number of deaths due to congenital anomalies (11.6%) and a higher number due to infections (38%) in the same period. However, the population of the previous study had a median GA of 34 weeks, which contrasts with the 29 weeks in the present study. Preterm NBs are a particularly vulnerable group to infection due to their immunological immaturity, longer hospital stay, frequent exposure to invasive procedures, and nonspecific clinical symptoms that may delay the beginning of treatment. Therefore, the higher percentage of deaths due to infection can be mainly related to a higher number of immature NBs included in the present study. The emergence of multidrug-resistant strains in the last decade may also play a role in this predominance of infection as a cause of mortality in recent years. A previous study conducted in our NICU, which analysed the infection by multidrug-resistant bacteria between 2008 and 2017 and included 64 infectious episodes, identified a case fatality rate of 10.9% for these infections, which was higher than the value of 7% identified for healthcare-associated infections[21].

In our study, most deaths due to congenital anomalies without PND occurred in the first 15 years. Besides that, we observed a decrease in the proportion of deaths due to congenital anomalies during the period of the study. This reflects the improvement of ultrasound diagnosis and quality of PND in the last decades and justifies the fact that most deaths due to undiagnosed congenital anomalies occurred in the first years of study. Furthermore, the improvement in prenatal diagnostic acuity has also led to the termination of many pregnancies whose fetus presented severe anomalies incompatible with life.

The importance of autopsy in NICUs has been analysed in recent years, with performance rates ranging between 39% and 82%[22]. In the current study, autopsy was performed in 45% of patients, with a higher prevalence in those with higher GA and BW. These are important factors in the final decision to request a pathological examination[23]; often reserved for cases of

Table 3. Distribution of causes of death in newborns according to adaptation of the Wigglesworth classification

Classification	n (%)	Cause of death	n (%)
Complications of prematurity	154 (39.5%)	Extreme immaturity	58 (14.9%)
		Necrotizing enterocolitis	45 (11.5%)
		CNS hemorrhage	29 (7.4%)
		Pulmonary hemorrhage	21 (5.4%)
		Spontaneous intestinal perforation	1 (0.2%)
Infection	93 (23.8%)	Late-onset neonatal sepsis	44 (11.3%)
		Early-onset neonatal sepsis	19 (4.9%)
		Sepsis with meningitis	8 (2.0%)
		Sepsis with pneumonia	6 (1.5%)
		Ventilator-associated pneumonia	5 (1.3%)
		TORCH infection	4 (1.0%)
		Endocarditis	4 (1.0%)
		Pneumonia	2 (0.5%)
		Meningitis	1 (0.2%)
Congenital anomalies	64 (16.4%)	Polymalformative syndrome	15 (3.8%)
		Cardiovascular disease	14 (3.6%)
		Chromosomal anomaly	10 (2.6%)
		Musculoskeletal system disease	9 (2.3%)
		CNS disease	8 (2.0%)
		Respiratory tract disease	4 (1.0%)
		Digestive tract disease	2 (0.5%)
		Urinary tract disease	2 (0.5%)
Perinatal asphyxia	47 (12.0%)		47 (12.0%)
Other causes	32 (8.2%)	Meconium aspiration syndrome	8 (2.0%)
		Pulmonary hypertension	5 (1.3%)
		Pneumotorax	3 (0.7%)
		Disseminated intravascular coagulation	2 (0.5%)
		Hemoperitoneum	2 (0.5%)
		Metabolic disease	2 (0.5%)
		Hydrops fetalis	2 (0.5%)
		Unknown cause	4 (1.0%)
		Others	4 (1.0%)
			390

CNS: central nervous system.

"unexpected" death, in which the classic risk factor arising from the immaturity of the NB is not present. Despite clinical and pathological agreement in 77% of cases, additional findings in 23% of autopsies demonstrates its importance in clarification of the cause of death. This offers the possibility of genetic counselling

Year	Total Deaths	Infections		Congenital Anomalies		Complications of Prematurity		Perinatal Asphyxia		Others	
	n	n	%	n	%	n	%	n	%	n	%
1992	20	3	15	2	10	6	30	3	15	6	30
1993	30	6	20	5	17	13	43	3	10	3	10
1994	25	6	24	4	16	9	36	5	20	1	4
1995	26	5	19	6	23	12	46	3	12	0	0
1996	23	3	13	5	22	10	43	3	13	2	9
1997	18	3	17	4	22	9	50	2	11	0	0
1998	18	3	17	4	22	6	33	3	17	2	11
1999	13	5	38	3	23	2	15	2	15	1	8
2000	19	4	21	4	21	9	47	2	11	0	0
2001	11	1	9	5	45	5	45	0	0	0	0
2002	15	1	7	2	13	4	27	5	33	3	20
2003	14	4	29	1	7	6	43	3	21	0	0
2004	18	6	33	2	11	8	44	1	6	1	6
2005	10	4	40	1	10	3	30	1	10	1	10
2006	12	5	42	1	8	6	50	0	0	0	0
2007	9	5	56	1	11	1	11	2	22	0	0
2008	11	3	27	2	18	5	45	1	9	0	0
2009	8	0	0	4	50	2	25	1	13	1	13
2010	4	0	0	2	50	1	25	0	0	1	25
2011	7	1	14	0	0	5	71	1	14	0	0
2012	11	3	27	1	9	5	45	2	18	0	0
2013	7	1	14	3	43	1	14	1	14	1	14
2014	13	1	8	1	8	8	62	1	8	2	15
2015	7	1	14	0	0	4	57	1	14	1	14
2016	10	4	40	0	0	4	40	0	0	2	20
2017	5	2	40	0	0	3	60	0	0	0	0
2018	8	4	50	0	0	3	38	0	0	1	13
2019	6	4	67	0	0	0	0	0	0	2	33
2020	12	5	42	1	8	4	33	1	8	1	8
p**–value** (χ^2)			0.01		0.04		0.99		0.11		0.56

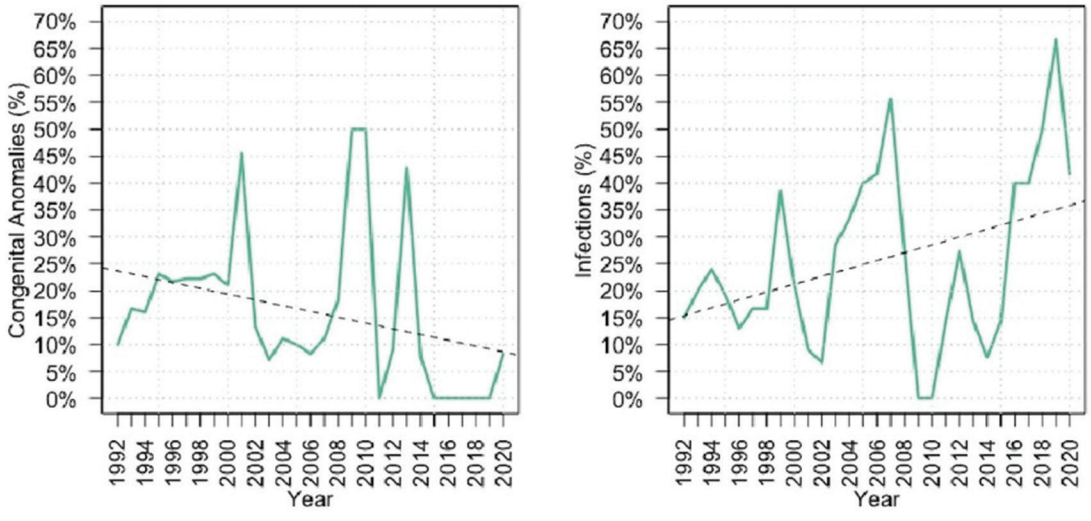

Figure 2. Distribution and trend of causes of death from 1992 to 2020.

Table 4. Additional findings identified in autopsies according to modified Goldman classification

Class	Additional findings identified in autopsies	n (%)
IA	Congenital heart disease	1 (3.7%)
	Sepsis with endocarditis	1 (3.7%)
	Constrictive pericarditis	1 (3.7%)
IB	Hereditary disease of metabolism (glycogenosis)	1 (3.7%)
IIA	Multiple organ thrombosis and ischemic changes in immediate postoperative period of intestinal atresia	1 (3.7%)
IIB	Congenital pneumonia	3 (11.1%)
	Hypoxia with multi-systemic repercussion	2 (7.4%)
	Heart and respiratory failure secondary to fetal anaemia	1 (3.7%)
III	CNS hemorrhage	10 (37%)
	Pulmonary hemorrhage	2 (7.4%)
	Hemoperitoneum	2 (7.4%)
IV	Hepatic subcapsular hematoma	1 (3.7%)
	Bilateral pulmonary lymphangiectasia	1 (3.7%)
		27

CNS: central nervous system.

and supplies important data for future approach to other patients.

The main limitations of our study are the retrospective design, which required reliance on review of medical records for details of care and the fact that it was performed in a single center, which makes it difficult to generalize the results.

Conclusion

The evolution of neonatal mortality in this NICU over three decades reflects the improvement in PND and maternal-fetal interventions. It also reflects the improvement of differentiated postnatal care, scientific, technical, and technological advances. Analysis of neonatal mortality has the potential to enable a refined clinical practice. The present study offers a reality of a single NICU, but with a long period of study, with data from immature NB. Besides the path achieved similar to other NICUs, it stands out that infection and post-neonatal mortality deserve our concern in the future. MR interpretation and comparison between NICUs are important for evolution of knowledge and care of NB. Multidisciplinary morbidity and mortality meetings can enhance the multidisciplinary communication and supports NICUs to achieve and maintain high standards of care[24].

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Observations

Study presented as Oral Communication at the 49th Portuguese Congress of Neonatology, which took place on 8 and 9 April 2021.

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None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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