The Importance of Autopsy in Early Neonatal Death in Portugal

A Importância da Autópsia na Morte Neonatal Precoce em Portugal

Marlene MIRANDA✉[1], Sandra COSTA[1,2], Henrique SOARES[1,2], Joselina BARBOSA[1,3,4], Filipa FLOR-DE-LIMA[1,2], Manuela RODRIGUES[2], Hercília GUIMARÃES[1,2,4]

Acta Med Port 2020 Dec;33(12):811-818 ▪ https://doi.org/10.20344/amp.12182

ABSTRACT

Introduction: The early neonatal period is the most critical for the newborn's life. The autopsy is important to understand the cause of death, and find other diagnoses not clinically identified. However, the rate of neonatal autopsy is declining worldwide. This study aims to characterize early neonatal death and the clinical importance of the autopsy, evaluating the concordance between clinical and pathological diagnosis.

Material and Methods: Retrospective study of the clinical records of all neonates admitted to a level III Neonatal Intensive Care unit in Portugal who died during the first week of life in 10 consecutive years (2008 – 2017). In order to classify the concordance found between clinical and pathological diagnoses, the modified Goldman classification was used.

Results: During the first week of life, 76 newborns died. The main causes of death were complications related with prematurity and congenital malformations. The autopsy was performed in 50 newborns. Additional findings were found in 62% of the cases, and in 12% findings with important implications for genetic counseling of future pregnancies. There was concordance between the clinical and pathological findings in 38% of cases.

Discussion: An autopsy was performed more frequently in newborns with greater gestational age. The number of additional diagnoses found at autopsy, including diagnoses with implications for genetic counseling, confirm the importance of performing them.

Conclusion: An autopsy should be proposed to all parents after early neonatal death, given its importance in clarifying the cause of death.

Keywords: Autopsy; Causes of Death; Infant Mortality; Infant, Newborn; Neonatal Intensive Care Unit

RESUMO

Introdução: O período neonatal precoce é o mais crítico para a vida do recém-nascido. A autópsia é importante para compreender a causa de morte e conhecer outros diagnósticos não identificados clinicamente. No entanto, a taxa de autópsia neonatal está a diminuir em todo o mundo. Este estudo pretende caracterizar a morte neonatal precoce e a importância clínica da autópsia, avaliando a concordância entre o diagnóstico clínico e o anatomopatológico.

Material e Métodos: Estudo retrospetivo dos processos clínicos de todos recém-nascidos admitidos numa unidade de Cuidados Intensivos Neonatais de nível III em Portugal e que faleceram durante a primeira semana de vida em 10 anos consecutivos (2008 - 2017). Para classificar a concordância encontrada entre os diagnósticos clínicos e anatomopatológicos foi usada a classificação de Goldman modificada.

Resultados: Na primeira semana de vida faleceram 76 recém-nascidos. As principais causas de morte foram complicações relacionadas com prematuridade e anomalias congénitas. A autópsia foi realizada em 50 (65,8%) recém-nascidos. Achados adicionais foram encontrados em 62% dos casos, sendo em 12% achados com implicações importantes no aconselhamento genético de futuras gestações. A concordância entre os achados clínicos e anatomopatológicos foi de 38% dos casos.

Discussão: A autópsia foi realizada com maior frequência em recém-nascidos com maior idade gestacional. O número de diagnósticos adicionais encontrados na autópsia, incluindo diagnósticos com implicações para aconselhamento genético, confirmam a importância da sua realização.

Conclusão: A autópsia deve ser proposta a todos os pais após a morte neonatal precoce, dada a sua importância no esclarecimento da causa de morte.

Palavras-chave: Autópsia; Causas de Morte; Mortalidade Infantil; Recém-Nascido; Unidade de Cuidados Intensivos Neonatais

INTRODUCTION

Early neonatal deaths are defined as those occurring between zero and seven days of life. Globally, 36% of neonatal deaths have occurred within the first 24 hours of life and about 75% within the first week.[1,2] A clear clinical diagnosis is often challenging in neonates, as many diseases are associated with nonspecific manifestations[3] and their critical condition often does not allow the timely use of any diagnostic testing that could clarify the clinical situation.

Post-mortem examination a very relevant tool, providing a significant contribution to medical education and increased accuracy of public health statistical data,[4] allowing the identification of additional findings that were not clinically suspected and improved diagnostic accuracy.[4] The autopsy is particularly relevant for parents, as the clarification

1. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
2. Serviço de Neonatologia. Centro Materno Pediátrico. Centro Hospitalar Universitário São João. Porto. Portugal.
3. Departamento de Ciências da Saúde Pública e Forenses e Educação Médica. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
4. Unidade de Investigação e Desenvolvimento Cardiovascular. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
✉ Autor correspondente: Marlene Miranda. lmarlenemirandas@gmail.com

Recebido: 16 de abril de 2019 - Aceite: 08 de janeiro de 2020

of the cause of death may give a significant contribution to assisting in the grieving process and may provide information on conditions potentially relevant to genetic counselling for future pregnancies.[5,6] Some authors have described that more parents who have refused an autopsy have more frequently regretted their decision when compared to those who gave their consent.[5]

Although many advantages have been described in literature as regards the pathological examination, a decline in the rate of autopsies in newborns admitted to neonatal intensive care units (NICUs) has been found in different countries. This could be explained by the difficulty in addressing the parents and giving the most adequate explanation for the relevance of an autopsy. Religious or cultural beliefs, the delay in the funeral and concerns about disfigurement also contribute to the difficulty in obtaining the parents' consent.[3] The development of diagnostic techniques allowing physicians to increase diagnostic accuracy may also explain this decrease.[4,7,8]

Non-invasive assessment methods have been developed as an alternative to autopsy. Post-mortem MRI has been one of the most frequently analysed, with better parental acceptance as it is less invasive. However, the limited resolution of MRI in the detection of certain disorders must be taken into consideration.[9] A comparison between the additional findings in autopsy with the possibility of detection by MRI has shown that more than 55% of the additional findings found at autopsy would probably have not been detected with post-mortem MRI.[3] Percutaneous needle biopsy has also been studied as an alternative because it is minimally invasive and therefore more easily accepted by parents; however, a high false negative rate has been found, as many abnormalities located within the organ could have not been detected.[10]

This study aimed to identify the cause of early neonatal death and to assess the importance of autopsy, by analysing the concordance between clinical and pathological diagnosis.

MATERIAL AND METHODS

This was a retrospective study carried out at the neonatology department of the Maternal Paediatric Centre of the *Centro Hospitalar Universitário São João*, a level-III hospital. All neonates admitted between 1 January 2008 and 31 December 2017 who died between zero and seven days of life were included in the study.

A consent for autopsy is systematically obtained from the patient's next of kin. The autopsy is usually performed by an experienced perinatal pathologist, according to a pre-established protocol.

Study data were obtained from the patient and mother's clinical record, referral notes, discharge notes and autopsy reports.

The following maternal variables were analysed: age, parity, history of miscarriages, foetal and neonatal death and medical history. Neonates' variables included gestational age, age at admission and at death, gender, birth weight and obstetric history (type of delivery and obstetric complications).

The cause of death was obtained from clinical records and discharge notes and the cause of death after the autopsy was obtained by analysing the pathology reports. The cause of death was ranked according to the Wigglesworth classification,[11] which is the most widely used and used for the Portuguese national registry of perinatal mortality. According to this classification, (i) congenital malformations, (ii) conditions associated with immaturity, (iii) asphyxia conditions developing in labour and (iv) other specific conditions were included as the four leading causes of neonatal death.

Table 1 – Agreement between ante- and post-mortem diagnosis*

Class	Description
IA	Diagnosis that, had it been 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 counselling
II	Diagnosis that, had it been detected before death, would probably not have led to change in management of survival, because: **A.** No appropriate therapy was available at the time **B.** Appropriate therapy was given even though the diagnosis was unknown at the time **C.** Patient had acute cardiopulmonary arrest that was appropriately managed, but patient did not survive for definitive management **D.** Patient had 'do not resuscitate' status
III	Diagnosis that may or may not have been related to disease process and was contributory cause of death
IV	Diagnosis unrelated to outcome and may or may not have affected eventual prognosis of the patient
V	Complete concordance between diagnosis before death and findings at autopsy

*: According to the classification developed by Brodlie *et al.*[12] (modified from Goldman and Kumar)

A modified Goldman classification[12] (Table 1) was used to assess the concordance between clinical diagnoses and pathological findings, by dividing the additional autopsy findings into major diagnoses (class I and II) including those of the primary cause of death or underlying diseases, and minor diagnoses (class III and IV) including any related diagnoses, causes associated with the cause of death or other relevant conditions. Neonatal deaths were classified according to the most relevant necropsy examination finding.

Data were analysed by use of IBM Statistic SPSS, version 25 software. Variables were described with absolute and relative frequencies for categorical variables and median, 25th percentile (p25) and 75th percentile (p75) for continuous variables. Comparison between groups was performed with the use of chi-square, Fisher's exact and Mann-Whitney tests.

Logistic regression analysis was aimed at the identification of neonate characteristics and clinical factors associated to the autopsy using the backward stepwise selection technique. All variables with a significance level of $p \leq 0.2$ in the univariate analysis were considered for the final model. Continuous variables were checked for linearity by using the Box-Tidwell procedure.[13] The strength of association was assessed by odds ratio (OR), considering a 95% confidence interval (CI) and *p*-values <0.05 were considered significant.

The study was approved by the Ethics Committee for Health of the *Centro Hospitalar Universitário São João* and an informed consent has been waived for this study.

RESULTS

A total of 4,026 neonates were admitted to the department and 157 died during the study period, corresponding to a 3.9% mortality rate. Seventy-six (48.4%) died within the first seven days of life, 52 (33.1%) died between 8 and 28 days of life and 29 (18.5%) upon the neonatal period; 59.4% from the 128 (81.5%) neonatal deaths have occurred within the early neonatal period. An autopsy was performed in 50 (65.8%) of those who died within the first week of life. Annual autopsy rates ranged between 87.5% in 2011 and 37.5% in 2015.

The causes of death according to the Wigglesworth classification are shown in Table 2.

Maternal age ≤34 was found in 57 (75.0%) neonates, 46 (60.5%) were primiparous mothers and no record of a relevant medical history was found in 61 (84.7%) cases. Regarding their clinical history, four presented with chronic arterial hypertension, three with thyroid disease, one with type-2 diabetes mellitus, one with epilepsy, one with hereditary thrombophilia and one with a history of deep vein thrombosis and pulmonary thromboembolism. A history of miscarriage was documented in 12 (15.8%) cases and two (2.7%) cases had a history of foetal or neonatal death.

Seventy-four (94.7%) pregnancies were monitored and 62 (81.6%) were single. The presence of complications has been found in 50 (68.5%) cases, including prenatal diagnosis of malformations (n = 19), clinical signs of suspected chorioamnionitis (n = 12), premature or prolonged rupture of membranes (n = 10), placental abruption (n = 10), pre-eclampsia (n = 7), altered flow in the umbilical artery (n = 7),

Table 2 – Causes of death of neonates included in the study, according to the classification of Wigglesworth[11]

Classification	n (%)		n
Congenital anomalies	**28 (36.8)**	CNS disorder	**2**
		Cardiovascular disorder	**6**
		Digestive disorders	**1**
		Urinary system disorders	**2**
		Musculoskeletal disorders	**6**
		Chromosomal anomalies	**1**
		Non-chromosomal polymalformative syndrome	**3**
		Others	**7**
Immaturity or preterm birth	**33 (43.4)**	Hyaline membrane disease	**12**
		Infection	**7**
		Necrotizing enterocolitis	**4**
		CNS haemorrhage	**9**
		Others	**1**
Intrapartum asphyxia	**11 (14.5)**	Placental abruption	**4**
		Others	**7**
Other specific causes	**4 (5.3)**	CNS disorder	**1**
		Cardiovascular disorder	**1**
		Metabolic disorder	**1**
		Maternal bacterial infection	**1**

CNS: central nervous system

intrauterine growth restriction (n = 7), gestational diabetes (n = 6), cervical insufficiency (n = 5), centralisation of the foetal circulation (n = 2), threatened preterm delivery requiring inpatient management (n = 2), genital infection (n = 1), HELLP syndrome (n = 1), placenta praevia (n = 1), foetal tachycardia (n = 1), amniotic sac prolapse (n = 1) and twin growth discordance (n = 1).

As regards neonate characteristics, 41 (53.9%) were male, 47 (61.8%) were born in our hospital, 64 (84.2%) were admitted to the NICU within the first 24 hours of life and died within an average of two days of life. The median gestational age was 31 weeks and 67.1% were premature (< 37 weeks gestation). The median birth weight was 1,525 g, with 53 (69.8%) neonates weighing less than 2,500 g.

Those who underwent an autopsy were compared with those who were not and gestational age, birth weight and congenital malformations as underlying cause of death were shown in the univariate analysis as predictors of having an autopsy (Table 3). Subsequently, a multivariate analysis showed an association between gestational age and having an autopsy (Table 4), with a higher frequency of autopsy in term neonates.

Additional findings were found in 62% of the autopsies (Table 5), based on the information obtained by the modified Goldman classification.

Major findings (class I and II) were found in 46% of neonates. Eight (16%) neonates were classified as class I; the autopsy findings, if known before death, could have

Table 3 – Clinical characteristics of neonates; comparison between those who underwent autopsy *vs.* those who did not

	Total (n = 76)	**Autopsy** (n = 50)	**No autopsy** (n = 26)	***p*-value**
Age at death (days) (median; p25/p75)	2 (0/4)	1 (1/3)	3 (0/6)	0.119*
< 24 hours n (%)	21 (27.6)	12 (24.0)	9 (34.6)	0.326**
Gestational age (weeks) (median; p25/p75)	31 (26/38)	35 (28/38)	27 (25/35)	**0.004***
Gestational age (weeks) n (%)				**0.013*****
23 - 28	32 (42.1)	15 (30.0)	17 (65.4)	
29 - 36	19 (25.0)	15 (30.0)	4 (15.4)	
≥ 37	25 (32.9)	20 (40.0)	5 (19.2)	
Birth weight (g) (median; p25/p75)	1525 (765/2613)	1945 (854/2980)	870 (665/2160)	**0.011***
Birth weight (g) (n;%)				**0.031*****
< 1500	37 (48.7)	19 (38.0)	18 (69.2)	
1500 - 2499	16 (21.1)	12 (24.0)	4 (15.4)	
≥ 2500	23 (30.3)	19 (38.0)	4 (15.4)	
Type of birth				
C-section, n (%)	41 (53.9)	30 (60.0)	11 (42.3)	0.155**
APGAR score,n (%)				
1-minute < 7	55 (72.4)	34 (68.0)	21 (80.8)	0.238**
5-minute < 7	37 (48.7)	21 (42.0)	16 (61.5)	0.106**
Resuscitation, n (%)	59 (78.7)	37 (74.0)	22 (88.0)	0.235**
Oxigen, n (%)	59 (78.7)	37 (74.0)	22 (88.0)	0.235**
Endotracheal tube, n (%)	49 (65.3)	29 (58.0)	20 (80.0)	0.074**
Adrenaline, n (%)	13 (17.6)	7 (14.3)	6 (24.0)	0.342**
Mechanical ventilation at hospital admission, n (%)	67 (90.5)	42 (87.5)	25 (96.2)	0.410**
Maternal age, (years) (median; p25/p75)	31 (27/35)	32 (27/35)	30 (26/33)	0.256*
Maternal age (years), n (%)				0.300*****
≤ 34	57 (75.0)	35 (70.0)	22 (84.6)	
35 - 39	15 (19.7)	11 (22.0)	4 (15.4)	
≥ 40	4 (5.3)	4 (8.0)	0	
Causes of death, n (%)				**0.029****
Congenital anomalies	24 (31.6)	20 (40.0)	4 (15.4)	
Other causes	52 (68.4)	30 (60.0)	22 (84.6)	

p25/p75: 25th percentile /75th percentile; *: Mann-Whitney's test; **: Chi-square test; ***: Fisher's exact test

increased survival of two (4%) neonates and the autopsy has shown relevant data in six (12%) neonates for genetic counselling of future pregnancies. Fifteen (30%) neonates were classified as class II and findings found at autopsy in two neonates would probably have not changed the outcomes, because no adequate treatment was available for that clinical situation (class IIA), eight neonates were on an adequate treatment despite no diagnosis of the clinical situation had been obtained (class IIB), four neonates presented with a cardiorespiratory arrest leading to their early death leaving no time for diagnosis, despite an attempted resuscitation (class IIC) and one neonate had a clinical indication not to be resuscitated (class IID).

Minor findings (class III and IV) were found in 16% of cases. Four (8%) neonates were classified as class III and four (8%) as class IV.

There was a complete agreement between clinical and pathological diagnosis (Table 5) in 19 (38%) cases.

Pneumonia (n = 8) went most frequently undiagnosed, although all the patients were under adequate antibiotic therapy due to a suspicion of another infection.

On the other hand, hyaline membrane disease was mostly overdiagnosed and this was not confirmed by autopsy in five cases.

Neonates classified as class I and II are shown in Table 6.

DISCUSSION

Out of the 157 neonates who died during the study period, 128 (81.5%) died within the neonatal period, mostly within the early neonatal period (59.4%).

The leading cause of death was related to complications associated with prematurity [33 (43.4%) neonates]. Even though the death of premature neonates was the leading cause of neonatal death, this has declined over the past 20 years in both Europe and North America.[2]

Congenital anomalies were the cause of death in 5-38% of neonatal deaths and these were found in a 36.8% rate in our study (28 neonates). These seem to play a greater role in early neonatal mortality in developed countries, in which there has been a decrease in mortality from other causes, namely infectious, due to an improved pregnancy monitoring.[2]

Asphyxia in the perinatal period is one of the main causes of early death worldwide, accounting for 7.1% of early neonatal deaths in developed countries.[2] A higher percentage of early neonatal deaths associated with asphyxia during labour (14.5%) has been found in our study, probably due to the fact that this hospital is a referral centre for induced hypothermia.

The importance of neonatal autopsy has already been discussed and shown in some studies carried out in neonatal intensive care units from different countries, with a neonatal autopsy rate ranging from 39% to 82%.[14] However, studies evaluating only the importance of autopsy in the early neonatal period are scarce. Early neonatal deaths represent an important percentage of deaths within the neonatal period, confirming that the first week of life is the most critical for newborns.[2] Mostly preterm neonates died within the first week of life and the cause of death is frequently considered to be related to complications of prematurity, leading to the conclusion that autopsy may have been regarded as redundant.[15] However, perinatal autopsy remains as the most useful way to understand the cause and mechanisms of death, changing the clinical diagnosis in 35% to 75% of cases.[5]

In our study, a 65.8% rate of early neonatal autopsy has been found, higher than what has been found by other authors (47.9%).[15] Post-mortem examination was performed more frequently in neonates with greater gestational age. Similar results have been found in studies that also included deaths after seven days of life.[8,12,16] These may be explained by the fact that an autopsy is less encouraged in extreme prematurity.[8,15] In addition, birth weight and the presence of congenital anomalies have also been described as having an influence on the decision to obtain a neonatal autopsy. As regards birth weight, it has been described that neonatal autopsy is performed more frequently in neonates with higher birth weight.[16] Very low birth weight neonates were mostly included in those who did underwent an autopsy in our study (Table 3), in line with literature.[15] There are conflicting results in literature as regards the presence of congenital anomalies. Some authors have shown that autopsy was performed more frequently in neonates with congenital anomalies,[16] while it was performed mostly in those with no congenital anomalies, according to other authors.[8]

Table 4 – Determinants for autopsy

Variables	OR*	95% CI	*p*-value
Gestational age (weeks)			
23 - 28	-		
29 - 36	4.77	1.17 - 17.68	**0.029**
≥ 37	5.78	1.33 - 16.17	**0.016**
5-minute Apgar score < 7	3.66	0.97 - 8.28	0.056

*: Multivariate analysis by logistical regression. OR: odds ratio; CI: confidence interval

Table 5 – Distribution of autopsy findings according to the modified Goldman classification

Class		n (%)
I		8 (16)
	A	2
	B	6
II		15 (30)
	A	2
	B	8
	C	4
	D	1
III		4 (8)
IV		4 (8)
V		19 (38)

Table 6 – Description class I and II cases

	Clinical diagnosis	Post-mortem diagnosis
Class IA		
Case 1	Prematurity with growth restriction	Pericardial effusion (pre-tamponade)
Case 2	Congenital diaphragmatic hernia	Coarctation of the aorta; congenital diaphragmatic hernia
Class IB		
Case 1	Bilateral pyelo-ureteral junction syndrome	Alveolar capillary dysplasia; bilateral pneumonia; bilateral pyelo-ureteral junction syndrome
Case 2	Liver failure of unknown aetiology	Congenital haemochromatosis; bilateral congenital pneumonia
Case 3	Congenital diaphragmatic hernia	Bone findings suggestive of osteochondrodysplasia; congenital diaphragmatic hernia
Case 4	Congenital heart disease	Pulmonary lymphangiectasia; bilateral pneumonia; congenital heart disease
Case 5	Congenital chylothorax related to hydrops fetalis	Lymphatic dysplasia; congenital chylothorax
Case 6	Probable pulmonary vascular malformation associated with pulmonary hypertension	Congenital pulmonary lymphangiectasia
Class IIA		
Case 1	Congenital heart disease (probable Ebstein anomaly)	Non-Ebstein congenital heart disease; non-compacted myocardium with dysfunction of the coronary microcirculation and tricuspid valve involvement
Case 2	Probable congenital heart disease	Complex heart disease – right isomerism
Class IIB		
Case 1	Congenital diaphragmatic hernia	Congenital diaphragmatic hernia; acute right pneumonia
Case 2	Hyaline membrane disease	Polymalformative syndrome
Case 3	Perforated necrotizing enterocolitis (PNE)	PNE with septic shock and acute peritonitis with disseminated intravascular coagulation (DIC) and cerebral ischaemia; incipient meningitis; infarction
Case 4	Hyaline membrane disease	Peripartum asphyxia with placental abruption; incipient hyaline membrane disease
Case 5	Severe hyaline membrane disease	Congenital pneumonia with pulmonary immaturity; pulmonary interstitial emphysema
Case 6	Edwards´ syndrome	Edwards' syndrome; bilateral pneumonia
Case 7	Hyaline membrane disease	Bilateral pneumonia bilateral; meningitis
Case 8	Hyaline membrane disease	Necrotizing pneumonia; right pneumothorax; hyaline membrane disease
Class IIC		
Case 1	Probable congenital heart disease	Congenital heart disease – complete transposition of great vessels
Case 2	Hyaline membrane disease	Interstitial pneumonitis with pulmonary hypoplasia and multifocal relative immaturity
Case 3	Disseminated intravascular coagulation (DIC)	Paravertebral congenital neoplasm (probable neuroblastoma); DIC
Case 4	Severe blood dyscrasia	Congenital neuroblastoma with liver metastases
Class IID		
Case 1	Meconium aspiration syndrome with refractory severe pulmonary hypertension; early neonatal sepsis. 'Do not resuscitate' clinical indication	Neonatal sepsis; bilateral pneumonia; acute encephalitis; pneumothorax

An autopsy was performed more frequently in neonates in whom the cause of death was associated with congenital anomalies, even though this was not significant in the multivariate analysis. Congenital anomalies are understood as clear manifestations of diseases that may be the cause of death and an autopsy may be less encouraged in this case.[8] However, even with clinically diagnosed congenital anomalies, the autopsy is very useful, improving the accuracy of clinical diagnosis.[3]

Additional autopsy findings (class I-IV) were found in 62% of the cases, in which 46% were major findings and 16% were minor findings. Had they been known before, they would probably have led to different outcomes in 4% of the cases (class IA). The autopsy findings were relevant for

genetic counselling of future pregnancies (class IB) in 12% of the cases, enhancing their importance.

Pneumonia was most frequently found in post-mortem examination, in line with other studies.[4,7]

Overdiagnosed hyaline membrane disease has also been found in five cases; the autopsy did not show any findings consistent with this clinical condition. However, all patients were treated with exogenous surfactant, which could explain its absence.

Similar results to those of this study were found by a previous study carried out in our NICU in 2010 and aimed to assess the agreement between ante- and post-mortem diagnosis in all neonates admitted to the unit, by using the same modified Goldman classification, showing a 66% rate of additional findings (53% major findings and 13% minor findings) and the presence of relevant information for genetic counselling in 9.4% of the cases.[4]

Six studies on the presence of diagnostic errors in neonatal intensive care units from different countries, according to Goldman's classification, were analysed by the systematic review by Custer *et al.*[14] Additional major findings were found in 19.2% of the cases (class I, 3.7%; class II, 15.5%). Class III findings were only described in five publications and were found in 37.2% of the cases. Class IV diagnoses were only described by three studies and these were found in 15.6% of the cases. A higher rate (46%) of major findings has been found in our study. This may be explained by the fact that neonatal deaths beyond seven days of life were included in this systematic review, with a higher probability of having a more accurate clinical picture, compared to those who died within the first week of life, although this fact did not occur when comparing our study with the one carried out in the same institution in 2010.[4] The subjectivity of the classification of cases according to Goldman's classification is a possibility that we cannot exclude. A lower rate of minor findings has been found in our study (class III - 8% and class IV - 8%). This may be explained by the fact that multiple findings were described per patient and the same case was included in different classes by some studies included in the review, leading to a slightly higher rate. In addition, it has been described that minor findings are more frequently found in neonates who died later.[3] Only early neonatal deaths were included in this study and this may have explained the lower number of minor findings.

An autopsy is particularly important in the neonatal period because, in addition to providing objective information about the cause of death, it allows the detection of important conditions for genetic counselling of future pregnancies.[6] In this study, the autopsy has shown relevant data for genetic counselling in 12% of the cases. Rates ranging between 2.4 and 26% have been found in other studies, while a 9.4% rate has been found in the previous study carried out in our NICU.[4,6,12] These results further enhance the importance of the autopsy within the early neonatal period.

This study has some limitations, including its retrospective design, with a small sample size and based on a single centre, reducing the ability to generalize from its results. Selection bias cannot be overlooked, since a consent for autopsy was more easily obtained from parents of neonates with unclear diagnosis.

The strengths of this study included the fact that it was carried out at a neonatology department of a level III hospital, which it is a referral centre for neonatal cardiac, surgical and neurological pathology and with a high autopsy rate (65.8%).

The rate of additional diagnoses found in recent studies and in the present study show that, despite the improvement in diagnostic testing in recent years, autopsy is still crucial to clarify the cause of death and to show other conditions that were not previously diagnosed, even in the presence of obvious cause-of-death factors, such as extreme prematurity or the presence of congenital anomalies. Since it is not possible to predict in which cases relevant data would have been obtained from an autopsy,[8] this should be proposed to parents after an early neonatal death.

CONCLUSION

Autopsy findings are crucial in clarifying the causes of early neonatal death, even in cases where the causes of death are explained by clinical diagnosis. The additional findings obtained in post-mortem examination are crucial for an accurate diagnosis and often allow genetic counselling. Therefore, an autopsy should be proposed to parents after an early neonatal death, explaining its importance and stressing how it may be relevant for future pregnancies.

HUMAN AND ANIMAL PROTECTION

The authors declare that this project complied with the regulations that were established by the Ethics and Clinical Research Committee, according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

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

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

FINANCIAL SUPPORT

The authors declare that there was no public or private financial support in writing this manuscript.

REFERENCES

1. UNIGME. Levels & trends in child mortality: report 2018, estimates developed by the United Nations Inter-agency Group for Child Mortality Estimation. New York: UNICEF; 2018.
2. Lehtonen L, Gimeno A, Parra-Llorca A, Vento M. Early neonatal death: a challenge worldwide. Semin Fetal Neonatal Med. 2017;22:153-60.
3. de Sevaux JLH, Nikkels PGJ, Lequin MH, Groenendaal F. The Value of Autopsy in Neonates in the 21st Century. Neonatology. 2019;115:89-93.
4. Costa S, Rodrigues M, Centeno MJ, Martins A, Vilan A, Brandão O, et

al. Diagnosis and cause of death in a neonatal intensive care unit--how important is autopsy? J Matern Fetal Neonatal Med. 2011;24:760-3.
5. Judge-Kronis L, Hutchinson JC, Sebire NJ, Arthurs OJ. Consent for paediatric and perinatal postmortem investigations: implications of less invasive autopsy. J Forensic Radiol Imaging. 2016;4:7-11.
6. Tamanaha F, Fuksman R, Pedraza A, Prudent L. What is the value of neonatal autopsy? Pathological and clinical correlation in 135 cases. Arch Argent Pediatr. 2017;115:490-2.
7. Feria-Kaiser C, Furuya ME, Vargas MH, Rodriguez A, Cantu MA. Main diagnosis and cause of death in a neonatal intensive care unit: do clinicians and pathologists agree? Acta Paediatr. 2002;91:453-8.
8. Swinton CH, Weiner J, Okah FA. The neonatal autopsy: can it be revived? Am J Perinatol. 2013;30:739-44.
9. Leadbetter KZ, Vesoulis ZA, White FV, Schmidt RE, Khanna G, Shimony JS, et al. The role of post-mortem MRI in the neonatal intensive care unit. J Perinatol. 2017;37:98-103.
10. Celiloglu OS, Celiloglu C, Kurnaz E, Ozdemir R, Karadag A. Diagnostic contribution of postmortem needle biopsies in neonates. Turk Patoloji Derg. 2013;29:122-6.
11. Wigglesworth JS. Monitoring perinatal mortality. A pathophysiological approach. Lancet. 1980;2:684-6.
12. Brodlie M, Laing IA, Keeling JW, McKenzie KJ. Ten years of neonatal autopsies in tertiary referral centre: retrospective study. BMJ. 2002;324:761-3.
13. Hosmer D, Lemeshow S. Regressão logística aplicada. 2ª ed. Nova Iorque: JohnWiley & Sons; 2000.
14. Custer JW, Winters BD, Goode V, Robinson KA, Yang T, Pronovost PJ, et al. Diagnostic errors in the pediatric and neonatal ICU: a systematic review. Pediatr Crit Care Med. 2015;16:29-36.
15. Bishop KL, Dupuis C, Nanton P, Clarke K, Bolt C, Chin-See C. Perinatal autopsy rates at the University Hospital of the West Indies: 2002-2008. West Indian Med J. 2013;62:35-8.
16. Pavon Delgado A, Salinas Martin MV, Losada Martinez A, Fontillon-Alberdi M, Nunez Solis JM, Zamarriego Zubizarreta C. Valor de la autopsia en una unidad de cuidados intensivos neonatológicos. An Pediatr. 2008;69:124-8.