End-of-life decisions in neonates and infants

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End-of-life decisions in neonates and infants: a nationwide mortality follow-back survey

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Summary box

What is already known?

- Deaths of infants are often preceded by possibly life-shortening end-of-life decisions such as withholding or withdrawing treatment or administering medication.
- The only available trend data worldwide is from the Netherlands and dates back almost a decade and indicates important shifts.

What are the new findings?

- Our nationwide evaluation of the prevalence of neonatal end-of-life decisions in Belgium in 1999-2000 and 2016-2017 showed that the prevalence of end-of-life decisions remained stable at 60%, with non-treatment decisions occurring in about 35% of all deaths.
- A non-negligible group of 7% of neonate and infant deaths at timepoint 1 and 10% at timepoint 2 was preceded by a decision to administer medication with an explicit life-shortening intention, which is clinically significant as it was contrary to both the expectations of consulted experts and the decreasing trend figures from the Netherlands.

What is their significance?

- Our findings call for an open multidisciplinary debate including for example nursing staff and family members, based on clinical as well as ethical and juridical reflections from different jurisdictions, and to discuss the need for international guidelines.

Abstract

Objectives: Neonatology has undergone important clinical and legal changes, however, the implications for end-of-life decision-making in seriously ill neonates to date are unknown. Our aim was to examine changes in prevalence and characteristics of end-of-life decisions in neonatology.

Methods: We performed a nationwide mortality follow-back survey in August 1999 to July 2000 and September 2016 to December 2017 in Flanders, Belgium. Data were linked to information from death certificates. For each death under the age of one, physicians were asked to complete an anonymous questionnaire about which end-of-life decisions were made preceding death.

Results: The response rate was 87% in 1999-2000 (253/292) and 83% in 2016-2017 (229/276). The proportion of deaths of infants born before 26 weeks' gestation increased (14% vs 34%, p=0.001). Prevalence of ELDs remained stable at 60%, with non-treatment decisions occurring in about 35% of all deaths. Use of medication with an explicit life-shortening intention was prevalent in 7-10% of all deaths. In early neonatal death (< 7 days old) medication with an explicit life-shortening intention decreased from 12% to 6%, in late neonatal death (7-27 days old) it increased from 0% to 26%, and in post neonatal death (>27 days old) it increased from 2% to 10%.

Conclusions: Over a timespan of 17-year the prevalence of neonatal end-of-life decisions has remained stable. A substantial number of deaths was preceded by the intentionally hastening of death by administrating medication. While surveying solely the physician perspective in this paper, there is a need for an open multidisciplinary debate including for example nursing staff and family members, based on clinical as well as ethical and jurisdictional reflections to discuss the need for international guidelines.

Introduction

Despite a rise in prenatal diagnostic procedures and neonatal interventions[1,2], about one in 100 live-born children in developed countries dies before the age of one[3,4]. Many of these deaths are preceded by a possibly life-shortening end-of-life decision (ELD)[5–9], including non-treatment decisions or administering pain and/or symptom relief medication[7,10]. Such medical decisions can be made taking the potentially life-shortening effect into account, co-intending the life-shortening effect without it being the main goal of the treatment, or explicitly intending to shorten the life of the infant[7,10].

As medical practice continued to evolve and new and improved treatment options have become available, changes in treatment have occurred, for example an increase in "active" treatment for extreme premature babies[11]. Such changes can lead to discussions about the usefulness of continuing therapies or ELD making, suggesting new information is required. Previous research is both outdated and usually has as an important limitation that the physician was often the unit of analysis and not the decedent, meaning that reliable estimates of ELDs were impossible[5–9,12–16]. Case-based studies are required with the total population of neonatal deaths as denominator. The only reliable trend figures available are from death certificate studies in 1995, 2001, 2005 and 2010[13] in the Netherlands, indicating an increase in the prevalence of non-treatment decisions and a decrease in the prevalence of drug administration with explicit life-shortening intention[13]. However, as these results come from the only country in the world in which intentionally hastening death in neonates with a severe condition under strict guidelines[17] are legally regulated via the Groningen protocol, we think that these findings are not valid for jurisdictions without such a legal regulation. Therefore, an evaluation of changes in prevalence of ELDs in neonatology in different jurisdictions is warranted.

We address following research questions: 1) to what extent has the prevalence of different ELDs in neonates changed over time 2) have the underlying reasons for the ELD changed over time and 3) have the socio-demographic and clinical profiles of infants whose death was preceded by these ELDs changed over time.

Methods

Design, setting and participants

We conducted a nationwide mortality follow-back survey based on a cohort of all infants under the age of one residing in Flanders who died between August 1999 and July 2000[7] (timepoint 1) and September 2016 and December 2017 (timepoint 2). Flanders is one of the three semi-autonomous regions of Belgium with autonomy over the quality of health care. We included only deaths of Flemish residents to provide prevalence rates in a set population within 1 semi-autonomous region. The design of both studies was identical. The longer inclusion period in timepoint 2 was specifically chosen to ascertain a population large enough to ensure significant power to provide reliable trend analysis, based on information from the central administration authority[18].

All deaths were processed by the central administration authority (the Flemish Agency for Care and Health). All cases were identified through the death certificates signed within the inclusion period. The physician fills out the main part of the certificate, indicating demographic information and clinical information e.g. cause of death[10]. For each death, within four months of its occurrence the attending physician was asked to complete a questionnaire. A robust method was implemented using a trusted third party as intermediary to ensure data protection and reidentification risk[10]. The Total Design Method was followed, including a maximum of three follow-up postal mailings[19].The study design, mailing and anonymity procedure are described elsewhere[10] (Appendix 1). STROBE guidelines were used for reporting (Appendix 2).

Questionnaire and variables

The questionnaires at timepoint 1 and timepoint 2 included questions about which ELDs were made, the accompanying decision-making process, the involvement of parents in this process, the involvement of colleagues and experts, and the ELD policy of the hospital. Questions on which decisions were made were identical to ensure comparability. On other aspects both questionnaires varied, as terminology and grammar was updated, term ambiguity and length of the questionnaire were reduced, and additional cognitive testing took place[10]. A Dutch version of questions used in this publication was added in Appendix 3.

Both questionnaires, at timepoint 1[7] and at timepoint 2, first asked whether death had been sudden and unexpected; if not, an ELD was considered possible and physicians were asked whether they had:

1. withheld or withdrawn life-prolonging medical treatment taking into account or explicitly intending hastening death
2. intensified administration of medication, taking into account or co-intending hastening the death or
3. prescribed, supplied or administered medication with the explicit intention of hastening death.

When more than one ELD was noted, that with the most explicit life-shortening intention was deemed most important and used for analysis; if more than one ELD with the same life-shortening intention was noted, administration of drugs ('active') prevailed over withholding or withdrawing treatment ('passive'). Also the most important reason for the ELD was asked. For a detailed description of the ELD categories and examples of which medical decisions could be included in each category, we refer to the published study protocol of this study[10].

The demographic and clinical patient data (place of death, sex, age at death, gestational age at birth and cause of death) were obtained from the death certificates. We used a deterministic linkage procedure to link death certificate with questionnaire data, and small cells analysis to ensure that linked death certificate data would prevent reidentification.

A clinically relevant categorization for the cause of death was developed to achieve homogenous groups with a similar cause of death. This categorization (box 1) was evaluated, in terms of completeness to classify all possible causes of death and clarity of descriptions, by four physicians working in neonatal and prenatal care. Cases were sorted into one of the categories by a FC and LDm based on the underlying cause of death (ICD-10 codes) on the death certificate. When main cause of death was inconclusive, ICD-10 codes of other associated causes of death were taken into account.

Statistical analysis

To examine non-response bias demographic variables were compared by means of chi-square tests, Fisher's exact tests or Kruskal Wallis tests. To compare changes over time in the prevalence of different types of ELDs and the socio-demographic and clinical characteristics (sex, age at death, gestational age at birth, and cause of death) associated with different types of ELDs Chi-square tests and two-tailed Fisher's exact tests were used. Multivariable binary logistic regression was performed with ELD (yes/no) as dependent variable, and study period, age at death, gestational age at birth and cause of death as independent variable to account for possible confounding of the demographical variables. Additionally, a multivariable binary logistic regression model with these main effects and the interaction effects of these with the study period was performed to examine shifts in prevalence of an ELD in certain demographical groups over both periods, controlling for confounding of study period, age at death, gestational age at birth and cause of death. Multivariable analysis for the separate types of ELDs were not made due to small sample sizes.

Results

We received 253 questionnaires for 292 deaths at timepoint 1 (87% response rate) and 229 completed questionnaires for 276 deaths at timepoint 2 (83% response rate). No significant differences in demographic characteristics between deaths with and without a response was found (Appendix 4), therefore weighing of results was not necessary.

The cohorts in both timepoints were similar in terms of place of death (respectively 89% vs 92% in hospital), age at death (50% vs 55% in the first seven days of life) and sex (Table 1). Statistically significant differences between both cohorts were found for gestational age (proportion of infant decedents born before 26 weeks of gestation was lower at timepoint 1 [14%] than at timepoint 2 [34%] than; p-value= 0.001) and cause of death (lower proportion of complications of pregnancy with [17 to 12%] and without repercussions for the foetus [15 to 8%], more 'other' causes of death [16 to 7%] at timepoint 1 than timepoint 2; p-value = 0.01).

No statistically significant differences in prevalence of types of ELDs were found between the timepoints in univariable and multivariable analyses (Table 2). An ELD was made in 57% at timepoint 1 and in 61% at timepoint 2. The most common ELD was a non-treatment decision (34% at timepoint 1 and 37% at timepoint 2). Administration of medication taking into account a possible life-shortening effect was intensified in 16% at timepoint 1 and 14% of deaths at timepoint 2. Medication with an explicit intention to shorten life was administered in 7% (17 cases) at timepoint 1 and 10% (24 cases) at timepoint 2. At timepoint 1 opioids were used in 14 cases; in five a muscle relaxant was administered in association. In three cases, potassium chloride was used. At timepoint 2, opioids were used in 20 cases, in 11 of those an additional sedative (barbiturates or benzodiazepines) and in four an additional muscle relaxant. In two cases a sedative only was given and in one a muscle relaxant only (not in table, type of drug info was missing for one case in 2016-2017).

Significant and substantial changes occurred within subpopulations depending on age at death (Table 3). At timepoint 2 ELDs were made significantly less often than at timepoint 1 in infants under the age of seven days (p-value = 0.01; 72% vs 55%). In those who died between seven and 27 days and those over 27 days, ELDs were made significantly more often at timepoint 2 than at timepoint 1 (50% vs 74% and 38% vs 64% respectively, p-values = 0.03 and 0.003). The increase can mostly be seen in those who died after withdrawal of treatment (9% vs 26% between 7-27 days and 16% vs 31% over 27 days old) and those who received intensified administration of medication with an explicit life-shortening intention (0% vs 26% between 7-27 days and 2% vs 10% over 27 days). The statistically significant differences between the two study periods in the prevalence of ELDs depending on the age of the infant were confirmed when controlling for possible confounding in the multivariable binary logistic regression (data not shown).

Univariate analysis revealed that, in infants born at full term (>37 weeks of gestation), the decision to withdraw treatment was made more often at timepoint 2 (34%) than at timepoint 1 (20%, p-value = 0.04) (table 3). No other differences in sociodemographic or clinical patterns for the specific ELDs were observed between cohorts.

In 60% of all ELD cases at timepoint 2, ‘no real chance of survival’ was indicated and in 50% ‘no hope of a bearable future’ (only available for timepoint 2, not in table). Where treatment was withheld or withdrawn, or medication without an explicit life-shortening intention was given, the main reason given was ‘no real chance of survival’ (62%, 76% and 62% respectively). Where medication was administered with an explicit life-shortening intention, the main reason was ‘no hope of a bearable future’ (91%).

Discussion

This nationwide mortality follow-back survey on end-of-life decisions in neonates and infants indicates that, when comparing a cohort of all infant decedents under the age of one between August 1999 and July 2000 and September 2016 and December 2017, modest changes occur in the prevalence of end-of-life decisions on population level, however, substantial changes occur within the subpopulations of age groups. Deaths preceded by an ELD remained at about 60%, with non-treatment decisions being about 35%. ELDs taken decreased in early neonatal deaths but increased in late and post neonatal deaths. In both study timepoints a non-negligible group of deaths was preceded by a decision to intentionally hasten death by administrating medication (7% in 1999-2000, 10% in 2016-2017).

We found a non-negligible proportion of infants who died after administration of medication with an explicit life-shortening intent, namely 7% of all deaths 17 years ago and 10% now. This result contrasts sharply with the decrease in the use of medication with explicit life-shortening intention which was seen in the Netherlands from 8% of all neonatal deaths in 2005 to 1% in 2010[13]. In the Netherlands, intentionally hastening death in extremely ill neonates is not prosecuted under strict guidelines in the Groningen protocol[17]. Evaluation of whether all due care criteria were applied in a specific case happens retrospectively, after which a decision is made whether or not a prosecution is warranted[17]. In Belgium such a protective framework is lacking and intentionally hastening death by means of medication is thus not legally permissible. Possibly, the Groningen protocol, by setting up specific and detailed rules and procedures, has discouraged physicians in the Netherlands from engaging in practices to intentionally hasten death. Alternatively, it might have led to a different understanding of what constitutes death-hastening medical interventions with and explicit life-shortening intention in extreme cases and administering medication taking into account a possible life-shortening effect in other cases. Evaluation of this practice of end-of-life care in other jurisdictions seems indicated, as it may provide input for a societal debate about the need for revised guidelines, protocols or laws to shape end-of-life practice in neonatal and infant care and about the need for further research and evaluation to monitor and understand these decisions.

Increased doses of sedatives and opioids were reported in the majority of cases where medication with an explicit life-shortening intention was administered. We can presume that this medication was administered to relieve the suffering of the neonates and infants for whom there was no hope of a bearable future or those who would not survive without life sustaining interventions, even when death was hereby hastened. This clinical practice fits within a palliative care context and decisions are probably made in the best interest of the child. It should be noted that the prevalence of administering medication with an explicit life-shortening intention in Flanders is considerably higher in neonates and infants (10%) as compared to minors (8%)[20] and adults (6%, including euthanasia)[21], raising the question of whether this practice needs to be subject of more monitoring and evaluation in neonatology.

We found increased amounts of ELDs in late and post neonatal deaths compared to 1999/2000. There is an increased availability of improved medical treatments[2] since that time, such as amongst others increased use of antenatal corticosteroid- and postnatal surfactant administration[2], lung-protective ventilation strategies (CPAP)[2] and hypothermia treatment for neonatal encephalopathy[22], leading to lower annual infant mortality rates in Flanders in 2016-2017 compared to 1999-2000[3,23]. This increased availability of treatment options might have led to more active initial therapeutic approaches in severely ill neonates, who previously would have died shortly after birth without initiation and hence also withdrawal of these treatments.

The decrease of the use of ELDs in the first week of life can possibly be related to the noticeable change in the population of neonatal deaths with a larger proportion of decedents now being extremely premature (<26 weeks of gestation). In contrast with 17 years ago, intensive care is now systematically offered to infants born at 24 weeks' gestation in Flanders[24]. Mortality in these extremely premature infants is still high, however[25], and they often die during the first week of life despite active treatment, without an ELD. In future research on end-of-life decisions in neonates, ample attention to extremely premature infants should therefore be given.

Despite changes in the prevalence of ELDs in specific age groups, the overall prevalence of ELDs stays relatively stable at about 60% of all neonatal deaths in Flanders, which is similar to that in the Netherlands (63%)[13]. Similarly, the proportion of ELDs is higher in neonates than in children aged one to 17 years (36%)[20] and adults (48%)[21]. This is not surprising since deaths occurring in adults and minors are more often sudden and unexpected, such as accidents or trauma, making ELDs impossible. The most prevalent neonatal ELDs are non-treatment decisions (35%), specifically withdrawing of life-prolonging treatment, which occurs in about one in four cases, a prevalence estimate comparable with non-population-based studies across Europe[6,14–16].

Conclusion

In conclusion, our nationwide surveys on ELDs showed that the proportion of infant deaths preceded by an ELD has remained relatively stable at about three in five, confirming that non-treatment decisions as well as intentionally hastening death by means of medication continue to be an integral part of medical practice in severely ill neonates in Flanders, Belgium. Our observed trend differs from those in the Netherlands, the only other country with reliable population-based prevalence rates. It could be questioned whether the prevalence of ELDs in the rest of the world are following the Belgian or the Dutch outcome. For Belgium neonatology practice, it should be debated whether guidelines or protocols should facilitate and improve the guidance of neonatologists and parents in taking end-of-life decisions for these extremely ill newborns and infants.

Strengths and limitations of the study

We achieved high response rates (83% and 87%) by using a design with a rigorous procedure, making conclusions valid for the entire population of deceased infants under the age of one irrespective of care setting or diagnosis. The questionnaire was developed based on existing questionnaires on ELDs in neonates[7,13], minors[20] and adults[26,27], ensuring comparability over time, settings, countries and age groups. Socially desirable answers or unwillingness to participate were reduced by ensuring anonymity. Recall and memory bias cannot be excluded since questionnaires were filled out up to four months after death. A questionnaire with closed multiple-choice answers is less suitable for in-depth study of the decision-making process, as it fails to reflect the depth and reasoning behind a decision. Although other actors in the decision-making process such as parents or nurses can provide useful information, we deemed the physician perspective as most important to report on the medical decisions made. However, our method is deemed the best method to study ELDs on a population level.

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Transparency: LD affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: Due to privacy issues our data cannot be made openly accessible.

Authors' contributions: All listed authors contributed to the writing and/or revision of the article and approved the final version of the manuscript.

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Box 1: Cause of death categories in neonatology

The following cause of death categories were identified:

- Prematurity and related disorders: Death due to a direct cause of prematurity, immaturity or disorders related to prematurity. For example, necrotizing enterocolitis, intraventricular hemorrhage, respiratory distress syndrome, or death due to (extremely) low birth weight or low gestational age.
- Congenital anomalies - singular: Death due to a single congenital anomaly with a defect in one organ or organ system. For example, a congenital malformation of the heart or a spina bifida.
- Congenital anomalies - multiple or systemic disorders: Death due to the presence of multiple congenital anomalies in different organ systems, or due to a disorder that affects multiple organ systems. For example, chromosomal disorders, multiple congenital malformations diagnosed in one infant, or an inborn error of metabolism.
- Complications of pregnancy with repercussions on foetal growth or development: Infant died due to complications of pregnancy that had an influence on the growth or the health of the baby prenatally. For example, a cytomegalovirus infection with congenital infection of the foetus, or pre-eclampsia with severe intrauterine growth restriction.
- Acute complications of pregnancy and/or birth in a previously healthy foetus. For example, a placental abruption or birth trauma causing oxygen deprivation.
- Disorders acquired after birth: Death due to a non-congenital disorder, acquired after birth of a previously healthy baby. For example, infectious diseases resulting in multiple organ failure.
- Other: Cause of death was sudden, without previous diagnoses. Examples are sudden infant death syndrome, accidents or trauma.

Table 1: demographic and clinical characteristics of deceased neonates and infants in 1999-2000 and 2016-2017

	1999-2000 12 months		**2016-2017** 16 months		
All infant and neonatal deaths in study period	293		276		
All infant and neonatal deaths for which a response was received (response percentage)	253 (86%)		229 (83%)		
	N	**%**	**N**	**%**	**P-value**
Place of death[a]					0.34[a]
Hospital	225	89	210	92	
NICU		N/A	115	50	
Other hospital ward		N/A	95	41	
Home	18	7	15	7	
Other	10	4	4	2	
Age at death[b]					0.11
Early neonatal death (<7 days)	127	50	125	55	
Late neonatal death (7-27 days)	34	13	43	19	
Post neonatal death (>27 days)	92	36	61	27	
Sex[c]					0.46
Male	147	58	135	59	
Female	106	42	94	41	
Gestational age at birth[b]					0.001
< 26 weeks	36	14	72	34	
26-28 weeks	38	15	28	13	
29-31 weeks	19	8	10	5	
32-36 weeks	57	23	25	12	
≥ 37 weeks	101	40	76	36	

Cause of death[d, e]					0.01
Prematurity and related disorders	47	19	47	21	
Congenital anomalies singular	39	16	38	17	
Congenital anomalies multiple or systemic disorders	48	19	34	15	
Complications of the pregnancy with repercussions on foetal growth or development	30	12	40	17	
Acute complications of pregnancy and/or birth in a previously healthy foetus	20	8	34	15	
Disorders acquired after birth	26	10	19	8	
Other	41	16	17	7	

Percentages are column percentages calculated with all cases for which a response was received as the denominator. Missing values were limited: dataset of 1999-2000: gestational age, n=2 (0.8%), cause of death, n=2 (0.8%). Dataset 2016-2017: gestational age, n=18 (7.9%). Percentages were calculated without these missing cases.

[a] Differentiation between NICU and other hospital wards was only possible in the 2016-2017 dataset. Chi-square analysis were performed with three categories (hospital, home, other).

[b] Kruskal Wallis tests were used to compare differences for age at death and gestational age at birth between both time periods

[c] Two-tailed Fisher's exact tests were used to compare differences in sex between time periods.

[d] Pearson Chi-square tests were used to compare differences in cause of death between time periods.

[e] See box 1 for description of the cause of death categories

N/A: not asked.

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Table 2: Prevalence of end-of-life decisions (ELDs) in neonatology in Flanders, Belgium in 2016-2017 vs 1999-2000

	1999-2000 (12 months) n= 253[b]		2016-2017 (16 months) n= 229[b]		p-value[a]
	N	%	N	%	
No ELD possible (death entirely sudden and unexpected)	59	23	46	20	0.23
ELD possible, but not made (death non-sudden)	51	20	43	19	0.73
ELD made	143	57	140	61	0.31
Non-treatment decision	86	34	85	37	0.51
Withholding treatment	32	13	27	12	0.78
Withdrawing treatment	54	21	58	25	0.33
Use of drugs	57	23	55	24	0.75
Medication with hastening death taken into account or co-intended	40	16	31	14	0.52
Medication with an explicit intention to hasten death	17	7	24	10	0.15

When more than one ELD was noted by physicians, only the most important decision was used. The most important decision is the decision with the most explicit life-shortening intention. When more than one ELD with the same life-shortening intention was noted, administration of drugs (active) prevailed over withholding or withdrawing treatment (passive).

[a] Fisher's exact test: independent variable = study period, dependent variable = ELD type present yes/no.

[b] Column percentages: percentage of cases in that study period with that type of ELD category.

Table 3: ELD prevalence in different patient groups by sociodemographic and clinical characteristics over time; 1999-2000 versus 2016-2017

	Any ELD[a]			Non-treatment decision[a]						Use of drugs[a]					
				Withholding			Withdrawing			Medication with a potentially life-shortening effect			Medication with explicit intention to hasten death		
	1999-2000	2016-2017	p-value[b]	1999-2000	2016-2017	p-value[b]	1999-2000	2016-2017	p-value[b]	1999-2000	2016-2017	p-value[b]	1999-2000	2016-2017	P-value[b]
Sex															
Male	58%	64%	0.33	14%	13%	0.86	20%	26%	0.32	16%	13%	0.40	7%	12%	0.15
Female	55%	57%	0.78	10%	10%	0.99	23%	24%	0.87	15%	15%	0.99	7%	9%	0.79
Age at death															
Early neonatal death (<7 days)	72%	55%	0.01	18%	18%	0.99	28%	22%	0.31	13%	10%	0.43	12%	6%	0.12
Late neonatal death (7-27 days)	50%	74%	0.03	15%	2%	0.08	9%	26%	0.08	26%	21%	0.60	0%	26%	N/A
Post neonatal death (>27 days)	38%	64%	0.003	4%	7%	0.71	16%	31%	0.05	15%	16%	0.99	2%	10%	0.06
Gestational age at birth															
< 26 weeks	61%	57%	0.84	25%	19%	0.62	11%	18%	0.41	17%	10%	0.35	8%	10%	0.99
26-28 weeks	74%	71%	0.99	16%	11%	0.72	29%	21%	0.58	18%	21%	0.77	11%	18%	0.48
29-31 weeks	68%	80%	0.67	16%	0%	N/A	11%	30%	0.31	21%	30%	0.66	21%	20%	0.99
32-36 weeks	49%	56%	0.64	9%	8%	0.99	28%	32%	0.79	11%	4%	0.43	2%	12%	0.08

≥ 37 weeks	51%	64%	0.07	9%	7%	0.78	20%	34%	0.04	17%	14%	0.84	5%	9%	0.37
Cause of death															
Prematurity and related disorders	64%	60%	0.83	15%	11%	0.76	23%	23%	0.99	15%	17%	0.99	11%	9%	0.99
Congenital anomalies singular	72%	74%	0.99	18%	16%	0.99	23%	34%	0.32	23%	16%	0.57	8%	8%	0.99
Congenital anomalies multiple	75%	71%	0.80	25%	12%	0.17	27%	29%	0.99	15%	21%	0.56	8%	9%	0.99
Complications of the pregnancy with repercussions for the foetus	67%	68%	0.99	13%	23%	0.37	17%	20%	0.77	30%	10%	0.06	7%	15%	0.45
Acute complications of the pregnancy and/or birth in a healthy foetus	75%	56%	0.24	10%	6%	0.62	30%	32%	0.99	30%	9%	0.06	5%	9%	0.99
Disorders acquired after birth	38%	63%	0.14	0%	5%	N/A	27%	16%	0.48	8%	16%	0.64	4%	26%	0.07
Other	10%	12%	0.99	0%	0%	N/A	7%	12%	0.62	0%	0%	N/A	2%	0%	N/A

Data was analyzed by means of individual chi-square tests for each demographic characteristic (example all females) with study period as independent variable and the prevalence of the type of ELD (any ELD, withholding treatment, withdrawing treatment, medication with a potentially life-shortening effect and medication with an explicit life-shortening effect) as dependent variable.

[a] Row percentages. Percentage of infants with that sociodemographic or clinical characteristic that received that type of ELD within each study period. Example: percentage of male infants in 1999-2000 that died with any ELD.

[b] P-values represent the significance of difference of the Chi-square test. When significant, the percentage of cases with that clinical or sociodemographic characteristic (ex. Male) is significantly different in that category of ELD (including no ELD) in 1999-2000 compared to 2016-2017.

Missing values in gestational age: 2 cases in 1999-2000 and 18 cases in 2016-2017. Missing values in cause of death: 2 cases in 1999-2000.

N/A: not applicable, one of the cells in the comparison was equal to zero.