Neonatal Mortality, Trends, and Risk Factors in a Tertiary Israeli Neonatal Intensive Care Unit: A 13-Year Retrospective Analysis

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ABSTRACT **Background:** This study provides valuable insight on the importance of antenatal follow-up, despite advances in medical capabilities.

Objectives: To provide current information on mortality rates and causes including demographic parameters.

Methods: A total of 3362 infants were admitted to the neonatal intensive care unit at Kaplan Medical Center between 2009 and 2021. Retrospective data were extracted from a computerized prospective database and further divided to two groups: 2009–2014 and 2015–2021. For sequential variables, we calculated the mean, standard deviation, and median. For categorical variables we calculated the prevalence and performed a chi-square test. The sequential variables did not show a normal distribution according to the Shapiro-Wilk test. Therefore, the A-parameter Mann-Whitney test was used. Results were considered significant when the *P*-value < 0.05.

Results: A decrease in the death rate was found, but when evaluating the infants who died, a decrease in full antenatal follow-up from 55.2% to 31.5% was seen (*P*-value = 0.06).

Conclusions: Despite advancements in medical knowledge and capabilities, an association was found between increased mortality and reduced antenatal follow-up.

IMAJ 2026; 28: 226–231

KEY WORDS: death rate, demographics, infant, mortality, neonatal

Live births resulting in death within the first year of life are defined as infant deaths. These deaths are characterized as neonatal (< 28 days) and further subdivided into early neonatal (< 7 days), late neonatal (7–27 days), or postneonatal (28–364 days) [1]. Mortality rates in the neonatal intensive care unit (NICU) represent the number of neonates who have died within the NICU at admittance.

According to the World Health Organization (WHO), 2.3 million newborns died in 2022 and nearly half (47%) of all deaths in children under 5 years of age occurred in the newborn period (the first 28 days of life). Neonatal mortality rates differ between countries, with the most significant difference being between developed and developing countries [2]. The mortality rate in Israel during 2021 was 2.8 deaths per 1000 live births [3,4].

According to the WHO, premature birth, birth complications (birth asphyxia/trauma), neonatal infections, and congenital anomalies remain the leading causes of neonatal deaths [2]. Prematurity as a cause of death is not informative enough when reported as the primary cause of death. Although most neonatal and postneonatal deaths can be attributed to complications of prematurity, classifying prematurity itself as the cause of death does not improve our understanding of preventable causes of death. The accurate reporting of infant death is a cornerstone of infant mortality. Accurate definitions are essential for understanding causes and finding potential solutions [1,5].

Newborn infants in need of critical medical attention are normally admitted to the NICU [4]. In our center, these infants tend to be one of the following: preterm born before 35 + 0 weeks gestation, low birth weight under 2000 grams, in need of oxygen/respiratory support, and/or having serious medical conditions. Deaths occurring during NICU admittance are a major contributor to total infant deaths and remain high, both in developed and developing countries. Determining the cause and factors associated with NICU mortality can greatly facilitate efforts to reduce infant deaths [5].

Major advances have occurred in neonatal care over the past 60 years, since the subspecialty of neonatology

emerged. These advances have brought remarkable improvements in survival. We would therefore expect that the leading causes of death might change with time, emphasizing the importance and reliance on good quality data for framing relevant research questions that hopefully result in improved care [6].

Additional demographic factors have an impact on infant deaths, including maternal age, lack of antenatal follow-up, maternal level of education, poor sanitation, and political and medical setup [7-9]. By acquiring good quality data and targeting relevant demographic risk factors in each country, the implementation of targeted educational programs in the community becomes possible.

In this study, we provide up-to-date information on the causes of death in our NICU, which is in a tertiary medical center in a developed country. In addition, we looked at demographics, morbidity, and care parameters to see if they influenced mortality risk.

PATIENTS AND METHODS

The data from this single-center descriptive retrospective cohort study, including data regarding infant deaths, was extracted from four different databases: a computerized prospective mortality database that has been routinely kept in our NICU since 2009; computerized routine patient records; a record of every admittance to the NICU including gestational age, diagnoses, and discharge/ death date; hospital admittance records of deceased infants. These records enabled us to validate our NICU records.

Data were collected for each neonatal death recorded between 2009, when our unit started keeping a computerized prospective mortality database, and 2021, the year our study was conducted. Two groups were then created for comparison by dividing the study period into two time periods. Statistical analysis was conducted on the entire group, for each group separately, and for comparing between the two groups.

Descriptive statistical analysis was used to characterize our study population. Relevant data included information about the mother, her pregnancy, the delivery, and the neonate. All infants born at our center for whom resuscitation was attempted even if not successful, or if they were admitted for any cause and at any point, were included in the study. We also included extremely premature infants who received palliative care only according to parental wishes. Still births were excluded from the study.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). Results were considered significant when the *P*-value was < 0.05. For sequential variables we calculated the mean, standard deviation, and median. For categorical variables, we calculated the prevalence and performed a chi-square test to find differences among the groups. The sequential variables did not show a normal distribution according to the Shapiro-Wilk test. Therefore, the A-parameter Mann-Whitney test was used instead to compare between the two groups.

ETHICS APPROVAL

Ethics approval was given by Kaplan Medical Center Helsinki committee, trial no. 0114-22-KMC. Informed consent was wavered.

RESULTS

Of 74,524 babies born in Kaplan Medical Center between the years 2009 and 2021, 3362 were admitted to the NICU. The death rate was 2.15/1000 live births and 4.7/100 NICU admissions.

When comparing the death rate between the two assigned time periods, 2009–2014 and 2015–2021, a decrease was seen [Table 1].

The leading cause of death was respiratory illnesses (34.5%) followed by infectious disease (18.9%), genetic abnormalities and congenital malformations (16.2%), hemorrhagic conditions (14.2%), and Prenatal asphyxia (12.8%).

Table 1. Mortality rate per 1000 live births and 100 NICU admissions between the years 2009 and 2021

Time period	Number live births	Number deceased	Number NICU admissions	Mortality rate per 1000 live births	Mortality rate per 100 NICU admissions
2009–2021	74,524	160	3362	2.15	4.7
2009–2014	33,067	87	1695	2.63	5.13
2015–2021	41,457	73	1667	1.76	4.37

NICU = neonatal intensive care unit

When comparing the cause of death between the two assigned time periods a decrease was seen in deaths related to genetic abnormalities and congenital malformations together, from 21% in the first time period to 10.4% in the second (*P*-value = 0.04) [Figure 1].

When comparing the demographic parameters of the infants who died during the two assigned time periods of our study, a statistically significant difference was seen in the following parameters: during the second time period the maternal age was older (*P*-value = 0.042), chorioamnionitis was more prevalent (*P*-value = 0.04), and maternal steroidal treatment was more prevalent (*P*-value = 0.029). Contrary to our expectations, the prevalence of full follow-up during pregnancy was reduced during the second time period (55.2% vs. 31.5%, *P*-value = 0.009) [Table 2].

When comparing infant morbidity between the two assigned study time periods, a statistically significant difference was seen in prevalence of intraventricular hemorrhage was reduced (*P*-value = 0.025) and in the prevalence of patent ductus arteriosus was reduced (*P*-value = 0.02). When comparing age by hours at time of death, a statistically significant difference can be seen. Infants born during the second period survived longer than during the first period (*P*-value = 0.042), even though the mean gestational age at birth was the same in the two groups. A trend toward early gestational age at birth was seen during the second period but it was not statistically significant [Table 3].

DISCUSSION

During the 13 years included in our study (2009–2021), 160 infants who had been admitted to the NICU at Kaplan Medical Center passed away. This death rate is 2.15 per 1000 live births, coinciding with the last calculated Israeli neonatal mortality rate [3]. After dividing the 13 years of the study into two separate time periods and comparing them, a decline in the death rate was seen from the first period to the second period. This finding is similar to a Mexican study conducted between 1990 and 2015, in which a decline was also seen in the death rate over the study's period [10]. When looking at the age of death in hours, a statistically significant increase can be seen between the two time periods (*P*-value = 0.04). This decline in the death rate and increase in death age is most likely due to medical advancements over the years, better pregnancy follow-up, improved prenatal care, and better understanding of the importance of keeping a healthy lifestyle during pregnancy.

In contrast, when looking at the death rate per 100 NICU admissions, we do not see a significant decline between the two time periods. This result is most likely because as medical abilities advanced, the gestational age of neonates treated declined. When comparing gestational age and birth weight of deceased neonates in the two time periods, a trend downward can be seen supporting

Figure 1. Cause of death: comparison between two time periods

*Other includes extreme prematurity receiving palliative care only, esophageal perforation, and metabolic acidosis without defined cause
abn = abnormalities, mal = malformations

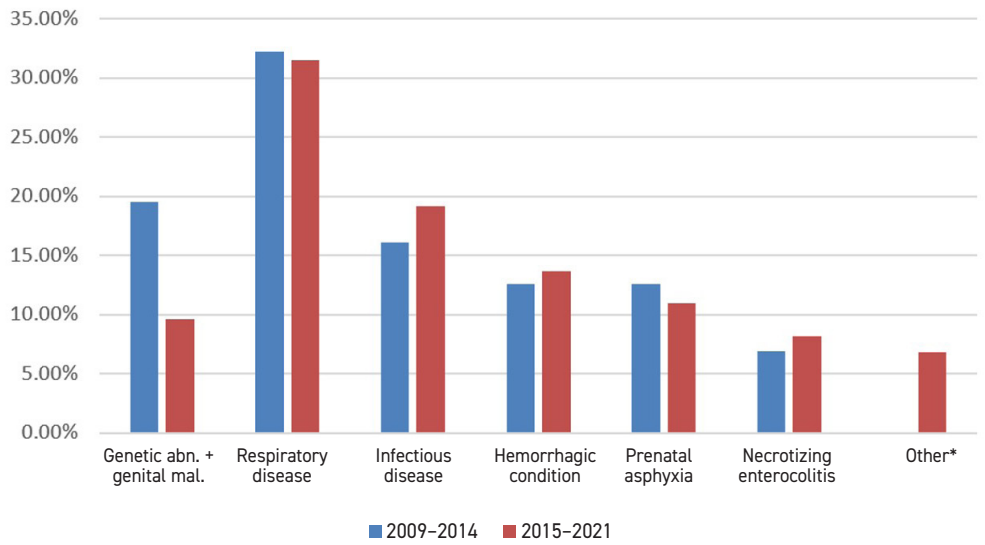

Table 2. Demographic parameters and morbidity risk factors in deceased infant cohort

Parameter	First time period 2009–2014 (n=87)	Second time period 2015–2021 (n=73)	Study duration 2021–2009 (n=160)	*P*-value
Number of deceased	87	73	160	
Female	41 (47.1%)	25 (35.2%)	66 (41.8%)	0.13
Male	46 (52.9%)	46 (64.8%)	92 (58.2%)	0.13
Mean gestational age	29.5 ± 6.3	28.4 ± 6.1		0.33
Mean birth weight (gram)	1392.5 ± 986.5	1229.7 ± 987.4		0.20
Age at death (hours)	14.3±24	18.1±22.8		0.04
Mean maternal age	29 ± 6.3	33 ± 6.5		0.04
Gestational diabetes	3 (3.4%)	2 (2.7%)	5 (3.1%)	0.80
Eclampsia	10 (11.5%)	8 (11.0%)	18 (11.2%)	0.91
Apgar score at 5 minutes	6.2 ± 2.7	5.2 ± 3		0.09
Apgar score at 5 minutes ≤ 5	31 (36.5%)	34 (50%)	65 (42.5%)	0.09
Maternal hypertension	6 (6.9%)	2 (2.7%)	8 (5.0%)	0.23
Group B streptococcus	4 (4.6%)	7 (9.6%)	11 (6.9%)	0.07
Chorioamnionitis	3 (3.4%)	9 (12.3%)	12 (7.5%)	0.03
Neonatal antibiotic treatment	73 (83.9%)	57 (87.1%)	130 (81.2%)	0.35
Maternal fever	3 (3.4%)	5 (6.8%)	8 (5.0%)	0.33
Prolonged rupture of membranes	11 (12.6%)	9 (12.3%)	20 (12.5%)	0.95
Neonatal resuscitation	70 (80.5%)	56 (67.7%)	126 (78.8%)	0.56
Emergency cesarean section	54 (62.1%)	44 (60.3%)	98 (61.3%)	0.82
Maternal Celestone treatment	41 (47.1%)	47 (64.4%)	88 (55%)	0.03
Meconium stained amniotic fluid	4 (4.6%)	6 (8.2%)	10 (6.3%)	0.35
Small for gestational age	21 (24.1%)	12 (16.4%)	33 (20.6%)	0.23
Twin pregnancy	23 (26.4%)	19 (26%)	42 (26.2%)	0.95
Maternal smoking	9 (10.3%)	2 (2.7%)	11 (6.9%)	0.06
No drug abuse	87 (100%)	73 (100%)	160 (100%)	
No consanguineous marriage	87 (100%)	73 (100%)	160 (100%)	
No alcohol abuse	87 (100%)	73 (100%)	160 (100%)	
Parents married	79 (90.8%)	59 (80.8%)	138 (86.2%)	
Spontaneous pregnancy	68 (78.2%)	51 (69.9%)	119 (74.4%)	0.37
Insemination	6 (6.9%)	5 (6.8%)	11 (6.9%)	0.36
In vitro fertilization	12 (13.8%)	17 (23.3%)	29 (18.1%)	0.36
Full antenatal follow-up	48 (55.2%)	23 (31.5%)	71 (44.4%)	0.01
Partial antenatal follow-up	28 (32.2%)	33 (45.2%)	61 (38.1%)	0.01
Placental abruption	13 (14.9%)	8 (11%)	21 (13.1%)	0.46
Asian and Israeli heritage	46 (52.9%)	37 (50.7%)	83 (51.9%)	0.16
European and American heritage	14 (16.1%)	20 (27.4%)	34 (21.2%)	0.16
African heritage	27 (31%)	16 (21.9%)	43 (26.9%)	0.16
Up to 12 years education	35 (55.6%)	30 (53.6%)	65 (54.6%)	0.82
Over 12 years education	28 (44.4%)	26 (46.4%)	54 (45.4%)	0.82

Table 3. Morbidity and treatment parameters in deceased infant cohort

Parameter	First time period 2009–2014 (n=87)	Second time period 2015–2021 (n=73)	Study duration 2021–2009 (n=160)	*P*-value
Neonatal respiratory support	81 (93.1%)	63 (68.3%)	144 (90%)	0.15
Nitric oxide	13 (14.9%)	11 (15.1%)	24 (15%)	0.98
Sildenafil	3 (3.4%)	3 (4.1%)	6 (3.8%)	0.83
Sodium bicarbonate	21 (24.1%)	20 (27.4%)	41 (25.6%)	0.64
Blood transfusion	51 (58.6%)	36 (49.3%)	87 (54.4%)	0.24
Ductal surgical closure	2 (2.3%)	1 (1.4%)	3 (1.9%)	0.66
Periventricular leukomalacia	2 (2.3%)	0 (0%)	2 (1.3%)	0.19
Intraventricular hemorrhage	32 (36.8%)	15 (20.5%)	47 (29.4%)	0.03
Late onset sepsis	19 (21.8%)	10 (13.7%)	29 (18.1%)	0.18
Early onset sepsis	6 (6.9%)	7 (9.6%)	13 (8.1%)	0.53
Necrotizing enterocolitis	8 (9.2%)	11 (15.1%)	19 (11.9%)	0.25
Patent ductus arteriosus	51 (58.6%)	25 (34.2%)	76 (47.5%)	0.002
Bronchopulmonary dysplasia	4 (4.6%)	2 (2.7%)	6 (3.8%)	0.54
Respiratory distress syndrome	48 (55.2%)	37 (50.7%)	85 (53.1%)	0.57
Persistent pulmonary hypertension	12 (13.8%)	11 (15.1%)	23 (14.4%)	0.82
Meconium aspiration syndrome	1 (1.1%)	0 (0%)	1 (0.6%)	0.36
Pneumothorax	14 (16.1%)	9 (12.3%)	23 (14.4%)	0.50
Inotropic treatment	39 (44.8%)	36 (49.3%)	75 (46.9%)	0.57

that fact. In line with the decrease in gestational age and birth weight with time, we did not see a decline in mortality due to respiratory illness, infection, or necrotizing enterocolitis between the two time periods.

When looking at the population of infants who died during our study period, the following findings are worth mentioning. The percentage of premature infants was the highest (79%), which is like the results reported by the WHO showing prematurity as one of the leading causes of death [2]. Within the preterm infant group, the main cause of mortality was due to prematurity complications. This finding was also seen in the Hadassah Medical Center study, which took place during the years 2000–2009 [11].

The most common cause of death remained respiratory illness throughout the two study periods. Interestingly, a decline of 10% was seen in genetic illness and congenital malformations as a cause of mortality between the first and second study periods. This finding can be explained by the increase in antenatal follow-up and genetic testing during pregnancies, causing in turn an increase in in utero diagnosis of life-threatening illnesses. One can assume that in parts of the Israeli population, a diagnosis of a life-threatening illness in utero will be followed by a termination of pregnancy; therefore, causing a reduction in infants born with life threatening genetic illnesses.

A statistically significant decline in full antenatal follow-up visits during pregnancy in the deceased infant population was seen from 55% in the first time period to 31.5% in the second time period (*P*-value = 0.01). In our study we did not check full antenatal follow-up in all NICU admissions. Therefore, we do not know if this decline is unique to the deceased infant population or a trend seen throughout our NICU population. The medical literature does not provide a direct, comprehensive statistic for full antenatal follow-up in Israel between our study periods. However, several indicators suggest that antenatal care coverage in Israel is exceptionally high. For example, in 2015, 97.7% of mothers were screened for hepatitis B during pregnancy, reflecting very high adherence to antenatal screening protocols [12]. In addition, the system of maternal and child health clinics, combined with universal health insurance, ensures that nearly all pregnant women have access to antenatal care services [13].

Our hospital is centrally located, ensuring good access to healthcare to most of our NICU population. Therefore, we assumed the decline in full antenatal follow-up is unique to the deceased infant population in our study and therefore strengthens the fact that poor antenatal follow-up coincides with increased mortality. Further studies are needed to solidify this assumption.

A comparison of maternal perinatal steroidal treatment showed a statistically significant increase in mothers treated before birth between the first and second time periods (47.1% vs. 64.4%, *P*-value = 0.03). This too is as expected due to the knowledge gained over the years as to the importance steroidal treatment in preventing respiratory distress syndrome and intraventricular hemorrhage [14,15]. Further strengthening the benefits of perinatal steroidal treatment is a statistically significant decrease in intraventricular hemorrhage in the deceased infants between the two time periods (38% vs. 21%, *P*-value = 0.02).

Our study supports the assumption that as medical knowledge advances, including perinatal and infant care, parental awareness of the importance of full pregnancy follow-ups, and improved healthy lifestyles, the neonatal death rate decreases. In contrast, an increase in poor antenatal follow-up was seen within the deceased infant cohort, which reinforced the importance of pregnancy follow-up for survival, despite medical advancements.

The limitations in our study include its retrospective design. Data were extracted from a computerized database and were reliant on the accuracy of medical records and follow-up. This procedure may have caused missing data or documentation bias. Our center receives a wide range of patient populations, but our results might not be generalizable to other centers or populations.

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Capsule

Recognizing food by T cells

Immunological tolerance to dietary antigens is essential for preventing food allergies and digestive disorders such as celiac disease. However, the specific food-derived antigens that contribute to immune tolerance remain poorly described. **Blum** and colleagues mapped the dietary epitopes recognized by food-responsive T cell receptors derived from murine intestinal regulatory T (T_{reg}) cells. Seed storage proteins from corn, wheat, and soy, including the maize protein αZein, were targets of food-responsive T_{reg} cell receptors. αZein-specific T_{reg} cells suppressed T cell responses to αZein ex vivo and after adoptive transfer into naïve mice. These findings provide insight into the dietary components recognized by the naturally occurring T_{reg} cells that mediate oral tolerance.

Sci Immunol 2026; 11 (117): eaeb4684
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