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Evaluation of neonatal intensive care unit mortality

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Abstract

Aim: To evaluate neonatal intensive care unit (NICU) deaths in one of the largest obstetrics centers in Turkey in order to determine the causes of death in this high-risk group.

Materials and Methods: We retrospectively analyzed all NICU deaths occurring between 2013 and 2018. The study included infants born alive at 22 weeks of gestation or older.

Results: Of 102374 babies born in our hospital, 14,768 infants (14.4%) were admitted to the NICU and 957 (6.48%) of those infants died before discharge. The most common causes of death were extreme prematurity or extremely low birth weight (31.5%), lethal anomalies (13.1%), and sepsis (8.2%). At younger gestational ages, causes associated with extreme prematurity and complications of prematurity were most common, while the death rate due to perinatal asphyxia and genetic or structural anomalies increased at older gestational ages.

Conclusion: The causes of NICU deaths are multifactorial and vary with gestational age. Efforts to reduce NICU mortality should include preventing or delaying preterm delivery and identifying the most appropriate treatment modalities that may reduce the risk of respiratory distress, intracranial hemorrhage, necrotizing enterocolitis, and sepsis. In more mature infants, the main goal should be to prevent and treat perinatal asphyxia and determine the most appropriate treatment modalities for non-lethal anomalies.

Introduction

Infant mortality is considered a key public health indicator and can be categorized as occurring during the neonatal period (≤ day 28) or the postneonatal period (day 29-364) [1]. The neonatal period is the riskiest in terms of survival. Although neonatal mortality fell globally by 52% from 38 to 17 deaths per 1000 live births between 1990 and 2019, the risk of death remains highest during the first month of life. In 2019, there were an estimated 2.4 million neonatal deaths globally, approximately a third of which occurred on the first day after birth and another quarter within the first week. Worldwide, the mortality rate has declined more rapidly among children aged 1 to 59 months than in those less than 1 month of age. As a result, the proportion of neonates among all deaths in children under the age of 5 years increased from 40% in 1990 to 47% in 2019. Approximately 1.5 million deaths (28%) in children under 5 years of age occurred between 1 and 11 months and 1.3 million (25%) occurred between 1 and 4 years of age [2]. Although the rate of neonatal mortality is decreasing globally, there are marked differences in neonatal mortality between regions and countries [3]. Rates and causes of neonatal mortality vary depending on countries' development status, societies' socioeconomic structure, and the quality of the health services provided. Prematurity, infection, and perinatal hypoxic insult are the most frequent causes of neonatal mortality in underdeveloped and developing countries, whereas most neonatal mortality in developed countries is due to prematurity and congenital anomalies [4]. After a long period of decline in neonatal and infant mortality rates in developed countries, these rates appear to have stabilized in recent years [5,6]. This suggests that research to understand the specific causes of these deaths is needed to enable more targeted initiatives to further reduce mortality. Although prematurity continues to be one of the most important causes of neonatal deaths, mortality rates due to respiratory distress syndrome and sepsis are steadily declining [7-9]. In addition, while the incidence of death due to congenital malformations has showed little change, there may be a relative decrease in deaths related to neural tube defects and an increase in some chromosomal abnormalities [10]. High-risk infants (extremely preterm, extremely low birth

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weight, having congenital anomalies) delivered in perinatal centers with high patient density constitute an important subgroup with higher hospitalization and mortality rates. Deaths that occur in neonatal intensive care units (NICU) are a major contributor to total infant deaths. Therefore, determining the causes and factors associated with NICU mortality can greatly facilitate efforts to reduce infant deaths [11]. In the present study, we retrospectively reviewed deaths in one of the largest obstetrics centers in Turkey in order to determine the causes of death in this high-risk group.

Material and Methods

The University of Health Sciences Zekai Tahir Burak Health Practice and Research Center is one of the largest perinatology and obstetrics centers in Turkey, with an average of 18000 births per year. Babies under follow-up in the perinatology clinic with low birth weight, risk of preterm birth, no prenatal follow-up, and antenatally diagnosed congenital anomalies are frequently born in our center. Risky pregnancies from the surrounding provinces are also referred to our center in the antenatal period. The NICU is one of the largest in the country, with 100 level III beds, 30 level II beds, and an average of 2,500 patient admissions per year. The hospital is also a reference center for therapeutic hypothermia, congenital heart disease, and neural tube defects, and receives referrals from surrounding hospitals. In this study, we retrospectively analyzed the medical records and death certificates of all neonates who died between 2013 and 2018. Ethical approval was taken by the Ankara City Hospital Ethics Committee (E2-21-1025). Infants who were born alive at 22 weeks of gestation or older, were admitted to the NICU, and did not survive until discharge were included in the study. For each case, the primary cause of death was determined. We also reviewed the NICU database to obtain data on total admissions and discharge survival during the study period. There were no significant institutional changes in the unit during this period. Gestational age was estimated based on the mother's last menstrual period. When this information was unreliable or unknown, gestational age was determined according to ultrasound and the new Ballard score [12]. The terms prematurity and extreme prematurity were defined as live birth between 28 and 37 weeks and before 28 weeks of gestation, respectively. Birth weight was measured using a digital infant scale and classified using the World Health Organization (WHO) weight classification [13]. Extremely low birth weight (ELBW) was defined as a birth weight less than 1000 g. Perinatal asphyxia was defined as low Apgar score, cord blood acidosis, multiple organ involvement (kidney, lungs, liver, heart, and intestines), and neonatal neurological sequelae (seizures, coma, and hypotonia) [14]. Respiratory distress syndrome (RDS) was diagnosed using clinical and radiological findings in neonates exhibiting respiratory distress after birth [15]. Persistent pulmonary hypertension of the newborn was defined as hypoxic respiratory failure resulting from failure of the normal decrease in pulmonary vascular resistance and transition to postnatal circulation after birth [16, 17]. Infection was diagnosed based on clinical signs and symptoms, laboratory findings, evidence of focal lesions, or positive blood culture. The diagnosis and grading of necrotizing enterocolitis (NEC) was performed according to the Bell criteria [18]. Spontaneous intestinal perforation (SIP) was also diagnosed using clinical and radiological findings [19]. Intracranial hemorrhage (ICH) was diagnosed based on cranial ultrasound findings. Congenital anomalies, heart defects, congenital diaphragmatic hernia, congenital metabolic diseases, genetic syndromes, and other abnormalities were diagnosed based on the infant's clinical presentation at admission and findings from X-ray, ultrasound, and echocardiography examinations, and in necessary cases, computed tomography scanning and genetic and metabolic testing. Congenital anomalies that were life-threatening or required surgical correction were classified as major anomalies. Major heart defects were defined as defects that required catheterization or surgical intervention within the first year of life [20]. SPSS version 24.0 software was used for statistical analyses. Descriptive statistical methods (mean, standard deviation, frequency) were used to summarize the data.

Table 1. Neonatal charasteristics of infants who died

Male, %	514 (53.7%)
Birth weight (g), median (min-max)	1020 (270-4830)
Gestational age (weeks), median (min-max)	28 (22-42)
Apgar 1 min, median (min-max)	4 (0-8)
Apgar 5, median (min-max)	6 (1-10)
Age at death (day), median (min-max)	4 (1-360)

Table 2. Causes of death

Cause of death	% (n)
Extreme prematurity or extreme low birth weight 31.5 (301)	31.5 (301)
Lethal anomaly	13.1 (125)
Sepsis	8.2 (79)
Genetic syndrome	8 (77)
Major hearth defects	5.4 (52)
Perinatal asphyxia	5 (48)
Necrotizing enterocolitis/ Spontaneous intestinal perforation	4.7 (45)
Pulmonary hemorrhage	4.7 (45)
Other	3.7 (35)
IVH or intracranial hemorrhage	3.6 (34)
Congenital diaphragmatic hernia	3.4 (32)
Respiratory distress syndrome	3 (29)
Airleak	2 (19)
Lung hypoplasia	2 (19)
Renal failure	0.7 (7)
Bronchopulmonary dysplasia	0.5 (5)
Pulmonary hypertension	0.5 (5)

Results

Demographics

Of 102,374 babies born in our hospital in the 6-year period of 2013 to 2018, 14,768 infants (14.4%) were admitted to the NICU and 957 (6.48%) of those infants died before discharge. Of the infants who died, 52.7% were male and 24.5% (n = 235) were born before 25 weeks of gestation. Twenty-two percent of the deaths occurred in the first 24 hours, 65.7% (n = 629) in the early neonatal period, 21.3%

Table 3. Causes of death by gestational age group

	Preterm <25 wk	Preterm 25-28 wk	Preterm 29-33 wk	Late preterm 34-36 wk	Term >37 wk
Total	237	264	172	102	182
Extreme PM or extreme LBW	204	90	7	-	-
Sepsis					
<7 days	1	5	13	6	2
>7 days	2	28	15	6	1
Lethal anomaliy	1	18	49	25	32
Genetic syndrome	-	2	15	20	40
Major hearth defects	1	2	9	12	28
NEC/ SIP	12	24	6	1	2
Perinatal asphyxia	-	1	1	9	37
Renal failure	-	5	1	-	1
Congenital diaphragmatic hernia	-	-	2	6	24
Other	-	7	17	3	8
Pulmonary hemorrhage	1	33	9	2	-
Respiratory distress syndrome	2	17	10	-	-
Airleak	4	8	5	2	-
IVH or intracranial hemorrhage	8	21	4	-	1
Lung hypoplasia	0	0	6	10	3
Bronchopulmonary dysplasia	1	3	1	-	-
Pulmonary hypertension	-	-	2	-	3

(n = 204) in the late neonatal period, and 13% (n = 124) in the postneonatal period. The demographic data of the 957 patients who died are shown in Table 1.

Primary cause of death

The most frequent causes of death were extreme prematurity or ELBW (n = 301, 31.5%), lethal anomalies (n = 125, 13.1%), and sepsis (n = 79, 8.2%). Causes of death are shown in Table 2. Of the patients who died, 237 (24.8%) were born before 25 weeks, 264 (27.6%) at 25 to 28 weeks; 172 (18%) at 29 to 32 weeks, 102 (10.7%) at 34 to 36 weeks and 182 (19%) after 37 weeks of gestation. Birth weight was less than 500 g in 69 (7.2%) of the infants who died, 500 to 750 g in 246 (25.7%), 750 to 1,000 g in 156 (16.3%), 1,000 to 2,500 g in 296 (30.9%), 2,500 to 4,000 g in 181 (18.9%), and more than 4,000 g in 9 infants (1%). At younger gestational ages, causes associated with complications of prematurity and extreme prematurity (RDS, ICH, NEC, and sepsis) were most common, while the death rate due to perinatal asphyxia and genetic or structural anomalies increased at older gestational ages. The causes of mortality by gestational week are presented in Table 3.

Factors contributing to death

Of the 298 extreme prematurity and ELBW infants, 203 (68.1%) were born before 25 weeks of gestation and 244 (81.8%) had a birth weight less than 750 g. Of the 79 infants (8.2%) who died due to sepsis, more deaths occurred after 7 days (n = 52, 5.4%) compared to those within the first 7 days (n = 27, 2.8%). Three of the infants in this group were born before 25 weeks of gestation. In addition, 8 of the 34 infants (3.6%) who died due to ICH and 4 of the 19 infants (2.0%) who died due to air leak were born before 25 weeks of gestation. Of the 45 infants who died due to NEC/SIP, 12 (26%) were born before 25 weeks and 21 (46%) had a birth weight below 750 g. Of 19 patients (2.0%) who died due to pulmonary hypoplasia, 9 had multicystic dysplastic kidneys, 7 had bilateral renal agenesis/Potter sequence, 2 had polycystic kidney, and 1 had renal agenesis/achondroplasia. Of the 125 infants who died due to lethal anomaly, 46 (37%) were diagnosed as having hydrops fetalis and 7 of these patients had cardiac problems (fetal arrhythmia in 2, Ebstein anomaly in 2, atrioventricular septal defect [AVSD] in 2, and complex cardiac anomaly in 1), and 1 patient had Rh incompatibility. Four patients in this group had trisomy 21. Thirty-three patients (26%) died due to CNS anomalies: 15 had meningomyelocele/hydrocephalus, 8 had massive hydrocephalus, 6 had anencephaly, 3 had lissencephaly, and 1 patient had holoprosencephaly. Twenty-four (19%) of the infants who died had multiple anomalies but no specific syndrome or genetic disease. Other lethal anomalies were skeletal dysplasia (n = 5), thanatophoric dysplasia (n = 5), ichthyosis (n = 4, with tricuspid valve dysplasia in 1), epidermolysis bullosa (n = 3), VACTERL association (n = 2), esophageal atresia (n = 2, with tetralogy of Fallot in 1), OEIS complex (n = 1), atrial isomerism (n = 1), and partial hydatidiform mole (n = 1). Of the 48 infants who died due to hypoxic-ischemic encephalopathy, 6 were born before 35 weeks of gestation and did not receive therapeutic hypothermia. All 42 infants born after 35 weeks of gestation received hypothermia. A total of 77 infants died due to major genetic syndromes: trisomy 18 (n = 25, 32.4%), trisomy 13 (n = 8, 10.4%), metabolic disease (n = 8, 10.4%), hypotonic infant (n = 6, 7.8%), nemaline rod myopathy (n = 2, 2.6%), myotonic dystrophy (n = 2, 2.6%), Pena-Shokeir syndrome (n = 2, 2.6%), Holt-Oram syndrome (n = 2, 2.6%), Fryns syndrome (n = 2, 2.6%), Jeune syndrome (n = 2, 2.6%), and 1 infant each with Meckel-Gruber syndrome, Klippel-Feil syndrome (with double-outlet right ventricle), Waardenburg syndrome, Cornelia

de Lange syndrome, Crouzon syndrome, Seckel syndrome, CHARGE syndrome, Bruck syndrome, Poland syndrome, Apert syndrome, tetraploidy, 3p deletion, 8q duplication, monosomy 5, Carmi syndrome, spinal muscular atrophy, Ellis-van Creveld syndrome, and Pierre Robin sequence. Ten infants with trisomy 21 died due to causes unrelated to their primary genetic anomaly. Of these patients, 4 had hydrops fetalis (with AVSD in 1), 5 had congenital heart disease (AVSD in 4, hypoplastic left heart in 1), and 1 had anal atresia. A total of 52 patients died due to major cardiac defects: hypoplastic left heart (n = 10), complex cardiac anomaly (n = 8), AVSD (n = 7), truncus arteriosus (n = 4), tetralogy of Fallot (n = 4), tetralogy of Fallot and pulmonary atresia (n = 4), double-outlet right ventricle (n = 3), large artery transposition (n = 3), pulmonary atresia (n = 2; with ventricular septal defect in 1 patient and AVSD in 1 patient), aortic coarctation (n = 2), hypoplastic aortic arch (n = 2), and 1 patient each with Ebstein anomaly, tricuspid atresia, and pulmonary stenosis. The prevalence of cardiac anomalies among all infants who died was 9.3% (n = 89). Thirty-five infants could not be categorized. Of these, cause of death was severe perinatal depression but not hypoxic-ischemic encephalopathy (n = 11), postoperative surgical complications (n = 9; intestinal atresia in 4, encephalocele in 1, esophageal atresia in 1, volvulus in 1, omphalocele in 1, and anal atresia and trisomy 21 in 1 patient), arrhythmia (n = 4), congenital airway anomaly preventing intubation (n = 3), shock (n = 2), hemophagocytic syndrome (n = 1), congenital rubella infection (n = 1), congenital cytomegalovirus infection (n = 1), spinal injury (n = 1), sudden cardiac arrest (n = 1), and esophageal atresia with respiratory failure (n = 1).

Potentially modifiable factors associated with death

More detailed data were obtained from the records of 462 infants who died in the years 2013 to 2015. Potentially modifiable factors associated with death were identified in 127 (27.4%) of the cases. Lack of prenatal care was the most common of these (n = 52, 11.2%). In this group, 4 infants (0.9%) had undiagnosed diaphragmatic hernia and 1 (0.2%) had undiagnosed Rh incompatibility. The second most common factor was the mother being less than 20 years of age (n = 46; 9.9%). Seventeen infants (3.7%) were born in centers with lower-level NICUs and required transport and 3 infants (0.6%) were born on route to the hospital. Pregnancy termination had been recommended for 9 infants (1.9%) in the antenatal period due to congenital anomalies.

Discussion

In this study, we compiled a large amount of mortality data from a 130-bed NICU in a perinatal center with a high volume of births and intensive care admissions. By analyzing this comprehensive sample of admissions, we aimed to both reveal the causes of NICU deaths and draw attention to this issue with regard to preventable causes. Every perinatal center should convene periodically to discuss this issue in committees formed from departments related to antenatal and perinatal care, NICU staff, and relevant branches, and try to develop strategies for preventable problems. The causes of NICU deaths are multifactorial and vary with gestational age. At earlier gestational ages, extreme prematurity and associated complications such as NEC, RDS, ICH, and sepsis are the primary causes. At later gestational ages, mortality is more frequently associated with genetic or structural anomalies and hypoxic-ischemic encephalopathy. Of the nonsurviving infants in this study, 81% were born before 37 weeks, 42.8% before 28 weeks, and 24.8% before 25 weeks of gestation. Globally, the preterm birth rate is estimated to be approximately 11%, resulting in approximately 15 million preterm births annually [21]. Eighty-four percent of these births occur at 32 to 36 weeks of gestation, 10% at 28 to 32 weeks of gestation, and 5% before 28 weeks of gestation. In preterm infants, lower birth weight and gestational age are major factors associated with increased mortality risk [22-26]. Therefore, extremely preterm and ELBW infants have the greatest impact on infant mortality [22]. A systematic review of 22 studies indicated that late preterm infants had a 6-fold higher neonatal mortality rate and a 4-fold higher postneonatal mortality rate compared to term infants [27]. Infants born at or before 28 weeks of gestation have the highest mortality, with reported rates of about 50%. However, survival of infants born at 24 to 26 weeks of gestation has improved with advances in prenatal and neonatal care [28-31]. General measures to reduce mortality in preterm infants include ensuring access to prenatal care, delivering at-risk babies in centers where appropriate stabilization and supportive treatment can be provided, and improving and ensuring the widespread availability of appropriate prenatal, perinatal, and postnatal support. However, more targeted interventions may be possible depending on the main causes of infant death. Prematurity is not particularly informative 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. Many infant deaths involve concomitant factors, and it can be difficult to identify a single cause of death. Having accurate information is of key importance when evaluating causes of death and researching possible solutions [32]. Therefore, it is recommended that these causes of death be documented in detail and classified accordingly. In the patient group with more detailed data that may be related to mortality, the two most common potential preventable factors were lack of prenatal care and low maternal age (<20 years). There were also infants who were born in centers with lower-level NICUs and required transport to our center, and infants for whom termination of the pregnancy was recommended in the antenatal period due to congenital anomalies. These findings once again highlight the importance of antenatal follow-up, the risk of low maternal age in terms of increasing neonatal mortality, the importance of delivering at an appropriate center, and the impact of termination due to the detection of congenital anomalies incompatible with life in antenatal follow-up in reducing neonatal mortality [33-38]. Of course, there are limitations of our study. It may not be possible to identify all of the factors involved in an infant's death in a single cause of death analysis. Data regarding potentially modifiable factors in mortality were not available for all of

our patient groups; more detailed data were only available for the first 3 years. However, even with these limitations, the large number of patients and sharing the available data will make an important contribution to the literature.

Conclusions

The causes of NICU deaths are multifactorial and vary with gestational age. At earlier gestational ages, extreme prematurity and associated complications such as NEC, RDS, ICH, and sepsis are the primary causes. In infants born at later gestational ages, mortality is more commonly caused by genetic or structural anomalies and hypoxic-ischemic encephalopathy. Therefore, efforts to reduce NICU mortality should include preventing or delaying preterm delivery and identifying the most appropriate treatment modalities to reduce the risk of common complications of prematurity. For infants born later in gestation, the main goal should be to prevent and treat perinatal asphyxia and determine the most appropriate treatment modalities for non-lethal anomalies.

Ethics approval

Ethical approval was taken by the Ankara City Hospital Ethics Committee (E2-21-1025).

References

1. Grand Rounds CDC; Centers for Disease Control and Prevention (CDC). CDC Grand Rounds: public health approaches to reducing U.S. infant mortality. MMWR Morb Mortal Wkly Rep. 2013;62(31):625–628.
2. Unicef. Levels and trends in child mortality 2020: Report 2020. Estimates developed by the UN Inter-agency Group for Child Mortality Estimation. Copyright © 2020 by the United Nations Children's Fund ISBN: 978-92-806-5147-8.
3. Shim JW, Kim MJ, Kim EK, et al. The impact of neonatal care resources on regional variation in neonatal mortality among very low birthweight infants in Korea. Paediatr Perinat Epidemiol. 2013 ;27(2):216-25.
4. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team. 4 milion neonatal deaths: when? Where? Why? Lancet. 2005; 365:891.
5. Kung HC, Hoyert DL, Xu J, Murphy SL. Deaths: final data for 2005. Natl Vital Stat Rep. 2008; 56(10):1–120.
6. Bell R, Glinianaia SV, Rankin J, et al. Changing patterns of perinatal death, 1982–2000: a retrospective cohort study. Arch Dis Child Fetal Neonatal Ed. 2004;89(6):F531–F536.
7. Goldenberg RL, Culhane JF, et al. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75– 84.
8. Hein AH, Lofgren MA. The changing pattern of neonatal mortality in a regionalized system of perinatal care: a current update. Pediatrics. 1999;104(5 pt 1):1064 –1069.
9. Stoll BJ, Holman RC, Schuchat A. Decline in sepsis-associated neonatal and infant deaths in the United States, 1979 through 1994. Pediatrics. 1998;102(2):e18.
10. Wen SW, Liu S, Joseph KS, et al. Patterns of infant mortality caused by major congenital anomalies. Teratology. 2000; 61(5):342–346.
11. Jacob J, Kamitsuka M, Clark RH, et al. Etiologies of NICU deaths. Pediatrics. 2015;135(1):e59–65.
12. Ballard JL, Khoury JC, Weding K, et al. New Ballard score, expanded to include extremely premature infants. J Pediatr. 1991;119:417–423.
13. WHO. Every Newborn Progress Report May 2015 [Internet]. Geneva 27, Switzerland: WHO Press, World Health Organization, 20 Avenue Appia,; 2015. Available from: www.everynewborn.org%0Awww.everynewborn.org.
14. John Hç Menkes and Harvey B. Sanrat. Perinatal Asphyxia and Trauma. Child Neurology 2000; 401-455.
15. Hermansen CL, Lorah KN. Respiratory distress in the new born. Am Fam Physician. 2007;76(7):987–994.
16. Kluckow CRaM. Pathophysiologically Based Management of Persistent Pulmonary Hypertension of the Newborn: Elsevier; 2018.
17. Hilgendorff A, Apitz C, Bonnet D, et al. Pulmonary hypertension associated with acute or chronic lung diseases in the preterm and term neonate and infant. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart. 2016;102 Suppl 2:ii49-56.
18. Neu J. Necrotizing enterocolitis: The search for a unifying pathogenic theory leading to prevention. Pediatr Clin North Am. 1996;43:409-32.
19. Pumberger W, Mayr M, Kohlhauser C, et al. Spontaneous localized intestinal perforation in very-low-birth-weight infants: a distinct clinical entity different from necrotizing enterocolitis. J Am Coll Surg. 2002; 195:796.
20. Zhang Y, Riehle-Colarusso T, Correa A, et al. Observed prevalence of congenital heart defects from a surveillance study in China. J Ultrasound Med. 2011;30:989–95.
21. Organization WHO. Newborns: improving survival and well-being. 2020; https://www.who.int/news-room/fact-sheets/detail/newborns-reducing-mortality (Accessed 09/09/2020).
22. Ely DM, Driscoll AK. Infant Mortality in the United States, 2017: Data From the Period Linked Birth/Infant Death File. Natl Vital Stat Rep. 2019; 68:1.
23. Cnattingius S, Johansson S, Razaz N. Apgar Score and Risk of Neonatal Death among Preterm Infants. N Engl J Med. 2020; 383:49.
24. Suttun L, Bajuk B. Population-based study of infants born at less than 28 weeks' gestation in New South Wales, Australia, in 1992-3. New South Wales Neonatal Intensive Care Unit Study Group. Paediatr Perinat Epidemiol. 1999; 13(3):288-301.
25. Schindler T, Koller-Smith L, Lui K, Bajuk B et al. Causes of death in very preterm infants cared for in neonatal intensive care units: a population-based retrospective cohort study. BMC Pediatrics. 2017; p. 59.
26. Watkins WJ, Kotecha SJ, Kotecha S. All-Cause Mortality of Low Birthweight Infants in Infancy, Childhood, and Adolescence: Population Study of England and Wales. PLoS Med. 2016; 13:e1002018.
27. Teune MJ, Bakhuizen S, Gyamfi Bannerman C, et al. A systematic review of severe morbidity in infants born late preterm. Am J Obstet Gynecol. 2011; 205:374.e1.
28. Field DJ, Dorling JS, Manktelow BN, et al. Survival of extremely premature babies in a geographically defined population: prospective cohort study of 1994-9 compared with 2000-5. BMJ. 2008;336:1221.
29. Itabashi K, Horiuchi T, Kusuda S, et al. Mortality rates for extremely low birth weight infants born in Japan in 2005. Pediatrics. 2009; 123:445.
30. Boel L, Banerjee S, Clark M, et al. Temporal trends of care practices, morbidity, and mortality of extremely preterm infants over 10-years in South Wales, UK, Scientific Reports. 2020;10:18738.
31. Battin MR, Knight DB, Kuschel CA, et al. Improvement in mortality of very low birthweight infants and the changing pattern of neonatal mortality: The 50-year experience of one perinatal centre. J Paediatr Child Health. 2012;48:596–9.
32. Barfield WD; Committee on Fetus and Newborn. Standard terminology for fetal, infant, and perinatal deaths. Pediatrics. 2011;128(1):177–181.
33. Tekelab T, Chojenta C, Smith R, et al. The impact of antenatal care on neonatal mortality in sub-Saharan Africa: A systematic review and meta-analysis. PLoS One. 2019;13;14(9):e0222566.
34. Neupane S, Doku DT. Association of the quality of antenatal care with neonatal mortality: meta-analysis of individual participant data from 60 low- and middle-income countries. Int Health. 2019;13;11(6):596-604.
35. Ribeiro FD, Ferrari RA, Sant'Anna FL, et al. [Extremes of maternal age and child mortality: analysis between 2000 and 2009]. Rev Paul Pediatr. 2014;32(4):381-8.
36. Kang G, Lim JY, Kale AS, et al. Adverse effects of young maternal age on neonatal outcomes. Singapore Med J. 2015;56(3):157-63.
37. Chien LY, Whyte R, Aziz K, et al. Improved outcome of preterm infants when delivered in tertiary care centers. Obstet Gynecol. 2001; 98:247.
38. Liu S, Joseph KS, Kramer MS, et al. Relationship of prenatal diagnosis and pregnancy termination to overall infant mortality in Canada. JAMA. 2002; 287:1561.