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HAS THE INCREASED SURVIVAL RATE OF PREMATURE NEW-BORNS BROUGHT ABOUT THE INCREASE IN LONG-TERM MORBIDITY?

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Abstract

Advances in perinatal and neonatal care are closely linked with the improvement in the survival rate of extremely low birth weight infants (ELBWI). Increased survival rate is the result of major changes in obstetrics and neonatal strategies and therapeutic procedures. The question is whether these changes in perinatal care have also brought about short-term and long-term positive results in morbidity in the child population. Despite the decrease in the neonatal morbidity rate, it appears that neonatal mortality remains stable. Frequently asked questions by parents aimed at medical professionals who are involved in the care of their child include questions on the incidence of adverse neurodevelopmental outcomes. In literature, there is a wide range of different data that interpret the incidence of disorders. We present a review of death rates and short and long-term morbidity in extremely premature infants.

Key words: *morbidity; death rate; survival rate; ELBWI*

REVIEW ARTICLE

INTRODUCTION

Children born prematurely are exposed to a higher risk of long-term disorders than full-term infants. The disorders may influence not only the infants in their childhood or adulthood, but also their families. The earlier a baby is born, the higher the risk of disorders.

According to the World Health Organization (WHO), every child born before the 37th gestational week (i.e. 36 weeks and 6 days at ***the earliest***, i.e. 258 days after the last menstruation period) is ***considered to be born prematurely (it is immature)***. Immaturity may be categorized according to the gestational week that, the baby is born, as shown in Table 1.

Different stages of immaturity may also be classified according to birth weight. The categories are shown in Table 2.

The incidence of preterm infants is almost 11% (15 million) and is rising all over the world (Battisti 2011). 84% of all preterm infants are infants born between the 32nd and 36th g.w., 10% are born between the 28th and <32nd g.w. and 5% are born in the <28th g.w. In Europe, almost half a million infants are born prematurely (1 out of 10). The USA operates with a similar number, 450,000–550,000 (1 out of 9). Since 1990, the number of preterm infants has increased by almost 21%. Currently, the incidence of preterm infants is about 11.5% (Glass et al. 2015). Globally, south Asia has the largest number of preterm infants and Africa has almost 18%.

A premature birth may happen spontaneously (with or without premature rupture of membranes), which happens in approximately 80% of cases. Medical causes (pre-pathological

Table 1 – Classification of infants according to gestation (Blencowe et al. 2013, Barfield 2016)

Classification of infants	Gestational week
Extremely preterm	24th–27th g.w.
Very preterm	28th–31st g.w.
Moderate preterm	32nd–33rd g.w.
Near term = "Late preterm"	34th–36th g.w.

Table 2 – Classification of infants according to birth weight (Gomella 2013)

Classification of infants	Birth weight
Low birth weight – LBW	less than 2500 g
Very low birth weight – VLBW	less than 1500 g
Extremely low birth weight – ELBW	less than 1000 g
Micro preemie	less than 800 g

conditions of the mother or foetus) occur in 20% of cases (Battisti 2011). A premature birth is influenced by many risk factors: demographic (ethnicity, family anamnesis, socio-economic status of the mother, smoking, drug abuse, environment and others), but primarily, they are mainly from the mother's side (urinary infections, sexually infectious diseases, vaginal infections, e.g. bacterial vaginitis, trichomoniasis, foetus abnormalities, pregnancy with *in vitro* insemination, undernourishment or obesity before pregnancy, short period between pregnancies, placenta praevia – the condition in which the placenta grows in the lowest part of the uterus and covers the whole or a part of the cervix, the danger of the rupturing of the uterus, high blood pressure, vaginal haemorrhage, diabetes or gestational diabetes, blood clotting and others). The result is a premature birth. The earlier the baby is born, the worse the prognosis of its condition is. The consequences of premature birth may be the death of the infant, and short-term or long-term illnesses.

The influence of the risk factors during pregnancy may lead ***to the death*** of the preterm infant. However, death may occur in any post-natal period due to the amount of illnesses connected to immaturity. The consequences of these illnesses may influence childhood and adulthood and cause death in the adult age as well. The morbidity of preterm infants indirectly responds to their gestational age, as well as to their birth weight (Table from up-to-date health statistics).

Premature birth complications are a direct cause of the death of infants. They are responsible for 35% out of 3.1 million infant deaths worldwide. The second indirect cause is infections (Blencowe et al. 2013).

The preterm infant ***survival rate*** and the number of surviving infants with an extremely low gestation or birth weight rises with better quality medical care and with the establishment of new therapeutic methods. Tables 4 and 5 show a summary of the data on survival rates, which were taken from various databases.

As external databases state, the survival of immature new-borns is rising in Czech Republic too. In 2015, Plavka et al. quote the figures concerning the incidence of new-borns with a birth weight of <1000 g – 0.42%, 1000–1499 g – 0.76% and new-borns with a birth weight under 1500 g – 1.15%.

In combination with the number of risk factors that influence the immature organism (infections, inflammations, hypoxia, ischemia, malnutrition, hyper hydration, oxygenic stress, mechanical ventilation, medicines, transfusions and others), prematurity significantly participates in infant morbidity. ***Morbidity*** which very immature new-borns carry into the next period influences their further life as well. The risk of long-term neurosensory disorders grows when diseases are overcome (BPD increases the risk of neurosensory disorders by 2.5 times, ROP by 3.7 times, IVH/cPVL by 3.9 times). A significant factor that participates in the quality of life of the living new-borns is the combination of nosological units in the new-born stage, which may increase the risk of a long-term impact (Schmidt et al. 2003).

Despite the higher quality of medical care in other stages, preterm new-borns are still exposed to the risk of ***ilness***. As well as death rate, the risk of morbidity is inversely connected to the gestational age. The most serious complications include intraventricular hemorrhage (IVH – stage III–IV), periventricular leukomalacia (PVL), persistent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing

Table 3 – Morbidity according to gestation

Gestational age (per week)	Death rate in 1000 live-births	Birth weight (g)	Death rate in 1000 live-births
40	1.75	>2500	2.1
37–39	2.41	2000–2499	9.9
34–36	7.23	1500–1999	24.7
32–33	16.02	1250–1499	39.9
28–31	35.70	1000 to 1249	61.7
<28	374.74	750 to 999	124.6
		500 to 749	394.3

Table 4 – Survival rate according to gestation ≤25 g.w. (AAP 2012)

Population	Year of birth	22 weeks	23 weeks	24 weeks	25 weeks	Notes
UK and Ireland (Costeloe et al. 2000)	1995	2%/9% (*n* = 138/22)	22%/20% (*n* = 241/131)	26%/34% (*n* = 382/298)	44%/52% (n = 424/357)	All live-births/ admitted in NICU
NICHD Network centres (Lemons et al. 2001)	1995 & 1996	21% (*n* = 56)	30% (*n* = 216)	50% (*n* = 301)	24% (n = 379)	All live-births; new-borns with inborn development disorders are excluded
Norway (Markestad et al. 2005)	1999 & 2000	5%/0% (*n* = 38/0)	16%/39% (*n* = 55/23)	44%/60% (*n* = 80/58)	66%/80% (n = 83/69)	All births/admitted in NICU
NICHD Network centres (Tyson et al. 2008)	1998–2003	5%	26%	56%	75%	4,466 new-borns from 19 centres; new-borns with birth weight >1000 g or those who did not need mechanical ventilation are excluded
Vermont Oxford Network centres	2003–2005	5% (*n* = 2.625)	29% (*n* = 5,481)	56% (*n* = 8.722)	73% (n = 9.795)	All new-borns born in hospitals or transported in the first ≤28 postnatal days

enterocolitis (NEC) and sepsis. The incidence of the complications significantly decreases with gestational age.

Co-morbidity increases the risk of long-term neurosensory disorders. Neurological, cognitive and behavioural disorders are potentially an emotional, psychological and economic burden for the child and the parents for their whole lives. The most severe disorders are blindness, deafness, cerebral palsy (CP), epilepsy, and very difficult handicaps for a child may be psychomotor retardation (PMR), autism, cognitive disorders, ADHD, other psychiatric disorders, alcohol or other substance abuse, and social behaviour disorders. The key part in the life of a child is adolescence. Approximately 25% of preterm new-borns may develop psychiatric disorders in the period of adolescence.

Table 5 – Survival rate according to birth weight under 1000 g (AAP 2012)

	Year of birth	<500 g		500–750 g		750–1000 g	Notes
UK and Ireland (Costeloe et al. 2000)	1995	6% (*n* = 33)		32% (*n* = 497)		56% (*n* = 276)	Admitted in NICU
NICHD Network centres (Lemons 2001)	1995–1996	11%		52% (500–800 g)		85%	All live-births; new-borns with inborn development disorders are excluded
Vermont Oxford Network units (Finer et al. 1999)	1994–1996	17% (*n* = 497)		60% (*n* = 5334)		90% (*n* = 6336)	All live-births; new-borns with lethal anomalies are excluded
Norway (Markestad et al. 2005)	1999 & 2000	10%/54% (*n* = 71/13)		42%/68% (*n* = 216/92)		78%/88% (*n* = 268/240)	All births/ admitted in NICU
United States (National Center for Health Statistics 2001)	2001	14% (*n* = 6450)		52% (*n* = 11.081)		85% (*n* = 11.847)	All live-births
Vermont Oxford Network centre	2003–2005	17% (*n* = 4.662)		56% (*n* = 22.649)		85% (*n* = 27.052)	All new-borns born in hospitals or transported in the first ≤28 postnatal days
NICHD Network centre (Lemons et al. 2001) (100 g increments)	1995–1996	501–600 g 29% (*n* = 317)	601–700 g 64% (n = 449)	701–800 g 74% (*n* = 439)	801–900 g 86% (n = 419)	901–1000 g 90% (*n* = 462)	All live-births; new-borns with inborn development disorders are excluded

Medicine made great progress during the 20th century. There were significant changes in gynaecology and obstetrics, neonatology and nursing. The implementation of many new therapeutic strategies and prevention (e.g. the centralization of patients with low birth weights, better quality lung ventilation, nutrition, precise check-ups of infectious diseases and others) significantly contributed to the progress. The result was a significant decrease in the death rate and an increase in preterm infant survival. In Czech Republic (Zoban et. al. 2015) the number of live-born babies with low birth weight grew (above all weight categories of 1500–2499 g; by 2.3% in 13 years); the specific new-born death rate (SNDR) decreased, including the category of <750 g/23.–26. g.w.; the prevalence of "high-risk" peri-/neonatal morbidity changed mostly in the category of <1000 g: cerebral morbidity and early infections decreased; however, the incidence of BPD and ROP increased again. The analysis published by Stoll et al. (2015) has shown significant changes in nursing care in the last 20 years in the USA, as well as in the death rate and morbidity. These changes included the increase of antenatal steroids (from 24% to 84%), which significantly reduced the risk of RDS and IVH; the number of caesarean sections in ELBWI increased

(from 44% to 64%), the number of intubations of new-borns in operating rooms decreased (from 80% to 65%), the use of CPAP increased from 7% to 11%, postnatal steroid use, which may influence brain development, decreased (from 29% to 13%). The number of new-borns surviving until discharge increased, mainly the groups of new-borns born in the 23rd, 24th, 25th and 27th g.w. There was a significant improvement in the survival of infants born between the 22nd and 24th g.w. without serious morbidity. There was also a significant decrease in serious IVH in new-borns who were born between the 26th and 28th g.w., however, not in the group of new-borns who were born in ≤25 g.w. Managing effective preventive anti-infectious measurements led to a decrease of later sepsis (LOS). The incidence of BPD did not decrease. There was a mild increase in the group of new-borns who were born between the 26th and 27th g.w.

Determining the level of viability is the basic factor when considering the treatment. Besides the level of maturity of the foetus and its health condition, the viability depends on the development of medical technologies. It also depends on the socio-economic and cultural factors. From the point of view of being born alive and surviving, the borderline of viability is between the 22nd and 24th g.w. The agreement of the professional community on providing active nursing care is based on the level of probability of survival and survival without serious impacts. In developed countries, resuscitation and intensive care are mostly obligatory from the 26th gestational week because children born in this week have a high chance of surviving without serious impacts and of living a good quality life. The period between the 22nd and 25th gestational week is marked as a grey zone, when the results of the care are uncertain and unpredictable. They depend not only on gestational age, but also on weight, gender, the frequency of pregnancies, the place of birth and the induction of lung maturity of the foetus by corticoids. The results are also influenced by the approach of the doctors and parents to the nursing care. Surviving the first week significantly changes the prognosis. When deciding about the type of nursing care, it is necessary to work on the complex idea of viability. Creating standards based only on gestational age, which we are often not able to determine exactly, would not correspond with the medical and ethical complexity of the situation and it would prevent medical staff from individual decision making (Zlatohlávková 2011).

We cannot predict long-term immaturity disorders; some consequences do not have to be obvious until school age. Smaller impacts such as learning disorders, bad co-ordination or an inability to pay attention, may be the consequence of premature birth.

Many cohort studies have established an increased survival rate of new-borns that were born before the 27th g.w. They, however, focused on monitoring the survival rate and its quality (Costeloe et al. 2012). The data from the EPICURE study confirm that the prevalence of psychomotor disorders was significantly connected to the length of pregnancy; a more serious impact was found in a shorter gestation (45% in the 22nd–23rd g.w., 30% in the 24th g.w., 25% in the 25th g.w. and 20% after the 26th g.w. (Moore et al. 2012). In this group, CP was found in 14% of the surviving infants. There is certain evidence that the incidence of poliomyelitis in preterm infants born between the 28th and the 31st g.w. is decreasing (Hack and Costello 2007).

A few recent cohort studies (NICHD – USA, EPIPAGE 2 – France, NRN – Japan, PBFT – Taiwan, EPICure – England, EXPRESS – Sweden and KKH – Singapore) have provided estimates of specific survival rates by gestational age that may be used as the basis for understanding the results and international differences in survival rates of extremely immature new-borns (Patel 2016). The data from the cohort studies (EXPRESS Group, EPICure) have provided the estimates of long-term psychomotor disorders in ELBWI in the age of 2.5 to 3 years, as well as the degree of seriousness of the disorders by gestational age. According to the published data from the ESPRESS study, Sweden (analysis of patients aged 2.5 years), 42% (99% CI, 36–48%) of extremely preterm infants did not suffer an impact on health, 31% (99% CI, 25–36%) suffered mild impacts, 16% (99% CI, 12–21%) suffered medium impacts and 11% (99% CI, 7.2–15%) suffered severe impacts on their health. Mild and severe impacts decrease with gestational age (22 weeks – 60%, 23 weeks – 51%, 24 weeks – 34%, 25 weeks – 27% and 26

weeks – 17%) (Serenius et al. 2013). Moore et al. (2012) published similar results for children aged 3 years. None or mild impacts occurred in 55% of new-borns with a gestation of 22–23 weeks (95% CI, 39–72%), in 70% of new-borns with a gestation of 24 weeks (95% CI, 61–80%), in 75% of new-borns with a gestation of 25 weeks (95% CI, 68–81%), in 80% of new-borns with a gestation of 26 weeks (95% CI, 75–85%). Medium impacts occurred in 18% of new-borns with a gestation of 22–23 weeks (95% CI, 8–34%), in 14% of new-borns with a gestation of 24 weeks (95% CI, 8–23%) in 11% of new-borns with a gestation of 25 weeks (95% CI, 6–16%), in 11% of new-borns with a gestation of 26 weeks (95% CI, 9–15%). Severe impacts occurred in 26% of new-borns with a gestation of 22–23 weeks (95% CI, 14–43%), in 15% of new-borns with a gestation of 24 weeks (95%, CI 9–24%), in 15% of new-borns with a gestation of 25 weeks (95% CI, 10–21%), in 10% of new-borns with a gestation of 26 weeks (95% CI, 6–14%).

The incidence of premature births is constantly increasing in ***SR*** as well. The number of live-born babies with a birth weight of 1500 g increased by 36.5% between 1999 and 2015 (up to 1.27% of all live-born babies in 2015). Outpatients' department for the new-borns with pathological and perinatal risks monitor and keep a record of new-borns with a very low birth weight for long-term morbidity. Details on all new-borns with a birth weight under 1500 g were gained retrospectively during 2015. The information was gained using a questionnaire. The percentage of identified children in the outpatients' department for infants with perinatal pathology and risk, who were born in 2013 and analysed in 2015 and who survived until discharge, was 69% in infants with a birth weight of ≤1000 g and 71% in infants with a birth weight of 1001–1500 g. In the monitored group of new-borns who had a birth weight of ***≤1000 g***, the number of healthy new-borns increased. In 2010, it was 60%, and in 2013, it was 79%, although the extremely low birth weight infant group (ELBWI) registered a small increase in survival rate, i.e. from 64% to 67%. There was a small decrease in the incidence of sight disorders, however, we registered an increase in hearing disorders in this weight group (2013: sight disorders 0.6%, hearing disorders 2.3%). The incidence of cerebral palsy (CP) and psychomotor retardation (PMR) is slightly oscillating; in 2013, the incidence of CP was 8.7% and the incidence of PMR was 11.2%. We also registered a slight increase in the number of healthy new-borns with a birth weight of ***1001–1500 g*** (2010: 81% vs. 2013: 85%), where the survival rate between the years improved from 92.7% to 96.1%. The incidence of sight disorders slightly decreased; there was a slight increase in hearing disorders in this weight group (2013: sight disorders 0.3%, hearing disorders 1.5%). The Slovak perinatology and neonatology registered a higher incidence of CP and PMR in the weight group from 1001 to 1500 g (in 2013, the incidence of CP was 10.3% and the incidence of PMR was 8.2%) (Magyarová et al. 2014).

CONCLUSION

The development of prenatal medicine has led to a decrease in the new-born death rate and to a progressive decrease in the gestational-week time necessary for new-borns to survive. The strongest predictors of long-term survival are the gestational age and the infant's birth weight. The probability of long-term results of intensive resuscitative care is also influenced by gender or the exposure to antenatal corticosteroids. New-borns with a birth weight higher than 1000 g and a gestational age of over 28 weeks have a positive prognosis, a low death rate and morbidity. New-borns with a gestation of 26 to 28 weeks face a relatively low death rate; this fact has not changed in the last 15 years. Considering national and international published data, the higher survival rate of extremely immature new-borns in Slovakia is not connected to the higher incidence of serious morbidity of new-borns or to long-term impacts on neurological development in later age.

CONFLICT OF INTERESTS

The authors have no conflict of interest to disclose.

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