e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15 (11); 1419-1425

Original Research Article

Development in Childhood after Very Preterm Birth: Relationships with Later Neurodevelopmental and Health Results

Pawan Kumar[1], Kaushalendra Kumar Singh[2], Safi Ahmad[3], Anil Kumar Tiwari[4]

[1]Senior Resident, Patna Medical College & Hospital, Patna, Bihar, India
[2]Assistant Professor, Patna Medical College & Hospital, Patna, Bihar, India
[3]Post Graduate Trainee, Patna Medical College & Hospital, Patna, Bihar, India
[4]Assistant Professor, Patna Medical College & Hospital, Patna, Bihar, India

Received: 25-08-2023 / Revised: 28-09-2023 / Accepted: 30-10-2023
Corresponding author: Dr. Anil Kumar Tiwari
Conflict of interest: Nil

Abstract:

Objective: The only information available on the long-term outcomes of preterm infants is frequently a cross-sectional assessment of neurodevelopmental impairment (NDI) at the corrected age of 23–35 months. However, individual trajectories in result over time may differ and impairments may not become obvious until infancy or disappear over time. This study's main objective was to describe NDI in very preterm newborns at the ages of 1, 4, and 7 years old. The individual longitudinal trajectories in NDI from 1 to 7 years of age were subjected to a longitudinal analysis as a secondary goal.

Method: This was a single-center prospective cohort research that tracked children through 2023 who were born between 2020 and 2021 at less than 31 weeks' gestation. NDI evaluations at ages 1, 2, and 7 served as the outcome measurement. In regard to the cognitive, neurological, visual, and auditory components of the NDI composite score, issues were classified as none, mild, moderate, or severe. Standardized psychometric tests were used to evaluate cognitive function, which was expressed as a total DQ/IQ score. The neonatologist evaluated the neonate's neurological, visual, and auditory abilities.

Results: 240 kids in total were eligible for follow-up and 170 (78% of them) were evaluated. 53, 53, and 61% of the children at 1, 4, and 7 years old had no NDI; 30, 35, and 31% showed mild NDI; and 14, 9.1, and 8.5% of the children at 1, 4, and 7 years old showed moderate-to-severe NDI. 62% of the kids stayed in the same NDI category from 1 to 7 years old, 21% got better and moved into a better NDI category, and 16% became worse and moved into a worse NDI group. There were no differences between infants whose baseline traits improved or worsened. There were no differences between infants whose baseline traits improved or worsened. At all-time points, extreme prematurity, male gender, and low parental education were linked to worse NDI status. Despite the fact that there was significant individual heterogeneity in NDI status across time, gestation, gender, and parental education did not affect the trajectory of NDI.

Conclusion: In order to offer the best and most individualized recommendations and care when necessary, continued follow-up until the start of the school year is crucial.

Keywords: Very preterm children, trajectories, neurodevelopmental outcome, longitudinal follow-up, and NDI.

Introduction

Preterm births below 31 weeks' gestation have grown during the past few decades, and preterm children now have higher survival rates (1; Figure 1). Even said, the rising proportion of preterm children who survive still raises concerns about unfavourable long-term outcomes. It is commonly recognised that premature babies are more likely to grow up with physical and cognitive difficulties [2]. Clinicians and families must be knowledgeable of the neurodevelopmental outcomes of infants born at these early gestational ages (GA), as these results may affect antenatal counselling, resuscitation policies, and NICU recommendations [3].

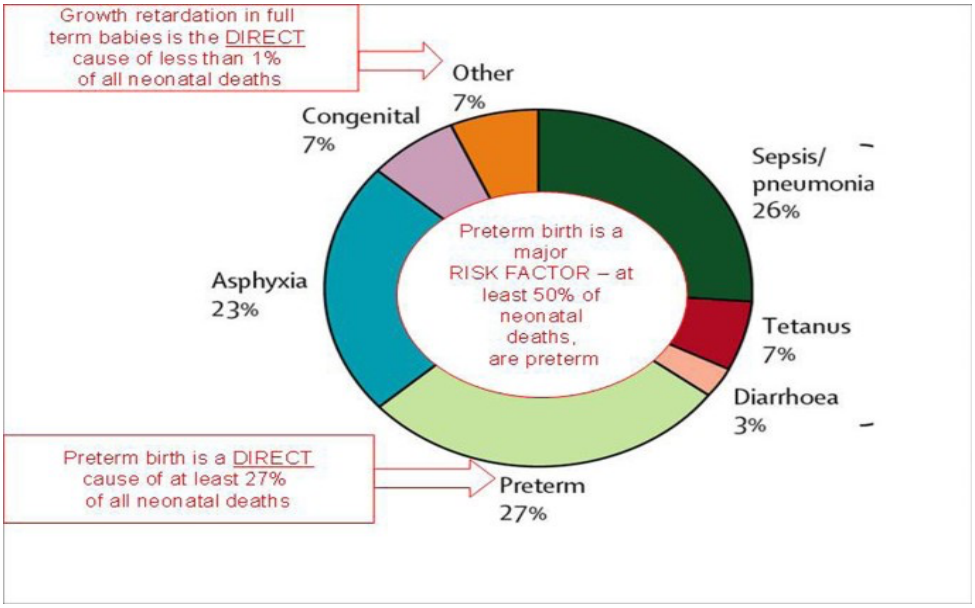

Figure 1: Risk Factor associated with Pre-term babies.

Studying development as a dynamic process is becoming more popular since the effects of developmental impairment may vary depending on the stage of development [4]. Infancy cross-sectional assessments make up a large portion of the outcome data currently accessible, but it is crucial to follow infants across time. Early signs of inadequate functioning may serve as a crucial warning sign for future issues or a call for early intervention, and impairments may last throughout childhood, adolescence, and adulthood [5]. Therefore, substantial variance in individual trajectories that cannot be seen in cross-sectional research may exist [6].

Research assessing preterm children's developmental trajectories frequently concentrates on particular developmental aspects, such as cognitive, behavioural, or social issues [7]. However, a composite outcome score incorporating many categories offers a broad perspective on the number and nature of problems experienced by preterm born children.

Evaluation of developmental trajectories using a composite result may yield extra information because developmental disorders can occur over a wide range of outcome measures. The composite measure of neurodevelopmental impairment (NDI), which considers cognitive, neurological, visual, and auditory function, is a frequently used indicator of a poor long-term result [8]. This outcome measure emphasises severe deficits and gives physicians and parents crucial prognostic data [9].

Preterm babies born under 31 weeks of gestation have been entitled to a thorough follow-up programme in the perinatal centre for the past three decades. This comprises visits to the neonatologist and psychologist's outpatient clinic at the corrected age of one year and the uncorrected ages of four and seven years, allowing for the possibility of an NDI assessment at three additional ages. Unique knowledge about the growth of very preterm children is provided by the data gathered over a period of more than 2 years. As a result, the main goal of this study was to describe NDI in very preterm born children who were assessed at three later ages of 1, 4, and 7. As a supplementary purpose, a longitudinal analysis was undertaken on the individual longitudinal trajectories in NDI's from 1 to 7 years of age

Method

This cohort research included all newborns with a gestational age under 31 weeks who were admitted within 20 hours following birth to the neonatal intensive care unit (NICU) at Patna Medical College & Hospital, Patna between 2020 and 2021 and followed through 2023. Children with parents who reside outside Patna Medical College & Hospital, Patna adherence area were excluded, as were children who were referred by other NICUs.

A prospective data collection method was used for the outpatient clinic visits. Neonatal information was gathered from each patient's medical file. Gender (male or female), birth weight in grammes, gestational age in days (based on ultrasound findings or, in the absence of ultrasound data, on the first day of last menstrual period), small for gestational age (defined as birth weight below the 10th percentile [10], multiplicity (dichotomized as single or multiple birth), mode of delivery (dichotomized as vaginal or by caesarean section), and complete course of antenata were among the individual characteristics Apgar score at five minutes postpartum, inborn or outborn NICU, rate

of artificial ventilation greater than twelve hours, days of endotracheal intubation on any mode of ventilation, surgical treatment of a persistent ductus arteriosus, intraventricular haemorrhage grade three or four according to ultrasound [11], cystic periventricular leukomalacia grade three [12], severe brain injury (defined as intraventricular haemorrhage grade three or four or cystic periventricular.

Using scores established by the Netherlands Institute for Social and Cultural Research (The Hague, Netherlands) based on postal code at birth, socioeconomic status was evaluated. An average score of 0 and a positive or negative score signifying a better or lower than average status were used [12]. Reasons for no-show were noted for children who were not seen for a follow-up visit.

Any preterm children below 31 weeks' gestation were eligible for our follow-up programme. These included appointments with the neonatologist and psychologist in an outpatient setting at the corrected age of one year and the uncorrected ages of four and seven years. The neonatologist evaluated the child's neurological, visual, and auditory capabilities as well as his or her overall health. According to the GMFCS classification, the neurological result was rated as normal, somewhat abnormal, or unilateral/bilateral CP [13]. The child's cognitive, emotional, and behavioural development were assessed by the psychologist.

A composite score based on cognitive, neurological examination, and the existence of visual and/or hearing impairment served as the outcome measure, called neurodevelopmental impairment (NDI). There were four levels of NDI: none, mild, moderate, and severe. If cognitive testing revealed an IQ or DQ between 71 and 83 (1 to 2 SD), visual or hearing loss without a device or with good correction, or faulty neurological tests without a neurological syndrome (such as posture, coordination, and tone dysregulation disorders), the NDI was categorised as light. If the cognitive DQ/IQ score fell between 54 and 68 (2 to 1 SD), there was a unilateral cerebral palsy, there was restricted vision or hearing, and aids were used. If a person had bilateral cerebral palsy, blindness, deafness, or a cognitive DQ/IQ score below 54 (>-2 SD), their NDI was classified as severe. Based on the poorest determinant in either of the four categories, the NDI score was calculated. NDI was categorised as missing if one category was absent. For examinations conducted at ages 1, 4, and 7, NDI was calculated.

Depending on how the data were distributed, the Student's T-test or Mann-Whitney U-test was used to compare children with and without follow-up, and the Chi-square test was used for categorical and dichotomous variables. The R multivariate imputation by chained equation (MICE) package was used to impute parental education for the 24% of the children whose data were missing. An interaction term between age and group was utilised in a continuation ratio model to examine NDI trajectory, testing whether different groups had distinct NDI trajectory. Together with gender (boys vs. girls), gestational age (extremely preterm (EP) vs. very preterm (VP), and parental education (low vs. middle-to-high), these group terms also included a dichotomized variable for each of these factors.

Results

500 infants born between 2020 and 2023 who were under 31 weeks' gestational age were admitted to the NICU. 260 (16%) of these infants passed away, leaving 240 infants who may have received follow-up care in the outpatient clinic. 170 (or 78%) of these kids were seen for follow-up. A total of 63 (74%), 59 (70%), and 48 (62%) children received follow-up at 1, 4, and 7 years, respectively.

Compared to children without follow-up, those who had it at birth were less mature. The socioeconomic status of children who were seen for follow-up was greater. Their admittance to the NICU was made substantially more frequently complicated by PDA and ROP, but significantly less frequently by a laparotomy. Children who received follow-up had lengthier stays in the NICU than those who did not.

At ages 1, 4, and 7, NDI could be computed for 63, 58, and 48 children, respectively (Table 1).

Table 1: NDI at each subsequent age

Follow-up	Age 1	Age 4	Age 7
Age at assessment			
Mean (SD)	2.27 (0.12)	5.07 (0.18)	8.10 (0.21)
Median (IQR)	2.24 (2.21-2.28)	5.02 (5.00-5.20)	8.02 (8.0-8.22)
NDI			
None (%)	53%	53%	61%
Mild (%)	20%	35%	31%
Moderate (%)	7.0%	6.1%	5.8%
Severe (%)	7.3%	3.1%	2.6%
NDI in EP (<27 weeks)			
None (%)	51%	46%	54%

Mild (%)	32%	44%	35%
Moderate (%)	9.0%	5.5%	6.7%
Severe (%)	8.1%	2.3%	2.5%
NDI in VP (27° -28° weeks)			
None (%)	57%	60%	67%
Mild (%)	31%	28%	24%
Moderate (%)	5.5%	6.8%	5.0%
Severe (%)	6.7%	3.4%	3.5%

53, 53, and 61% of the infants at 1, 4, and 7 years old did not have any NDI, while 14, 9.1, and 8.5% of the children had moderate-to-severe NDI. 21 (12.3%) of the 23 infants with minor disabilities at 1 years of age exhibited mild impairments in both domains.

None of the newborns had more than two impairments. Among the group of 12 infants who had minor disabilities at age 4, 23 (21.7%) had a mild disability in two domains, 21 (3%) in three domains, and 2 (0.3%) had a mild disability in all domains. Seven (17.3%) of the 11 babies with minor disabilities at age seven had mild impairments in two domains, two (0.5%) had mild impairments in three domains, and two (0.5%) had mild impairments in every domain.

More children were examined in a clinic as they grew older for rehabilitation medicine and stopped receiving follow-up care. When these kids were included in the moderate-to-severe NDI category, the percentage at 7 years old rose to 15%. The original data was used in further research to classify this subgroup as missing. When NDI rates for EP and VP newborns were presented separately, it was seen that the rates of "no NDI" and "mild NDI" were lower in EP infants than in VP infants, but the rates of moderate-to-severe NDI were identical (Table 1).

NDI for 1-7 Age Group

At 1, 4, and 7 years of age, 35% of children showed no NDI for the entire trajectory, and 80% of children showed either no NDI or mild NDI across the entire trajectory. 4.1% of children experienced moderate-to-severe NDI during the course of their whole trajectory. 62% of these kids stayed in the same NDI category from 1 to 7 years, 21% got better and moved into a better NDI category, and 16% became worse and moved into a worse NDI category. 75% of all kids who had normal NDI at 1 years old were still in that category at 7. For newborns with mild impairments, 42% remained in the same NDI group, while for infants with moderate to severe impairments, 51% did. From 1 to 8 years old, there were no variations in the traits of newborns that stayed in the same group, got better, or got worse.

Individual Longitudinal NDI Trajectories

The continuation ratio model revealed that, compared to extremely preterm-born children, very preterm-born children had, on average, 1.94 (95% CI 1.27-2.97) times' higher odds of being in a better NDI group. Children from parents with middle-to-high education had 3.36 (95%CI 2.00-5.63) times higher odds of being in a better NDI category compared to children from parents with low education, and female children had a 2.01 (95%CI 1.31-3.04) times higher likelihood of being in a better NDI category than male children. When the trajectories were compared to these traits, it was discovered that children with EP and VP traits, as well as male and female children and children with low vs. middle-high educational backgrounds, displayed similar trajectories.

Discussion

In this study, neurodevelopmental damage in very and extremely preterm children born below 31 weeks gestation was assessed at ages 1, 4, and 7. Also, the progression of each longitudinal trajectory across time was examined. In 36% of the kids, we saw individual changes in NDI status over time, with 16% showing a move into a more concerning category and 21% showing an improvement. But over time, 62% of the kids stayed in the same category.

The severity of NDI was clearly correlated throughout time with gestation, gender, and parental education, according to longitudinal research. There were no distinctions between the traits of children who improved and those who got worse, and gestation, gender, and parental education had no bearing on the NDI trajectories. We noted greater rates for kids without or with mild NDI compared to prior studies. At ages 5 and 8, 54 and 62%, respectively, of the survivors demonstrated normal neurodevelopment, while 30% and 36 survivors demonstrated modest neurodevelopmental damage. At 5 and 8 years old, respectively, the normal development rate for EP children was 47 and 55%, while the mild NDI rate was 45 and 36%. Children born under 27 weeks' GA had rates of 36 and 30% for children without and with mild NDI at 6.5 years old, respectively, according to the Swedish EXPRESS study [14]. Children born below 26 weeks' GA had a rate of 75% for none-to-mild NDI at 6 years and a rate of 53% for none-to-mild NDI in 53% at 11 years,

according to the UK's EPICure study [3]. However, differences in follow-up age, the diagnosis of neurodevelopmental disability, and study population prevent worldwide comparisons [15]. One moderate-to-severe impairment in one domain may have the same severity as several mild deficiencies in other domains. At ages 1, 4, and 7, 12.3, 25.1, and 18.5% of infants with mild NDI had minor issues in more than one domain, respectively. It seems that as people become older, more modest deficiencies start to show. Unfortunately, the NDI definition does not take into account the possibility of compounded long-term impacts from multiple impairments across domains. Further research on the significance of milder neurocognitive impairments may be necessary [16].

There are few longitudinal follow-up studies, despite the abundance of cross-sectional follow-up investigations. The results of this study revealed that 16% of all children got worse by the time they turned 8 and that roughly 2/3 of the children examined at 2 years old were still in the same NDI group. Similar findings have previously been published in the EXPRESS study, which found that from the ages of 2 to 6.5, 47% of all children remained in the same NDI group and 32% of all children worsened towards a poorer NDI category [17]. These findings show significant individual heterogeneity over time, even if average NDI rates remained comparable throughout time. In fact, this highlights the significance of maintaining follow-up with individuals throughout their time in school.

At all-time points, it was discovered that the severity of NDI was related to the EP/VP status, gender, and parental education. These data were consistent with other research reports of gender disparities in neurodevelopmental outcomes favouring females [18]. Also, the associations between parental education and neurodevelopmental outcome as well as the previously documented associations between gestational age and neurodevelopmental outcome are strengthened by these results [11]. Although it was discovered that EP/VP status, gender, and parental education were related with NDI, these relationships remained constant across time and the trajectories' paths were unaffected by these variables. So, it appears that kids with these traits have the same potential for growth and development as kids without them [18].

Moreover, no changes in the traits of infants who got better or worse between the ages of 1 and 7 were discovered. Nonetheless, significant individual variability in trajectories were observed. This emphasises the significance of additional elements that may have an impact on development over time, such as early childhood interventions like a comprehensive physiotherapy programme or special education support. Moreover, socio-environmental elements like the strength of the parent-child bond are crucial for growth [16].

The added advantage of a composite result is that it gives a general sense of the outcomes following very preterm delivery, despite the importance of thorough investigation of individual domains. It's crucial to avoid concentrating on just one developmental domain because issues following preterm birth might arise throughout a variety of developmental domains. The majority of the youngsters in this study showed no impairment when examining the individual domains separately. Yet, when the several domains were combined to create the NDI composite outcome, a minority of 35% of all children showed no NDI across the whole trajectory. It appears that the majority of very preterm kids do have some obvious issues at some point in their lives. Also, the study's composite outcome measure is the longer-term result that is most usually utilised for comparisons both within and between nations [19].

International comparisons can aid clinician judgement and give families predictive information. In this study, preterm was taken into account when calculating cognitive scores at age 1, but not at ages 4 or 7. The majority of worldwide recommendations and the current Dutch national guideline on follow-up both suggest using corrected scores for preterm children up to 2-3 years. Nonetheless, a substantial difference between corrected and uncorrected IQ scores was identified in very preterm children at age 5, with adjusted values naturally being higher than uncorrected ones [20]. It is advised that future studies consistently reflect cognitive outcomes based on corrected scores [21]. The study's total follow-up rate was 79%, which is comparable to other studies' follow-up rates, which ranged from 71 to 92% at various ages [3, 5]. Also, during the longitudinal follow-up programme, more than 61% of the children completed follow-up at all-time points, showing a high follow-up rate when compared to other longitudinal studies like the just-released EPICure2 study [22]. These kids, who had no further care, had healthy birth weights, no significant brain damage, and straightforward NICU admissions.

This explains why babies with follow-up visits were more immature at delivery and spent longer time in the NICU than babies without follow-up visits. On the other hand, there was a noticeable difference in socioeconomic level between infants who had follow-up and those who did not, with a higher SES score in the latter group. This result is consistent with other research' conclusions that dropout rates were higher in households with social difficulties and that preterm children from such

families would have less favourable neurodevelopment [3].

Conclusion:

This study investigated neurodevelopmental impairment in extremely preterm children at three distinct ages up to the age of 8 along with the longitudinal trajectories of these outcomes.

The severity of NDI was found to be clearly correlated with gestation, gender, and parental education at all time periods. Despite the fact that we saw significant individual heterogeneity in NDI status across time, gestation, gender, and parental education had no effect on the NDI trajectory.

The significance of other (unknown) variables on developmental trajectories is indicated by these findings. Very prematurely born children must be followed up with until they start school in order to offer the best, personally tailored referrals and care possible.

References:

1. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, Eunice kennedy shriver national institute of child health. Human Development Neonatal Research NetworkTrends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA. 2015; 314:1039-51.
2. Patel RM, Kandefer S, Walsh MC, Bell EF, Carlo WA, Laptook AR, Sánchez PJ, Shankaran S, Van Meurs KP, Ball MB, Hale EC. Causes and timing of death in extremely premature infants from 2000 through 2011. New england journal of medicine. 2015 Jan 22; 372(4):331-40.
3. Tanvetyanon T. Talking about death with dying children. The New England journal of medicine. 2005 Jan 1; 352(1):91-2.
4. Anderson P, Doyle LW. Victorian Infant Collaborative Study Group: Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s. jama. 2003 Jun 25; 289(24):3264-72.
5. Linsell L, Johnson S, Wolke D, O'Reilly H, Morris JK, Kurinczuk JJ, Marlow N. Cognitive trajectories from infancy to early adulthood following birth before 26 weeks of gestation: a prospective, population-based cohort study. Archives of disease in childhood. 2018 Apr 1; 103(4):363-70.
6. Raju TN, Mercer BM, Burchfield DJ, Joseph Jr GF. Periviable birth: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of child health and human development, Society for Maternal-Fetal medicine, American Academy of pediatrics, and American College of obstetricians and Gynecologists. American journal of obstetrics and gynecology. 2014 May 1; 210(5):406-17.
7. Perlman J. Periviable Birth: Executive Summary of a Joint Workshop by the: Eunice Kennedy Shriver: National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists. Obstetrics & Gynecology. 2014 Sep 1; 124(3):635.
8. Younge N, Smith PB, Gustafson KE, Malcolm W, Ashley P, Cotten CM, Goldberg RN, Goldstein RF. Improved survival and neurodevelopmental outcomes among extremely premature infants born near the limit of viability. Early human development. 2016 Apr 1; 95:5-8.
9. Ding S, Lemyre B, Daboval T, Barrowman N, Moore GP. A meta-analysis of neurodevelopmental outcomes at 4–10 years in children born at 22–25 weeks gestation. Acta Paediatrica. 2019 Jul; 108(7):1237-44.
10. Hoftiezer L, Hof MH, Dijs-Elsinga J, Hogeveen M, Hukkelhoven CW, van Lingen RA. From population reference to national standard: new and improved birthweight charts. American journal of obstetrics and gynecology. 2019 Apr 1; 220(4):383-e1.
11. Papile L, Burstein J, Burstein R, Koffler H, Koops B. Relationship of intravenous sodium bicarbonate infusions and cerebral intraventricular hemorrhage. The Journal of pediatrics. 1978 Nov 1; 93(5):834-6.
12. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. Behavioural brain research. 1992 Jul 31; 49(1):1-6.
13. Statusscores SC. Available online at: http://www. scp. nl/Formulieren. Statusscores_opvragen (accessed March 1, 2019). 2017.
14. Palisano R, Rosenbaum P, Walter S, Russel D, Madera E, Galuppi B. Desarrollo y fiabilidad de un sistema para clasificar función de motor gruesa en niños con parálisis cerebral. Dev Med Child Neurol. 1997; 39:214-23.
15. Pieters S, Dek JE, Kooij AP. RAKIT-2 psychometrische eigenschappen deel 2.
16. Van Beek PE, Van De Par K, Van Der Horst IE, Van Baar AL, Vugs B, Andriessen P. The Need for Special Education among ELBW and SGA Preterm Children: A Cohort Study. Frontiers in Pediatrics. 2021 Oct 20; 9:719048.
17. Hortensius LM, Janson E, van Beek PE, Groenendaal F, Claessens NH, Swanenburg de Veye HF, Eijsermans MJ, Koopman-Esseboom C, Dudink J, van Elburg RM, Benders MJ. Nutritional intake, white matter integrity, and neurodevelopment in extremely

preterm born infants. Nutrients. 2021 Sep 27; 13(10):3409.
18. Suir I, Oosterhaven J, Boonzaaijer M, Nuysink J, Jongmans M. The AIMS home-video method: parental experiences and appraisal for use in neonatal follow-up clinics. BMC pediatrics. 2022 Jun 11; 22(1):338.
19. Serenius F, Ewald U, Farooqi A, Fellman V, Hafström M, Hellgren K, Maršál K, Ohlin A, Olhager E, Stjernqvist K, Strömberg B. Extremely preterm infants in Sweden study group neurodevelopmental outcomes among extremely preterm infants 6.5 years after active perinatal care in Sweden. JAMA Pediatr. 2016 Oct 1; 170(10):954-63.
20. Marlow N, Ni Y, Lancaster R, Suonpera E, Bernardi M, Fahy A, Larsen J, Trickett J, Hurst JR, Morris J, Wolke D. No change in neurodevelopment at 11 years after extremely preterm birth. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2021 Jul 1; 106(4):418-24.
21. Adams-Chapman I, Heyne RJ, DeMauro SB, Duncan AF, Hintz SR, Pappas A, Vohr BR, McDonald SA, Das A, Newman JE, Higgins RD. Neurodevelopmental impairment among extremely preterm infants in the neonatal research network. Pediatrics. 2018 May 1; 141(5).
22. Goldstein RF, Cotten CM, Shankaran S, Gantz MG, Poole WK. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Influence of gestational age on death and neurodevelopmental outcome in premature infants with severe intracranial hemorrhage. J Perinatol. 2013; 33(1):25-32.