Int J Clin Exp Med 2017;10(3):5372-5380
www.ijcem.com /ISSN:1940-5901/IJCEM0034549

Original Article

Analysis of high-risk factors and effect of early intervention on preterm infant neurodevelopment

Fang He[1], Qiu-Ping Li[2], Nan-Ping Li[1], Li Yao[1], Xiu-Wei Ma[2], Zhi-Chun Feng[2]

[1]*Children Health Clinic, Army General Hospital Affiliated Bayi Children's Hospital, Beijing 100071, China;* [2]*Army General Hospital Affiliated Bayi Children's Hospital, Beijing 100071, China*

Received June 27, 2016; Accepted September 5, 2016; Epub March 15, 2017; Published March 30, 2017

Abstract: Objective: This study aims to determine the influence of high-risk factors and the effect of early intervention on abnormal neurodevelopmental outcomes in preterm infants with certain risk factors. Methods: The outcome of neurodevelopment was confirmed by Gesell scores. Associations between high-risk factors and neurodevelopmental outcome were examined by chi-square test and logistic-regression analysis. The effect of early intervention on the neurodevelopmental outcome of preterm infants with certain risk factors was determined by two independent sample *t*-tests. A $P<0.05$ was considered statistically significant. Results: We found that both maternal age (OR: 25.477; 95% CI: 4.870-133.290; $P<0.001$) and education level (OR: 0.287; 95% CI: 0.120-0.686; $P=0.005$) were significant prenatal risk factors for abnormal neurological outcomes. Significant perinatal risk factors that were identified included gestational diabetes (OR: 0.127; 95% CI: 0.022-0.752; $P=0.023$), preeclampsia (OR: 54.405; 95% CI: 12.442-237.888; $P<0.001$) and meconium (OR: 38.260; 95% CI: 10.935-133. 864; $P<0.001$). Significant postnatal risk factors included gestational age (OR: 9.170; 95% CI: 2.454-34.265; $P=0.001$), birth weight (OR: 20.960; 95% CI: 4.285-102.519; $P<0.001$) and multiple birth (OR: 114.853; 95% CI: 13.209-998.612; $P<0.001$). The DQ value in the early intervention group was significantly higher than in the non-early intervention group for all five aspects of the Gesell score ($P<0.05$). Conclusions: Maternal age and educational level, gestational diabetes preeclampsia, meconium, gestational age, birth weight and multiple births are risk factors for abnormal neurodevelopmental outcomes among preterm infants. A positive effect of early intervention was identified on the neurodevelopmental outcomes of preterm infants with certain risk factors.

Keywords: Early intervention, high-risk factors, neurodevelopmental outcomes, preterm infants

Introduction

The 2012 World Health Organization (WHO) official data revealed that the number of global preterm infants has reached 15 million cases annually, which accounts for 10% of the total number of neonates. China ranks second in the world for the number of preterm infant cases. Although the survival rates of preterm infants have progressively increased in recent years, the 12-32% prevalence of major neurodevelopmental handicaps in surviving preterm children represents a growing public health concern [1, 2]. Thus, survival is not an adequate measure of success in infants who remain at high risk for neurodevelopmental morbidities. More attention should be given on primary and even long-term neurodevelopmental outcomes.

Cerebral palsy (CP), a group of nonprogressive neurological disorders, cognition and perception disturbances caused by lesions of the brain, arises during early development; and occurs in 1-2.4 cases per 1,000 live births [3]. Severe CP can be predicted with high probability shortly after birth by cranial ultrasonography, magnetic resonance imaging (MRI) and other imaging techniques. As the child develops, early warning signs include delay in meeting motor milestones, seizures, poor sucking ability, a persistently fisted hand, and decreased rate of head growth [4]. However, the majority of cases do not present unequivocal symptoms early in current practice, and most children with CP are diagnosed around the age of 1-2 years.

CP may destroy a child and even the whole family. Hence, the early discovery of the risk of CP is

very important. Population-based studies suggest that low birth weight and small gestational age increase the prevalence of CP [5]. Birth asphyxia such as the 5-minute Apgar score was previously considered to be the most common etiology of CP. Furthermore, some published studies have focused on preterm infants with a high risk of CP due to bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and intraventricular hemorrhage (IVH) [6, 7]. Moreover, previous studies have identified several high-risk factors for the development of CP. However, these studies focused on the incidence of CP, and were limited by either a small sample size or the absence of statistical significance. In this study, the investigators aimed to observe the incidence of its abnormal neurodevelopmental outcome (pre-CP) and high risk factors.

Another fundamental question is whether these children would benefit from being identified earlier and receiving specific, early intervention. Various early intervention (EI) strategies have been developed to improve long-term outcomes. Fredrik Serenius observed 1,011 infants born before 27 completed gestational weeks, and found that among children born extremely preterm and receiving active perinatal care, 73% of them had mild or no disability, and neurodevelopmental outcome improved with each week of gestational age [8]. In another study, Arne Ohlsson assessed the effectiveness of the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) through a systematic review and meta-analyses of randomized controlled trials that included 627 preterm infants; and revealed that there was no evidence to prove that NIDCAP improved long-term neurodevelopmental or short-term medical outcomes [9].

Hence, in this study, we analyzed 1,337 preterm infants at the prenatal, perinatal and postnatal periods to determine the relationship between certain potential risk factors and the incidence of abnormal neurodevelopmental outcomes. At the same time, we focused on the role of early intervention on the neurodevelopmental outcome of preterm infants with certain risk factors to provide precise evidence for the promotion of the neurodevelopment of preterm infants.

Methods

Subjects and ethics

From 2010 to 2012, a total of 2,374 preterm infants were discharged from Bayi Children's Hospital and received follow-up examinations. Among these infants, 1,027 infants who only had one follow-up were excluded from the study. Finally, 1,337 preterm infants were enrolled into this study. These infants were within the gestational age of 26-36 weeks, and their birth weight was within 650-2350 g. Furthermore, among these 1,337 preterm infants, 823 infants had no major neurological disability (case group); and the remaining 514 infants had abnormal developmental quotients (DQs, <75; control group). Infants in the control group were matched for age, gender and parental educational and occupational status. A complete neuropsychological profile was conducted for each infant by assessing parameters from the time of discharge until two years of age.

Written informed consent was obtained from all guardians of these patients, and the study protocol was approved by the Ethics Committee of our hospital.

Neurodevelopment evaluation

Neurodevelopmental outcomes were qualitatively defined using Gesell developmental schedules including adaptive, gross motor, fine motor, language comprehension, and expression and personal social parameters [10]. Preterm infants were normally assessed at 18 months corrected age.

Early intervention methods

Early intervention methods that were referred to NIDCAP intervention after discharge were reviewed. NIDCAP consisted of nutrition and feeding guidance, as well as developmental guidance for gross motor, fine motor and adaptive parameters; which include a rich environment for early intelligence development, tactile stimulation by massage, skin and physical touch, and attention development training [11].

Statistical analysis

Data were encoded for computer analysis by double entry, and compared to the original

Table 1. Univariate analysis for high risks

Variable	Gesell normal	Gesell abnormal	Statistic	*P*
Prenatal risks				
Maternal age				
<25	163	113	-13.427#	<0.001
25-35	171	350		
>35	489	51		
Maternal educational level				
Illiterate	2	26	-8.824#	<0.001
Primary school	199	21		
High school	74	20		
College	469	337		
Graduate	79	110		
History of adverse pregnancy				
No	680	409	1.951*	0.162
Yes	143	105		
Perinatal risks				
Gestational diabetes				
No	454	383	50.599*	<0.001
Yes	369	131		
Preeclampsia/pregnancy-induced hypertension				
No	771	41	-30.895#	<0.001
I	38	201		
II	14	272		
Maternal fever				
No	592	320	-4.311#	<0.001
<38	171	110		
38-39	40	58		
>39	20	26		
Rupture of membrane			-27.424#	<0.001
No	680	44		
<24 h	136	257		
24-48	1	100		
>48	6	113		
Natural delivery				
No	540	160	150.842*	<0.001
Yes	283	354		
Cesarean delivery				
No	283	354	150.842*	<0.001
Yes	540	160		
Meconium				
No	641	2	-31.134#	<0.001
I	172	77		
II	0	230		
III	10	205		
Tight nuchal cord				
No	517	299	2.874*	0.09
Yes	306	215		
Postnatal risks				

Sex				
Male	599	199	152.602*	<0.001
Female	224	315		
Gestational age				
32-37	774	57	-30.118#	<0.001
28-32	45	377		
<28	4	80		
Birthweight				
>2500	184	10	-29.260#	<0.001
1500-2500	601	30		
1000-1500	35	437		
<1000	3	37		
5-minute Apgar score <7				
No	565	254	49.324*	<0.001
Yes	258	260		
Neonatal seizures				
No	771	479	0.125*	0.723
Yes	52	35		
Fraction of inspired oxygen 1st 48 h				
No	769	239	375.781*	<0.001
Yes	54	275		
Intraventricular hemorrhage				
No	795	252	-20.670#	<0.001
I	24	124		
II	4	61		
III	0	77		
Retinopathy of prematurity				
No	578	387	-0.776#	0.438
I	238	71		
II	7	22		
III	0	34		
BPD				
No	769	224	-20.772#	<0.001
I	48	117		
II	5	109		
III	1	64		
Multiple births				
No	817	233	546.070*	<0.001
Yes	6	281		

#Wilcoxon rank sum test, statistic: Z; *chi-square test, statistic: chi-square.

medical files for accuracy. Chi-square test and logistic regression analysis were performed to assess associations with high-risk factors and abnormal neurodevelopmental outcomes, and statistical significance was determined using Wald 2 or F tests. Results from comparisons between cases and controls were presented as odds ratios (OR) with 95% confidence intervals (95% CI). Student's *t*-test for two independent samples was performed to assess the influence of early intervention on preterm infants with certain risk factors. $P<0.05$ was considered statistically significant.

Results

The high-risk factors considered in this study were obtained from the review of literature, and

Table 2. Logistic-regression analysis

Variable	Regression coefficient	Standard error	Wald	P	OR (95% CI)
Maternal age	3.238	0.844	14.707	<0.001	25.477 (4.870, 133.290)
Maternal education	-1.248	0.445	7.881	0.005	0.287 (0.120, 0.686)
Gestational diabetes	-2.061	0.906	5.172	0.023	0.127 (0.022, 0.752)
Preeclampsia/pregnancy-induced hypertension	3.996	0.753	28.188	<0.001	54.405 (12.442, 237.888)
Meconium	3.644	0.639	32.528	<0.001	38.260 (10.935, 133.864)
Gestational age	2.216	0.673	10.855	0.001	9.170 (2.454, 34.265)
Birthweight	3.043	0.810	14.112	<0.001	20.960 (4.285, 102.519)
Multiple births	4.744	1.103	18.481	<0.001	114.853 (13.209, 998.612)
Constant	-20.318	3.638	31.189	<0.001	

Variable selection: stepwise regression. Variables included criteria were P<0.05, and excluded criteria were P>0.10. Univariate analysis of P<0.4 variables as candidate variables into logistic regression. Considering whether vaginal delivery and cesareandelivery are the same cocept, we choose keep cesarean delivery.

Table 3. The DQ value of two groups with certain high-risk factors

Group	N	Adaptive	Gross motor	Fine motor	Language	Personal social
Early intervention group	362	86.09 ± 1.543*	91.72 ± 1.849*	86.11 ± 1.939*	85.68 ± 1.849*	89.33 ± 1.819*
Non-early intervention group	465	60.71 ± 2.586	69.69 ± 2.649	58.31 ± 3.111	55.35 ± 2.753	61.13 ± 2.726
P value		<0.01	<0.01	<0.01	<0.01	<0.01

*Compared with non-early intervention group, early intervention group had a statistically significant effect on the neurodevelopmental outcomes.

these were classified into three groups: prenatal, perinatal and postnatal risks (**Table 1**) [12, 13].

Analysis of prenatal risk factors on abnormal neurodevelopmental outcomes

There was a significant relationship between maternal age/educational level and neurodevlopment outcomes. Logistic regression analysis revealed the following: OR: 25.477, 95% CI: 4.870-133.290, *P*<0.001; OR: 0.287, 95% CI: 0.120-0.686, *P*=0.005; and no significant relationship was identified between the outcome and history of adverse pregnancy (*K*=1.951, *P*=0.162). These results indicate that a higher maternal educational level was associated with better neurodevelopmental outcome, while a maternal age within 25-35 years old was more related with abnormal neurodevelopmental outcome.

Analysis of perinatal risk factors on abnormal neurodevelopmental outcomes

Univariate analysis revealed that all perinatal risk factors (*P*<0.001), except the tight nuchal cord (*K*=2.874, *P*=0.09), had significant associations with neurodevelopmental outcome. However, subsequent logistic regression analysis revealed that only gestational diabetes (OR: 0.127; 95% CI: 0.022-0.752; *P*=0.023), preeclampsia (OR: 54.405; 95% CI: 12.442-237.888; *P*<0.001) and meconium (OR: 38.260; 95% CI: 10.935-133.864; *P*<0.001) were high-risk factors for abnormal neurodevelopmental outcomes. There was no obvious effect of maternal fever, rupture of membrane and delivery method by logistic regression analysis (*P*>0.10).

Analysis of postnatal risk factors on abnormal neurodevelopmental outcomes

Table 1 shows the postnatal risk factors that were assessed in this study. It was found that gestational age (OR: 9.170; 95% CI: 2.454-34.265, *P*=0.001), birth weight (OR: 20.960; 95% CI: 4.285-102.519, *P*<0.001) and multiple births (OR: 114.853; 95% CI: 13.209-998.612; *P*<0.001) were significant risk factors for abnormal neurodevelopmental outcomes (**Table 2**). In addition, infants with younger gestational age and lower birth weight were more likely to have abnormal neurodevelopmental outcomes. Gender, neonatal seizures, the fraction of inspired oxygen during the first 48 hours, a five-minute Apgar score of <7, as well as ROP, BPD and IVH, were not significant risk factors.

The effect of early intervention on the neurodevelopmental outcome of preterm infants with certain risk factors

Table 3 shows the Gesell scores in the early and non-early intervention groups. It was found that DQ values in the early intervention group were higher than in the non-early intervention group for adaptive (86.09 ± 1.543 and 60.71 ± 2.586), gross motor (91.72 ± 1.849 and 69.69 ± 2.649), fine motor (86.11 ± 1.939 and 58.31 ± 3.111), language (85.68 ± 1.849 and 55.35 ± 2.753) and personal social (89.33 ± 1.819 and 61.13 ± 2.726) categories, respectively (all categories, $P<0.01$).

Discussion

As survival continues to increase for preterm infants due to advancements in clinical medicine and greater availability for healthcare, more information has been obtained on short- and long-term neurodevelopmental outcomes. The most common occurring outcome after birth of early preterm infants is CP. In this study, 38.44% (514/1,337) of preterm children had an abnormal neurodevelopmental outcome based on Gesell scores. Studies have suggested that a combination of biologic and environmental factors contribute to the abnormal neurodevelopmental outcome of preterm infants [14]. The order of effects of these high risk factors from high to low in this study was multiple birth, preeclampsia, meconium, maternal age, birth weight, gestational age, maternal education and gestational diabetes.

Prenatal risk factors on neurodevelopmental outcome

Both maternal age and education had a clear association with the prognosis of high-risk preterm infants. We found that mothers within the age of 25-35 years old were more likely to have preterm infants with abnormal neurodevelopmental outcomes, compared with the other two groups. The reason may be the majority of this group and the less attention given to these preterm infants. Mothers with higher educational levels had children with better neurodevelopmental outcomes, compared to mothers with lower educational level; although statistical data revealed the OR value was only 0.287. This is possibly due to better follow-up compliance, which allows for the easy identification of problems and the initiation of earlier intervention.

Perinatal risk factors on neurodevelopmental outcome

Preeclampsia is associated with a significant developmental delay in gross motor, fine motor, and visual motor functions in early childhood. Epidemiological studies have also shown that the incidences of preeclampsia and intrauterine growth retardation are significantly elevated in children with CP, compared with the normal population [15, 16]. Importantly, our findings were in agreement with previous studies; which revealed that severe preeclampsia was significantly associated with worse neurological outcomes (OR=54.405).

Infants born with meconium-stained amniotic fluid were more likely to have neurodevelopmental impairment than normally born infants, and this is attributable to intrauterine hypoxia and subsequent infection [17]. We found that meconium was significantly correlated with abnormal neurodevelopmental outcomes (OR= 38.260).

Postnatal risk factors on neurodevelopmental outcome

We found that gestational age and birth weight were significant risk factors for the development of abnormal neurodevelopmental outcomes, and a decrease in these factors led to an increase in the rate of disabilities. Documented improvements in survival in very low birth weight (VLBW) and extremely low birth weight (ELBW) infants (22-25 weeks gestation and less than 800 g) over the past 20 years have not been accompanied by proportional reductions in the incidence of disability in this population [18, 19]. Neonates that most likely have long-term disability are those who were born before 26 weeks or who have an ELBW of ≤771.1 g. Rates of CP in ELBW infants vary within the range of 5-30%, but are most commonly cited as 15-23% [20]. In extremely preterm infants, the prevalence of CP at two years of age is likely to be higher [21]. Infants born at 34-36 weeks of gestation are 1.25 times more likely to have cognitive impairment than term infants [22]. In this study, we found that infants born below 28 weeks were 13 times correlated with abnormal neurodevelop-

mental outcomes, when compared with infants born within 32-37 weeks of gestation; while infants born with a weight below 1,000 g were 19 times correlated with these outcomes, than an infant with a birth weight within 1,500-2,500 g.

Extremely preterm infants are born during a period of active brain development and maturation, placing them at extremely high risk for brain injury from hypoxia, ischemia, malnutrition and infection; and these are associated with IVH. Severe IVH is the strongest predictor of CP [23]. Multiple studies have reported a 2-6-fold increase in risk of CP in patients with severe IVH [6]. However, we found in this study that IVH was not significantly associated with abnormal neurological outcomes. There were only 10.6% preterm infants with moderate or severe IVH, when compared with other high risk factors; the influence of IVH was negligible.

Common neonatal morbidities including BPD and ROP have been shown to be associated with poor cognitive function and academic abilities in infancy and at school age [24]. However, our study revealed that BPD and ROP were not significant risk factors for abnormal neurological outcomes. The reason might be the same with IVH. Furthermore, 4.7% and 13.4% preterm infants had moderate or severe ROP and BPD, respectively.

Previous reports have indicated that the rate of neurodevelopmental impairment at 18-22 months (after correcting for age) is directly proportional to the duration for mechanical ventilation requirement in the neonatal intensive-care unit (NICU) [7]. However, in our study, the fraction of inspired oxygen during the first 48 hours post-birth was not significantly associated with the risk of developing neurodevelopmental impairment. The possible reason maybe that some preterm infants did not have any severe organic pathology such as neonatal respiratory distress syndrome (NRDS) or BPD, and the time of inspired oxygen did not last long.

Multiple births is an important risk factor for both death and neurodevelopment impairments (NDI) among VLBW infants [25]. In a National Institute of Child Health and Human Development (NICHD) Neonatal Network study, ELBW twins born between 1997 and 2005 had increased risk of moderate to severe CP (8.4% *vs.* 6.3%), a mental developmental index (MDI) less than 70 based on Bayley Scales of Infant Development, Second Edition (BSID II, 39% *vs.* 29.9%), NDI (45.1% *vs.* 36.0%) and death (64% *vs.* 53%), when compared with singletons, respectively [26]. In this study, the incidence of abnormal neurodevelopmental outcome in multiple birth infants was 97.9% (OR=114.853).

The effect of early intervention on preterm infants

We focused on the effect of early intervention on preterm infants based on our previous findings. We found that 362/827 of preterm infants, who were exposed to one or more certain risk factors, had normal DQ values at 18 months (after correcting for age) after receiving NIDCAP intervention upon discharge. In contrast, a total of 465 preterm infants who had one or more certain risk factors, and did not receive any intervention until one year of age or later, or had only received rehabilitation therapy when diagnosed with CP, always had an abnormal DQ value. Gesell scores were statistically significant between these two groups ($P<0.01$), which suggest that early intervention had a positive effect on the neurodevelopmental outcome of preterm children. Some reports have also indicated a positive effect on early intervention in children with brain damage [27]. Another study found that integrated intervention, including medication, hyperbaric oxygen, body massage, passive gymnastics, as well as visual, listening and tactile stimulation administered to children with hypoxic ischemic encephalopathy (HIE), significantly improved the developmental and intellectual index of children, compared to controls [28].

Although the non-early intervention group had abnormal DQ values, they belonged to the mild neurodevelopmental lag. In this study, we confirmed the neurodevelopmental outcome of children through Gesell developmental schedules at 18 months (after correcting for age) by analyzing medical records in the follow-up system of our hospital. Most authorities recommend that the correction of chronological age for preterm children should be continued until two years of age. At this age, for infants born at 28 weeks gestation, this correction produces a 12% difference in terms of developmental age [29, 30]; which represents an important clinical

difference, compared to assessment based on chronological age. In addition, there is currently increasing evidence of abnormal outcomes in school age children and adolescents [31]. For more immature children, this correction could be continued for a longer period of time, since the difference would be significant up to three years (24 weeks gestation: 11% difference) [32]. However, the observation of the neurodevelopment in preterm infants can be extended to the school age: if without early intervention, these preterm infants may exhibit differences with peers of the same chronological age. Under this situation it is difficult to reduce the gap in Gesell scores [33].

Future studies should explore additional factors for increased risk of abnormal neurological outcomes with longer and more suitable observation periods, as well as additional intervention methods, in a large group of preterm infants. These studies would provide a more precise indication of preterm infant neurodevelopmental outcomes, and would minimize the incidence of disability in children with the identified risk factors.

Disclosure of conflict of interest

None.

Address correspondence to: Zhi-Chun Feng, Army General Hospital Affiliated Bayi Children's Hospital, Chaoyangmen No. 2 North Street, Dongcheng District, Beijing 100071, China. Tel: +86 13321154215; Fax: +86 010-66721786; E-mail: zhjfengzc@126.com; drfeng_zc@163.com

References

[1] Muglia LJ, Katz M. The enigma of spontaneous preterm birth. N Engl J Med 2010; 362: 529-35.

[2] Iams JD, Romero R, Culhane JF, Goldenberg RL. Preterm birth: primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet 2008; 371: 164-75.

[3] Panteliadis CP, Hagel C, Karch D, Heinemann K. Cerebral palsy: A lifelong challenge asks for early intervention. Open Neurol J 2015; 26: 45-52.

[4] Bonnier C. Evaluation of early stimulation programs for enhancing brain development. Acta Paediatr 2008; 97: 853-58.

[5] Wilson-Costello D, Friedman H, Minich N, Siner B, Taylor G, Schluchter M, Hack M. Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000-2002. Pediatrics 2007; 119: 37-45.

[6] Lee JY, Kim HS, Jung E, Kim ES, Shim GH, Lee HJ, Lee JA, Choi CW, Kim EK, Kim BI, Choi JH. Risk factors for periventricular-intraventricular hemorrhage in preterm infants. J Korean Med Sci 2010; 25: 418-24.

[7] Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sauve RS, Whitfield MF; Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. JAMA 2003; 289: 1124-9.

[8] Serenius F, Källén K, Blennow M, Ewald U, Fellman V, Holmström G, Lindberg E, Lundqvist P, Maršál K, Norman M, Olhager E, Stigson L, Stjernqvist K, Vollmer B, Strömberg B; EXPRESS Group. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. JAMA 2013; 309: 1810-20.

[9] Ohlsson A, Jacobs SE. NIDCAP: A Systematic Review and Meta-analyses Randomized Controlled Trials. Pediatrics 2013; 131: e881-93.

[10] Wang G, Chen Y, Zeng R. The value of neurobehavior tests on the assessment of brain function in infants with hypoxic ischemic encephalopathy. Chin J Nat Med 2010; 12: 9-12.

[11] Als H, Butler S, Kosta S, McAnulty G. The Assessment of Preterm Infants Behavior (APBI): furthering the understanding and measurement of neurodevelopmental competence in preterm and full term infants. Ment Retard Dev Disabil Res Rev 2005; 11: 94-102.

[12] Bastek JA, Sammel MD, Paré E, Srinivas SK, Posencheg MA, Elovitz MA. Adverse neonatal outcomes examining the risks between preterm, late preterm and term infants. AM J Obstet Gynecol 2008; 199: e361-8.

[13] Thompson DK, Warfield SK, Carlin JB, Pavlovic M, Wang HX, Bear M, Kean MJ, Doyle LW, Egan GF, Inder TE. Perinatal risk factors altering regional brain structure in the preterm infant. Brain 2007; 130: 667-77.

[14] Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism: a review and integration of findings. Arch Pediatr Adolesc Med 2007; 161: 326-33.

[15] Zetterström K, Lindeberg S, Haglund B, Magnuson A, Hanson U. Being born small for gestational age increases the risk of severe pre-eclampsia. BJOG 2007; 114: 319-24.

[16] Class MJ, de Vries LS, Bruinse HW. Maternal characteristics of a cohort of preterm infants

with a birth weight ≤750 g without major structural anomalies and chromosomal abnormalities. Am J Perinatol 2011; 28: 367-75.
[17] Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-Analysis of Neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics 2009; 124: 717-28.
[18] Narchi H, Skinner A, Williams B. Small for gestational age neonates-are we missing some by only using standard population growth standards and does it matter? J Matern Fetal Neonatal Med 2010; 23: 48-54.
[19] Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, Bauer CR, Donovan EF, Korones SB, Laptook AR, Lemons JA, Oh W, Papile LA, Shankaran S, Stevenson DK, Tyson JE, Poole WK; NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol 2007; 196: 147, e1-8.
[20] Taylor HG, Klein N, Drotar D, Schluchter M, Hack M. Consequences and risks of <1000 g birth weight for neuropsychological skills, achievement, and adaptive functioning. J Dev Behav Pediatr 2006; 27: 459-69.
[21] Vohr BR, Wright LL, Poole WK, McDonald SA. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. Pediatrics 2005; 116: 635-43.
[22] Petrini JR, Dias T, McCormick MC, Massolo ML, Green NS, Escobar GJ. Increased risk of adverse neurological development for late preterm infants. J Pediatr 2009; 154: 169-76.
[23] McRea HJ, Men LR. The diagnosis management and postnatal prevention of intraventricular hemorrhage in the preterm neonate. Clin perinatol 2008; 35: 1882-4.
[24] Chyi LJ, Lee HS, Gould J, Sutcliffe T. School outcomes of late preterm infants:special needs and challenges for infants born at 32 to 36 weeks gestation. J Pediatr 2008; 153: 25-31.
[25] Pharoah PO. Neurological outcome in twins. Semin Neonatol 2002; 7: 223-30.
[26] Wadhawan R, Oh W, Perritt RL, McDonald SA, Das A, Poole WK, Vohr BR, Higgins RD. Twin gestation and neurodevelopmental outcome in extremely low birth weight infants. Pediatrics 2009; 123: e220-7.
[27] Cameron EC, Maehle V, Reid J. The effects of an early physical therapy intervention for very preterm, very low birth weight infants:a randomized controlled clinical trial. Pediatr Phys Ther 2005; 17: 107-19.
[28] Parkes J, Hill N, Dolk H, Donnelly M. What influences physiotherapy use by children with cerebral palsy? Child Care Health Dev 2004; 30: 151-60.
[29] Stephens BE, Bann CM, Poole WK, Vohr BR. Neurodevelopmental impairment: predictors of its impact on the families of extremely low birth weight infants at 18 months. Infant Ment Health J 2009; 29: 570-87.
[30] Marlow N, Hennessy EM, Bracewell MA, Wolke D. Motor and executive function at 6 years of age after extremely preterm birth. Pediatrics 2007; 120: 793-804.
[31] Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 2002; 288: 728-37.
[32] Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005; 352: 9-19.
[33] Itabashi K, Mishina J, Tada H, Sakurai M, Nanri Y, Hirohata Y. Longitudinal follow-up of height up to five years of age in infants born preterm small for gestational age, comparison to full--term small for gestational age infant. Early Hum Dev 2007; 83: 327-33.