



Original Research

Midterm Neuromotor Development Results of Preterm Babies less than 34 Weeks Gestational Age

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Abstract

Objectives: This study aimed to evaluate the neuromotor development of premature babies and to determine the risk factors affecting neuromotor development in the middle time (3 years).

Methods: All babies with ≤ 34 weeks gestational age and born between 2011-2014 and hospitalized in our neonatal clinic were included in this study. Prenatal, perinatal and postnatal features of the babies were recorded. Consent was obtained from the families who had an outpatient follow-up and agreed to participate in this study. Neurological examination and Denver II Developmental Screening Test (DDST-II) were applied to babies and their results were recorded. Factors affecting neurodevelopment were evaluated.

Results: Complete data for 96 of the study infant were obtained. Fifty (52.1%) of the cases were female. The mean birth weight was 1542 ± 518 grams. The mean corrected age was 20.9 ± 10.7 months at the time of the examination. It was found cerebral palsy in 11 babies (11.5%) with the neurological examination and developmental retardation in 15 babies (15.6%) with DDST-II. Low birth weight, a gestational period of 25-26 weeks, Apgar score at 5th minute < 7 were found to be the main risk factors for cerebral palsy and abnormal DDST-II result ($p < 0.05$). In babies with abnormal neurological examination, the frequency of bronchopulmonary dysplasia, sepsis and intraventricular hemorrhage were found to be high ($p < 0.05$), and in babies with abnormal DDST-II results the frequency of respiratory distress syndrome, bronchopulmonary dysplasia and sepsis were found to be high ($p < 0.05$).

Conclusion: In our study, abnormal neurological examination rate was found 11.5% in preterm infants with gestational age ≤ 34 weeks, and the rate of abnormal DDST-II was found 15.6%. The main factors affecting neuromotor development were gestational week, birth weight and 5th minute Apgar score. The frequency of bronchopulmonary dysplasia, sepsis and intraventricular hemorrhage in babies with abnormal neurological examination, and the frequency of respiratory distress, bronchopulmonary dysplasia and sepsis were found to be high in babies with abnormal DDST-II.

Keywords: Premature; neuromotor development; morbidity.

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Mortality rates in preterm infants have decreased significantly thanks to the improvements in service provision in neonatal intensive care units, especially in surfactant and antenatal steroid treatment.^[1,2] It has been recently reported

that average survival rate of babies born at 25th gestational week is 56%, and the survival rate in babies born at 22nd-25th gestational weeks gradually increases with improved health care services.^[3] The increase in survival rates and premature

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births has not been accompanied by a decrease in long-term neurodevelopmental retardation. Survived premature babies constitute an important risk group for neurodevelopmental problems, such as cerebral palsy (CP) and mental retardation (MR). Especially neonates and extremely low-birth weight (ELBW) newborns constitute a high risk group for neurodevelopmental retardation. Today, it is accepted that the success criteria of neonatal intensive care units worldwide are related to neurodevelopmental outcomes.^[4]

The incidence of CP in preterm babies is higher than term babies.^[5] In the United States, preterm babies constitute approximately 45% of the children with cerebral palsy, 35% of the children with visual impairment and 25% of children with cognitive impairment or hearing impairment.^[6] In addition, problems in domains of cognitive functions, language, attention and behavior that affect the success of school performance may emerge in preterm infants during childhood.^[7] In studies performed, CP, MR, blindness, deafness and hydrocephalus have been accepted as major neurological sequelae.^[7, 8] The minor neurological sequelae affecting higher number of the premature children include delayed speech, learning difficulties, perception problems, attention disorders, and behavioral problems. Minor neurological disorders are generally not detected until school age.^[9]

Long-term follow-up of babies at appropriate intervals and suitable methods according to the risks detected in the prenatal period; allows early detection of morbidity, taking necessary precautions and planning treatments.

In our study, our primary objective was to determine the risk factors affecting the neuromotor development of the babies born at ≤ 34 gestational weeks in our hospital between 2011-2014, and hospitalized in our Neonatal Clinic. Our second objective was to investigate the mid-term (first 3 years of life) evaluation of neuromotor development of babies using neurological examination and Denver II Developmental Screening Test (DDST-II).

Methods

A prospective, cross-sectional study was planned. This study was carried out in two stages. In the first stage, all babies born at ≤ 34 gestational weeks between 2011-2014 in our hospital, and hospitalized in the Neonatal Intensive Care Unit were included in this study. Information of the babies during hospitalization was recorded. In the second stage, our patients who attended the control visits at outpatient clinics were informed about this study and invited to our hospital for neurological examination and application of Denver II Developmental Screening Test. This study was completed with the patients who agreed to participate in this study.

Exclusion Criteria

Babies born in an external center, babies born in our hospital and referred to an external center, infants lost during hospitalization, cases with major congenital anomalies (e.g., cyanotic congenital heart disease, neural tube defect) and congenital metabolic disease were excluded from this study.

Data Collection:

Ethical approval for this study was obtained from the Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee (05/06/2014-317).

In the first stage, the characteristic features of the babies whose data can be accessed were scanned from the patient registry files and the electronic database of the neonatal intensive care unit.

Information about gestational age, gender, birth weight, height and head circumference; 1st and 5th min Apgar scores, type of delivery, length of hospital stay, oxygenation status of the patients, resuscitation applied at birth (if any), duration of adherence to mechanical ventilator, and CPAP (Continuous Positive Airway Pressure) application time, use of surfactant, caffeine, and antibiotic therapy (if any), whether or not the patient had been diagnosed as respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), sepsis, necrotizing enterocolitis (NEC) and intraventricular bleeding (IVC), and received postnatal steroids for bronchopulmonary dysplasia have been recorded.

In the second stage, the families of the babies who could be reached and accepted to participate in this study were informed about this study, and the families were called for control. The cases brought to the Well Child Outpatient Clinic and undergoing neurodevelopmental evaluation constituted the study group. Voluntary consent forms were obtained from the families, then, the neurological examination and DDST-II tests were performed. Neurological examination was performed by a pediatrician. Patients with pathological findings were reevaluated by the pediatric neurologist. DDST-II test was applied by the certified Child Development Specialist. The cases with abnormal neurological examination and DDST-II results were followed up by the pediatric neurology and child development specialist.

Mid-term Results: Babies whose corrected age did not exceed three years (36 months) were included in this study.

Statistical Analysis

IBM SPSS Statistics 22 program was used for statistical analysis of the information obtained from this study. While evaluating the study data, the fitness of the parameters to

normal distribution was evaluated with the Shapiro- Wilks test. While evaluating the study data, descriptive statistical methods (mean, standard deviation, frequency) were used. Regarding quantitative data Oneway Anova test was used for intergroup comparison of the parametres with normal distribution. Tukey test was employed to determine the group that caused the difference. Student's t-test was used for comparisons of normally distributed parameters between two groups, and Mann- Whitney U test was used for comparisons of non-normally distributed parameters between two groups.

In the comparison of qualitative data, Chi-square test, Fisher's Exact Chi-Square test and Continuity (Yates) Correction were used. Pearson correlation analysis was used to examine the relationships between parameters that show normal distribution. Significance was evaluated at the level of $p < 0.05$.

Results

The data of the cases that meet the study criteria, patients without missing data who were brought to the outpatient clinic of our Newborn Clinic for examination within the period determined were recorded. Flow diagram of this study is given in Figure 1. The prenatal, natal and postnatal features of the patients included in this study and their demographic features during hospitalization in the neonatal period are presented in Table 1. There were 51 (53.1%) mothers who received antenatal steroid treatment; it was found that 29 of them (30.2%) were administered a single dose and 22 of them (22.9%) were on full cure steroid treatment. The chronological ages of the babies ranged between 5 and 39 months, and the mean chronological age was 22.1 ± 9.7 months, and the adjusted age was 20.9 ± 10.7

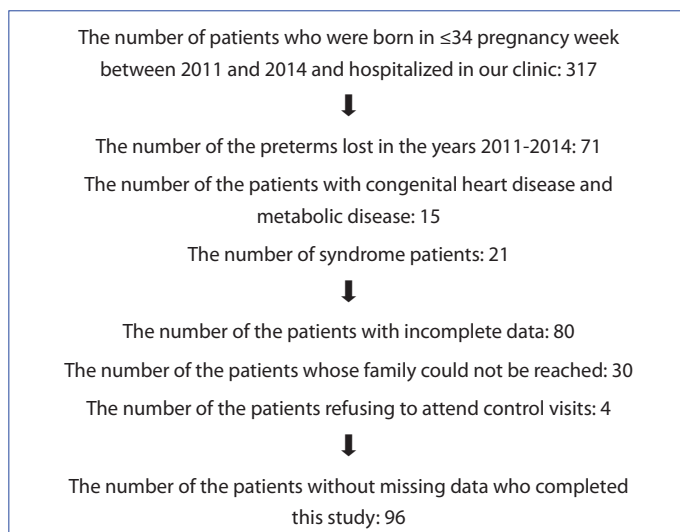


Figure 1. Flow diagram of the study.

months. Neurological examination and DDST-II results of the cases are presented in Table 2. Based on neurological examination findings, 11 patients were diagnosed with cerebral palsy.

The evaluation of the risk factors of the patients and the results of the neurological examination are presented in Table 3. There was a significant relationship between abnormal neurological examination findings, low- birth weight and gestational week ($p=0.02$, $p=0.03$). According to the results of the neurological examination, a statistically significant difference was found between the distributions of the gestational weeks ($p=0.031$). As a result of the pairwise comparisons made to determine the gestational week that caused the difference, the higher number of babies with abnormal neurological examination findings had been delivered between 25th and 26th gestational weeks. The incidence of BPD, sepsis and IVC was higher in patients with abnormal neurological examination findings ($p=0.009$, $p=0.009$, $p=0.026$).

Any significant difference was not found between the frequency of RDS and NEC among patients with abnormal and normal neurological examination findings. Requirement for mechanical ventilator was found to be significantly higher in patients with abnormal neurological examination findings ($p=0.01$). Duration of oxygen therapy and CPAP application time were increased in patients with abnormal neurological examination findings ($p=0.01$, $p=0.024$).

The comparison of DDST-II results with the demographic characteristics of the cases is presented in Table 4. There was a significant relationship between abnormal DDST-II results and low- birth weight and gestational week ($p=0.001$, $p=0.002$). As a result of the pairwise comparisons made to determine the gestational week that caused the difference, higher number of the babies born between 25th-26th gestational weeks was found to have abnormal DDST-II results. No significant correlation was found between abnormal DDST-II results, weight groups (SGA, AGA, LGA), mode of delivery and gender of babies.

The frequency of RDS, BPD and sepsis were found to be higher in patients with abnormal DDST-II results ($p=0.028$, $p=0.001$, $p=0.014$). No significant difference was found between the frequency of NEC and IVC among patients with abnormal or abnormal DDST-II results (Table 4). In patients with abnormal DDST-II results, requirement for mechanical ventilation was found to be significantly higher ($p=0.05$). Frequency of surfactant treatment in patients with abnormal DDST-II results was higher than patients with normal DDST-II results ($p=0.028$).

Table 1. The prenatal, natal and postnatal features of the cases and their demographic characteristics during hospitalization in the neonatal period

	Mean±SD	Lower and upper limits
Birth weight, g	1542.1±518.5	625-2950
Gestational weeks	n	%
25-26	11	11.5
27-28	5	5.2
29-30	19	19.8
31-32	42	43.8
33-34	19	19.8
Antenatal steroid use	51	53.1
Apgar score, (1. min <7)	54	56.3
Apgar score (5. min <7)	12	12.5
Mode of delivery, cesarean	86	89.4
Diagnoses at hospitalisation		
Respiratory Distress Syndrome	27	28.1
Bronchopulmonary Dysplasia	20	20.8
Mild	17	17.7
Moderate	3	3.1
Sepsis	20	20.8
Necrotizing Enterocolitis	25	26
Stage 1	20	20.8
Stage 2	5	5.2
Intraventricular bleeding	24	25
Stage 1	16	16.6
Stage 2	4	4.2
Stage 3	4	4.2
Treatments administered at admission		
Oxygen support	88	91.7
Mechanical ventilation support	42	43.8
Continuous positive airway pressure	68	70.8
Surfactant	27	28.1
Caffeine	45	46.9
Antibiotics	88	91.7
Steroid therapy with the indication of bronchopulmonary dysplasia		
Once	15	15.6
Twice	5	5.2
Characteristic features of hospital stay	Mean±SD	Lower and upper limits
Length of hospital stay, days	40±28.9	5-166
Oxygen requirement time, days	20.1±27.3	1-166
Duration of mechanical ventilation, days	10.5±17.4	1-83
Duration of CPAP application, days	5.6±6.3	1-33
Duration of antibiotherapy, days	14.3±11.8	3-74

SD: Standard deviation.

Table 2. Midterm (for a period of three years) results of neurological examination, and DDST-II tests of the cases

	n	%
Neurological examination results		
Normal	85	88.5
Abnormal	11	11.5
DDST-II		
Normal	81	84.4
Abnormal	15	15.6
Distribution of DDST-II test results		
Abnormal Personal–Social Development	4	4.2
Abnormal fine motor development	6	6.3
Abnormal development of language	5	5.2
Abnormal gross motor development	9	9.4

DGTT-II: Denver II Developmental Screening Test.

Discussion

In recent years, through the developments in perinatology and neonatal intensive care services, the life span of premature babies has increased significantly.^[10] Despite all these favourable advances, the number of premature and LBW babies could not be reduced. Premature babies, especially very and extremely preterm babies, constitute a significant risk group for neurodevelopmental problems, such as cerebral palsy and mental retardation. In the USA, preterm infants constitute 45% of children with CP, 35% of the visually impaired and 25% of the children with impaired hearing and cognitive functions.^[6]

CP is a non-progressive disease of the central nervous system, which occurs when prenatal and perinatal events affect the developing brain tissue, including posture and movement disorders.^[11] In studies conducted on the frequency of cerebral palsy by gestational week, the highest rate has been reported in patients who were born at the 22nd gestational week (21.7%) and at the 23rd gestational week (17.8%), while in 4.%, and 0.7 % of the babies born at the 33th, and 34th gestational weeks, respectively.^[12, 13] The incidence of CP was 14.2% at the age of six in the evaluation of these 183 preterm children regardless of their gestational weeks at birth.^[14] In our country, the incidence of CP in premature babies was determined to be between 8.5-24.2%.^[15, 16] In our study, it was seen that the frequency of CP was similar to the results reported in our country.

In a study in which neurological evaluation was performed using DDST-II tests, in babies with abnormal DDST-II results, the frequency of severe RDS and requirement for surfactant was significantly higher.^[17] Similarly, in our study, higher rates were found in babies with abnormal DDST-II results. BPD plays a significant role in clinical diseases that nega-

Table 3. Evaluation of neurological examination results, and risk factors of the cases

	Neurological examination results		p
	Normal n=85	Abnormal n=11	
	Mean±SD		
Birth weight, g	1598.8±503.9	1103.8±427.8	<0.001
Gestational weeks	30.9±2.3	28.6±2.6	0.003
	n (%)	n (%)	
Gestational weeks		0.031	
25-26	7 (7.3)	4 (4.2)	
27-28	4 (4.2)	1 (1)	
29-30	16 (16.7)	3 (3.1)	
31-32	39 (40.6)	3 (3.1)	
33-34	19 (19.8)	0 (0)	
Apgar score (1 st min <7)	44 (45.8)	10 (10.4)	0.021
Apgar score (5 th min <7)	7 (7.3)	5 (5.2)	0.004
Bronchopulmonary dysplasia	14 (14.6)	6 (6.3)	0.009
Sepsis	14 (14.6)	6 (6.3)	0.009
Intraventricular bleeding	18 (18.8)	6 (6.3)	0.026
Requirement for mechanical ventilation	32 (33.3)	10 (10.4)	0.001
Surfactant treatment	21 (21.9)	6 (6.3)	0.069
Duration of oxygen therapy	15.5±19.4 (7)	52.8±47.9 (40)	0.001
Duration of CPAP application	5.3±6.4 (3)	7.7±5.3 (6)	0.024

CPAP: Continuous Positive Airway Pressure.

Table 4. Evaluation of the factors effective on DDST-II results

	DDST-II test results		p
	Normal n=81	Abnormal n=15	
	Mean±SD		
Birth weight g	1616.4±497	114.9±456.8	0.001
Gestational weeks	31±2.2	28.5±2.8	0.001
	n (%)	n (%)	
Gestational weeks			0.002
25-26	5 (5.2)	6 (6.3)	
27-28	4 (4.2)	1 (1)	
29-30	15 (15.6)	4 (4.2)	
31-32	39 (40.6)	3 (3.1)	
33-34	18 (18.8)	1 (1)	
Apgar score (5 th min <7)	6 (6.3)	6 (6.3)	0.003
Respiratory distress syndrome	19 (19.8)	8 (8.3)	0.028
Bronchopulmonary dysplasia	11 (11.5)	9 (9.4)	0.001
Sepsis	13 (13.5)	7 (7.3)	0.014
Requirement for mechanical ventilation	30 (31.3)	12 (12.5)	0.005
Surfactant treatment	19 (19.8)	8 (8.3)	0.028

DDST-II: Denver II Developmental Screening Test; SD: Standard deviation.

tively affect neurodevelopmental prognosis. In studies conducted in preterm infants in our country, the frequency of BPD has been reported to range between 13.1% and 30%.^[17, 18] The BPD is thought to negatively affect growth and development because it impairs nutrition, causes frequent lung infections and increases the frequency of hospitalizations.

In the study conducted by Kavuncuoğlu et al.,^[19] patients with and without the diagnosis of BPD were compared, and abnormal DDST-II results were detected in 32%, and 6% of the patients diagnosed with BPD and the patients in the control group, respectively. However, there was no difference in the development of CP among patients with BPD. Similarly, in our study, the frequency of BPD was high in patients who were abnormal as a result of DDST-II. In our study, the frequency of BPD was found to be significantly higher in patients with CP.

Use of antenatal steroids in preterm infants reduces the incidence of RDS mortality, NEC and IVC.^[20, 21] However, some studies have reported that the use of antenatal steroids causes cystic developments in white matter.^[22] It has been reported that the administration of single-cycle antenatal steroids in preterm infants is a safe procedure regarding the nervous system of the newborn and an effective method in preventing the development of cerebral palsy and decreasing the frequency of death and IVC.^[23] It has been reported that there is no significant relationship between abnormal DDST-II results and antenatal steroid administration.^[15] Similarly, in our study, no statistically significant relationship was found between abnormal DDST-II results and antenatal steroid administration.

Based on the results of metaanalysis, it was seen that the use of systemic postnatal dexamethasone reduced the frequency of BPD, but its use was limited due to the neurocognitive side effects it may cause. When early and late term postnatal steroid use was evaluated separately, it was suggested that early steroid use increases the risk of CP. Thus, recommendations did not favour its use. However, its long-term use has been suggested because it does not significantly increase the risk of development of neurological sequelae in the long-term, so its limited use has been recommended due to its side effects.^[24] The results of this study on the effects of postnatal steroid use on neuromotor development are contradictory and there is no clear consensus.

When the neuromotor development of 2-year-old babies who received postnatal systemic dexamethasone treatment was evaluated, the incidence of neuromotor dysfunction was reported to decrease by 40 percent.^[25] In another study, 366 of the 2358 premature babies were adminis-

tered postnatal systemic corticosteroid treatment, and as a result of this study, a reduction of 2.0 points in the mental development index and a 40% increase in CP risk in each 1 mg/kg dose of steroid administered.^[26] In a study in which premature babies were evaluated at the age of seven, in patients with BPD who received postnatal steroids in the early and late periods; it was reported that there was no difference concerning the frequency of CP and behavioral disorders between both groups.^[27] In our study, 20 (20.8%) patients diagnosed with BPD received late postnatal steroid (dexamethasone) treatment. There was no significant difference between patients with CP and patients with normal neurological examination findings in terms of steroid treatment.

Infections have been shown to negatively affect neurodevelopmental prognosis in very-low-birth-weight (VLBW) preterm infants.^[28] The main mechanism causing developmental disorders in sepsis is white matter damage that arises from the effects of inflammatory cytokines induced by infections in the perinatal and postnatal periods.^[29] In our study, the incidence of sepsis was found to be higher in patients with CP. In the study conducted by Sütçüoğlu et al.,^[17] when the babies were evaluated at the age of two, the detection rate of abnormal DDST-II results was found to be statistically significantly higher when compared with the patients who did not have sepsis. In accordance with the other studies cited herein, the frequency of sepsis was found to be higher in patients with abnormal DDST-II results. It has been reported that the development of stage ≥ 3 NEC in preterm babies with a birth weight below 1000 g is an independent risk factor for developmental problems seen in 18-22 months of life.^[30] In our study, unlike the literature, there was no significant relationship between NEC and abnormal neurological examination and abnormal DDST-II results. This situation can be explained that the babies in our study had a higher gestational week at birth.

One of the most significant factors contributing to the unfavourable neurodevelopmental prognosis is considered as intraventricular bleeding. Psychiatric problems and dysfunction in management functions are seen in approximately 1/3 of infants with stage 3 and 4 intraventricular bleeding.^[31, 32] In a study in which 128 VLBW babies in our country were evaluated in adjusted 12-18 months, the detection rate of IVC was found to be statistically significantly higher in patients diagnosed with CP.^[33] In our study, there was a positive relationship between the frequency of IVC and the diagnosis of the CP.

In babies with a birth weight below 1250 g, caffeine treatment has been shown to shorten their stay in mechanical ventilation and reduce the incidence of BPD in these ba-

bies.^[34] A total of 2006 babies with birth weights between 500-1250 grams, were evaluated at corrected 18-21 years of age and at the age of five months; higher survival rate was detected for babies who used caffeine and any significant difference in terms of neurodevelopmental retardation was not reported between both groups.^[35, 36] In our study, there was no positive effect of caffeine treatment on neurological development.

As the gestational weeks at birth and birth weight decrease, the rate of neurodevelopmental retardation increases. In a study where babies were evaluated at the age of 2.5, CP was detected in 7% of the babies born at a gestational age less than 27 weeks and in 0.1% of term babies.^[37] In our study, the mean gestational age at birth and birth weight of the patients diagnosed with CP were significantly lower as expected. In our study, the mean gestational week at birth and birth weight were found to be significantly lower in babies with abnormal DDST-II results.

It has been reported that unfavourable neurodevelopmental prognosis in VLBW infants is associated with male gender, and the incidence of moderate to severe CP is higher in males.^[38] In a study conducted in our country, the male gender was found to be a significant risk factor for abnormal neurodevelopment based on the evaluation of DGTT-II results.^[15] However, similar to our study, it was observed in different studies that there was no relationship between male gender and abnormal DDST-II results.^[33]

In a study evaluating premature babies with DDST-II, there was no relationship between 1st minute Apgar scores and abnormal DDST-II results, while a statistically significant relationship was found between the 5th minute Apgar scores and abnormal DDST-II results.^[15] In our study, there was no relationship between 1st minute Apgar scores and abnormal DDST-II results, whereas 5th minute Apgar scores were found to be significantly lower in cases with abnormal DDST-II results.

In our study, the neurodevelopmental evaluation was performed with the neurological examination and DGTT-II tests. In abnormal neurological examination, findings can be detected in 58% preterm babies at the age of 2.5.^[37] In our study, the low detection rate of abnormal neurological examination results can be explained by that our babies were born at higher gestational weeks.

In a study with 367 VLBW infants with a corrected age of 15 months, abnormal DDST results were detected in 10.9% of these cases. In addition, retardation was reported in the personal-social development domain in 7.1%, in the fine motor domain in 7.9%, in language domain in 8.8% and in the gross motor domain in 10.7% of the cases.^[39] In our country, DDST-II test was performed in VLBW infants with a

corrected age of 12-18 months, and retardations were detected in the personal-social domain in 7-13%, in fine motor domain in 9.4-13%, in language domain in 7.8-23.1%, and in gross motor domain in 10.3-12.5% of the cases. In our study, it was thought that the rates of abnormal conditions detected in the domains of personal-social, fine motor, language and gross motor functions were lower than the incidence rates reported in our country, and this situation could have a positive reflection on the developing newborn health care of babies.

Conclusion

In conclusion, in our study, abnormal neurological examination findings, and DDST-II test results were found in 11.5% and 15.6% of preterm infants born at <34th gestational weeks, respectively. The main factors affecting neuromotor development were gestational week, birth weight and the 5th min Apgar scores. Higher frequency of the BPD, sepsis and IVC were found in babies with abnormal neurological examination findings, while the frequency of RDS, BPD and sepsis was higher in babies with abnormal DDST-II results. It was found that the babies who had abnormal neurological examination findings and DDST-II results required mechanical ventilator and oxygen therapy and prolonged adherence to a mechanical ventilator.

Disclosures

Ethics Committee Approval: Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee (05/06/2014-317).

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Conflict of Interest: None declared.

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