Original Article

A Decade of Risk Factors in Cerebral Palsy: A Retrospective Review at Thammasat University Hospital, Thailand

Chueluecha C, MD[1], Deeprasertdamrong W, MD[1], Sritipsukho P, MD[2,3]

[1] Department of Rehabilitation Medicine, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand

[2] Department of Pediatric, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand

[3] Center of Excellence in Applied Epidemiology, Thammasat University, Pathum Thani, Thailand

Background: Cerebral palsy (CP) causes patients to experience developmental delays, affecting self-help. CP has many risk factors, unfortunately, no total risk summarization exists now.

Objective: To study the risk factors for neonate CP, making it possible to diagnosis early and reduce complications.

Materials and Methods: The present study was a retrospective case control study in children aged 0 to 2 years, born at Thammasat University Hospital, Thailand between 2005 and 2014. Multivariable logistic regression compared perinatal period risks between normal children (control) and those with CP (case).

Results: Within the multivariable logistic regression evaluation, CP risk factors were cerebral and non-cerebral malformations, low birthweight, neonatal sepsis, with adjusted odds ratio 250.43, 16.04, 32.60, and 63.15, respectively.

Conclusion: Cerebral and non-cerebral malformations, low birthweight, and neonatal sepsis are CP predictive risks. However, multi-fetal gestation, preterm birth, low Apgar score, fetal distress, uterine and cord anomalies, maternal infection, neonatal seizure, neonatal encephalopathy, congenital infections, and use of ventilator remain undetermined. A multicenter research incorporating the other events is needed.

Keywords: Cerebral palsy, Risk factors, Prenatal, Perinatal, Postnatal

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Cerebral palsy (CP) is a permanent disorder of movement, muscle tone, or posture caused by non-progressive damage to the immature, developing brain. Disturbances of sensation, perception, cognition, communication, and behavior are often combined[1]. As such, the patient can experience developmental delays, especially in gross motor functions. It affects the patient's self-help and socialization, creating family problems and increasing the cost of patient care. Current studies believe that CP has many risk factors[2,3]. Prenatal risks include fetal growth restriction (FGR)[4] and multi-fetal gestation[5]. Perinatal risk factors are more extensive. They may be preterm birth, fetal distress[2], birthweight less than 2,500 g[6], and an Apgar score at five minutes under 7 points[7]. Obstetric complications such as abnormal fetal presentation, uterine rupture, cord prolapse, placenta abruption, placenta previa, premature rupture of membrane (PROM)[8], chorioamnionitis, maternal sepsis, maternal fever of 38 degrees Celsius or higher, or urinary tract infection (UTI)[9] are also included in the perinatal factors. Finally, postnatal variables encompass neonatal jaundice[10], neonatal seizure, neonatal encephalopathy[11], congenital infections covering cytomegalovirus (CMV), rubella, and toxoplasmosis infections[12], and neonatal sepsis[13]. In addition, steroid therapy to reduce ventilator duration[14], ventilator use for more than seven days[15], infants of male gender[16], and cerebral and non-cerebral congenital malformations[17] are significantly correlated with CP. Furthermore,

Correspondence to:

Chueluecha C.

Department of Rehabilitation Medicine, Faculty of Medicine, Thammasat University, Pathum Thani 12120, Thailand.

Phone: +66-2-9269834, **Fax**: +66-2-9269793

Email: puaichuenchom@hotmail.com

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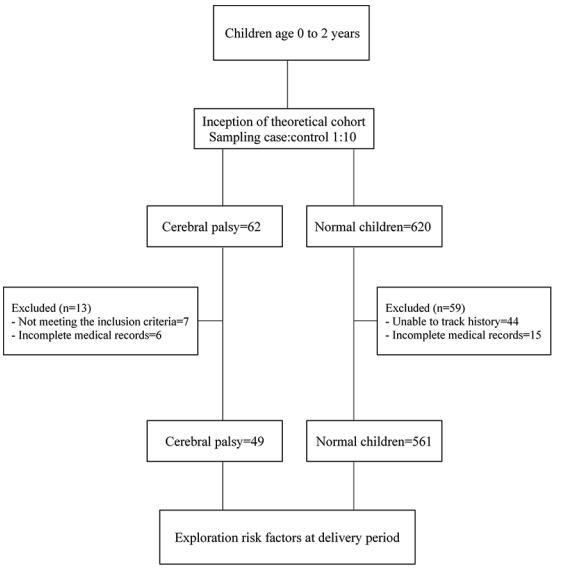

Figure 1. Participant flow of the study.

maternal attributes such as age over 35 years[18] and pregnancy complications such as preeclampsia[19] and gestational diabetes mellitus[20] are found to elevate the chances of CP.

As there is currently no summary of total risks for CP in neonates, considerable under-surveillance is likely resulting in treatment delays and possible irreversible complications. If awareness of monitoring requirements is heightened for vulnerable babies, the ideal outcomes would be early diagnosis and reduced complications. A study to establish all the risk factors for predicting neonatal CP before discharge has inherent utility for medical professionals, as well as for patients in small hospitals without specialized doctors and lower numbers of staff.

Materials and Methods

The present study was an exclusive retrospective case control study of neonatal CP risk factors in children aged 0 to 2 years, born at Thammasat University Hospital, Thailand between 2005 and 2014. The present population was those children diagnosed with CP with no neurological disorders from neonatal stroke, intracerebral hemorrhage, subgaleal hematoma, thrombotic disease, or other disorders of the nervous system that might later prove to be progressive conditions. In addition, the patients who suffered an accident or infection fatal to the nervous system after discharge from the hospital, or patients appearing to have nervous system disorders noticed upon physical examination before discharge were excluded. CP cases were identified using the standard criteria[1]. Normal babies who were born in the same day or nearly as the target population were used as the authors' control group, having a target of normal population of 1:10. The present study sample size was calculated using the odds ratio and probability of exposure among non-case patients in accordance with various risk factor data[15,18]: α was defined as 0.05. A power of 80% was used in a two-sided test. The sample size was determined to be at least 40 cases with 400 controls. Statistical analysis was done using Stata, version 14 (StataCorp LP, College Station, TX, USA). Logistic regression was used, or a penalized maximum likelihood estimation if there was no event in the control group. Both methods had a confidence interval (CI) of 95. As such, neonatal and maternal characteristics, as well as prenatal, perinatal, and postnatal risks were compared (Figure 1). The present research was approved by the Research Ethics Subcommittee on Human Research, Faculty of Medicine, Thammasat University on November 24, 2016 (Research Project Code: MTU-EC-RM-1-181/59).

Definitions

FGR: birthweight of newborn under the tenth percentile for weight as compared to the same population at the time of gestation[4]

Term: babies born at or after 37 weeks of pregnancy[21]

Preterm: babies born before 37 weeks of pregnancy[21]

Low birthweight: birthweight less than 2,500 g, regardless of gestational age[22]

Fetal distress: fetus that does not receive oxygen adequately during labor with the signs or symptoms characterized by an abnormal fetal heart rate (FHR) using an electronic monitoring or the meconium-stained amniotic fluid[23]

Chorioamnionitis: pregnancy with "inflammatory or an infectious" disorder of the chorion, amnion, or both, diagnosed based on fever presenting with one or more of the following[24]:

1. Fetal tachycardia (greater than 160 bpm for 10 minutes or longer)
2. Maternal white blood cell (WBC) count of more than 15,000 per microliter in the absence of corticosteroids
3. Purulent fluid from the cervical os (cloudy or yellowish thick discharge confirmed visually on a speculum exam coming from the cervical canal)

4. Biochemical or microbiologic amniotic fluid consistent with a microbial invasion of the amniotic cavity

Premature rupture of the membranes or prelabor rupture of the membranes (PROM): the rupture of the chorioamnionic membrane before the onset of labor[25], both in term and preterm labor

Maternal sepsis: two or more Systemic Inflammatory Response Syndrome (SIRS) criteria associated with proven or clinically suspected infection in pregnancy during labor[26]

1. Temperature above 38°C or below 36°C
2. Heart rate greater than 90 per minute
3. Respiratory rate greater than 20 per minute or $PaCO_2$ of less than 32 mmHg (4.3 kPa)
4. WBC count greater than 12,000/mm^3, less than 4,000/mm^3, or greater than 10% immature bands

Maternal UTI: pregnancy-related UTI includes all clinical types[27]

1. Asymptomatic bacteriuria (ASB)
2. Acute cystitis
3. Acute pyelonephritis

Neonatal sepsis: a clinical infection or sepsis diagnosed and treated by a physician with or without positive hemoculture[28]

1. Difficulty feeding
2. Convulsions
3. Movement only when stimulated
4. Respiratory rate greater than 60 per minute
5. Severe drawing in of breath (chest) and axillary temperature more than 37.5°C or less than 35.5°C
6. Cyanosis and grunting

Results

The present study had 49 patients diagnosed with CP and 561 normal children. Neonatal and maternal characteristics, prenatal, perinatal, and postnatal risks, evidence of differences (measured as p-value) are in Table 1 and 2. Significant differences occurred in both groups ($p<0.05$). Neonatal characteristics included cerebral and non-cerebral malformations, and prenatal factors included FGR, preterm delivery and multi-fetal gestation. Similarly, perinatal risks, such as low Apgar score (<7) at five minutes, fetal distress, uterine and cord abnormalities, and maternal infections during delivery, were noted. The postnatal risks of neonatal jaundice, neonatal seizure, neonatal encephalopathy, congenital infections, neonatal sepsis and using a mechanical ventilator were also pertinent (Table 1).

Univariate and multivariable analyses of CP risk are listed in Table 3. Cerebral and non-cerebral malformations, multi-fetal gestation, preterm, low birthweight, fetal distress, neonatal jaundice, and neonatal sepsis were deemed risks, with an adjusted odds ratio (OR) of 250.43, 16.04, 5.42, 4.00, 32.60, 5.19, 4.56, and 63.15, respectively.

Discussion

The primary aim of the present study was to improve awareness of CP risk factors, especially for non-specialized doctors. All factors stated are commonly seen in clinical practice and in non-case studies. Theoretically, there are a multitude of variables to a neonate's potential to develop CP. The authors attempted to reduce confounding factors in associated events, while exploring all the possible causes. Accordingly, there is only one category for each factor (Table 1): "yes" (having the risk factor), and "no" (not having), without any hierarchy. As mentioned in the Methods, the adjusted OR was determined by logistic regression when there were significant differences ($p<0.05$) between the two groups. However, Apgar score at five minutes with a lower score than 7, uterine and cord abnormalities, neonatal seizure, neonatal encephalopathy, congenital infection, and ventilator use, only appeared in the case group. Therefore, penalized maximum likelihood estimation for these variables was used instead.

In view of the neonatal characteristics, there was no particular type of cerebral malformation (adjusted OR 250.43). In the normal group, microcephaly was the only one. It is reasonable to believe that some kind of cerebral malformation would present the highest risk for CP in the present study, as also delineated in other research[17,29]. The associated risk noted was more prevalent in term versus in preterm[17]. With non-cerebral malformations (adjusted OR 16.04), the most common anomalies in CP cases were cardiovascular disorders (78.5%), while for non-cases it was hydrocele (100%), again, this was in accordance with other studies[17,29,30].

Multi-fetal gestation was the most evident prenatal factor (adjusted OR 5.42). However, with the CI approaching 1 (95% CI 0.55 to 52.88), there was an implication of no statistically significant difference ($p=0.146$). This might be due to the present data as twins were the only form of multi-fetal gestation seen. Twin pregnancy[5,31] has a strong relationship with CP, but triplets have an even stronger connection[5]. Recent increases in multi-fetal gestation, particularly with triplets and quadruplets due to the popularity of infertility treatments[32], should encourage doctors

Table 1. Neonatal characteristics of cases vs non-cases with evidence of differences (p-value)

Characteristics	Cases (n=49) n (%)	Non-cases (n=561) n (%)	p-value
Neonatal characteristics			
Sex: male	26 (52.0)	307 (54.34)	0.769
Cerebral malformations	7 (14.29)	1 (0.18)	<0.001
• Microcephaly	2	1	
• Schizencephaly, absence of septum pellucidum, and corpus callosum	1	0	
• Porencephaly	1	0	
• Hydrocephalus	2	0	
• Hydrocephalus, agenesis of corpus callosum	1	0	
Non-cerebral malformations	14 (28.57)	5 (0.89)	<0.001
• Ocular albinism	1	0	
• Cleft lip/cleft palate	1	0	
• Heart	11	0	
• Jejunal atresia	1	0	
• Hydrocele	0	5	
Prenatal events			
Fetal growth restriction	11 (22.45)	42 (7.68)	0.002
Multi-fetal gestation	10 (20.00)	6 (1.06)	<0.001
• Twins	10	6	
• Triplets	0	0	
• Quadruplets	0	0	
Perinatal events			
Preterm (GA <37 weeks)	24 (48.98)	13 (2.30)	<0.001
Low birthweight (<2,500 g)	26 (52.00)	3 (0.53)	<0.001
Apgar score at 5-minute, score <7	6 (12.24)	0 (0.00)	<0.001
Fetal distress	5 (10.00)	15 (2.65)	0.018
Uterine and cord abnormalities	3 (6.00)	0 (0.00)	0.001
• Cord prolapse	2	0	
• Uterine rupture	1	0	
Maternal bleeding in 3rd trimester	3 (6.00)	10 (1.77)	0.142
• Placenta abruptio	0	1	
• Placenta previa	3	9	
Maternal infection	9 (18.00)	2 (0.35)	<0.001
• Chorioamnionitis	1	0	
• PROM	7	2	
• Maternal sepsis	0	0	
• Temp >38 during labor	0	0	
• UTI	1	0	
Postnatal events			
Neonatal jaundice	12 (24.00)	4 (0.71)	<0.001
• MB of phototherapy threshold	12	4	
• MB > ETT 0 to 10	0	0	
Neonatal seizure	3 (6.00)	0 (0.00)	0.001
Neonatal encephalopathy	3 (6.00)	0 (0.00)	0.001
Congenital infection	3 (6.38)	0 (0.00)	<0.001
• CMV	3	0	
• Rubella	0	0	
• Toxoplasmosis	0	0	
Neonatal sepsis	17 (34.00)	1 (0.18)	<0.001
Exposure to postnatal steroids	0 (0.0)	0 (0.0)	NA
Duration of mechanical ventilator	14 (29.17)	0 (0.00)	<0.001
• ≤7 days	8	0	
• >7 days	6	0	

GA=gestational age; PROM=premature rupture of membrane; UTI=urinary tract infection; MB=microbilirubin; ETT=exchange transfusion threshold; CMV=cytomegalovirus; NA=not applicable (frequency of valid data too small or not applicable for prediction purposes)

Table 2. Maternal characteristics of cases vs non-cases, with evidence of differences (p-value)

Characteristics	Cases (n=49) n (%)	Non-cases (n=561) n (%)	p-value
Maternal underlying diseases	3 (6.00)	13 (2.30)	0.152
Preeclampsia	2	5	
GDM	1	7	
DM type 1/2	0	1	
Maternal age			0.20
<20 years	7 (14.29)	37 (6.78)	
>35 to 40 years	5 (10.20)	88 (16.12)	
>40 years	0 (0.00)	10 (1.83)	

GDM=gestational diabetes mellitus; DM=diabetes mellitus

to be extra vigilant after delivery and monitor this population very closely. FGR was found to be a common prenatal risk factor[4] with a far greater risk in the presence of other major birth defects, mainly cerebral and cardiac[4]. Surprisingly, extra-uterine growth (as known as "catch-up growth") does not decrease CP incidence[33]. Yet, when it was included in the multivariable logistic regression calculation with the other factors, a modifier effect occurred. This initiated a huge change in its and other odds ratio, possibly skewing FGR and other variables such as congenital malformation, preterm, and low birthweight, therefore, it was not calculated.

For perinatal factors, low birthweight (adjusted

Table 3. Univariate and multivariable analysis of cerebral palsy risk factors

Risk factors	CP (n=49) n (%)	No CP (n=561) n (%)	Univariate analysis		Multivariable analysis	
			OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Neonatal characteristics						
Cerebral malformation	7 (14.29)	1 (0.18)	93.83 (11.28 to 780.66)	<0.001	250.43 (26.29 to 2385.48)	<0.001
Non-cerebral malformation	14 (28.57)	5 (0.89)	44.71 (15.24 to 131.25)	<0.001	16.04 (2.83 to 90.86)	0.002
Prenatal events						
Fetal growth restriction	11 (22.45)	42 (7.68)	3.48 (1.66 to 7.30)	0.001		
Multi-fetal gestation	10 (20.00)	6 (1.06)	23.29 (8.06 to 67.35)	<0.001	5.42 (0.55 to 52.88)	0.146
Perinatal events						
Preterm	24 (48.98)	13 (2.30)	40.69 (18.56 to 89.21)	<0.001	4.00 (0.66 to 24.34)	0.132
Low birthweight	26 (52.00)	3 (0.53)	172.91 (52.82 to 565.99)	<0.001	32.60 (5.31 to 199.96)	<0.001
Apgar score 5minute, score <7	6 (12.24)	0 (0.00)	167.21 (9.27 to 3,017.42)*	<0.001		
Fetal distress	5 (10.00)	15 (2.65)	4.07 (1.42 to 11.72)	0.009	5.19 (0.88 to 30.66)	0.069
Uterine and cord abnormalities	3 (6.00)	0 (0.00)	83.36 (4.24 to 1,637.36)*	0.004		
Maternal infection	9 (18.00)	2 (0.35)	61.79 (12.92 to 295.43)	<0.001		
Postnatal events						
Neonatal jaundice	12 (24.00)	4 (0.71)	44.29 (13.63 to 143.89)	<0.001	4.56 (0.26 to 80.01)	0.299
Neonatal seizure	3 (6.00)	0 (0.00)	83.34 (4.24 to 1,637.36)*	0.004		
Neonatal encephalopathy	3 (6.00)	0 (0.00)	83.34 (4.24 to 1,637.36)*	0.004		
Congenital infection	3 (6.38)	0 (0.00)	88.96 (4.52 to 1,749.34)*	0.003		
Neonatal sepsis	17 (34.00)	1 (0.18)	290.55 (37.51 to 2,250.41)	<0.001	63.15 (5.03 to 793.09)	0.001
Use mechanical ventilator	14 (29.70)	0 (0.00)	475.35 (27.77 to 8,136.42)*	<0.001		

CP=cerebral palsy; OR=odds ratio; CI=confidence interval

* Penalized maximum likelihood estimation

OR 32.60) played a major role, followed by fetal distress and preterm. Low birthweight was documented as a notable risk and found in conjunction with an increased CP prevalence, especially for children weighing 1,000 to 1,499 g to 59.18 per 1,000 live births[6]. Other indicated perinatal factors included fetal distress and preterm. These had an adjusted OR of 5.19 and 4.00, respectively, however, with the CI crossing 1 (95% CI 0.88 to 30.66 and 0.66 to 24.34), no statistically significant difference was seen (p=0.069, 0.132). Later evidence had demonstrated that fetal distress played a relatively minor role in less than 10%[34] of the cases. In a large, prospective, population-based study, of term and near-term singletons with CP, 91.5% did not show fetal distress[35].

Being preterm has been confirmed[2,21] to be the strongest CP predictor. After the 1980s, preterm birth survival rates dramatically increased, the CP discovery rate in preterm births also rose[36,37]. The lower the gestational age, the higher the risk of CP[2], especially in less than 32 weeks[21]. From the present study data, all 13 (2.30%) preterm babies in the control group were at a gestational age of 36 weeks. This is in contrast with the case group in which the 24 (48.98%) preterm infants varied in gestational age from 23 to 36 weeks. Surprisingly, the authors' calculations did not show preterm births as a significant risk for CP. Importantly, the authors would add that for the present study data specifically, however, this may not offer a complete perspective. Lacking any preterm cases under 36 weeks in the control group appeared to have skewed the present study data, with 95% CI crossing 1 and an insignificant p-value. There was also notable variation in determining correlation with certain risk factors where the OR of preterm birth was 40.69 (95% CI 18.56 to 89.21, p<0.001) but the adjusted OR as only 4.00. Clearly, the greatest issue with the present study data lies in having only term and preterm events in the control group versus the case group had extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks), and moderate to late preterm (32 to 37 weeks)[38]. Similarly, having an Apgar score at five minutes of less than 7 (OR 167.21) was a strong risk

factor for the case group, however, this low Apgar score was absent in the control group. The present study CP group had six cases (12.24%)[7].

Maternal infection also has increased risk (OR 61.79) and is associated with other factors, such as congenital infection and various infectious conditions after birth, as such, multivariable logistic regression was not used. In the present study data, chorioamnionitis, PROM, and UTI were seen without maternal fever or sepsis in preterm babies, much like other studies[9]. The authors did not separately calculate preterm and term, which may explain the increased, but not statistically significant, risk.

Neonatal sepsis was the most important postnatal event (adjusted OR 63.15). The typical sequela after neonatal sepsis was neurodevelopmental impairment (14%), 8% had CP and growth retardation[13]. This is reported as a strong risk for CP in all gestational age groups[39]. Regarding neonatal jaundice, the authors had only infants requiring phototherapy, but no newborns received exchange transfusion. CP, especially athetoid type, is believed to be caused by bilirubin stains in the bilateral globus pallidus, subthalamic nuclei, brainstem, and cerebellum when serum levels are very high[40]. However, recent long-term studies of serum bilirubin levels and CP development display no association[41]. This association has only been seen with high exchange transfusion (ETT) in conjunction with two or more other CP risk factors[10]. The present study showed an increased OR (adjusted OR 4.56), even with benign serum bilirubin and jaundice from hemolytic disease. Most likely this is because of low birthweight and other risk factors associated with CP[42].

Limitation

At present, there is no data for assessing the whole risk of neonatal CP before an infant returns home. To the best of the authors' knowledge, this is the first exploration of newborn CP risks. Clearly elucidating these risks will help general practitioners screen patients, making it possible to determine risk groups requiring in-depth monitoring. This needs to be highlighted for patients in small community hospitals without specialized doctors or suffering from an insufficient supply of medical personnel. The authors must point out that, however, this is a retrospective case control study, and the present study results and interpretations reflect this. As such, there were very few or no events for some risk factors in the present study controls; thus, the authors were not able to calculate their adjusted OR value.

Conclusion

Cerebral and non-cerebral malformations, low birthweight, and neonatal sepsis are predictive risks for CP. However, multi-fetal gestation, preterm birth, low Apgar score, fetal distress, uterine and cord anomalies, maternal infection, neonatal seizure, neonatal encephalopathy, congenital infections, and use of ventilator are still in question. As noted, because of the present study was retrospective study that used normal neonates as the control, there were very few or absent events or risk factors. Further long-term multicenter research would increase these events in both control and case groups to permit a clearer analysis of the possible associations with CP.

What is already known on this topic?

CP has many known risk factors from neonatal and maternal characteristics as well as within the prenatal, perinatal, and postnatal periods. Most risk factors are sorted into preterm and term conditions.

What this study adds?

At present, no summary of all the possible risks for CP in neonates exists. Establishing a list of all the risk factors commonly seen in clinical practice to predict neonatal CP before discharge is crucial to provide early care. Discounting divisions by gestational age, cerebral and non-cerebral malformations, low birthweight, and neonatal sepsis are predictive risks for CP.

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Conflicts of interest

The authors declare no conflict of interest.

References

1. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl 2007;109:8-14.
2. Sukhov A, Wu Y, Xing G, Smith LH, Gilbert WM. Risk factors associated with cerebral palsy in preterm infants. J Matern Fetal Neonatal Med 2012;25:53-7.
3. Himmelmann K, Ahlin K, Jacobsson B, Cans C, Thorsen P. Risk factors for cerebral palsy in children born at term. Acta Obstet Gynecol Scand 2011;90:1070-81.
4. Blair EM, Nelson KB. Fetal growth restriction and

risk of cerebral palsy in singletons born after at least 35 weeks' gestation. Am J Obstet Gynecol 2015;212: 520.e1-7.
5. Petterson B, Nelson KB, Watson L, Stanley F. Twins, triplets, and cerebral palsy in births in Western Australia in the 1980s. BMJ 1993;307:1239-43.
6. Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol 2013;55:509-19.
7. Moster D, Lie RT, Irgens LM, Bjerkedal T, Markestad T. The association of Apgar score with subsequent death and cerebral palsy: A population-based study in term infants. J Pediatr 2001;138:798-803.
8. Gilbert WM, Jacoby BN, Xing G, Danielsen B, Smith LH. Adverse obstetric events are associated with significant risk of cerebral palsy. Am J Obstet Gynecol 2010;203: 328.e1-5.
9. Neufeld MD, Frigon C, Graham AS, Mueller BA. Maternal infection and risk of cerebral palsy in term and preterm infants. J Perinatol 2005;25:108-13.
10. Wu YW, Kuzniewicz MW, Wickremasinghe AC, Walsh EM, Wi S, McCulloch CE, et al. Risk for cerebral palsy in infants with total serum bilirubin levels at or above the exchange transfusion threshold: a population-based study. JAMA Pediatr 2015;169:239-46.
11. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. BMJ 1988;297:1304-8.
12. McMichael G, MacLennan A, Gibson C, Alvino E, Goldwater P, Haan E, et al. Cytomegalovirus and Epstein-Barr virus may be associated with some cases of cerebral palsy. J Matern Fetal Neonatal Med 2012;25:2078-81.
13. Haller S, Deindl P, Cassini A, Suetens C, Zingg W, Abu SM, et al. Neurological sequelae of healthcare-associated sepsis in very-low-birthweight infants: Umbrella review and evidence-based outcome tree. Euro Surveill 2016;21:30143.
14. Powell K, Kerkering KW, Barker G, Rozycki HJ. Dexamethasone dosing, mechanical ventilation and the risk of cerebral palsy. J Matern Fetal Neonatal Med 2006;19:43-8.
15. Himpens E, Oostra A, Franki I, Vansteelandt S, Vanhaesebrouck P, den Broeck CV. Predictability of cerebral palsy in a high-risk NICU population. Early Hum Dev 2010;86:413-7.
16. Johnston MV, Hagberg H. Sex and the pathogenesis of cerebral palsy. Dev Med Child Neurol 2007;49:74-8.
17. Rankin J, Cans C, Garne E, Colver A, Dolk H, Uldall P, et al. Congenital anomalies in children with cerebral palsy: a population-based record linkage study. Dev Med Child Neurol 2010;52:345-51.
18. Soleimani F, Vameghi R, Biglarian A. Antenatal and intrapartum risk factors for cerebral palsy in term and near-term newborns. Arch Iran Med 2013;16:213-6.
19. Mor O, Stavsky M, Yitshak-Sade M, Mastrolia SA, Beer-Weisel R, Rafaeli-Yehudai T, et al. Early onset preeclampsia and cerebral palsy: a double hit model? Am J Obstet Gynecol 2016;214:105-9.
20. Nahum SK, Friger M, Shoham-Vardi I, Abokaf H, Spiegel E, Sergienko R, et al. Prenatal exposure to gestational diabetes mellitus as an independent risk factor for long-term neuropsychiatric morbidity of the offspring. Am J Obstet Gynecol 2016;215:380-7.
21. Palmer L, Blair E, Petterson B, Burton P. Antenatal antecedents of moderate and severe cerebral palsy. Paediatr Perinat Epidemiol 1995;9:171-84.
22. WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. Acta Obstet Gynecol Scand 1977;56:247-53.
23. American Pregnancy Association. Fetal distress: Diagnosis, conditions & treatment [Internet]. 2015 [cited 2018 May 25]. Available from: https://americanpregnancy.org/labor-and-birth/fetal-distress/.
24. Higgins RD, Saade G, Polin RA, Grobman WA, Buhimschi IA, Watterberg K, et al. Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis: Summary of a workshop. Obstet Gynecol 2016;127:426-36.
25. Beckmann C. Premature rupture of membranes. In: Beckmann C, Ling FW, Barzansky BM, Herbert W, Laube DW, Smith RP, editors. Obstetrics and gynecology. 6thed. Baltimore: Lippincott Williams & Wilkins; 2010. p. 213-17.
26. Morgan J, Roberts S. Maternal sepsis. Obstet Gynecol Clin North Am 2013;40:69-87.
27. Szweda H, Jóźwik M M. Urinary tract infections during pregnancy - an updated overview. Dev Period Med 2016;20:263-72.
28. Opiyo N, English M. What clinical signs best identify severe illness in young infants aged 0-59 days in developing countries? A systematic review. Arch Dis Child 2011;96:1052-9.
29. Nelson KB, Blair E. Prenatal factors in singletons with cerebral palsy born at or near term. N Engl J Med 2015;373:946-53.
30. Blair E, Al Asedy F, Badawi N, Bower C. Is cerebral palsy associated with birth defects other than cerebral defects? Dev Med Child Neurol 2007;49:252-8.
31. Grether JK, Nelson KB, Cummins SK. Twinning and cerebral palsy: experience in four northern California counties, births 1983 through 1985. Pediatrics 1993;92:854-8.
32. Dickey RP. The relative contribution of assisted reproductive technologies and ovulation induction to multiple births in the United States 5 years after the Society for Assisted Reproductive Technology/ American Society for Reproductive Medicine recommendation to limit the number of embryos transferred. Fertil Steril 2007;88:1554-61.
33. Guellec I, Lapillonne A, Marret S, Picaud JC, Mitanchez D, Charkaluk ML, et al. Effect of intra- and

extrauterine growth on long-term neurologic outcomes of very preterm infants. J Pediatr 2016;175: 93-99.e1.
34. Jacobsson B, Hagberg G. Antenatal risk factors for cerebral palsy. Best Pract Res Clin Obstet Gynaecol 2004;18:425-36.
35. McIntyre S, Blair E, Badawi N, Keogh J, Nelson KB. Antecedents of cerebral palsy and perinatal death in term and late preterm singletons. Obstet Gynecol 2013;122:869-77.
36. Winter S, Autry A, Boyle C, Yeargin-Allsopp M. Trends in the prevalence of cerebral palsy in a population-based study. Pediatrics 2002;110:1220-5.
37. Pharoah PO, Cooke T, Cooke RW, Rosenbloom L. Birthweight specific trends in cerebral palsy. Arch Dis Child 1990;65:602-6.
38. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162-72.
39. Greenwood C, Yudkin P, Sellers S, Impey L, Doyle P. Why is there a modifying effect of gestational age on risk factors for cerebral palsy? Arch Dis Child Fetal Neonatal Ed 2005;90:F141-6.
40. Watchko JF, Tiribelli C. Bilirubin-induced neurologic damage--mechanisms and management approaches. N Engl J Med 2013;369:2021-30.
41. Scheidt PC, Graubard BI, Nelson KB, Hirtz DG, Hoffman HJ, Gartner LM, et al. Intelligence at six years in relation to neonatal bilirubin levels: follow-up of the National Institute of Child Health and Human Development Clinical Trial of Phototherapy. Pediatrics 1991;87:797-805.
42. Culley P, Powell J, Waterhouse J, Wood B. Sequelae of neonatal jaundice. Br Med J 1970;3:383-6.