PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Neonatal Morbidities and Developmental Delay in Moderately Preterm-Born Children

Jorien M. Kerstjens, Inger F. Bocca-Tjeertes, Andrea F. de Winter, Sijmen A. Reijneveld and Arend F. Bos

Pediatrics 2012;130;e265; originally published online July 9, 2012;
DOI: 10.1542/peds.2012-0079

Neonatal Morbidities and Developmental Delay in Moderately Preterm-Born Children

AUTHORS: Jorien M. Kerstjens, MD,[a] Inger F. Bocca-Tjeertes, MD,[a] Andrea F. de Winter, PhD,[b] Sijmen A. Reijneveld, MD, PhD,[b] and Arend F. Bos, MD, PhD[a]

[a]*Division of Neonatology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; and* [b]*Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen, Netherlands*

KEY WORDS
moderately preterm, late preterm, neurodevelopment, Ages and Stages Questionnaire, neonatal morbidity, hypoglycemia, follow-up

ABBREVIATIONS
ASQ—Ages and Stages Questionnaire
CI—confidence interval
Lollipop—Longitudinal Preterm Outcome Project
OR—odds ratio
PCHC—preventive child health care center
SGA—small for gestational age

This trial has been registered with the ISRCTN Register (http://isrctn.org) (identifier ISRCTN80622320).

www.pediatrics.org/cgi/doi/10.1542/peds.2012-0079

doi:10.1542/peds.2012-0079

Accepted for publication Apr 20, 2012

Address correspondence to Jorien M. Kerstjens, MD, Division of Neonatology, Beatrix Children's Hospital, University Medical Center, University of Groningen, Groningen, Netherlands. E-mail: j.m.kerstjens@umcg.nl

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

FUNDING: The Longitudinal Preterm Outcome Project (Lollipop) study is supported by grants from the Research Foundation of the Beatrix Children's Hospital, the Cornelia Foundation for the Handicapped Child, the A. Bulk Preventive Child Health Care Research Fund, the Dutch Brain Foundation, and unrestricted investigator-initiated research grants from Friso Infant Nutrition, FrieslandCampina, and Pfizer Europe. The financers had no role at any stage of the project or in the decision to submit the article.

WHAT'S KNOWN ON THIS SUBJECT: Moderately preterm-born children (32–$35^{6/7}$ weeks' gestation) are at risk for both neonatal morbidities after birth and developmental delays in early childhood. It is unknown whether neonatal morbidities contribute to the developmental delays of this particular group.

WHAT THIS STUDY ADDS: Of all neonatal morbidities commonly seen in moderately preterm-born children, only hypoglycemia increased the risk of developmental delay after moderately preterm birth. A concerted effort to prevent hypoglycemia after birth might enhance developmental outcome in this group.

abstract

BACKGROUND AND OBJECTIVE: Children born moderately preterm (32–$35^{6/7}$ weeks' gestation) are at increased risk of both neonatal morbidities and developmental delays in early childhood. It is unknown whether neonatal morbidities contribute to the increased risk of developmental delay. The objective of this study was to determine the effect of neonatal morbidities after moderately preterm birth on development at preschool age.

METHODS: In a community-based, stratified cohort, parents of 832 moderately preterm children born in 2002 or 2003 completed the Ages and Stage Questionnaire when their child was 43 to 49 months old. Data on Apgar scores, asphyxia, tertiary NICU admission, hospital transfer, circulatory insufficiency, hypoglycemia, septicemia, mechanical ventilation, continuous positive airway pressure, apneas, caffeine treatment, and hyperbilirubinemia were obtained from medical records. We assessed associations of neonatal characteristics with developmental delay, adjusted for gender, small-for-gestational-age status, gestational age, and maternal education.

RESULTS: Hypoglycemia and asphyxia were associated with developmental delay; odds ratios (ORs) were 2.42 (95% confidence interval [CI]: 1.23–4.77) and 3.18 (95% CI: 1.01–10.0), respectively. Tertiary NICU admission and hyperbilirubinemia had positive but statistically borderline nonsignificant associations with developmental delay: ORs were 1.74 (95% CI: 0.96–3.15) and 1.52 (95% CI: 0.94–2.46), respectively. No other neonatal morbidities were associated with developmental delay. In multivariate analyses, only hypoglycemia was associated with developmental delay (OR: 2.19; 95% CI: 1.08–4.46).

CONCLUSIONS: In moderately preterm-born children, only hypoglycemia increased the risk of developmental delay at preschool age. A concerted effort to prevent hypoglycemia might enhance developmental outcome in this group. *Pediatrics* 2012;130:e265–e272

Moderately preterm-born children (32–$35^{6/7}$ weeks' gestation)[1,2] have a relatively high rate of neonatal morbidities.[3] These neonatal morbidities include asphyxia, respiratory insufficiency, circulatory insufficiency, septicemia, hypoglycemia, hyperbilirubinemia, apnea, hypothermia, and feeding problems.[3–6] Some of these morbidities are severe enough to warrant admission to a tertiary NICU. Apart from the risk of neonatal morbidities, moderately preterm-born children are also more likely to have developmental delays at preschool age.[7–9] Particularly in moderately preterm-born children, it remains unclear whether these neonatal morbidities are associated with the increased risk of developmental delay.[9]

In the general population, male gender, small-for-gestational-age (SGA) status at birth, decreasing gestational age, and low maternal education increase the risk of developmental delay. It might, therefore, be important to correct for these biological and environmental variables when studying the association between neonatal morbidities and developmental delays in moderately preterm-born children.[10–13] First, insight into the impact these neonatal morbidities have on this particular group of preterm-born children might help to direct future research on optimizing postnatal care for this group.[14] Second, it might help to predict which children in this group might be more likely to have developmental delays in early childhood.

The aim of the authors of this study was to determine for moderately preterm-born children which neonatal morbidities were associated with developmental delay at preschool age. We hypothesized that several neonatal morbidities would have an association with developmental delays in this group, independent of SGA status, gender, gestational age (within the moderately preterm range), and maternal level of education.

METHODS

Population and Participants

This study was part of the Longitudinal Preterm Outcome Project (Lollipop) on growth and development in preterm children.[9,15,16] In a community-based cohort of 45 455 children born in 2002 and 2003, all children with a gestational age between $32^{0/7}$ and $35^{6/7}$ weeks' gestation were sampled. We based the size of our cohort on the estimates for the numbers needed to compile growth curves for Dutch preterm-born children, because for that part of the Lollipop study we needed the largest number of children. To detect a difference in growth restraint of 10% between term and preterm children per week of gestation, separately for boys and girls, with a power of 80% at $P = .05$, we needed to include 1000 moderately preterm-born children.[16] In this context, growth restraint was defined as <10th percentile for term children, which led to a planned inclusion of 1000 moderately preterm-born children.

All the children were included during their regular visit to a preventive child health care center (PCHC) at the age of 43 to 49 months (inclusion from October 2005–September 2007). At this age, 95% to 97% of all Dutch children are seen routinely at a PCHC.[17] Children with major congenital malformations, congenital infections, and all children with syndromes were excluded. Eventually, after removal of the excluded children, 1145 moderately preterm-born children were included in the study.

The study was approved by the local institutional review board, and written informed consent was obtained from all parents. A detailed description of how the Lollipop study was conducted has been described previously.[9,15,16]

Variables and Procedures

Parents completed several questionnaires, including the Dutch version of the 48 months Ages and Stages Questionnaire (ASQ) before their planned visit to the PCHC. The ASQ is a parent-completed developmental screening tool.[18,19] Its reliability and validity have been documented in several studies.[19–22] The ASQ measures development in 5 domains: communication, fine motor, gross motor, problem-solving ability, and personal-social functioning.[18] The scores on each domain add up to an ASQ total-problems score. A score of >2 SDs below the mean score for the Dutch reference group was considered to indicate developmental delay (dichotomous yes/no). Reliability, validity, mean scores, and cut-off values of the Dutch 48 months ASQ version had been determined earlier in a larger part of the Lollipop cohort consisting of a sample of 1510 early and moderately preterm-born children and 562 term-born controls.[15] For the purpose of this study and in accordance with the ASQ manual and American Academy of Pediatrics recommendations, the ASQ scores were based on the children's uncorrected calendar age.[15,23]

Data on neonatal morbidities of children participating in this part of the Lollipop study were collected from hospital records, bedside charts, and preventive child health care records. We based our choice of neonatal morbidities to be collected on general clinical knowledge on the admission of moderately preterm-born children and on a search of the available literature.[3] In the Netherlands, deliveries between 32 and 37 weeks' gestation are conducted in regional hospitals. After birth, glucose values, oral intake, daily weight gain, and jaundice are monitored according to local protocols. Only when the mother is critically ill or the expected birth weight of the child is <1200 g will mothers be admitted antenatally to a tertiary hospital center. Whenever a child needs mechanical ventilation after birth or is otherwise critically ill,

the child is stabilized in the regional hospital and then transferred to a tertiary NICU.

Neonatal morbidities were categorized as birth-related, admission-related, and other neonatal variables. Definitions of the variables are described in Table 1. We did not include rare neonatal morbidities (morbidities with a prevalence of <0.5% in moderately preterm-born children) in the analyses because of a lack of power to detect their effects, however severe. Such rare morbidities include high-grade intraventricular hemorrhages, bronchopulmonary dysplasia, necrotizing enterocolitis, and convulsions.

Glucose values are measured routinely several times during the first 24 hours of life and longer whenever necessary for all infants born at <36 completed weeks of gestation. This practice is common in the Netherlands, even for children staying in the maternity ward with their mothers. In most hospitals, glucose values were monitored by bedside analyses and only sent to the laboratory if they were <3.0 (54 mg/dL) or 2.5 mmol/L (45 mg/dL), according to local protocol. Children without recorded laboratory data and no mention of low plasma glucose values in discharge letters or bedside charts were considered to have had blood glucose values of >2.5 mmol/L (45 mg/dL).

Data on biological and environmental variables included maternal educational level, gender, and SGA status. Data on maternal education were collected from a general parental questionnaire and data on birth weight and gestational age were collected from discharge letters, preventive child health care records, and obstetrical data. SGA status, as a proxy for intrauterine growth, was defined as a birth weight <10th percentile of the Dutch Kloosterman growth curves.[24]

Owing to local differences among hospitals in the manner in which data were stored and retrieved, we cross-checked data on both neonatal morbidities and biological and environmental variables in all available data sources.

TABLE 1 Definitions of Variables Concerning Neonatal Morbidities Grouped into Birth-Related, Admission-Related, and Other Neonatal Variables, and the Definitions of the Biological and Environmental Variables

Variable	Definition
Birth-related	
Low Apgar score	Apgar score <7 after 5 min
Asphyxia	Asphyxia documented in the conclusion of the discharge letter
Admission-related	
Not admitted	Not admitted to any pediatric ward; stayed with mother in the maternity ward
Tertiary NICU	Admission to a tertiary NICU
Transportation	Transfer from a regional hospital to a tertiary NICU within 72 h after birth
Other neonatal	
Circulatory insufficiency	Inotropics, including dopamine, dobutamine, or (nor)adrenaline
Respiratory insufficiency	
CPAP	CPAP for longer than initial stabilization in the delivery room only
Ventilation	Mechanical ventilation for a longer duration than initial stabilization in the delivery room only
CPAP and/or ventilation	CPAP and/or mechanical ventilation with same definitions
Apnea	Apnea in discharge letter or documented on bedside charts
Caffeine	Treatment with caffeine for apnea
Septicemia	Both clinical symptoms and at least 1 positive blood culture result
Hypoglycemia	At least 1 plasma glucose value <1.7 mmol/L (30 mg/dL), within first 72 h of life
Hyperbilirubinemia	Peak bilirubin value of >340 μmol/L (20 mg/dL) and/or any value requiring phototherapy
Biological and environmental factors	
SGA	Birth wt <10th percentile according to the Dutch growth curves
Male gender	Male gender
Low gestational age	<34 weeks' gestation (ie, 32^{+0}–33^{+6} weeks)

CPAP, continuous positive airway pressure.

Analyses

We first analyzed the prevalence rates of all birth-related, admission-related, and other neonatal variables as well as the prevalence rates of biological and environmental variables of our study group. Subsequently, we analyzed the association between all the variables and rates of abnormal ASQ total-problems scores in univariate logistic regression analyses. Finally, all risk factors with univariate associations of $P < .10$ were included simultaneously in a multivariable logistic regression model. Because we expected to find an association between SGA status and several neonatal morbidities, such as hypoglycemia, we had decided beforehand to repeat the analyses without the children who were SGA. For those neonatal morbidities that had significant associations in the multivariate analyses, we also assessed which ASQ domains were involved and carried out further investigations concerning the variable and the children affected. All analyses were done by using SPSS version 18.0 (SPSS Inc, Chicago, IL).

RESULTS

The parents of 84% ($N = 960$) of the 1145 participating moderately preterm-born children completed the ASQ. The median age of these children was 46 months. Of these 960 questionnaires, 97% ($N = 927$) were completed within the time window, which we had set at 43 to 49 months. We did not retrieve data on neonatal morbidities for 10% ($N = 95$) of these 927 children. This fact was partly due to logistic reasons, because

we did not visit small regional hospitals that were very far away from the coordinating research center, and partly due to missing records. The final sample eventually consisted of 832 children with ASQ data within the set time window and neonatal data. The nonincluded children in the final sample ($N = 313$) more often had mothers who were non-Dutch (15.0% vs 5.4%, $P < .001$). They did not differ significantly concerning gender, gestational age, SGA status, maternal education, or percentage of multiples (results not shown). Demographics of the children in the final sample are shown in Table 2. The prevalence rates of the neonatal morbidities we studied ranged from 1.1% to 46%.

Univariate Analyses

Within our total study group of 832 moderately preterm-born children, 73 (9.1%) had abnormal ASQ total-problems scores, as opposed to 4.2% of the term-born children in the original Lollipop cohort.[9] Table 3 shows the results of both the univariate and multivariate logistic analyses. Two neonatal morbidities, hypoglycemia and asphyxia, had a positive association with developmental delay as measured by the ASQ total-problems score in the univariate analyses; odds ratios (ORs) were 2.42 (95% confidence interval [CI]: 1.23–4.77) and 3.18 (CI: 1.01–10.0), respectively. Tertiary NICU admission and hyperbilirubinemia had positive albeit statistically nonsignificant associations with developmental delay ($0.05 < P < .10$). No other neonatal morbidities were associated with developmental delay. Regarding biological and environmental risk factors, both gender and SGA were associated strongly with developmental delay, whereas maternal educational level and a lower gestational age (within the age range for moderately preterm-born children) were not. Repeating our analyses with gestational age as a continuous variable did not change our results with respect to the effect of gestational age.

TABLE 2 Prevalence Rates for All Birth-Related, Admission-Related, Other Neonatal, Biological, and Environmental Variables for Different Gestational Groups

Variable	32–35 wk, $N = 832$		32–33 wk, $N = 268$		34–35 wk, $N = 564$	
	N[a]	%	N	%	N	%
Birth-related						
Low Apgar score	32	3.7	14	5.2	18	3.2
Asphyxia	17	2.0	8	3.0	9	1.6
Admission-related						
Not admitted to a pediatric ward	5	0.6	0	0	5	0.9
Tertiary NICU	119	14.3	74	27.6	45	8.0[b]
Transportation	37	4.4	22	8.2	15	2.7[b]
Other neonatal						
Circulatory insufficiency	25	3.0	12	4.5	13	2.3
Respiratory insufficiency						
CPAP (0–13 d)	139	16.7	82	30.6	57	10.1[b]
Ventilation (0–23 d)	62	7.5	40	14.9	22	3.9[b]
CPAP and/or ventilation	153	18.4	91	34.0	62	11.0[b]
Apnea	193	23.3	119	44.4	74	13.2[b]
Caffeine	94	11.4	74	27.6	20	3.6[b]
Septicemia	30	3.6	17	6.3	13	2.3[b]
Hypoglycemia[c]	67	8.1	24	9.0	43	7.7
Hyperbilirubinemia[d]	361	46.4	147	55.1	214	38.0[b]
Biological and environmental factors						
SGA (<10th percentile)	76	9.1	25	9.3	51	9.0
Male gender	471	56.6	145	54.1	326	57.8
Low maternal education	246	29.7	91	34.1	155	27.7[b]

CPAP, continuous positive airway pressure.

[a] All variables: ≤9 children with missing data.

[b] $P < .05$ for differences between both gestational groups in χ^2 analysis.

[c] At least 1 recorded plasma glucose value <1.7 mmol/L (30 mg/dL). Range, lowest recorded value: 0.4–6.4 mmol/L.

[d] Peak bilirubin value of >340 μmol/L (20 mg/dL) or any value requiring phototherapy. Range, highest recorded value: 34–421 μmol/L.

Multivariate Analyses

As shown in Table 3, hypoglycemia remained associated with an increased risk of developmental delay as measured by the ASQ total-problems score in the multivariate model, with an OR of 2.19 (CI: 1.08–4.46). Male gender and SGA status also retained strong associations with developmental delay in the multivariate model. The multivariate analyses without the children who were SGA showed similar results; in the model without the children of SGA status, the OR of hypoglycemia for abnormal ASQ total scores was 2.64 (CI: 1.23–5.65).

Looking at the group of children with hypoglycemia ($N = 67$) in more detail, we found that >90% had not been admitted to a tertiary NICU, and none had had asphyxia, circulatory insufficiency, or a bilirubin value of >340 μmol/L. Two children (3%) with hypoglycemia were mechanically ventilated, 4 children (6%) had a septicemia, and 8 (12%) were born SGA. Rates of SGA status, tertiary NICU admittance, hyperbilirubinemia, septicemia, mechanical ventilation, and asphyxia did not differ statistically between children with and without documented hypoglycemia. Twelve of 67 children with a glucose value <1.7 mmol/L (30 mg/dL) had abnormal ASQ total-problems scores; 12 of 73 children with abnormal ASQ total-problems scores had a glucose value <1.7 mmol/L (30 mg/dL). In a subanalysis, we found that ORs for abnormal ASQ total-problems scores increased with decreasing glucose values (Table 4). Finally, we examined the association between hypoglycemia and underlying ASQ domains. Hypoglycemia had

TABLE 3 ORs, 95% CIs, and *P* Values for Abnormal ASQ Total-Problems Scores for Birth-Related and Admission-Related or Other Neonatal Variables and Biological and Environmental Variables

Variable	Univariate Analyses		Multivariate Analyses[a]	
	OR (CI)	*P*	OR (CI)	*P*
Birth-related				
Low Apgar score	1.11 (0.33–3.75)	.87	—	—
Asphyxia	3.18 (1.01–10.0)	.05	2.67 (0.74–9.60)	.13
Admission-related				
Not admitted to a pediatric ward	0.81 (0.10–6.59)	.85	—	—
Tertiary NICU	1.74 (0.96–3.15)	.07	1.22 (0.61–2.42)	.57
Transportation	1.26 (0.43–3.15)	.67	—	—
Other neonatal				
Circulatory insufficiency	0.47 (0.05–3.05)	.38	—	—
Respiratory insufficiency				
CPAP	0.85 (0.44–1.67)	.65	—	—
Ventilation	1.04 (0.45–2.64)	.84	—	—
CPAP and/or ventilation	0.76 (0.39–1.48)	.65	—	—
Apnea	0.85 (0.44–1.67)	.65	—	—
Caffeine	0.76 (0.39–1.48)	.41	—	—
Septicemia	1.56 (0.53–4.60)	.42	—	—
Hypoglycemia[b]	2.42 (1.23–4.77)	.01	2.19 (1.08–4.46)	.03
Hyperbilirubinemia[c]	1.52 (0.94–2.46)	.09	1.48 (0.89–2.46)	.13
Biological and environmental factors				
SGA (<10th percentile)	3.30 (1.78–6.12)	<.001	2.62 (1.36–5.05)	<.001
Male gender	3.54 (1.94–6.46)	<.001	3.12 (1.70–5.75)	<.001
Low gestational age[d]	0.95 (0.57–1.60)	.85	—	—
Low maternal education	1.31 (0.79–2.18)	.30	—	—

CPAP, continuous positive airway pressure.

[a] All variables with univariate associations at $P < .10$ were entered in the multivariate model simultaneously.

[b] At least 1 plasma glucose value <1.7 mmol/L (30 mg/dL).

[c] Peak bilirubin value of >340 μmol/L (20 mg/dL) or any value requiring phototherapy.

[d] Low gestational age within the study group; that is, $32^{0/7}$ to $33^{6/7}$ weeks' gestation.

TABLE 4 ORs, 95% CIs, and *P* Values for Abnormal ASQ Total-Problems Scores for Different Ranges of Hypoglycemia

Variable	*N*	OR	CI	*P*
Glucose value <1.1 mmol/L (20 mg/dL)	25	3.04	1.03–9.00	.045
Glucose value of 1.1–1.7 mmol/L (20–30 mg/dL)	42	2.50	0.98–6.40	.055
Glucose value of 1.7–2.2 mmol/L (30–40 mg/dL)	120	1.40	0.66–3.00	.38
Glucose value of 2.2–2.8 mmol/L (40–50 mg/dL)	109	1.31	0.59–2.92	.41

positive but statistically nonsignificant associations with all 5 underlying ASQ domains, as shown in Table 5.

TABLE 5 ORs, 95% CIs, and *P* Values for Abnormal ASQ Domain Scores for Hypoglycemia

ASQ Domain	OR (CI)	*P*
Fine motor	1.7 (0.81–3.61)	.16
Gross motor	2.0 (0.87–4.71)	.10
Communication	1.7 (0.81–3.40)	.16
Problem-solving	2.1 (0.94–4.37)	.07
Personal-social	2.2 (0.93–5.05)	.08

DISCUSSION

The authors of this study demonstrated that in a group of moderately preterm-born children, only hypoglycemia was associated with parent-reported developmental delay at preschool age, controlling for SGA status and gender. No other neonatal morbidities we studied were associated with developmental delay in this group.

Our finding that only hypoglycemia was associated with an increased developmental risk in moderately preterm-born children was unexpected. A documented glucose value <1.7 mmol/L (30 mg/dL) was rather common (8.1%) and increased the risk of developmental delay from 9.1% to almost 20%. There is no consensus among pediatricians on the absolute threshold values for hypoglycemia that will lead to brain injury.[25–28] There also is no consensus on specific operational thresholds for different gestational ages below which extra measures to prevent hypoglycemia should be undertaken.[25,26] There is considerable debate on the effect of short-lasting low plasma glucose levels at higher values than 1.7 mmol/L, that is, in the range between 1.7 and 2.5 mmol/L (30–45 mg/dL).[25–27] We chose a relatively low cut-off point to enable us to study even short periods of hypoglycemia.

Hypoglycemia is only a proxy for energy failure in the brain. The effect of hypoglycemia on the brain, even if it occurs only during a short period, also depends on many other factors. These factors include cerebral blood flow, cerebral glucose utilization, and the presence of alternative substrates such as lactate and ketone bodies.[25–29] Comorbidity among the children with hypoglycemia was not increased significantly, suggesting that they were not the sicker children. Moreover, excluding children of SGA status from the analyses did not change our results. The effects on development of hypoglycemia in moderately preterm-born children seemed to be due to the hypoglycemia in itself. Furthermore, risk of developmental delay increased with decreasing glucose values, with a steeper incline below 1.7 mmol/L (30 mg/dL), suggesting an increased risk of brain injury below this value. There are relatively few studies published on the effect of neonatal hypoglycemia on development in early childhood. In a systemic review on this subject, the authors concluded that no valid estimate of the effect of neonatal hypoglycemia on development could be given based on the 18 studies included in their review.[30]

Data on the underlying pathologic substrate of hypoglycemia on the brain are rare and derive mostly from adult studies, animal studies, or studies on term-born infants.[27,28] MRI findings in these few studies have shown that both diffuse cortical and subcortical injuries, hemorrhages, infarction, and basal ganglia and thalamus abnormalities are related to hypoglycemia.[27,28] Our findings on the effects of hypoglycemia on developmental delay across all 5 developmental domains measured by the ASQ are in agreement with these findings of injuries in a wide range of cerebral regions.

The high risk for hypoglycemia in moderately preterm-born infants can be explained by the fact that in comparison with healthy term-born infants, they have less glucose stores, less alternative substrates, and less well-developed hormonal counter-regulatory mechanisms to sustain adequate glucose levels after birth.[25–29] They also have more difficulties in starting to feed orally and in achieving adequate feedings than term-born infants do.[3,5] Moreover, in contrast to early preterm-born infants, moderately preterm-born infants do not always routinely receive intravenous glucose infusions after birth.

In our moderately preterm-born study group, we found no association between other common neonatal morbidities such as respiratory insufficiency, circulatory insufficiency, and septicemia and developmental delay. This finding is contrary to our hypothesis and in contrast with findings on early preterm-born children, for whom several of these neonatal morbidities were linked to an increased risk of developmental delay.[31–33] The differences in the effects of these neonatal morbidities on developmental delays in both groups might be due to the fact that the severity of several neonatal morbidities is usually lower in the moderately preterm-born group. No child was ventilated for >2 weeks, and bilirubin values of >340 μmol/L (20 mg/dL) were rare. Furthermore, we speculate that the brain of moderately preterm-born children is perhaps more resilient to injury caused by neonatal morbidities than the brain of early preterm-born children.

The strengths of our study were the community-based approach and the large number of children who participated. We also recognize several limitations of our study. We measured developmental outcome with a parent-completed screening tool instead of submitting the children to extensive neuropsychological tests. Nevertheless, developmental screeners are considered to be reliable measures for identifying developmental problems in high-risk populations.[34] A second limitation was the retrospective design for collecting data on neonatal morbidities. It is possible that for some children, hypoglycemia had not been measured according to the national guidelines or had been recorded in sources we were unable to trace. A third limitation concerned the low prevalence of some of the risk factors, such as asphyxia, circulatory insufficiency, not being admitted to neonatal care, and intraventricular hemorrhages. This low prevalence leads to a relatively low power to detect differences in developmental outcome. Still larger population-based studies are needed to estimate the effect of such severe, but rare, neonatal morbidities on risk of developmental delay. Finally, more children who were not included in the final analyses had mothers born outside the Netherlands. The latter children are unlikely to have had different neonatal morbidities. Furthermore, all children born in the Netherlands get equal medical care at birth regardless of the insurance of their parents. We therefore think these differences in rates of mothers born outside the Netherlands will not have influenced our results.

Our study may have important implications. We were surprised to find that 8.1% of the moderately preterm-born children we studied had at least 1 documented glucose value of <1.7 mmol/L (30 mg/dL), which occurred despite the guidelines to prevent hypoglycemia in this group. These guidelines include recommendations to monitor glucose regularly during the first 24 hours, and administering early, frequent enteral feedings. Controlled, prospective studies with interventions aiming at enhanced prevention of severe hypoglycemia in moderately preterm-born children are needed to confirm that the chance of developmental delay can be modified by stricter glucose control.[35] The next implication is that our results might help to further unravel the complex cascade of biological, environmental, prenatal, perinatal, and postnatal events that might all lead to developmental delay in moderately preterm-born children.[2,10,12] We found that the effects of SGA status and male gender were more important than all the neonatal morbidities we examined. Our study, therefore, does not support the view that neonatal morbidities have a large influence on developmental outcome in the group of moderately preterm-born children.

CONCLUSIONS

Hypoglycemia after moderately-preterm birth is associated with an increased risk of parent-reported developmental delay at age 4. Stricter monitoring and timely treatment of hypoglycemia after birth might benefit the large group of moderately preterm-born children.

ACKNOWLEDGMENTS

This study is part of a larger cohort study on development, growth, and health of preterm children, known as the Lollipop study. It is part of the study

program of the Postgraduate School of Behavioral and Cognitive Neurosciences, University of Groningen, Groningen, Netherlands.

The authors thank all participating PCHC physicians for their contribution to the field work of the study. In particular, we thank the preventive child health care physicians E. ten Vergert, B. van der Hulst, and M. Broer van Dijk for coordinating the field work. We thank Dr. T. Brantsma-van Wulfften Palthe for correcting the English manuscript.

The ASQ 48 months form was translated into Dutch with permission from the author and is available from the authors on request.

REFERENCES

1. Jensen LV, Mathiasen R, Mølholm B, Greisen G. Low 5-min Apgar score in moderately preterm infants; association with subsequent death and cerebral palsy: a register based Danish national study. *Acta Paediatr*. 2012;101(2):e80–e82
2. van Baar AL, Vermaas J, Knots E, de Kleine MJ, Soons P. Functioning at school age of moderately preterm children born at 32 to 36 weeks' gestational age. *Pediatrics*. 2009; 124(1):251–257
3. Teune M, Bakhuizen S, Gyamfi Bannerman C, et al. A systematic review of severe morbidity in infants born late preterm. *Am J Obstet Gynecol*. 2011;205(4):374, e1–e9
4. Altman M, Vanpée M, Cnattingius S, Norman M. Neonatal morbidity in moderately preterm infants: a Swedish national population-based study. *J Pediatr*. 2011;158(2):239–244, e1
5. 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(4):367, e1–e8
6. Boyle JD, Boyle EM. *Born just a few weeks early: does it matter* [published online ahead of print August 24, 2011]? *Arch Dis Child Fetal Neonatal Ed*. doi:10.1136/archdischild-2011-300535
7. McGowan JE, Alderdice FA, Holmes VA, Johnston L. Early childhood development of late-preterm infants: a systematic review. *Pediatrics*. 2011;127(6):1111–1124
8. Woythaler MA, McCormick MC, Smith VC. Late preterm infants have worse 24-month neurodevelopmental outcomes than term infants. *Pediatrics*. 2011;127(3). Available at: www.pediatrics.org/content/127/3/e622
9. Kerstjens JM, de Winter AF, Bocca-Tjeertes IF, ten Vergert EM, Reijneveld SA, Bos AF. Developmental delay in moderately preterm-born children at school entry. *J Pediatr*. 2011; 159(1):92–98
10. Talge NM, Holzman C, Wang J, Lucia V, Gardiner J, Breslau N. Late-preterm birth and its association with cognitive and socioemotional outcomes at 6 years of age. *Pediatrics*. 2010; 126(6):1124–1131
11. Latal B. Prediction of neurodevelopmental outcome after preterm birth. *Pediatr Neurol*. 2009;40(6):413–419
12. Aarnoudse-Moens CSH, 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(2):717–728
13. Wolke D, Schulz J, Meyer R. Entwicklungslangzeitfolgen bei ehemaligen, sehr unreifen fruhgeborenen. *Monatsschr Kinderheilkd*. 2001;149:S53–S61
14. Jain L. School outcome in late preterm infants: a cause for concern. *J Pediatr*. 2008; 153(1):5–6
15. Kerstjens JM, Bos AF, ten Vergert EMJ, de Meer G, Butcher PR, Reijneveld SA. Support for the global feasibility of the Ages and Stages Questionnaire as developmental screener. *Early Hum Dev*. 2009;85(7): 443–447
16. Bocca-Tjeertes IFA, Kerstjens JM, Reijneveld SA, de Winter AF, Bos AF. Growth and predictors of growth restraint in moderately preterm children aged 0 to 4 years. *Pediatrics*. 2011;128(5). Available at: www.pediatrics.org/content/128/5/e1187
17. Crone MR, Vogels AGC, Hoekstra F, Treffers PDA, Reijneveld SA. A comparison of four scoring methods based on the parent-rated Strengths and Difficulties Questionnaire as used in the Dutch preventive child health care system. *BMC Public Health*. 2008;8(1): 106–115
18. Squires J, Bricker D, Potter L. *Ages and Stages Questionnaires User's Guide*. 2nd ed. Baltimore, MD: Paul H. Brookes Publishing; 1999
19. Squires J, Bricker D, Potter L. Revision of a parent-completed development screening tool: Ages and Stages Questionnaires. *J Pediatr Psychol*. 1997;22(3):313–328
20. Skellern CY, Rogers Y, O'Callaghan MJ. A parent-completed developmental questionnaire: follow up of ex-premature infants. *J Paediatr Child Health*. 2001;37(2):125–129
21. Yu LM, Hey E, Doyle LW, et al; Magpie Trial Follow-Up Study Collaborative Group. Evaluation of the Ages and Stages Questionnaires in identifying children with neurosensory disability in the Magpie Trial follow-up study. *Acta Paediatr*. 2007;96(12): 1803–1808
22. Heo KH, Squires J, Yovanoff P. Cross-cultural adaptation of a pre-school screening instrument: comparison of Korean and US populations. *J Intellect Disabil Res*. 2008;52 (pt 3):195–206
23. Bernbaum JC, Campbell DE, Imaizumi SO, McInerny T. Follow-up care of the graduate of the neonatal intensive care unit. In: McInerny TK, Adam HM, Campbell DE, Kamat DM, Kelleher KJ, eds. *American Academy of Pediatrics Textbook of Pediatric Care*. Elk Grove Village, IL: AAP; 2008
24. Kloosterman GJ. On intrauterine growth: the significance of prenatal care. *Int J Gynaecol Obstet*. 1970;8(6):895–912
25. Rozance PJ, Hay WW Jr. Describing hypoglycemia—definition or operational threshold? *Early Hum Dev*. 2010;86(5): 275–280
26. Adamkin DH; Committee on Fetus and Newborn. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics*. 2011;127(3):575–579
27. Rozance PJ, Hay WW. Hypoglycemia in newborn infants: features associated with adverse outcomes. *Biol Neonate*. 2006;90(2):74–86
28. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. *Pediatrics*. 2008;122(1):65–74
29. Adamkin DH. Late preterm infants: severe hyperbilirubinemia and postnatal glucose homeostasis. *J Perinatol*. 2009;29(suppl 2): S12–S17
30. Boluyt N, van Kempen A, Offringa M. Neurodevelopment after neonatal hypoglycemia: a systematic review and design of an optimal future study. *Pediatrics*. 2006;117 (6):2231–2243
31. Schlapbach LJ, Aebischer M, Adams M, et al; Swiss Neonatal Network and Follow-Up Group. Impact of sepsis on neurodevelopmental

outcome in a Swiss National Cohort of extremely premature infants. *Pediatrics*. 2011;128(2). Available at: www.pediatrics.org/content/128/2/e348

32. Kuint J, Barak M, Morag I, Maayan-Metzger A. Early treated hypotension and outcome in very low birth weight infants. *Neonatology*. 2009;95(4):311–316
33. Watchko JF, Jeffrey Maisels M. Enduring controversies in the management of hyperbilirubinemia in preterm neonates. *Semin Fetal Neonatal Med*. 2010;15(3):136–140
34. Glascoe FP. Evidence-based approach to developmental and behavioural surveillance using parents' concerns. *Child Care Health Dev*. 2000;26(2):137–149
35. Hay WW Jr, Raju TNK, Higgins RD, Kalhan SC, Devaskar SU. Knowledge gaps and research needs for understanding and treating neonatal hypoglycemia: workshop report from Eunice Kennedy Shriver National Institute of Child Health and Human Development. *J Pediatr*. 2009;155(5):612–617

Neonatal Morbidities and Developmental Delay in Moderately Preterm-Born Children

Jorien M. Kerstjens, Inger F. Bocca-Tjeertes, Andrea F. de Winter, Sijmen A. Reijneveld and Arend F. Bos

Pediatrics 2012;130;e265; originally published online July 9, 2012;
DOI: 10.1542/peds.2012-0079