Sleep in high risk infants

Sleep duration and nocturnal awakenings in children born prematurely, low birth weight and/or small for gestational age.

Mari Hysing[1], PhD, Ted Reichborn-Kjennerud[2,3], PhD MD, Trond Markestad[4,5], PhD MD, Irene Elgen[5,6], PhD MD, Børge Sivertsen[1,2,7]

[1] Department of Psychosocial Science, Faculty of Psychology, University of Bergen, Bergen, Norway, Regional, Centre for Child and Youth Mental Health and Child Welfare, NORCE Norwegian Research Institute, Bergen,Norway

[2]Division of Mental Health, Norwegian Institute of Public Health, Oslo & Bergen, Norway

[3] Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[4] Department of Pediatrics, Haukeland University Hospital, Bergen, Norway

[5] Department of Clinical Medicine, University of Bergen, Bergen, Norway

[6] Department of Child and Adolescent Psychiatry, Haukeland University Hospital, Bergen, Norway

[7] Department of Research and innovation, Helse Fonna HF, Haugesund, Norway;

Objective: Infants born with gestation-related risks (low birth weight, small for gestational age and premature born infants) are faced with a cascade of developmental issues. The aim of the present study was to investigate if infants with gestation-related risks have different patterns of parent reported sleep duration and nocturnal awakenings than children without these risk factors.

Method: Information on sleep duration and nocturnal awakenings were obtained by parental report at 6 and 18 months of age in the Norwegian Mother and Child Cohort Study, which is a population-based longitudinal pregnancy cohort conducted at the xxx. Birthweight and gestational age were obtained from the Medical Birth Registry of Norway. Outcomes were related to birthweight, prematurity and to being born small for gestational age (SGA).

Results: A total of 75,531 of mother – child dyads were included. Compared to children without gestational risks, children born SGA and with LBW had shorter sleep, duration, while children born prematurely had longer sleep duration at both time points. The infants born SGA and LBW, but not the prematurely born children had less nocturnal awakenings at 6 months, but all had more awakenings at 18 months.

Conclusion: Infants with gestation-related risks show distinct sleep patterns. We suggest that sleep assessment is included in the follow- up of high-risk infants. Future studies are needed to investigate the predictive value and functional importance of the sleep patterns for infants with gestational related risk.

Key terms: sleep, infants, prematurity, small for gestational age, low birth weight, gestation -related risk

INTRODUCTION

Infants with gestation-related risks, including infants born prematurely, small for gestational age (SGA) and with low birth weight (LBW), are at increased risk of neurodevelopmental and mental health problems [1]. They are faced with a cascade of developmental issues, but whereas the main focus of previous studies has been on daytime behavior, less is known about nighttime sleep behavior. Addressing sleep issues in these risk populations may be of great significance, due to the importance of sleep for child development. For instance, there is evidence that sleep problems in toddlers increases the risk of later behavioral and emotional problems [2], as well as lower cognitive performance [3, 4]. Problems with sleep-wake transitions in children with gestation-related risks have been linked to both negative developmental outcomes [5] and neurological dysfunction [6]. Furthermore, circadian sleep patterns in children born preterm have been associated with delayed cognitive functioning and increased health care visits [7]. Therefore, improving our understanding of sleep in infants with gestation-related risks, is of importance when predicting future challenges, and also key in designing intervention studies.

Sleep in infants born prematurely and full term have been extensively studied, but the results remain conflicting. Some longitudinal studies following the children for the first five and ten years of life, have failed to find differences between children born prematurely and at term across a range of sleep variables, including sleep duration and nightly awakenings [8, 9]. Other studies found that prematurely born children have shorter sleep duration at 12 months of age [10], longer sleep duration later in childhood [11], and lower sleep quality at 20 months as measured by actigraphy [12]. These mixed results warrant further studies on the associations between specific gestational risks and later sleep patterns. For instance, developmental outcomes have been found to vary according to the degree of prematurity and intrauterine growth [13-15]. For outcomes such as cognition, there have been differences across gestational risk groups and this may also be the case for rate and type of sleep problems[16], but sleep behaviors across groups with different gestational risks remain largely unexplored. Furthermore, longitudinal studies in the first two years are needed to assess if the sleep patterns are specific for the various developmental stages, since sleep undergoes major changes during this period

Our aim was to investigate whether sleep duration and nightly awakenings at 6 and 18 months of age differed between children born prematurely, SGA or with LBW than for children without these gestation-related risks. The study was based on a large population-based Norwegian birth cohort that prospectively followed mothers from early pregnancy.

METHODS

Population

This study was based on The Norwegian Mother and Child Cohort Study (MoBa). In short, MoBa is a prospective population-based pregnancy cohort study conducted by xxx.[17] Women were recruited from all over Norway at 17-19 weeks of pregnancy between June 1st 1999, and December 31rd 2008, and 108 841 (42.7%) consented to participate. The women were followed regularly during pregnancy and the mothers and their children were later seen at regular intervals. The current study was based on version 9 of the quality-assured data files released for research in September 2015. The data were obtained from MoBa Questionnaires 1 (gestational week 17), 4 (6 months after birth), and 5 (18 months after birth) and the Medical Birth Registry of Norway (MBRN). As of September 2015, the study contained a longitudinal sample with valid data on the sleep variables of 75,531 of the included mother-child dyads. We excluded children born at less than 22 and more than 43 weeks' gestation, yielding an eligible sample of 74,880 women and 75,205 children; 1223 were twins (1.6%), 38,455 (51.1%) were girls, 4397 (5.9%) were born prematurely [GA < 28 weeks: n=116 (0.2%), 28-31 weeks: n=374, (0.5%), and 32-36 weeks: n=3907 (5.2%)], and 2900 (3.9%) children had LBW [BW< 1000 g: n=125 (0.2%), BW 1000-1499 g: n=284 (0.4%), and 1500-2499 g: n=2491 (3.3%)] (Table 1).

Measures

Demographical and clinical measures

Information on maternal age and sex, BW and GA of the children, were obtained from the MBRN. Information on maternal education was obtained from MoBa questionnaire 1, on breastfeeding from Questionnaire 4 (6 months) and on sleep from Questionnaire 4 and 5 (6 and 18 months). The introduction of and sustainment of breastfeeding, bottle feeding, and solids was reported by the mothers at six months. Breastfeeding was categorized into three groups: predominant breastfeeding, breastfeeding, and bottle-feeding/no breastfeeding. This is largely in accordance with the classification system of the World Health Organization [[18]]. This categorization is described in detail in an earlier study on breastfeeding derived from this cohort [19]. Predominant breastfeeding is when the infant’s predominant source of nutrition is breast milk. Partial breastfeeding is continued breastfeeding up to six months postpartum, supplemented by formula or solids. Bottle-feeding referred to those mothers who stopped breastfeeding completely and used only milk supplementation and solids.

Birth status

LBW was defined as BW < 2500 grams. We also studied sleep characteristics according to the commonly used BW subcategories, i.e. <1000 grams (extremely low birth weight - ELBW), 1000-1499 grams (Very low birth weight -VLBW), 1500-2499 grams (low birth weight - LBW), 2500-4200 grams, and > 4200 grams. *SGA* was defined as BW below the 2.5^{th}

percentile for sex and GA according to Norwegian percentiles.[20] Appropriate BW for GA (AGA) was defined as BW within 2.5^{th} to 97.5^{th} percentile for GA and large for gestational age (LGA) as a BW above the 97.5^{th} percentile for GA. *Premature birth* was defined as 23-36 weeks' GA.

Sleep outcomes

Sleep duration was assessed with the question: "How many hours does your child sleep during 24 hours?" Response categories at 6 months were: "Less than 8 hours", "8-10 hours", "11-12 hours", "13-14 hours" and "15 hours or more", and at 18 months: "10 hours or less", "11-12 hours", "13-14 hours" and "15 hours or more". In the present study, the 6-month responses of "Less than 8 hours" (n=289) and "8-10 hours" (n=1968) were combined to allow for comparison at 18 months. The most frequently answered category was13-14 hours, which was chosen as the reference category in the analysis.

The American Academy of Sleep Medicine (AASM) recently published new recommendations on sleep duration. For infants (4-11 months old) 12-15 hours is recommended, 11-12 hours may be appropriate while less than 10 hours is insufficient. The corresponding recommendations for toddlers (1-2 years) are 11-14, 9-10 and less than 9 hours. Based on these recommendations, and as we wanted to keep the same cut-offs for both 6 and 18 months, short sleep duration was defined as ≤10 hours or 11-12 hours, respectively.

Nocturnal awakenings were assessed with the question "How often does your child wake up?" Response categories were "3 or more times per night", "1-2 times per night", "Several times a week", and "Seldom or never". The two latter response options were the most frequently answered categories (n=26,982 and n=27,562, respectively) and were combined as the reference category in the analysis.

Data analysis

All analyses were performed using the SPSS statistical software package version 25 (SPSS Inc., Chicago, IL, USA). Independent samples t-tests and chi-squared tests were used to examine differences in demographic, clinical and sleep variables between children born at term and preterm, and between SGA and non-SGA. Multinomial logistic regression analyses were conducted separately for preterm birth, LBW and SGA to examine the predictive effect of these variables on sleep duration and nocturnal awakenings. Both crude and adjusted models were examined, the latter adjusting for the following covariates entered in one block: gender, parity, maternal age maternal education and breastfeeding. For sensitivity purposes, we additionally adjusted for prematurity when examining the effect of SGA and BW on sleep outcomes. All tests were two-tailed with the significance level set at $p<0.05$.

Ethics

Informed consent was obtained from all MoBa participants upon recruitment. The study was approved by The Regional Committee for Medical Research Ethics xxx.

RESULTS

Demographics and overall sleep characteristics

The mean age of the mothers was 30.1 years and 62.4% of them reported an educational level beyond high school (Table1)

At both 6 and 18 months, the majority of the children slept 13- 14 hours, while respectively 3.3% and 2.1% slept 10 hours or less. Nightly awakenings occurred in 69.9% of the children at 6 and in 27.3% at 18 months. There were no significant sex differences for any of the sleep variables. Sleep characteristics stratified by prematurity vs. term birth, BW categories and SGA are presented in Table 1.

Please insert Table 1 about here

Determinants of sleep duration

Determinants of sleep for infants with gestation-related risk are presented in table 2. *Premature birth* was significantly associated with *long* sleep duration (≥ 15 hours) at both 6 months (adjusted OR=1.45, 95% CI: 1.35-1.56) and 18 months (adjusted OR=1.31, 95% CI: 1.11-1.54), but not with shorter sleep duration when compared to infants born at term.

LBW was also significantly associated with long sleep duration at 6 months (adjusted ORs ranging from 1.46-2.51), but not at 18 months. Within the LBW category, children with ELBW (BW< 1000 grams) had a 2.5 to 3-fold increased odds at both time points of sleeping less than 10 hours in comparison to the reference group, both in the crude and adjusted models. Additional adjustment for premature birth only slightly attenuated the ORs, and all significant associations remained (Supplementary Table).

SGA babies were more likely to have short sleep duration than AGA babies. At 6 months, the adjusted odds of sleeping less than 10 hours was 1.31 (95% CI: 1.01-1.70). The association between SGA and short sleep duration (<10 hours) was also significant at 18 months (adjusted OR=1.54, 95% CI: 1.15-2.07). Additional adjustment for premature birth in these analyses did not attenuate the ORs (Supplementary Table).

Please insert Table 2 about here

Determinants of nocturnal awakenings

Determinants of nocturnal awakenings are presented in table 3. Being *born premature* significantly *reduced* the odds of nocturnal awakenings at 6 months (adjusted OR=0.52, 95% CI: 0.47-0.58), but *increased* the odds at 18 months (adjusted OR=1.19 95% CI: 1.01-1.41) in comparison to infants born at term. For the *children with LBW* the odds were also reduced at 6 months, but did not differ from the reference at 18 months. However, for those born with ELBW the adjusted OR of being awake 3 or more times per night was particularly low at 6 months (OR=0.22;95% CI: 0.11-0.45), but the nocturnal awakenings were increased at 18 months (adjusted OR=2.94, 95% CI: 1.46-5.90). Additional adjustment for premature birth had no effect on the magnitude of the OR (Supplementary Table).

SGA birth was not significantly associated with nocturnal awakenings at 6 months, but the odds of 3+ awakenings was increased at 18 months (adjusted OR=1.33, 95% CI: 1.04-1.71). Additional adjustment for premature birth in these analyses did not attenuate the ORs (Supplementary Table).

Please insert Table 3 about here

DISCUSSION

In this large population-based study, infants with gestation-related risks showed some characteristic sleep patterns. There was a distinct developmental pattern of *less* parental reported nocturnal awakenings at 6 months, while there was *more* parent reported nocturnal awakenings one year later, compared to children without these risk factors. For sleep duration, the associations were more complex, with distinct sleep patterns across the gestational risk groups.

The observed developmental shift of increased parent reported nocturnal awakenings in infants with gestational risk in comparison to peers, has previously also been found among very preterm infants during the same developmental period [21]. The reason for this developmental shift is not certain. According to the Transactional theory of development in relation to sleep in premature infants, parental interactions are a key factor for night waking in infants born with gestational risk [22]. Nocturnal awakenings are more susceptible to parental influence later in development, with a critical window at 18 months [23]. The high rate of depressive symptoms among parents of infants born with gestational risk [24], which again is related to infant nocturnal awakenings at this age [25], may be another contributory factor. Neurodevelopmental disabilities (NDD) are also prevalent among infants born preterm [26], and there is support for a graded pattern of association, with increasing rate of sleep problems with increasing NDD. This was demonstrated in a Norwegian study of 11-year-old children [27], a study which also found that children born extremely preterm without NDD had more sleep problems than their peers. The current study sample did not include any information on NDD, but future waves of data collection could shed light on these associations.

Sleep duration differed across the groups of infants with gestation-related risks and changed over time, with both short and long sleep duration occurring more often among infants with high risks, compared to infants with low gestational risk. The short sleep duration observed among children born SGA is in line with findings from a small study of actigraphy assessed sleep in one-year-old premature-born children [10].

The long sleep duration that was observed for LBW and infants born prematurely, has also been demonstrated previously in premature born children [11]. However, our results differ from other epidemiological studies, including a 10-year follow-up study which found no differences in average sleep duration between term and preterm infants [8]. There may be several explanations for these conflicting findings. First, the inclusion of infants born SGA and ELBW/VLBW may constitute a more high-risk sample than the study by Iglowstein et al. [8]. Second, the observed curvilinear association, including higher risk of both short and long sleep duration among the ELBW group, may explain why some previous studies have not found any mean differences in overall sleep duration. The high-risk groups examined in the current study often occur together, and despite our very large sample size, the included groups of gestation-related risk were still relatively small, precluding us from investigating different combinations of high-risk groups. To investigate if prematurity per se could account for the associations in the SGA and LBW groups, we conducted sensitivity analysis that additionally adjusted for prematurity. This, however, did not change the pattern or magnitude of associations between SGA, LBW and sleep, indicating that these risk factors are associated with sleep, independent of prematurity.

Furthermore, the long sleep duration in these infants may be an indication of normal sleep length in accordance with the gestational age of the infants. Infant sleep evolves rapidly during the first year of life, with a decrease in sleep need [8]. As such, these differences would expectedly decrease over time, and therefore also explain why most associations observed at 6 months were no longer present one year later. The low rate of nocturnal awakenings in the infants with gestation-related risks may reflect a need for more sleep due to their relative immaturity. Another possible explanation for the long sleep duration, which has also been included in theoretical models of sleep in premature infants [22], is the feeding route. Being bottle-fed, as opposed to breast-fed, has been found to be a predictor of sleep problems in infants [9, 28]. Similarly, in the general population, frequent nocturnal awakenings have been linked to breastfeeding at six months, but not at 18 months [29]. In the current study, we included breastfeeding in the adjusted analysis, but this had no effects on the results. Thus, feeding route was not supported as a main factor accounting for the increased sleep problems in these high-risk infants.

At the same time, short sleep duration has been found to be associated with different neurodevelopmental markers, and has been linked to both later emotional and behavioral problems [2, 30], and poor cognitive functioning [7]. Sleep problems may be a result of shared neurological risks, e.g. neonatal cerebral hemorrhage, which has been related to later sleep problems among prematurely born children or children born with LBW. Alternatively, it may be contributing to the development of emotional regulation or negative cognitive development[7], and thus be an important target for interventions. The transactional pattern between development and sleep for infants born with gestational risk, might be elucidated through longitudinal studies. Further, it would be of interest to investigate if the differences in sleep patterns are evident later in childhood, or if these differences are most notable in the first few years of life.

Limitations

The present study was restricted to investigate sleep patterns and nocturnal awakenings in premature, SGA and LBW children. The possible functional consequences of these sleep characteristics were beyond the scope of the present study. Future studies should investigate how these distinct sleep patterns are related to later neurodevelopment and/ or emotional and behavioral problems. There are some methodological limitations that should be considered when interpreting the results. First, the measures of sleep are crude and based on parental report, and are restricted to sleep duration and nocturnal awakening. The reported awakenings are thus the signaled night time awakenings that are identified by the parents, and the results cannot be generalized to other brief awakenings that are not signaled. Sleeping arrangement may also bear influence if the parent is made aware of the nocturnal awakenings.

Other sleep problems that are associated with LBW, such as sleep disordered breathing, were not included.[31] Also, there may be unmeasured genetic and/or environmental confounding[32] that may explain the link between prematurity/ LBW/SGA and sleep problems. Finally, parental sleep related behavior that is associated with nocturnal awakenings such as staying with the child until it falls asleep may be more frequent among parents with high-risk infants. [9, 33]

The strength of the present study is the large-scale population-based design that allows for comparison of low frequent groups, while comparing them to peers. The longitudinal design was an opportunity to assess the developmental changes in sleep, and to our knowledge this is the first study to assess sleep over an extended period of time in these high- risk infants.

Conclusions and implications

In a large-scale population-based study, infants with gestation-related risk did show a significant difference in sleep pattern compared to controls. The pattern was complex and age specific. While the results need replication in future studies and the long-term functional significance of the sleep problems for infants born with gestation related risk warrant further investigation, the results do indicate that sleep could be included in the assessment and follow up of high-risk infants.

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