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The Effects of Prenatal Alcohol and Marijuana Exposure: Disturbances in Neonatal Sleep Cycling and Arousal[1]

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ABSTRACT. Neonatal EEG and sleep findings are presented from a longitudinal study of the effects of maternal alcohol and marijuana use during pregnancy. Infant outcome has been examined relative to the trimester(s) of pregnancy during which use occurred. Disturbances in sleep cycling, motility, and arousals were noted that were both substance and trimester specific. Alcohol consumed during the first trimester of pregnancy was associated with disruptions in sleep and arousal, whereas marijuana use affected sleep and motility regardless of the trimester in which it was used. Although these findings are preliminary and based on a small sample of women exhibiting only moderate substance use during pregnancy, they do suggest that specific neurophysiological systems may be differentially affected by prenatal alcohol or marijuana exposure even in the absence of morphological abnormalities. (*Pediatr Res* 24: 101–105, 1988)

Abbreviations

EEG, electroencephalogram
EKG, electrocardiogram
EMG, electromyogram
REM, rapid eye movement
NREM, non-REM

EEG sleep patterns have been used to assess cerebral maturation and neurophysiological organization of the developing CNS in premature, full-term, and older infants (1–9). Abnormal EEG-sleep patterns have been associated with specific clinical conditions identified in either the prenatal or perinatal periods. Among the clinical conditions associated with abnormal EEG-sleep patterns are seizures (10, 11), untreated hypothyroidism (12), maternal diabetes (4) and toxemia (13, 14), trisomy 21 (15), asphyxia (11, 16–18), and drug addiction (19). Several investigators contend that EEG-sleep abnormalities can predict medical and behavioral difficulties in neonates and infants even in the absence of clinical abnormalities (10, 11, 20, 21).

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There has been considerable research on the effects of maternal alcohol and marijuana use during pregnancy on the infant's physical and morphological development, but only a few studies have monitored sleep cycling and arousal as a neurophysiological measure independent of other clinical and/or neurobehavioral assessments. Those studies that have investigated the effects of prenatal alcohol exposure on neurophysiological development have found disturbances in the sleep or EEG patterns. Rosett *et al.* (22) reported that the infants of mothers who drank heavily throughout pregnancy had a greater proportion of quiet sleep, were more restless, and had more major body movements. EEG power spectra analyses of infants of alcoholic mothers have shown hypersynchrony of the EEG as well as an increase in the integrated power in all sleep states, with the greatest increase seen in active sleep (23, 24).

These studies (22–24), however, have methodological limitations. For example, information on alcohol use was frequently obtained from only one interview, which may have been conducted at varying times during pregnancy and, in some cases, only after delivery. To measure either alcohol or marijuana use accurately and with adequate control for the common sources of bias associated with interviewing methods, a more frequent and fixed interviewing schedule is required. In addition, studies have generally not quantified the various subtypes of active (REM) and quiet (NREM) sleep, or their cycling within sleep periods. Also, the descriptions of arousal and motility have been inadequate, presenting only differences in overall EEG power. No EEG-sleep findings have been reported, to our knowledge, for neonates with prenatal exposure to marijuana.

The discussion of EEG-sleep findings herein is limited to the first neonatal recording obtained on these infants at 24 to 36 h of life. Subsequent reports will describe sleep findings assessed later in the infants' development.

METHODS

Study design. The sample for this study is part of a larger cohort of women and their infants participating in a longitudinal study of substance use during pregnancy at a large, urban, university-affiliated obstetrical hospital. Written consent was obtained for both mothers and infants according to guidelines established by the University's Institutional Review Board for Biomedical Research.

Women were first interviewed during their fourth prenatal month to ascertain the use of alcohol, marijuana, tobacco, and other drugs for 1 yr before pregnancy and for the 1st trimester of pregnancy. A description of the methods used in this study for measuring alcohol and marijuana use, along with the development and reliability of the measures, has been reported elsewhere (25).

Women were reinterviewed at 7 months gestation about their substance use during the 2nd trimester, and were questioned again at 24 h postdelivery regarding 3rd trimester substance use. All study infants underwent comprehensive physical examination by study clinicians at birth.

Subjects. From a total of 763 live singleton deliveries, 55 newborns (27 males and 28 females) were selected for EEG-sleep studies. An infant was selected for a sleep study if his/her mother consumed one or more drinks or marijuana cigarettes per day during the 1st trimester. The next infant born after that whose mother drank or smoked a lesser amount was also selected. This subsample of infants had mean Apgar scores of 8.1 and 8.7 at 1 and 5 min, respectively. The average birth weight was 3438.6 g (range 2100–4400) and the average gestational age was 40.5 wk (range 37–43 wk) as determined by the Ballard et al. (26) modification of the Dubowitz assessment. The mothers of these infants were representative of the larger study cohort. They were of lower socioeconomic status, with an average educational level of 11.8 yr (range 9–16 yr) and a median reported income of $300–$399/month. Their mean age was 22.2 yr (range 18–32 yr). A total of 53% of the mothers were white, 47% were black, 71% were single, and 50% were primiparous. Table 1 summarizes the distribution of maternal substance use during each trimester of pregnancy for this subsample.

Procedures for recording and scoring neonatal EEG-sleep. For each infant included in this sample, a 2- to 2½-h EEG-sleep recording was obtained 24 to 36 h after birth. These recordings were obtained on swaddled infants, who were placed in a prone position, approximately 45 min to 1 h after a morning feeding. Male infants were studied before circumcision. All neonatal EEG sleep recordings were conducted in a quiet, environmentally controlled room designated for neonatal and infant sleep studies.

Neonatal sleep-EEG were recorded using a Nihon Kohden (model 4200) 21 channel polygraph. Sixteen channels were devoted to EEG and five channels recorded additional physiologic measures: one channel recorded submental EMG, two channels monitored eye movement activity (right and left outer canthi, offset slightly above one eye and below the other eye to optimize visualization of both horizontal and vertical eye movements), and the remaining two channels recorded cardiorespiratory measures (cardiopneumograph). Electrode placement for the newborn recordings followed the standard international 10/20 system with modifications as recommended for neonates (11). All recordings were obtained at a paper speed of 15 mm/s and at low linear filter settings of 0.3 Hz (EEG), 0.03 Hz (EKG and eye movements), and 0.1 Hz (EMG). EEG sensitivity was 7 μV/mm at the beginning of the recording and was adjusted when necessary. Throughout the recording period, behavioral observations were noted on the recording paper by the EEG technician. Such observations included eyes open, eyes closed, eye movements, body movements, jerks and twitches with indication of the body part(s) involved, startles, sucking, vocalizations, respiratory irregularities such as sighs and pauses, and the infant appearing quiet. Environmental noises were noted in order to differentiate evoked from spontaneous arousals.

The neonatal EEG-sleep recordings were scored independently by an electroencephalographer who was not aware of the prenatal substance exposure of these infants. Recordings were scored for EEG state, rapid eye movements, arousals, and body movements using 1-min scoring epochs. Scoring was based on operational definitions using representative neonatal EEG recording samples of each of the above areas. The scoring manual used existing standardized definitions for awake, active, and quiet sleep states in the neonate (27, 28). Additional sleep behaviors, including indeterminate or transitional sleep, arousals, and phasic rapid eye movement activity, have also been included in the scoring manual. Criteria used for scoring neonatal EEG-sleep recordings are summarized in Appendix A (scoring manuals are available from M.S.S. upon written request).

Table 1. *Frequency of maternal substance use during each trimester of pregnancy (n = 55)*

	1st trimester	2nd trimester	3rd trimester
Alcohol use			
Abstainers	23.6%	65.4%	52.7%
Less than 1 drink/mo	5.5%	7.7%	12.7%
1–3 drinks/mo	7.3%	11.5%	9.1%
1–6 drinks/wk	30.9%	9.6%	12.7%
1 or more drinks/day	32.7%	5.8%	12.7%
Mean drinks/day	1.3	0.37	0.49
Range	0–7.8	0–12	0–5.3
Marijuana use			
Abstainers	52.7%	73.1%	78.2%
Less than 1 joint/mo	10.9%	1.9%	1.8%
1–3 joints/mo	9.1%	3.8%	0.0%
1–6 joints/wk	7.3%	5.8%	10.9%
1 or more joints/day	20.0%	15.4%	9.1%
Mean joints/day	0.78	0.38	0.32
Range	0–7.4	0–6.5	0–7.9
Cigarette smoking			
Nonsmokers	37.0%	48.1%	47.3%
Less than ½ pack/day	22.2%	17.3%	9.1%
½–1 pack/day	24.1%	19.2%	25.5%
More than 1 pack/day	16.7%	15.4%	18.2%

RESULTS

A stepwise regression procedure was used to investigate the effects of maternal alcohol, marijuana, and tobacco use during the 1st, 2nd, and 3rd trimesters of pregnancy on the EEG-sleep variables. The alcohol and marijuana variables were expressed in terms of average drinks or marijuana cigarettes per day and tobacco cigarette smoking in terms of quantity of cigarettes smoked per day. The sleep states were expressed in percent of time the infant spent in each particular state over the course of the 120-min recording. Body movements, arousals, and rapid eye movements were expressed in number of occurrences per min.

Separate regressions were run by trimester to assess the independent effects of exposure during each trimester. Inasmuch as the substance use measures from trimester to trimester were highly correlated, it was not possible to include all trimesters in the same regression.[2] The following variables were entered as covariates into the equations along with alcohol, marijuana, and tobacco use for the appropriate trimester: maternal age, education, income, race, marital status, and other illicit drug use during each of the trimesters,[3] infant sex, birth weight, Dubowitz score, ponderal index; and EEG technician.[4]

The results of the 1st, 2nd, and 3rd trimester regressions are presented in Tables 2, 3, and 4, respectively. The effect of alcohol was specific to 1st and 2nd trimester exposure, and in general was associated with an increase in the number of arousals. Other variables affected by alcohol use were low voltage irregular active sleep and trace alternant quiet sleep, both of which were decreased in relation to 1st trimester alcohol use, and indeterminate sleep which was increased by 1st trimester alcohol use.

[2] As one step in the analyses, we tested for the interactions between alcohol, marijuana, and tobacco; the interaction terms, in general, were not significant predictors of infant outcome and were not included in further regression analyses.

[3] Two women were heavy drug users, both were on methadone throughout their pregnancies. The regression analyses were run eliminating these women and the results were unchanged. Therefore, these two women were included in the analyses presented herein.

[4] Differences were noted between the two EEG technicians in recording infant body movements during the EEG-sleep study. Therefore, EEG technician was included as a covariate in the regression analyses. Babies assigned to the two technicians did not differ on the previously defined covariates.

Marijuana use during each of the three trimesters of pregnancy predicted increased body movements, decreased total quiet sleep and decreased trace alternant quiet sleep (Tables 2, 3, and 4). Other effects predicted by the regression analyses were an increase in mixed active sleep with 1st and 3rd trimester use and decreases in low voltage irregular active sleep and the number of rapid eye movements with 1st trimester use.

To illustrate these findings with respect to actual mean differences, smaller group analyses compared infant sleep measures in abstainers and users for 1st trimester alcohol and marijuana use. An analysis of covariance was used to calculate adjusted means for the EEG-sleep variables. These means were adjusted for covariates on which the comparison subgroups differed on a preliminary analysis of variance. Results of these comparisons are presented in Table 5.

Two groups were selected for illustration, women who drank at least one drink a day during the 1st trimester ($n = 18$) and women who did not use alcohol at all during the 1st trimester ($n = 13$). The mean number of total arousals was 0.3/min for the offspring of users compared to 0.2 for the infants of the abstainers. Similar rates were found for the mean number of spontaneous arousals (0.3 *versus* 0.2). The mean duration of spontaneous arousals was different by a factor of two (4.9 s for the exposed *versus* 2.4 for the unexposed).

Table 2. *Regression analysis for 1st trimester substance use*

Outcome variable	Significant predictors	R^2	Standardized β
Awake (%)	Dubowitz score	0.10	0.34
	Maternal age	0.08	0.28
Total active sleep (%)	Birth wt	0.09	0.30
Mixed	1st trimester marijuana	0.08	0.29
Low voltage irreg.	1st trimester marijuana	0.10	−0.33
	1st trimester alcohol	0.09	−0.30
Total quiet sleep (%)	1st trimester marijuana	0.23	−0.41
	Maternal age	0.12	−0.46
	Education	0.06	0.27
Trace Alternant	1st trimester marijuana	0.22	−0.46
	1st trimester alcohol	0.10	−0.29
	Maternal age	0.07	−0.27
Indeterminate sleep (%)	1st trimester alcohol	0.20	0.29
	Birth wt	0.10	−0.30
	1st trimester drugs	0.08	0.29
Total arousals (no./min)	1st trimester alcohol	0.12	0.34
No. spontaneous	1st trimester alcohol	0.11	0.33
Duration spontaneous (s)	1st trimester drugs	0.15	0.39
Total body movements (no./min)	EEG technician	0.33	0.62
	1st trimester tobacco	0.07	0.26
Head movements	EEG technician	0.26	0.47
	Income	0.18	0.39
	1st trimester drugs	0.07	0.26
Face/suck movements	EEG technician	0.19	0.44
Small body movements	1st trimester marijuana	0.10	0.31
Large body movements	1st trimester marijuana	0.25	0.50
REM (no./min)	1st trimester marijuana	0.09	−0.32
	Education	0.08	−0.29

Table 3. *Regression analysis for 2nd trimester substance use*

Outcome variable	Significant predictors	R^2	Standardized β
Awake (%)	Dubowitz score	0.10	0.34
	Maternal age	0.08	0.28
Total active sleep (%)	Birth wt	0.10	0.31
Mixed	None		
Low voltage irreg.	None		
Total quiet sleep (%)	2nd trimester marijuana	0.18	−0.43
	Ponderal index	0.12	−0.35
Trace alternant	2nd trimester marijuana	0.16	−0.32
	Maternal age	0.08	−0.41
	Education	0.07	0.28
Indeterminate sleep (%)	2nd trimester drugs	0.18	0.33
	Birth wt	0.09	−0.31
Total arousals (no./min)	2nd trimester drugs	0.13	0.57
	2nd trimester alcohol	0.09	−0.36
No. spontaneous	2nd trimester drugs	0.13	0.57
	2nd trimester alcohol	0.08	−0.36
Duration spontaneous (s)	2nd trimester drugs	0.16	0.69
	2nd trimester alcohol	0.16	−0.49
Total body movements (no./min)	EEG technician	0.34	0.66
	2nd trimester tobacco	0.11	0.34
Head movements	EEG technician	0.27	0.47
	Income	0.20	0.42
	Dubowitz score	0.06	−0.26
Face/suck movements	EEG technician	0.22	0.53
	2nd trimester tobacco	0.09	0.31
Small body movements	EEG technician	0.09	0.29
Large body movements	2nd trimester marijuana	0.12	0.34
REM (no./min)	Education	0.10	−0.32

Similar groups were defined for the description of marijuana effects. Women who used marijuana at the rate of once a day or more often during the 1st trimester ($n = 11$) were compared to women who abstained from marijuana during the 1st trimester ($n = 29$). The rate of small and large body movements in users was 0.2 and 0.6/min, respectively, compared to 0.02 and 0.2/min, respectively, in the offspring of nonusers. Overall, 15.1% of the time was spent in total quiet sleep in the marijuana-exposed group and 27.8% was spent in total quiet sleep in the nonexposed group. The percent of time spent in trace alternant quiet sleep was 11.6% in the users and 23.8% in the nonusers. All of the above differences were significant at $p < 0.05$ (see Table 5).

DISCUSSION

EEG-sleep disturbances among infants in our study existed in the absence of evidence of the fetal alcohol syndrome or clinical withdrawal states. Maternal substance use among women in our sample was generally moderate. Nevertheless, disturbances in sleep cycling, motility, and arousals were shown to be associated with this use.

Our findings generally reaffirm previously published reports of disturbances in EEG-sleep states among neonates exposed to

Table 4. *Regression analysis for 3rd trimester substance use*

Outcome variable	Significant predictors	R^2	Standardized β
Awake (%)	Dubowitz score	0.10	0.34
	Maternal age	0.08	0.27
Total active sleep (%)	Birth wt	0.09	0.30
Mixed	3rd trimester marijuana	0.09	0.30
Low voltage irreg.	None		
Total quiet sleep (%)	Maternal age	0.15	−0.56
	3rd trimester marijuana	0.15	−0.36
	Education	0.07	0.29
Trace alternant	Maternal age	0.11	−0.38
	3rd trimester marijuana	0.12	−0.34
Indeterminate sleep (%)	Birth wt	0.16	−0.41
Total arousals (no./min)	3rd trimester drugs	0.13	0.36
No. spontaneous	3rd trimester drugs	0.13	0.36
Duration spontaneous (s)	3rd trimester drugs	0.08	0.28
Total body movements (no./min)	EEG technician	0.32	0.65
	3rd trimester tobacco	0.10	0.32
Head movements	EEG technician	0.25	0.46
	Income	0.19	0.41
	Dubowitz score	0.06	−0.25
Face/suck movements	EEG technician	0.19	0.51
	3rd trimester tobacco	0.10	0.32
Small body movements	3rd trimester marijuana	0.13	0.36
Large body movements	3rd trimester marijuana	0.33	0.57
REM (no./min)	None		

Table 5. *Adjusted means for EEG-sleep variables*

	Alcohol*		Marijuana†	
Outcome variable	Abstainer‡ (n = 13)	User§ (n = 18)	Abstainer‡ (n = 29)	User§ (n = 11)
Awake (%)	7.4	0.9	1.3	6.7
Total active sleep (%)	50.1	42.2	46.2	38.0
Mixed	31.6	28.9	26.4	31.3
Low voltage irregular	18.4	13.3	19.7	6.7‖
Total quiet sleep (%)	25.0	27.0	27.8	15.1‖
Trace alternant	21.3	21.3	23.8	11.6¶
Indeterminate sleep (%)	17.5	29.9	24.8	40.1¶
Total arousals (no./min)	0.2	0.3‖	0.4	0.3
No. spontaneous	0.2	0.3‖	0.3	0.3
Duration spontaneous (s)	2.4	4.9‖	4.5	4.5
Total body movements (no./min)	1.0	1.3	1.2	1.6
Head movements	0.1	0.2	0.1	0.1
Face/suck movements	0.6	0.8	0.8	0.8
Small body movements	0.1	0.1	0.02	0.2‖
Large body movements	0.4	0.3	0.2	0.6¶
REM (no./min)	3.9	3.9	4.6	2.5‖

* Means are adjusted for 1st trimester tobacco and EEG technician.
† Means are adjusted for birth weight, race, 1st trimester other illicit drug use, and EEG technician.
‡ Did not use during the 1st trimester.
§ Used more than once per day during the 1st trimester.
‖ $p < 0.05$.
¶ $p < 0.01$.

alcohol prenatally (22–24). Our findings on the effects of marijuana use during pregnancy on infant sleep are entirely new as to our knowledge these measures have not been previously examined. However, decreases in the amount of trace alternant quiet sleep, such as those observed in our marijuana-exposed infants, have been reported by Beckwith and Parmelee (29) in selected groups of high-risk neonates.

Considered in the context of current knowledge regarding the organization and development of sleep states, these findings are thought provoking. Whereas the mechanisms of sleep regulation have been only partially elucidated, different neuronal systems have been associated with the expression of the active (REM) and quiet (NREM) sleep states. Although considerable overlap among multiple neurochemical systems may well occur, noradrenergic neurons, particularly those within the brain stem in the area of the locus coeruleus, appear to be important in the regulation of motor activity during active (REM) sleep, whereas serotonergic neurons, concentrated in the area of the raphe nucleus, are important in arousal mechanisms and in the maintenance of wakefulness (30). Furthermore, monoaminergic systems have been shown to have different rates of development in animal populations (31–33).

Consideration of these aspects of the ontogeny of the neurotransmitter systems may assist in some preliminary speculations regarding our findings. Noradrenergic neurons are anatomically present and presumably functionally active throughout fetal life, whereas serotonergic neurons appear to develop later in gestation. Our data on infants exposed prenatally to marijuana suggest that this use may contribute to an overelaboration of the noradrenergic system that is reflected in increased motility and longer active sleep segments in exposed infants at birth. However, disturbances found among alcohol-exposed infants suggest an exaggerated serotonergic effect that may be expressed in the later development of arousal mechanisms and reflected in increases in both the number and the duration of arousals and in longer periods of indeterminate sleep in exposed infants.

In summary, sleep continuity and architecture in infants is complex and dependent on both the level of maturation and the level of organization of specific brain regions that contribute to the neurophysiological expression of sleep. Data presented herein suggest that certain neurophysiological systems may be adversely affected, and differentially so, by prenatal exposure to alcohol or marijuana as reflected in specific disturbances in sleep cycling and arousal in exposed infants. The present findings indicate only differences present at birth. Examination of additional measures obtained in the course of a longitudinal design is underway to assess the persistence of these sleep disturbances relative to the overall maturation and development in these infants.

REFERENCES

1. Dreyfus-Brisac C 1964 The electroencephalogram of the premature infant and full-term newborn: normal and abnormal waking and sleeping patterns. In: Kellaway P, Peterson, I (eds) Neurological and Electroencephalographic Correlative Studies in Infancy. Grune & Stratton, New York, pp 186–207
2. Dreyfus-Brisac C 1986 Sleep ontogenesis in early human prematurity from 24 to 27 weeks of conceptional age. Dev Psychobiol 1:162–169
3. Dreyfus-Brisac C 1970 Ontogenesis of sleep in human prematures after 32 weeks of conceptional age. Dev Psychobiol 3:91–121
4. Dreyfus-Brisac C 1979 Neonatal electroencephalography. In: Scarpelli EM, Cosmi EV (eds) Reviews in Perinatal Medicine, vol 3. Raven Press, New York, pp 397–472
5. Parmelee AH, Wenner WH, Akiyama Y, Schultz MA, Stern E 1967 Sleep states in premature infants. Dev Med Child Neurol 9:70–77
6. Parmelee AH, Akiyama Y, Schultz MA, Wenner WH, Schulte FJ, Stern E 1968 The electroencephalogram in active and quiet sleep in infants. In: Kellaway P, Peterson I (eds) Clinical Electrocephalography of Children. Grune & Stratton, New York, pp 77–88
7. Prechtl HFR, Akiyama Y, Zinkin P, Grant DK 1968 Polygraphic studies of the full-term newborn: I. Technical aspects and quantitative analysis. In: MacKeith R, Bax M (eds) Studies in Infancy (Clinics in Developmental Medicine no. 27). Spastics International Medical Publications and Heinemann Medical Books, Lavenham, Suffolk, England pp 1–21
8. Ellingson RJ, Peters JF 1980 Development of EEG and daytime sleep patterns in normal full-term infants during the first three months of life: longitudinal observations. Electroencephal Clin Neurophysiol 49:112–124
9. Lombroso CT 1979 Quantified electrographic scales on 10 pre-term healthy newborns followed up to 40–43 weeks conceptional age by serial polygraphic recordings. Electroencephal Clin Neurophysiol 46:460–474
10. Lombroso CT 1982 Some aspects of EEG polygraphy in newborns at risk for neurological disorders. In: Buser PA, Cobb WC, Okuma T (eds) Kyoto Symposia (EEG Suppl. no. 36). Elsevier Biomedical Press, Amsterdam, pp 652–663
11. Tharp BR, Cukier F, Monod N 1981 The prognostic value of the electroencephalogram in premature infants. Electrocephal Clin Neurophysiol 51:219–236
12. Schultz MA, Schulte FJ, Akiyama Y, Parmelee AH 1968 Development of electroencephalographic sleep phenomena in hypothyroid infants. Electroencephal Clin Neurophysiol 25:351–358
13. Schulte FJ, Heinze G, Schrempf G 1971 Maternal toxemia, fetal malnutrition, and bioelectric brain activity of the newborn. Neuropaediatrie 2:439–460
14. Hass GH, Prechtl HFR 1977 Normal and abnormal EEG maturation in newborn infants. Early Hum Dev 1:69–90
15. Ellingson RJ, Peters JF 1980 Development of EEG and daytime sleep patterns in Trisomy-21 infants during the first year of life: longitudinal observations. Electroencephal Clin Neurophysiol 50:457–466
16. Monod N, Pajot N, Guidasci S 1972 The neonatal EEG: statistical studies and prognostic value in full-term and preterm babies. Electroencephal Clin Neurophysiol 32:529–544
17. Watanabe K, Miyazaki S, Hara K, Hakamade S 1980 Behavioral state cycles, background EEGs and prognosis of newborns with perinatal hypoxia. Electroencephal Clin Neurophysiol 49:618–625
18. Holmes G, Rowe J, Hafford J, Schmidt R, Testa M, Zimmerman A 1982 Prognostic value of the electroencephalogram in neonatal asphyxia. Electroencephal Clin Neurophysiol 53:60–72
19. Schulman C 1969 Alterations of the sleep cycle in heroin addicted and "suspect" newborns. Neuropaediatrie 1:89–100
20. Thoman EG, Denenberg VH, Sievel J, Zeidner L, Becker P 1980 Behavioral state profiles in infancy are predictive of later medical or behavioral dysfunction. Neuropaediatrie 12:45–54
21. Crowell DH, Kapuniai LE, Boychuk RB, Light MJ, Hodgman JE 1982 Daytime sleep state organization in three-month-old infants. Electroencephal Clin Neurophysiol 53:36–47
22. Rosett HL, Snyder P, Sander LW, Lee A, Cook P, Weiner L, Gould J 1979 Effects of maternal drinking on neonate state regulation. Dev Med Child Neurol 21:464–473
23. Chernick V, Childiaeva R, Ioffe S 1983 Effects of maternal alcohol intake and smoking on neonatal electroencephalogram and anthropometric measurements. Am J Obstet Gynecol 146:41–47
24. Ioffe S, Childiaeva R, Chernick V 1984 Prolonged effects of maternal alcohol ingestion on the neonatal electroencephalogram. Pediatrics 74:330–335
25. Day NL, Wagener DK, Taylor PM 1985 Measurement of substance use during pregnancy: methodologic issues. In: Pinkert TM (ed) Consequences of Maternal Drug Abuse. NIDA Research Monograph no. 59, US Government Printing Office, Washington, DC
26. Ballard JL, Novak KK, Driver BA 1979 A simplified score for assessment of fetal maturation of newly born infants. J Pediatr 95:769–774
27. Werner SS, Stockard JE, Bickford RG 1977 Atlas of Neonatal Electroencephalography. Raven Press, New York
28. Anders T, Emde T, Parmelee AH (eds) 1971 A Manual of Standardized Terminology, Techniques, and Criteria for Scoring of States of Sleep and Wakefulness in Newborn Infants. UCLA Brain Information Service/BRI Publication Office, Los Angeles
29. Beckwith L, Parmelee AH 1986 EEG patterns of preterm infants, home environment, and later IQ. Child Dev 57:777–789
30. Jacobs BL 1985 Overview of the activity of brain monoaminergic neurons across the sleep-wake cycle. In: Wauguier A, Monti JM, Gaillard JM, Radilovacki M (eds) Sleep-Neurotransmitters and Neuromodulators. Raven Press, New York, pp 1–14
31. Coyle JT 1973 The development of catecholaminergic neurons of the central nervous system. Neurosci Res 5:35–52
32. Bloom FE 1984 The functional significance of neurotransmitter diversity. Am J Physiol 246:184–194
33. Crawford IL, Connor JD, Doller HJ 1984 Monoamine concentrations in brain regions of the developing rabbit. Int J Dev Neurosci 2:415–419

APPENDIX A

EEG-SLEEP VARIABLES—DEFINITIONS

Code	Criteria
AW	1. Low voltage irregular background 2. Eyes open 3. Irregular respirations 4. Vocalization and/or body movements 5. Sustained EMG tonus with activity bursts
AS	1. Two EEG backgrounds can be noted: a mixed pattern of high and low voltage components (*i.e.* 25–50 μV) and an admixture of θ, α, and β range frequencies with a frontal predominant δ; a second pattern (low voltage irregular) would be a low amplitude with rare δ and predominantly α and β with intermixed θ rhythms. 2. At least one eye movement independent of chin and gross body movements. 3. Irregular respirations 4. Presence of small and large body movements with sustained EMG tonus and activity bursts. 5. Absence of trace alternant
QS	1. Two EEG backgrounds can be noted: 50 to 100 μV predominantly δ intermixed θ background that is continuous (high voltage slow); or a discontinuous tracing (trace alternant) comprised of high amplitude bursts of 50 to 200 μV admixture of predominantly δ and θ activity with superimposed α and β activity separated by a low amplitude with intermixed θ, α, and β range frequencies. Burst intervals are from 3 to 8 s in duration and interburst intervals 4 to 8 s in duration. No asynchrony or excessive interburst intervals of more than 20 s. 2. No more than one isolated eye movement, body movement, or arousal. 3. Regular respirations 4. Sustained EMG tonus without activity bursts
IS	1. EEG-sleep interval in which criteria for active or quiet sleep are not fulfilled, or during 1 min in which these criteria are fulfilled for less than 30 consecutive seconds. Two or more discordant physiologic parameters (*i.e.* respirations, REM, body movements, eye opening, arousals) when compared to the predominant EEG pattern.
A	1. Discernable desynchronization of the EEG background for at least 2 s in duration with or without movements, unassociated with a discontinuous quiet sleep portion. Two or more brain regions simultaneously involved. Whole body myoclonic movements, startle movements or crying may accompany this electrographic change.

AW, awake; AS, active sleep; QS, quiet sleep; IS, indeterminate sleep; A, arousal.