

# A Longitudinal Study of Prenatal Marijuana Use

## *Effects on Sleep and Arousal at Age 3 Years*

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**Objective:** To test the hypothesis that sleep disruptions would be evident in 3-year-old children with a history of prenatal marijuana exposure.

**Design:** A prospective study using stratified random sampling beginning in the fourth month of pregnancy. Marijuana and other substance use were assessed by interviews at multiple time points. Offspring were followed up through age 3 years with multidomain assessments at fixed time points, including electroencephalographic sleep studies in the newborn period and at age 3 years.

**Setting:** Primary care, prenatal clinic at a university hospital.

**Subjects:** The sample included 18 children with prenatal marijuana exposure (mean [ $\pm$ SD] age, 39.0 $\pm$ 4.4 months) and 20 control children (mean [ $\pm$ SD] age,

39.7 $\pm$ 4.4 months). The two groups were similar in relationship to maternal age, race, income, education, or maternal use of alcohol, nicotine, and other substances in the first trimester.

**Main Outcome Measure:** Sleep variables from polysomnographic recordings at age 3 years.

**Results:** Children with prenatal marijuana exposure showed more nocturnal arousals (mean [ $\pm$ SD], 8.2 $\pm$ 5.3 vs 3.2 $\pm$ 4.6;  $P < .003$ ), more awake time after sleep onset (mean [ $\pm$ SD], 27.4 $\pm$ 20.0 vs 13.7 $\pm$ 12.4 min;  $P < .03$ ), and lower sleep efficiency (mean [ $\pm$ SD], 91.0 $\pm$ 3.8 vs 94.4 $\pm$ 2.1;  $P < .03$ ) than did control children.

**Conclusion:** Prenatal marijuana exposure was associated with disturbed nocturnal sleep at age 3 years.

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**M**ARIJUANA (cannabis) is one of the most frequently used illicit substances in our society among women of childbearing age.<sup>1</sup> The teratogenic effects of prenatal exposure to cannabis on the developing brain, however, are not well understood. Among the few well-controlled investigations, prenatal exposure to marijuana has been associated with impaired visual responsiveness and increased startles and tremors in newborns<sup>2</sup>; impaired cognitive function in children aged 48 months<sup>3</sup>; and deficits in visual-perceptual tasks, language, and behavior in children aged 6 to 9 years.<sup>4</sup> In a larger study<sup>5</sup> from which this sleep study sample was drawn, significant effects on the IQ were reported when the children were 3 years old. Other studies have failed to find evidence of central nervous system dysfunction at birth,<sup>6-8</sup> and the study by Streissguth et al<sup>9</sup> failed to find cognitive and developmental impairment at age 4 years.

Physiological studies have also yielded preliminary evidence for prenatal marijuana effects on central nervous system function. Lester and Dreher<sup>10</sup> found altered acoustic cries in infants exposed to marijuana in utero. Our research group found altered sleep cycling, with greater awake time, more body movements, and more indeterminate sleep, associated with marijuana exposure in the first trimester as reflected in electroencephalographic (EEG) sleep measures obtained in the newborn period.<sup>11</sup> Those studies were performed 24 to 36 hours after birth, and consisted of 3 hours of EEG sleep recording on swaddled infants in the nursery.

The present study is a follow-up in-

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## SUBJECTS AND METHODS

These data are from the Maternal Health Practices and Child Development Project,<sup>12</sup> which included three studies; the design, methods, instruments, and personnel were consistent across studies. The first two studies were designed to assess the effects of alcohol and marijuana exposure on the fetus. To select subjects for the first two studies, 1360 women were interviewed in their fourth month of pregnancy. The participation rate at this phase was 85%. This interview assessed substance use in the year before pregnancy and during the first trimester. Women who reported alcohol consumption of three or more drinks per week and the next woman who reported a lesser amount were selected for the study of alcohol effects. Women who reported marijuana use of two or more joints per month and the next woman who reported a lesser amount were selected for the study of marijuana effects. In addition, a third study was begun to increase the number of children available for newborn EEG studies.<sup>11</sup> In this protocol, women who reported alcohol consumption of one or more drinks per day or marijuana use of one or more joints per day during the first trimester were selected, as well as the next woman who reported a lesser amount.

In all studies, women were interviewed in their fourth and seventh months of pregnancy and at delivery. Women were selected from a general obstetrical population and therefore represent the entire spectrum of substance use. Their substance use during pregnancy was, in general, light to moderate. The women were healthy and of lower socioeconomic status. At the fourth-month interview, for the combined alcohol and marijuana studies (N=763), 461 (60%) women had completed high school; their mean age was 23 years (range, 18 to 42 years); 513 (67%) women were not married, and 245 (32%) were primigravidas. For the third study (N=108), 62 (57%) women had completed high school; their mean age was 24.5 years (range, 18 to 37 years);

84 (78%) women were not married, and 27 (25%) were primigravidas.

The sample for the 3-year-old sleep study consisted of 38 subjects—half of the subjects were drawn from a sample of 763 subjects from the first two studies and the other 19 subjects were drawn from a sample of 108 subjects from the third study. For the sleep study, all subjects in the group exposed to prenatal marijuana had mothers who reported marijuana use of at least one joint per week during the first trimester. Control subjects had mothers with reported marijuana use of less than one joint per month. Mothers of children who were selected for the sleep study at age 3 years did not differ from mothers of children in the larger cohorts with respect to maternal age, education, race, marital status, parity, or drug use other than marijuana.

The use of marijuana, alcohol, tobacco, and other illicit drugs was assessed for each trimester of pregnancy and for each month of the first trimester. Marijuana use was expressed as average daily joints for each trimester of pregnancy. Hashish and sensemilla use were rare to infrequent in this population; they were combined with the marijuana group. Hashish use was estimated as being equivalent to three joints, and sensemilla was counted as two joints, based on the amount of  $\Delta^8$ -3,4-*trans* tetrahydrocannabinol.<sup>13-15</sup> Prescription medication use was also assessed during pregnancy and at labor and delivery.

The interviewing techniques used to ascertain this information have been described previously.<sup>16</sup> A bogus pipeline technique was used to increase the accuracy of reporting. This method uses a bluff to convince the subject that separate laboratory evidence was being collected that would allow the investigators to check the validity of the interview report. Pilot data from the project indicated an increased rate of reported marijuana and illicit drug use with this technique.<sup>17</sup> Research project staff did not provide direct treatment or counseling; however, appropriate referral information was pro-

vestigation of EEG sleep measures when the children were 3 years old. The age of 3 years was chosen as the earliest that children are able to reliably cooperate with naturalistic, all-night sleep studies. The primary hypothesis of the study was that abnormalities in the regulation of sleep and arousal would be evident in well-controlled measures of EEG sleep at age 3 years.

## RESULTS

### SAMPLE

The sample included 18 children with prenatal marijuana exposure and 20 control children. In the group with prenatal marijuana exposure, the average use was 2.8 joints per day during the first trimester (range, 0.3 to 5.0 joints per day). There was also one outlier whose mother reported using an average of 23 joints per day through the first trimester. Analyses were performed with and without this outlier. The results did not change. In the control group, 18 children had no

marijuana exposure in utero and two had exposure of less than 0.01 joints per day.

Comparisons between the mothers of the group with prenatal marijuana exposure and the mothers of the control group revealed no significant differences in maternal age, education, income, race, marital status, nicotine use, alcohol use, or other drug use (**Table 1**). We also compared groups on the following psychosocial variables: maternal depression, maternal self-esteem, anxiety and/or hostility, attitudes toward the child, household structure, household environment, social support, and life events. The only significant group difference observed was in life events, with the group with prenatal marijuana exposure having fewer life events than the control group (mean [ $\pm$ SD] number of events,  $3.6 \pm 2.4$  in the group with marijuana exposure vs  $5.5 \pm 2.8$  in the control group;  $F=2.3$ ,  $df=36$ ,  $P=.003$ ). The mean ( $\pm$ SD) age of the children at the time of the sleep recording was  $39.0 \pm 4.4$  months in the group with prenatal marijuana exposure and  $39.7 \pm 3.3$  months in the control group (no significant differences).

vided on a case-by-case basis. This study received approval from the University of Pittsburgh (Pa) Psychosocial Institutional Review Board and the institutional review board of the Magee Womens Hospital, Pittsburgh.

### LONGITUDINAL FOLLOW-UP

At 8, 18, and 36 months after the birth of the infant, the mothers and the offspring were assessed. For the mothers, this included an assessment of current marijuana, alcohol, tobacco, and other drug use, including illicit drugs and over-the-counter medications. At each time point, demographic information was obtained, including lifestyle; psychosocial information; assessment of depression, anxiety, hostility, and self-esteem; and measures of life events and social support. Further details of specific instrumentation, methods, reliability assessment, and results of other outcome measures have been described elsewhere.<sup>17</sup>

### EEG SLEEP METHODS

The mothers completed sleep-wake diaries summarizing sleep-wake-related habits and behaviors in the home environment before the sleep studies. All children were healthy and free of illness and medications at the time of the study. They came to the Child and Adolescent Sleep Laboratory (Pittsburgh) for 3 consecutive nights of recordings. The laboratory is a comfortable, child-oriented environment designed to obtain naturalistic measures of sleep with minimal stress in young children. The staff is experienced in handling young children. Electrodes were placed using standard polysomnographic techniques 2 hours before the child's usual bedtime. Often, the electrode applications were performed in conjunction with videotape movies and rewards assisting the children to cooperate with the procedures. The children slept in the laboratory on their usual (home) schedule for 3 consecutive nights. A parent remained with the child throughout the studies. The families were paid for their participation.

### SLEEP VARIABLES

Summary sleep variables comparing the two groups are shown in **Table 2**. The group with prenatal marijuana exposure showed significantly lower sleep efficiency, more awake time after sleep onset, and more frequent arousals after sleep onset. There were no significant differences in the number of minutes in each sleep stage, latency to rapid eye movement period, total sleep time, bedtime, or wake-up time. Although naps were not recorded with EEG, estimates from maternal reports revealed no significant differences in the number or duration of daytime naps between groups. Approximately 50% of each group averaged one daily nap, lasting 30 to 60 minutes near the middle of the day. There were also no significant differences in maternal reports of sleep-wake schedules at home between groups.

There were no significant differences between groups in any of the major demographic variables or in alcohol, nicotine, or other substance exposure. Analyses using

### DATA ANALYSES

Summary sleep variables were generated based on sleep-stage scoring of the EEG record by trained technicians. Each page of multichannel recording (encompassing a 30-second interval) was assigned a stage of sleep or wakefulness according to standard criteria.<sup>18</sup> Reliability measures across the five raters in the laboratory were obtained bimonthly, with  $\kappa$  values of 0.85 and above. All staff in the sleep laboratory were blind to the status of the subjects. Summary sleep variables for each night of recording were generated using computer programs that created counts of the total minutes of sleep, minutes in each sleep stage, minutes awake, number of arousals, latency to sleep onset, latency to first rapid eye movement period, and percentage of recording period spent asleep (sleep efficiency). The precise definition of individual sleep variables and reliability data on sleep-stage scoring have been reported elsewhere.<sup>19,20</sup>

The major independent variable was prenatal marijuana use, while other variables, including marijuana use subsequent to pregnancy, other drug use, education, social support, mother's perception and expectations of child, and psychiatric status, were considered as possible secondary variables related to outcome. The primary dependent variables consisted of summary sleep variables averaging values on nights 2 and 3 (night 1 is considered adaptation data). The primary analyses compared sleep variables between the children with a history of prenatal exposure and the control children.

Many of the demographic and sleep variables did not fit gaussian distributions, and for some sleep variables, transformations such as log or square root failed to normalize the distributions. Therefore, we used nonparametric tests (Mann-Whitney *U* tests) to compare continuous variables. For the same reason, we used Spearman's rank correlations. Differences in demographic factors between the two groups were compared using Student's *t* tests for continuous variables and Fisher's Exact Test for categorical comparisons. All statistical tests were two tailed with  $\alpha_2 = .05$ .

these variables as covariates yielded the same pattern of results as did analyses that dropped individuals with alcohol or other substance exposure.

In addition, the correlation between first trimester marijuana exposure and summary sleep variables was also examined. Marijuana exposure in the first trimester showed a significant negative correlation with sleep efficiency (Spearman's  $\rho = -0.41$ ,  $P < .01$ ) and a positive correlation with the number of arousals (Spearman's  $\rho = 0.46$ ,  $P < .004$ ). There were no significant correlations between these sleep variables and estimates of marijuana exposure later in the pregnancy or with current maternal marijuana use.

### INDIVIDUAL NIGHT DATA

As described, planned analyses focused on summary variables based on the average of nights 2 and 3 (regarding night 1 as an adaptation night). However, subsequent to the primary analyses, we examined each night of data individually. These results are shown in **Table 3**. As il-

lustrated, the number of arousals was significantly increased in the group exposed to prenatal marijuana in each of the 3 nights of recording. Measures of sleep efficiency and awake time showed consistent patterns across nights but did not reach statistically significant differences on all nights.

Thirty-one children (15 exposed to prenatal marijuana and 16 controls) in this 3-year-old study had data available from the neonatal recordings reported by Scher et al.<sup>11</sup> The process of examining the relationship between neonatal sleep variables and sleep measures obtained at 3 years is complicated since the methods of quantifying sleep are completely different at these ages. The neonatal studies consisted of a single 3-hour nap recording with 16 channels of EEG using staging criteria based on the active/quiet/indeterminate sleep staging described by Anders et al.<sup>21</sup> The 3-year-old children were studied in all night, naturalistic sleep studies over 3 consecutive nights with two channels of EEG and staging based on criteria by Rechtschaffen and Kales<sup>18</sup> (stages 1, 2, 3, and 4 and rapid eye movement sleep).

To explore the relationship, however, we chose three variables reflecting neonatal sleep disruptions and three variables quantifying disruptions in the 3-year studies and examined the correlations within the group with prenatal marijuana exposure. Specifically, we compared percentage awake time, small body movements, and large body movements (from the newborn study) with number of arousals, sleep efficiency, and awake time after sleep onset (from the 3-year-old data). These analyses showed small body movements in the neonatal study were significantly correlated with the number of arousals in the 3-year-old study (Spearman's  $\rho=0.67$ ,  $P<.006$ ). Other correlations ranged from 0.04 to 0.32 and were not statistically significant.

COMMENT

In this study, 3-year-old children with a history of marijuana exposure during the first trimester showed significant disruptions within sleep. The specificity of the sleep changes is consistent with an interpretation of a physiologic cause. That is, the findings indicate disruptions within sleep, with no group differences in bedtime, time to fall asleep, total sleep time, individual sleep stages, or overall sleep architecture. This pattern of findings is difficult to explain based on behavioral or environmental effects since the common behaviorally based sleep problems seen at this age typically manifest as difficulty going to sleep and/or difficulty returning to sleep following normal nocturnal arousals. The increase in arousals

**Table 1. Demographic and Maternal Data at Phase 1 Assessment (Fourth Month of Pregnancy)\***

	Children With Prenatal Marijuana Exposure (n=18)	Control Children (n=20)
Maternal age, y	23.3±4.4	22.1±4.6
Maternal education, y	11.6±1.4	11.7±1.4
Income, \$ per mo	620±170	570±170
Race (white/African American)	5:13	11:9
First trimester: ever used		
Cigarettes (cigarettes per day)	11.7±11.3	8.3±11.0
Alcohol (drinks per day)	0.92±2.0	0.89±1.2
Other illicit drug (present/absent)	1/17	2/18
Marijuana (joints per day)†	2.8±5.1	0.001±0.003

\*Data are given as mean±SD except where noted. All differences are nonsignificant at  $P<.05$ , except (by design) marijuana use during the first trimester.  
† $P<.00001$ .

**Table 2. Summary Sleep Variables at Age 3 Years\***

Sleep Variable	Children With Prenatal Marijuana Exposure (n=18)	Controls (n=20)
Sleep efficiency, % of recording period spent asleep†	91.0±3.8	94.4±2.1
Awake time after sleep onset, min†	27.4±20.0	13.7±12.4
No. of arousals‡	8.2±5.3	3.2±4.6
Stage 1, min	15.3±12.9	14.7±12.1
Stage 2, min	242.8±44.1	263.3±54.9
Stage 3, min	53.2±29.4	48.8±27.9
Stage 4, min	118.9±27.1	117.3±32.1
Stage REM, min	133.5±29.8	122.6±24.5
REM latency, min	105.9±39.7	112.3±42.8
Total sleep time, min	563.9±60.1	566.7±49.0
Bedtime	21.6±0.7	21.7±0.5
Awake time	7.9±0.9	7.7±0.8

\*Data are given as mean±SD. REM indicates rapid eye movement.  
† $P<.05$ .  
‡ $P<.005$ .

**Table 3. Individual Night Data\***

Sleep Variable	Night 1			Night 2			Night 3		
	Children With Prenatal Marijuana Exposure (n=18)	Controls (n=20)	$P\leq$	Children With Prenatal Marijuana Exposure (n=18)	Controls (n=20)	$P\leq$	Children With Prenatal Marijuana Exposure (n=18)	Controls (n=20)	$P\leq$
No. of arousals	8.3±7.5	2.8±4.4	.008	8.9±6.1	3.4±5.2	.005	7.1±5.2	2.7±4.5	.005
Sleep efficiency, % of recording period spent asleep	88.6±7.1	92.7±3.8	NS	90.8±5.4	94.6±2.8	.03	91.2±4.5	94.2±3.7	NS (.08)
Awake time, min	26.6±22.9	20.8±16.8	NS	33.4±30.8	12.4±14.6	.01	21.1±17.9	15.1±16.7	NS

\*Data are given as mean±SD. NS indicates nonsignificant.

showed significant correlation with marijuana use during the first trimester, but did not correlate with use at other times or current use, consistent with a teratogenic model. Furthermore, there were no group differences in psychosocial variables (except lower rates of stressful life events in the group with prenatal marijuana exposure). Also, the findings at 3 years were consistent with an earlier report on this cohort showing sleep disruptions at birth,<sup>11</sup> and the increase in body movements during newborn sleep correlated with increased arousals within sleep at age 3 years.

The issue of potential influence of stress or anxiety contributing to disrupted sleep can also be addressed by examining adaptation (first night) effects within-group. That is, the first night of EEG sleep data are usually discarded because of the adaptation effects of sleeping in a strange place, adapting to EEG wires attached to the scalp and face, and the presence of strangers—all of which can

### ***Thus, these findings appear to be most consistent with a physiologic change in sleep and arousal regulation***

cause sleep disruptions. As reflected in Table 3, the first night effects were quite small in each study group. Despite the acute stress of strange environment, people, and wires, the control children had a mean ( $\pm$ SD) number of only  $2.8 \pm 4.4$  arousals on the first recording night (whereas the group with prenatal marijuana exposure had a mean [ $\pm$ SD] of  $8.2 \pm 5.3$  arousals on the second and third nights in the laboratory). Thus, the effects of a moderately acute stressor on EEG sleep measures appear to be very small compared with the group differences. Furthermore, there was no evidence of greater chronic stressors in the group with prenatal marijuana exposure and no evidence for group differences in sleep-wake schedules or habits to account for observed differences in the laboratory. Thus, these findings appear to be most consistent with a physiologic change in sleep and arousal regulation.

Marijuana use has been shown to cause direct changes in sleep and arousal patterns in a variety of studies in humans and animals.<sup>22-28</sup> Since marijuana exerts direct effects on areas of the brain that regulate sleep and arousal, it would not be surprising to find that prenatal marijuana use may affect the development of these same neural areas. Such a teratogenic effect could result in permanent alterations in sleep and arousal patterns.

Although these findings are provocative, they should be viewed cautiously. It is possible that prenatal marijuana itself is not the sole cause of the observed differences in the sleep studies at age 3 years. While all measured domains of demographic, social, and other substance use failed to explain the sleep differences, it is possible that other factors not assessed could have contributed to these findings. It is also possible that women may have underreported their marijuana use, as there was no objective measure of substance use independent of the interviews. However, if true, this bias would tend to de-

crease the estimate of the differences in sleep variables between the two groups.

These findings also raise a number of important questions. For example, what are the consequences of chronically disrupted sleep during early development? Although the total amount of sleep was normal, evidence from sleep research indicates that even brief repeated disruptions interfere with the restorative nature of sleep.<sup>29,30</sup> The most common daytime effects of disturbed sleep in children are detriments in focused attention and emotional and behavioral difficulties. Thus, chronic sleep problems in children can mimic attention deficit disorders and other child psychiatric disorders.<sup>31,32</sup> It is possible that some cognitive impairment<sup>5</sup> seen in these children could be secondary to chronically disrupted sleep. Additional studies will be necessary to further evaluate this association between sleep continuity disturbances and prenatal marijuana and possible links to cognitive function and emotional and behavioral domains.

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