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Pediatrics 2002;110;1182-1192
DOI: 10.1542/peds.110.6.1182

This information is current as of December 4, 2005

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The Maternal Lifestyle Study: Effects of Substance Exposure During Pregnancy on Neurodevelopmental Outcome in 1-Month-Old Infants

Barry M. Lester, PhD*; Edward Z. Tronick, PhD‡; Linda LaGasse, PhD*; Ronald Seifer, PhD§; Charles R. Bauer, MD∥; Seetha Shankaran, MD¶; Henrietta S. Bada, MD∥; Linda L. Wright, MD**; Vincent L. Smeriglio, PhD∥∥; Jing Lu, PhD∥∥∥; Loretta P. Finnegan, MD∥∥∥; and Penelope L. Maza, PhD∥∥∥

ABSTRACT. Objective. This was a prospective longitudinal multisite study of the effects of prenatal cocaine and/or opiate exposure on neurodevelopmental outcome in term and preterm infants at 1 month of age.

Methods. The sample included 658 exposed and 730 comparison infants matched on race, gender, and gestational age (11.7% born <33 weeks' gestational age). Mothers were recruited at 4 urban university-based centers and were mostly black and on public assistance. Exposure was determined by meconium assay and self-report with alcohol, marijuana, and tobacco present in both groups. At 1 month corrected age, infants were tested by masked examiners with the NICU Network Neurobehavioral Scale and acoustical cry analysis. Exposed and comparison groups were compared adjusting for covariates (alcohol, marijuana, birth weight, social class, and site). Separate analyses were conducted for level of cocaine exposure.

Results. On the NICU Network Neurobehavioral Scale, cocaine exposure was related to lower arousal, poorer quality of movement and self-regulation, higher excitability, more hyper-tonia, and more nonoptimal reflexes with most effects maintained after adjustment for covariates. Some effects were associated with heavy cocaine exposure, and effects were also found for opiates, alcohol, marijuana, and birth weight. Acoustic cry characteristics that reflect reactivity, respiratory, and neural control of the cry sound were also compromised by prenatal exposure, including cocaine, opiates, alcohol, and marijuana and by birth weight. Fewer cry effects remained after adjustment for covariates.

Conclusions. Cocaine effects are subtle and can be detected when studied in the context of polysubstance use and level of cocaine exposure. Effects of other drugs even at low thresholds can also be observed in the context of a polysubstance model. The ability to detect these drug effects requires a large sample and neurobehavioral tests that are differentially sensitive to drug effects. Long-term follow-up is necessary to determine whether these differences develop into clinically significant deficits.

ABBREVIATIONS. MLS, Maternal Lifestyle Study; NICHD, National Institute of Child Health and Human Development; NIDA, National Institute on Drug Abuse; MISU, Maternal Interview of Substance Use; NNNS, NICU Network Neurobehavioral Scale; NBAS, Neonatal Behavioral Assessment Scale; ANOVA, analysis of variance; SES, socioeconomic status.

Substance abuse is a major public health problem that affects millions of children and places enormous financial and social burdens on society. Eleven percent of children (8.3 million) live with at least 1 parent who is either alcoholic or in need of treatment for the abuse of illicit drugs.1 Of these, 3.8 million live with a parent who is alcoholic, 2.1 million live with a parent whose primary problem is with illicit drugs, and 2.4 million live with a parent who abuses alcohol and illicit drugs in combination.1 Furthermore, substance use by pregnant women continues to be a serious problem.2 The most recent report from the National Household Survey on Drug Abuse estimated that in 1999, the rate of drug use among pregnant women was 3.4% for illicit drugs, 17.6% for tobacco and 13.8% for alcohol.3 In the United States in 1999, there were 3,944,450 births to women aged 15 to 44 years.4 Using National Household Survey on Drug Abuse estimates of substance use during pregnancy, the approximate numbers of births in 1999 complicated by maternal use of illicit drugs, tobacco, and alcohol were 134,110, 694,220, and 544,330, respectively. Thus, from the public health perspective, the impact of substance use during pregnancy extends far beyond maternal health to that of a large number of the unborn population.

It is now well-documented that early scientific reports in the 1980s that portrayed children who were exposed to cocaine in utero as irreparably damaged were inaccurate.5–8 The 1990s brought concern with overinterpretation of the findings9,10 coupled with the recognition of methodological problems in published studies that limited our understanding of co-
caine effects. Current research suggests that, although there are effects of cocaine on child development, these effects are inconsistent and subtle and need to be understood in the context of polydrug use and the caregiving environment. However, even subtle effects can affect substantial numbers of school-age children at an annual estimated cost to society of upwards of $350 million for additional special education services for these children.

The Maternal Lifestyle Study (MLS) was developed in the early 1990s against the backdrop of debate and controversy about the effects of prenatal cocaine exposure on child outcome. The MLS is an interagency collaborative effort involving the National Institute of Child Health and Human Development (NICHD); the National Institute on Drug Abuse (NIDA); the Administration on Children, Youth and Families; and the Center for Substance Abuse Treatment. The MLS is the largest clinical prospective longitudinal study of acute neonatal events and long-term health and developmental outcomes associated with cocaine use during pregnancy. The MLS was developed with the recognition that cocaine use by pregnant women is a marker variable for 2 critical factors that can affect child outcome in addition to prenatal cocaine exposure: use of drugs other than cocaine and an inadequate caregiving environment. The MLS was designed to address many of the methodological issues in the field. They include, in addition to polydrug use and the role of the caregiving environment, sample size, methods of drug detection, prematurity, other confounding variables (eg, medical factors, interventions, protective services), and neurodevelopmental assessments that are sensitive to putative drug effects.

In this report, we present the first neurobehavioral findings from the MLS. We describe the effects of cocaine/opiate exposure on neurobehavioral outcome at 1 month of age in a large sample that was diverse with respect to geography, setting (urban/rural), race, and social class. The study used measures in neurobehavioral domains of neurologic integrity, behavior, stress/abstinence signs, and cry, which were selected for their sensitivity to cocaine effects. Drug exposure in all subjects was documented with meconium assay and self-report, preterm as well as term infants were included, and other confounding variables were controlled. We also conducted analyses to determine thresholds for cocaine effects and for the effects of other drugs.

METHODS

Study Design

The MLS was conducted at 4 NICHD Neonatal Research Network sites (Brown University, University of Miami, Wayne State University, and the University of Tennessee at Memphis). The study was approved by the institutional review board at each site. The study was conducted in 2 phases, acute outcome (phase I) and longitudinal outcome (phase II). After a summary of phase I, we present the first neurodevelopmental findings from phase II.

Phase I was conducted between May 1993 and May 1995. During phase I, 19,079 mother-infant dyads were screened. Maternal exclusion criteria were age <18 years, identified psychosis or history of institutionalization for retardation or emotional problems, or language barriers that prevented her from giving informed consent or understanding the study. Infant exclusion criteria were born (not born at one of the participating hospitals), multiple gestation (birth weight <501 g, gestational age >42 weeks, or if in the judgment of the attending physician the infant was unlikely to survive. A NIDA Certificate of Confidentiality was obtained by each site that assured confidentiality of information regarding the subjects’ drug use. The certificate superseded the mandatory reporting of illegal substance use that was in effect in the Florida and Rhode Island sites. The certificate was explained to the mother during the recruitment and informed consent procedure, including the condition that the certificate did not exclude reporting of evidence of child abuse or neglect. After informed consent was obtained, a maternal interview determined and current drug use and sociodemographic information. A physical examination of the infant was conducted; meconium was collected. Before mothers and infants were discharged, their charts were abstracted to collect selected medical data. Of the 19,079 subjects screened, 16,988 met the eligibility criteria and 11,811 mothers consented to participate in the study.

Meconium samples were collected in the nursery and shipped to a central laboratory (EISohl et al); Oxford, MS) for analysis of metabolites of illicit drugs (see ElSohly et al and Lester et al for details). The assay consisted of an enzyme-multiplied immunoassay technique screen for cocaine, opiates, tetrahydrocannabinol, amphetamines, and phencyclidine followed by gas chromatography/mass spectroscopy confirmation for presumptive positive screens.

The study definition of “exposure” was maternal admission of cocaine or opiate use during this pregnancy based on the hospital interview or positive gas chromatography/mass spectroscopy confirmation of cocaine or opiate metabolites. Although our primary interest was in cocaine, opiates were included in the exposed group because of hospital reports indicating that many cocaine users were also using opiates. “Unexposed” was defined as denial of cocaine or opiate use during this pregnancy and a negative enzyme-multiplied immunoassay technique screen for cocaine and opiates metabolites. A history of maternal alcohol, marijuana, and nicotine use during the pregnancy was recorded during the hospital interview and considered as background variables in both the exposed and unexposed groups.

Participants

The phase II longitudinal study began at the infant’s first follow-up visit at 1 month (age corrected for prematurity). Mothers signed a separate consent for phase II. Infants were excluded from phase II when they had a chromosomal abnormality or TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis) infection confirmed before the 1-month visit or when the mother planned to move out of the catchment area. A list of possible comparison infants from the unexposed group within each center that matched an infant in the exposed group on race, gender, and gestational age was sent by the data center to each study site. Mothers were called on the list in sequence to confirm consent for phase II and to schedule the 1-month visit. When an infant in the comparison group did not attend the 1-month visit, another match was generated for each exposed infant until a comparison infant was successfully enrolled in phase II or the recruitment period ended. Recruitment of all exposed infants was attempted. It was possible for either an exposed or comparison infant to be in the study without a match. This procedure resulted in 2 groups that were matched on race, gender, and gestational age. The 1388 mother-infant dyads (658 in the exposed group and 730 in the comparison group) who came to the 1-month visit were enrolled in the longitudinal study.

The 1-month visit included neurobehavioral, medical, and physical status measures of the infant; social and demographic questionnaires; and the Maternal Interview of Substance Use (MISU). The MISU provides information about the frequency and quantity of substance use for each trimester during this pregnancy and was administered only to the biological mothers who brought their infant to the 1-month visit. The MISU was completed by 1255 biological mothers who brought their infants to the 1-month visit within the 2-week time frame, and the neurobehavior examination was completed on 1211 of those infants, which is the final sample in this study. Analyses of heavy cocaine effects (n = 1032) excluded opiate users (n = 91) and mothers who were identified as
using cocaine by initial hospital interview or meconium but de-
nied use on the MISU (n = 88).

Measures

A neurodevelopmental assessment battery was specifically de-
signed for this study through 3 years of age based on hypoth-
esized mechanisms of action of the effects of cocaine on the “four
A’s of infant behavior”: arousal, attention, affect (including social
interaction), and action (motor patterning).8,30 All infants were
examined between 42 and 44 weeks postconceptional age by
trained personnel who were masked to infant exposure status. In
this report, we present results of 1-month neurodevelopmental
findings on 2 measures: the NICU Network Neurobehavioral
Scale (NNNS)31 and acoustic cry analysis.

NNNS

The NNNS was administered by psychometrists who were
certified on the examination. The NNNS was developed for the
MLS and has been used in studies of intrauterine exposure to
cocaine,32 opiates,30,34 and nicotine.38 The NNNS provides an
assessment of neurologic, behavioral, and stress/abstinence
neurobehavioral function. The neurologic component includes active
and passive tone, primitive reflexes, and items that reflect the
integrity of the central nervous system and maturity of the infant.
The behavior component is based on items from the Neonatal
Behavioral Assessment Scale (NBAS)36 modified to be sensitive to
infants awake at the beginning of the examination. The
NNNS items are sum-
morized into the following scales: Habituation, Attention,
Arousal, Regulation, Number of Handling Procedures, Quality of
behavior (motor patterning).8,30 All infants were

Cry Analysis

After completion of the NNNS, the infant was placed in the
isotile and maintained in a noncrying state for 30 seconds before
the cry was elicited. A Marantz PMD201 cassette recorder and
Radio Shack Dynamic Unidirectional Microphone were used to
record the cry for 30 seconds after stimulation to the sole of the infant’s
right foot. If the infant did not cry, then a second stimulus
was applied. The infant was supine with the microphone sus-
pended 5 inches above the infant’s mouth. A specially designed
stimulator and tone box automatically placed a tone on the tape to
coincide with the time of the cry stimulus. A computer system
used in other studies58–61 was designed specifically to perform the
cry analysis (Cry Research Inc, Brookline, MA). Each 30-second
cry signal was filtered above 5 kHz and digitized at 10 kHz by the
cry computer. For each cry utterance (defined as a cry during the
expiratory phase of respiration lasting at least 0.5 seconds), we
used the Fast Fourier Transform to compute the log magnitude
spectrum for each 25-ms block of the cry utterance. The following
14 cry variables were analyzed based on previous work38,39,41:

- First cry duration (seconds), duration to second cry utter-
ance (seconds), change (seconds, stimulus to cry onset), number of
utterances, number of short utterances (<0.5 seconds), duration (seconds)
of first cry utterance, duration (seconds) of second cry utterance, inspiratory
period (interval in seconds between first and second cry utter-
ance), dysphonation (percentage of 25-ms blocks with a low signal
noise ratio, ie, aperiodic sound), number of mode changes
(between phonation and dysphonation), energy (dB level), funda-
mental frequency (Hz, voice pitch), hyperphonation (percentage
of 25-ms blocks with fundamental frequency >1000 Hz), and first
and second formants (Hz, resonance frequencies).

Statistical Analysis

Analysis of variance (ANOVA) and χ² were used to compare
the cocaine-exposed and comparison groups on medical and ma-
eternal characteristics. The dependent neurobehavioral measures
were tested with 4 sets of analyses. Analysis 1 is a 2-way ANOVA
that tests 2 factors: cocaine exposure (exposed/not exposed) and
opiate exposure (exposed/not exposed). The ANOVA (type 3 sum
of squares) tests each factor after adjustment for the other. Anal-
ysis 2 is a 2-way ANOVA that tests cocaine and opiate effects after
controlling for the standard covariate set described below. Anal-
ysis 3 is a univariate analysis of drug use and the NNNS. Heavy
cocaine use was defined as ≥3 days per week during the first
trimester similar to criteria used by others.20 Any other co-
caine use was considered some use. For this analysis, subjects (n = 91)
were excluded when there was any opiate use during preg-
nancy based on initial hospital interview, toxicology, or self-report
on the MISU. Opiate use was excluded because opiate use could
co-occur with heavy, some, or no cocaine use and potentially
confound level of cocaine exposure effects. Thus, the sample for
the third analysis consisted of 1032 subjects. Analysis 4 is a 1-way
ANOVA that contrasts the 3 quantity of cocaine use groups after
controlling for the standard covariate set described below.

Standard Covariate Set

Analyses 2 and 4 included covariates selected either for con-
ceptual reasons or because they met the following statistical cri-
teria: the variable is correlated with both drug exposure and
NNNS or cry outcome (p < .05) and not highly correlated with
other covariates (Pearson r < 0.70).12,42–44 Variables in Tables 1
and 2 were examined for possible inclusion as covariates. The
covariates that were used in the adjusted analysis included
11 variables that controlled for the Index of Social Position Score
from the Hollingshead scale (socioeconomic status [SES]), birth weight,
a birth weight by cocaine interaction term, and site (not inter-
preted in this study) and 7 polydrug use variables. The extent and
type of drug use reported in the MISU was used to generate
polydrug covariates for alcohol, marijuana, and tobacco by aver-
ing reported use across the 3 trimesters of pregnancy. Because
all of the drug variables had nonnormal distributions, each was
reduced to 3 categories of use (heavy, some, and no use). Cutoffs
were based on thresholds for detecting effects that have been
reported by others.45–50 For alcohol, heavy use was ≥0.5 oz of
absolute alcohol per day (1 standard drink). For marijuana, heavy
use was defined as ≥0.5 joints per day. For tobacco, heavy use was
defined as ≥10 cigarettes per day. Each 3-category drug variable
was then used to construct 2 effect codes that served as planned

| TABLE 1. Medical Characteristics of Cocaine- or Opiate-Exposed and Comparison Groups |
|-------------------------------|-----------------|-----------------|---------------------|-----------------|
| Cocaine-Exposed               | Opiate-Exposed   |                      |
| Yes (N = 600)                  | No (N = 788)    | Yes (N = 115)      | No (N = 1273)      |
| Best obstetric gestational age (wk) | 36.07 (4.02) | 36.39 (4.02) | .142 | 36.58 (4.08) | 36.23 (4.02) | .369 |
| Birth weight (g)               | 2544 (749)      | 2695 (862) | .001 | 2619 (637) | 2637 (816) | .888 |
| Length (cm)                    | 46.26 (4.75)    | 47.11 (5.18) | .027 | 46.72 (5.18) | 47.77 (4.99) | .538 |
| Head circumference (cm)        | 32.91 (2.89)    | 32.37 (3.12) | .026 | 32.05 (3.24) | 32.12 (3.01) | .801 |
| Appgar 1 (median)              | 8               | 8                | .405 | 8           | 8           | .055 |
| Appgar 5 (median)              | 9               | 9                | .227 | 9           | 9           | .446 |
| Male (%)                       | 306 (51.0%)     | 421 (53.4%) | .370 | 54 (47.0%)  | 673 (52.9%) | .224 |
comparisons (orthogonal contrasts). One effect code contrasted heavy use versus some and no use. The second effect code contrasted some use versus no use. When the no use versus some use comparison is statistically significant and the high versus no use comparison is not significant, the interpretation is that there is no additional effect of the higher use group. That is, the threshold for the effect is at the cutoff for the low use group. In addition, a separate indicator variable (yes/no) for binge drinking was defined as >5 drinks at 1 time or on any 1 day.

RESULTS

Medical and Maternal Characteristics

Medical characteristics of the infants are presented in Table 1. There were no statistically significant (P > .05) differences between the exposed and comparison groups on gestational age, birth weight, length, head circumference, Apgar scores, and gender. Preterm infants (<38 weeks) accounted for 41% (n = 270) of the cocaine/opiate-exposed group and 43% (n = 314) of the comparison group (not significant). The percentages of preterm infants who were born at <33 weeks was 10.8% (n = 71) in the cocaine/opiate-exposed group and 12.5% (n = 91) in the comparison group (not significant). The percentages of preterm infants who used cocaine during pregnancy (n = 461 [70.3%]) than in the comparison group (n = 361 [49.5%]; P < .001). On the basis of the MISU interview, Table 3 describes patterns of cocaine use for admitted users. As expected, cocaine use declined during the 3 trimesters. For example, the percentage of women who reported daily use decreased from 17% in the first trimester to 7% in the third trimester with a corresponding increase in the percentage of women who were not using, from 16% in the first trimester to 33% in the third trimester. The 117 (33.2%) women who used cocaine ≥3 days per week during the first trimester compose the heavy use group in the study.

The results of the categorization of the drug covariates showed 15.4% heavy alcohol use, 48.4% some alcohol use, 36.1% no alcohol use, and 21.1% binge. For marijuana, there was 6.9% heavy use, 21.9% some use, and 71.2% no use. For tobacco, there was 23.6% heavy use, 30.9% some use, and 45.5% no use. Opiate use occurred in 4.9% of the sample.

Neurodevelopmental Outcome on the NNNS

Results of analysis of NNNS measures (Tables 4 and 5) are presented as unadjusted before covariates were used and adjusted with covariates included. The adjusted means are shown in the tables.

<table>
<thead>
<tr>
<th>TABLE 2. Maternal Characteristics of Cocaine- or Opiate-Exposed and Comparison Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine-Exposed</td>
</tr>
<tr>
<td>Yes (N = 600; %)</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Other (non-Hispanic)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>18–25</td>
</tr>
<tr>
<td>26–35</td>
</tr>
<tr>
<td>36–49</td>
</tr>
<tr>
<td>Marital status</td>
</tr>
<tr>
<td>Married</td>
</tr>
<tr>
<td>Never married</td>
</tr>
<tr>
<td>Divorced/widowed</td>
</tr>
<tr>
<td>Insurance</td>
</tr>
<tr>
<td>Medicaid</td>
</tr>
<tr>
<td>Self-pay</td>
</tr>
<tr>
<td>Private/HMO</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Education</td>
</tr>
<tr>
<td>&lt;12 y</td>
</tr>
<tr>
<td>≥12 y</td>
</tr>
<tr>
<td>Prenatal care (any)</td>
</tr>
</tbody>
</table>

HMO indicates health maintenance organization.
TABLE 4.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Prenatal Cocaine-Exposed N Mean ± SE</th>
<th>Prenatal Opiate-Exposed N Mean ± SE</th>
<th>P</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>423 Mean 5.42 ± 0.10</td>
<td>686 Mean 5.34 ± 0.09</td>
<td>.748</td>
<td>.313</td>
<td></td>
</tr>
<tr>
<td>Arousal</td>
<td>457 Mean 4.37 ± 0.05</td>
<td>741 Mean 4.44 ± 0.05</td>
<td>.341</td>
<td>.038</td>
<td></td>
</tr>
<tr>
<td>Regulation*</td>
<td>450 Mean 4.91 ± 0.06</td>
<td>732 Mean 4.93 ± 0.06</td>
<td>.480</td>
<td>.050</td>
<td></td>
</tr>
<tr>
<td>Handling</td>
<td>430 Mean 0.55 ± 0.02</td>
<td>713 Mean 0.56 ± 0.02</td>
<td>.407</td>
<td>.124</td>
<td></td>
</tr>
<tr>
<td>Quality of movement</td>
<td>455 Mean 4.43 ± 0.06</td>
<td>740 Mean 4.49 ± 0.05</td>
<td>.044</td>
<td>.208</td>
<td></td>
</tr>
<tr>
<td>Excitability*</td>
<td>460 Mean 4.12 ± 0.17</td>
<td>751 Mean 4.03 ± 0.15</td>
<td>.369</td>
<td>.032</td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td>460 Mean 3.37 ± 0.16</td>
<td>751 Mean 3.31 ± 0.14</td>
<td>.069</td>
<td>.167</td>
<td></td>
</tr>
<tr>
<td>Nonoptimal reflexes</td>
<td>460 Mean 4.48 ± 0.16</td>
<td>751 Mean 4.37 ± 0.14</td>
<td>.836</td>
<td>.688</td>
<td></td>
</tr>
<tr>
<td>Asymmetrical reflexes</td>
<td>460 Mean 1.00 ± 0.08</td>
<td>751 Mean 0.90 ± 0.07</td>
<td>.735</td>
<td>.223</td>
<td></td>
</tr>
<tr>
<td>Hypertonicity</td>
<td>460 Mean 0.53 ± 0.08</td>
<td>746 Mean 0.63 ± 0.06</td>
<td>.060</td>
<td>.410</td>
<td></td>
</tr>
<tr>
<td>Hypobitucity</td>
<td>460 Mean 0.18 ± 0.04</td>
<td>746 Mean 0.20 ± 0.04</td>
<td>.542</td>
<td>.993</td>
<td></td>
</tr>
<tr>
<td>Stress/abstinence</td>
<td>460 Mean 0.18 ± 0.01</td>
<td>751 Mean 0.18 ± 0.01</td>
<td>.501</td>
<td>.520</td>
<td></td>
</tr>
</tbody>
</table>

SE indicates standard error.

* Significant cocaine by birth weight interaction (reported in text).
damental frequency, and a lower second formant than the cry of infants who were not exposed to cocaine (Table 6, unadjusted). There were no effects on cry with adjustment for covariates. With no adjustment for covariates, opiate-exposed infants had fewer short utterances than infants who were not exposed to opiates (Table 6, unadjusted). With adjustment for covariates, the effects of opiate exposure on short utterances remained, and there was more hyperphonation in opiate-exposed than in infants who were not exposed to opiates (Table 6, adjusted). There were also significant cocaine by opiate interactions on energy and fundamental frequency with the highest energy ($P = .023$) and fundamental frequency ($P = .020$) in infants who were exposed to both cocaine and opiates.

Covariate Effects for Cocaine and Opiate Exposure

Low birth weight was correlated with fewer utterances ($P = .001$), fewer short utterances ($P = .001$), less energy ($P = .002$), and a higher second formant ($P < .001$). Infants in the some alcohol use group had a lower cry threshold than infants in the no alcohol use group ($P = .011$). Infants in the high marijuana use group showed more mode changes ($P = .019$) and a higher second formant ($P = .019$) than infants in the some and no marijuana use groups.

Level of Cocaine Exposure

With no adjustment for covariates, there was more dysphonia in the cries of infants with heavy cocaine exposure than in the cries of infants with some or no cocaine exposure (Table 7, unadjusted). With adjustment for covariates, the duration of the second cry utterance was longer in heavy compared with some or no cocaine exposure (Table 7, adjusted).

Covariate Effects for Level of Cocaine Exposure

The birth weight by level of exposure interaction showed that the infants in the low birth weight, heavy exposure group had longer second duration utterances than the other groups ($P = .043$). Lower birth weight was associated with fewer cry utterances ($P = .019$), fewer short utterances ($P = .002$), shorter latency ($P = .021$), less energy ($P = .001$), a higher second formant ($P = .002$), and a longer duration of the second cry utterance ($P = .023$). Infants in the some alcohol use group showed a lower cry threshold than infants in the no alcohol use group ($P = .026$). Infants in the high alcohol use group showed a higher proportion of hyperphonation ($P = .040$). Infants in the binge group had a lower first formant ($P = .033$). Infants in the some alcohol use group had a lower cry threshold than infants in the no alcohol use group ($P = .038$). Infants in the high marijuana use group showed more mode changes ($P = .010$) and a higher second formant ($P = .005$) than infants in the no and some marijuana use groups.

Additional Covariate Effects

SES and site were included as covariates in all of the analyses reported above. Therefore, the exposure effects reported above were not attributable to SES or site differences. However, for reporting purposes, we note that there were only 6 SES covariate effects out of the 74 analyses. However, site effects were observed 72 times. We did test the exposure status by site interaction term for each dependent variable to determine whether we needed to explore further the site effects. However, none of the interaction terms was statistically significant.

We also repeated the analyses with covariates (analysis 2 and 4) excluding birth weight and the birth weight by cocaine interaction from the list of covariates because it has been argued that if cocaine affects birth weight, then the inclusion of birth weight as a covariate will mask the effects of cocaine. Results showed that for the NNNS, the exclusion of birth weight and the interaction term as covariates did not result in additional statistically significant effects in analysis 2 or 4. In fact, all 3 effects in analysis 2 and 2 of 4 effects in analysis 4 were no longer statistically significant with these terms excluded. For cry, 2 effects were observed in analysis 1 (unadjusted for covariates) that were observed when birth weight and the interaction term were excluded in analysis 2. However, in analysis 4, there were no statistically significant effects when these covariates were excluded.
### TABLE 6.
Cry Variables in Cocaine- and Opiate-Exposed and -Nonexposed Infants

<table>
<thead>
<tr>
<th>Measure</th>
<th>Prenatal Cocaine-Exposed</th>
<th></th>
<th></th>
<th>Prenatal Opiate-Exposed</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>Mean ± SE</td>
<td>No</td>
<td>Mean ± SE</td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Threshold (n)</td>
<td>352</td>
<td>1.97 ± 0.02</td>
<td>544</td>
<td>1.96 ± 0.01</td>
<td>0.65</td>
<td>0.23</td>
</tr>
<tr>
<td>Latency (sec)</td>
<td>352</td>
<td>2.50 ± 0.27</td>
<td>547</td>
<td>2.47 ± 0.25</td>
<td>0.92</td>
<td>0.54</td>
</tr>
<tr>
<td>Utterances (n)</td>
<td>352</td>
<td>11.77 ± 0.53</td>
<td>547</td>
<td>11.11 ± 0.49</td>
<td>1.70</td>
<td>0.59</td>
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<tr>
<td>Short utterances (n)</td>
<td>352</td>
<td>15.07 ± 0.77</td>
<td>547</td>
<td>15.06 ± 0.72</td>
<td>4.35</td>
<td>0.48</td>
</tr>
<tr>
<td>Duration first utterance (sec)</td>
<td>352</td>
<td>2.23 ± 0.14</td>
<td>547</td>
<td>2.16 ± 0.13</td>
<td>5.12</td>
<td>0.36</td>
</tr>
<tr>
<td>Duration second utterance (sec)</td>
<td>344</td>
<td>1.42 ± 0.07</td>
<td>525</td>
<td>1.46 ± 0.07</td>
<td>0.82</td>
<td>0.36</td>
</tr>
<tr>
<td>Inspiratory period (sec)</td>
<td>344</td>
<td>2.58 ± 0.25</td>
<td>525</td>
<td>2.50 ± 0.24</td>
<td>0.75</td>
<td>0.11</td>
</tr>
<tr>
<td>Mode changes (%)</td>
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<td>12.82 ± 1.24</td>
<td>547</td>
<td>13.03 ± 1.14</td>
<td>0.32</td>
<td>0.48</td>
</tr>
<tr>
<td>Energy (dB)</td>
<td>352</td>
<td>4225.74 ± 235.32</td>
<td>547</td>
<td>3465.63 ± 212.98</td>
<td>0.01</td>
<td>0.19</td>
</tr>
<tr>
<td>Fundamental frequency (Hz)*</td>
<td>351</td>
<td>479.53 ± 8.86</td>
<td>545</td>
<td>453.31 ± 7.90</td>
<td>0.03</td>
<td>0.59</td>
</tr>
<tr>
<td>Hyperphonation (%)</td>
<td>352</td>
<td>2.90 ± 0.85</td>
<td>547</td>
<td>3.46 ± 0.66</td>
<td>0.32</td>
<td>0.10</td>
</tr>
<tr>
<td>First formant (Hz)</td>
<td>351</td>
<td>1640.69 ± 29.47</td>
<td>545</td>
<td>1615.67 ± 27.26</td>
<td>0.17</td>
<td>0.59</td>
</tr>
<tr>
<td>Second formant (Hz)</td>
<td>351</td>
<td>3950.86 ± 29.74</td>
<td>545</td>
<td>3959.86 ± 27.51</td>
<td>0.04</td>
<td>0.69</td>
</tr>
</tbody>
</table>

SE indicates standard error.

* Significant cocaine by opiate interaction for analyses with and without covariates (reported in text).
exposed group, and other studies have also reported opiate effects on the NBAS.56–60 We also found more stress/abstinence signs in the some marijuana use group and higher excitability scores in the heavy marijuana use group. Marijuana effects have also been reported on the NBAS61 but not using thresholds as in the present study. The finding of stress/abstinence effects in infants who were exposed to opiates and marijuana confirms the sensitivity of the NNNS to measure these effects and supports the null finding of no stress/abstinence effects in the cocaine-exposed infants.

Our finding that opiate-exposed infants had better orientation scores was not found with adjustment for covariates, suggesting that this may not be an opiate effect. There was also a covariate effect showing that lower orientation scores were attributable to binge drinking. Effects of prenatal alcohol exposure have been reported on the NBAS61–65 using estimates that measure regular drinking but at higher levels (averages of 1.7–2.32 oz of absolute alcohol per day) than in the present study. These studies did not use a binge variable that may prove useful in future studies in which the average drinking is at lower levels. Note also that the infants in our study were tested at 1 month of age. A few studies used repeated tests during the first month and found stronger effects of cocaine as infants approached 1 month.21,66,67 suggesting that the effects of cocaine and other drugs may be more easily detected after the immediate newborn period.

Cry

In previous work, acoustical analysis of cry has been related to prenatal cocaine exposure,38,39 opiates,68,69 marijuana,40 tobacco,41 and alcohol.41,70 Measures of cry acoustics reflect mechanisms that mediate cry production, including central nervous system reactivity (threshold, latency), respiratory control (energy, dysphonation, and utterances), and sound characteristics related to neural control of the vocal tract (fundamental frequency, hyperphonation, formant frequencies, and mode changes).

We found a louder cry (more energy), a higher pitched cry (fundamental frequency), with less resonance in the upper vocal tract (second formant) in cocaine-exposed infants and more turbulence or noise (dysphonation) in the cry signal with heavy cocaine exposure. However, these effects were not observed when adjusted for covariates, suggesting that they are not attributable only to cocaine. The second cry utterance was longer in the heavy cocaine use group with adjustment for covariates. The opiate effects on cry were more short utterances and more hyperphonation (very high pitch, >1000 Hz), and these were maintained with adjustment for covariates. Infants who were exposed to both cocaine and opiates had the loudest and highest pitched cries.

We also found effects of other drugs on cry acoustics. Infants in the some alcohol use group were more reactive, requiring fewer stimuli to elicit the cry (lower threshold), than infants with no alcohol exposure. There was more hyperphonation in the high alcohol use group and a lower first formant in the binge alcohol group. Infants in the high marijuana use group had more glottal instability (mode changes) and a higher second formant.

These findings demonstrate general effects of prenatal drug exposure on the reactivity, respiratory, and neural control components of the cry. In addition, there may be more specific effects that could help identify subgroups of infants at greater risk. For example, high-pitched and hyperphonated cries have been reported in infants with neurologic involvement.71 This could suggest that the opiate, cocaine plus opiate, and high alcohol use groups are at higher neurologic risk than other infants in our study. Finally, we found, as have others,70,71 effects of birth weight on cry. Most of the birth weight effects that we observed were related to the respiratory control aspect of cry production (utterance measures and energy).

General Issues

The statistical power of this sample coupled with sensitive neurobehavioral measures enabled us to

### TABLE 7. Cry Variables in Heavy, Some, and No Cocaine Exposure Groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Heavy N</th>
<th>Mean ± SE</th>
<th>Some N</th>
<th>Mean ± SE</th>
<th>None N</th>
<th>Mean ± SE</th>
<th>Unadjusted P</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold</td>
<td>89</td>
<td>1.94 ± 0.02</td>
<td>166</td>
<td>1.97 ± 0.02</td>
<td>506</td>
<td>1.95 ± 0.01</td>
<td>.221</td>
<td>.131</td>
</tr>
<tr>
<td>Latency (sec)</td>
<td>89</td>
<td>2.48 ± 0.39</td>
<td>166</td>
<td>2.93 ± 0.29</td>
<td>508</td>
<td>2.76 ± 0.19</td>
<td>.837</td>
<td>.084</td>
</tr>
<tr>
<td>Utterances (n)</td>
<td>89</td>
<td>10.58 ± 0.76</td>
<td>166</td>
<td>12.30 ± 0.57</td>
<td>508</td>
<td>11.21 ± 0.36</td>
<td>.285</td>
<td>.511</td>
</tr>
<tr>
<td>Short utterances (n)</td>
<td>89</td>
<td>15.85 ± 1.16</td>
<td>166</td>
<td>16.18 ± 0.84</td>
<td>508</td>
<td>15.92 ± 0.53</td>
<td>.676</td>
<td>.361</td>
</tr>
<tr>
<td>Duration first utterance (sec)</td>
<td>89</td>
<td>2.31 ± 0.20</td>
<td>166</td>
<td>2.31 ± 0.15</td>
<td>508</td>
<td>2.25 ± 0.10</td>
<td>.833</td>
<td>.350</td>
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<tr>
<td>Duration second utterance (sec)*</td>
<td>86</td>
<td>1.56 ± 0.10</td>
<td>161</td>
<td>1.42 ± 0.08</td>
<td>488</td>
<td>1.47 ± 0.05</td>
<td>.426</td>
<td>.046</td>
</tr>
<tr>
<td>Inspiratory period (sec)</td>
<td>86</td>
<td>2.79 ± 0.36</td>
<td>161</td>
<td>2.87 ± 0.28</td>
<td>488</td>
<td>2.73 ± 0.18</td>
<td>.936</td>
<td>.089</td>
</tr>
<tr>
<td>Dysphonation (%)</td>
<td>89</td>
<td>14.60 ± 1.74</td>
<td>166</td>
<td>10.46 ± 1.32</td>
<td>508</td>
<td>11.86 ± 0.85</td>
<td>.050</td>
<td>.105</td>
</tr>
<tr>
<td>Mode changes (%)</td>
<td>89</td>
<td>2.49 ± 0.28</td>
<td>166</td>
<td>2.05 ± 0.21</td>
<td>508</td>
<td>2.46 ± 0.13</td>
<td>.086</td>
<td>.938</td>
</tr>
<tr>
<td>Energy (dB)</td>
<td>89</td>
<td>3733.97 ± 274.43</td>
<td>166</td>
<td>3745.75 ± 206.00</td>
<td>508</td>
<td>3673.04 ± 131.04</td>
<td>.679</td>
<td>.162</td>
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<tr>
<td>Fundamental frequency (Hz)</td>
<td>89</td>
<td>461.74 ± 10.50</td>
<td>166</td>
<td>473.04 ± 7.89</td>
<td>508</td>
<td>471.88 ± 5.03</td>
<td>.906</td>
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<td>Hyperphonation (%)</td>
<td>89</td>
<td>1.42 ± 0.98</td>
<td>166</td>
<td>1.72 ± 0.74</td>
<td>508</td>
<td>2.27 ± 0.47</td>
<td>.719</td>
<td>.172</td>
</tr>
<tr>
<td>First formant (Hz)</td>
<td>89</td>
<td>1682.16 ± 41.05</td>
<td>166</td>
<td>1640.75 ± 30.84</td>
<td>506</td>
<td>1632.06 ± 19.69</td>
<td>.326</td>
<td>.657</td>
</tr>
<tr>
<td>Second formant (Hz)</td>
<td>89</td>
<td>3960.62 ± 42.10</td>
<td>166</td>
<td>3916.03 ± 31.63</td>
<td>506</td>
<td>3938.95 ± 20.19</td>
<td>.217</td>
<td>.465</td>
</tr>
</tbody>
</table>

SE indicates standard error.

* Significant cocaine by birth weight interaction (reported in text).
detect drug effects that were not previously possible. Dividing the cocaine sample into heavy versus some use improved the detection of cocaine effects by showing that some effects were attributable only to heavy cocaine exposure. The use of cut points to identify thresholds for drug covariates also improved detection by showing some effects at lower thresholds and some effects only at higher thresholds. These findings underscore the importance of using multiple, neurobehavioral measures to help identify subgroups of infants who are at greater risk and for studying neurobehavioral effects in the context of polydrug use. Our analysis for heavy use was based on a postnatal self-report measure. Postnatal self-report measures of maternal cocaine use has been found to be as effective as antenatal measures in predicting neurobehavioral outcome. It also avoids the limitations of antenatal measures that rely on clinic-based samples that may limit generalizability. It is also interesting that in the context of polydrug use, we found no evidence of cigarette smoking on NNNS or cry. Other studies have reported effects of cigarette smoking but not in the context of illegal and polydrug use.

Role of Birth Weight

Context also needs to include low birth weight. We found independent effects of birth weight on NNNS and cry as well as cocaine by birth weight interactions. Birth weight is probably a moderator variable, meaning that effects of cocaine may be different in low birth weight infants than in normal birth weight infants. We also tested the hypothesis that cocaine effects could be masked by the inclusion of birth weight and the cocaine by birth weight interaction. We found more evidence that the effects of cocaine on NNNS and cry are more visible when these variables were used as covariates than when they were not. We suggest that the use of these factors as covariates controls error variance that serves to unmask further the effects of cocaine on behavior.

Understanding Subtle Effects

The effects reported here are small in magnitude. We did not adjust for multiple comparisons. Adjustment for multiple comparisons protects against rejecting the null hypotheses when it is correct (type I error). However, as suggested by Rothman, the cost of this protection is to increase the type II error that findings are attributable to chance when they are not. Minimizing type II error or maximizing sensitivity to find effects is especially critical in studies such as ours in which effects are subtle and could easily be missed. It is important that we understand the implications of these subtle effects because they can affect not only our scientific understanding but also public policy and treatment. We found reliable but small differences attributable to drugs that are not necessarily deficits. Although our findings do not provide evidence of a clinically significant disorder or disease process, they do have both short-term and long-term implications.

The short-term importance of these differences is that they reflect neurobehavioral vulnerability that may be exacerbated by the caregiving environment. Many drug-exposed infants grow up in nonoptimal environments. Therefore, what start out as small differences can become exaggerated and develop into deficits. Our findings suggest certain neurobehavioral characteristics that could provide markers for later deficits, such as poor self-regulation, in cocaine-exposed infants, and the high pitched, hyperphonic cries in cocaine/opiate- and alcohol-exposed infants. Clinically, the drug-exposed infant is probably best thought of as an infant “at risk” rather than as an infant with a known disorder. In addition, environmental risk may interact with neurobehavioral risk. We might expect the lethargic infant to be more at risk for neglect and the excitable infant to be more at risk for abuse. This is said with 2 caveats. The first is the understanding that the concept of “at risk” is vague. Second, our findings are limited to the population studied and may not represent all drug-exposed infants. Most of the pregnant women who use cocaine and most of the subjects in research studies, including ours, are referred to as “recreational users” rather than “hard-core addicts.” Even our “heavy users” were rarely daily users, and heavy use was limited to the first trimester only as cocaine use declined throughout pregnancy. The clinical implications of considering these infants as “at risk” infants are that with intervention, later deficits can be prevented.

The long-term implications of these findings are that cocaine may affect areas of the brain that are not manifest until these children reach school. For example, in adult cocaine users, problems with executive function (decision making, judgment, attention, planning, and mental flexibility) are the most frequently reported cognitive deficits. The site of action for cocaine in the brain involves several brain areas that are thought to subserve these functions, including the nucleus accumbens/subcallosal cortex, prefrontal cortex, and limbic prefrontal cortex including the anterior cingulate. Functional magnetic resonance imaging studies and other imaging techniques show response to cocaine infusion in these locations as well as associated areas, including the basal ganglia and parietal cortex. Cocaine may have latent effects that are not yet observed in infancy. It may be that cocaine affects areas of the brain that we cannot evaluate in infancy or that are not manifested until children are older, such as executive function. There are many examples of problems that are undetected in early infancy (attention-deficit/hyperactivity disorder, autism, schizophrenia) that could provide alternative models for understanding prenatal exposure effects. Therefore, it is imperative that these children continue to be followed and that public policy allow for the possibility that even subtle findings in infancy may be a harbinger of more serious long-term deficits.

ACKNOWLEDGMENTS

This study was supported by the NICHD through cooperative agreements U10 HD 27904 (to Dr Lester), U10 HD 21397 (to Dr Bauer), U10 HD 21385 (to Dr Shankaran), and U10 HD 27856 (to Dr Bada) and NICHD contract N01-HD-2-3159 (to Drs Lester and
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THROWING MONEY AT HEALTH SERVICES WILL MEAN MORE TESTS AND TREATMENTS, BUT IT WON’T NECESSARILY PROLONG PEOPLE’S LIVES, WARNS JOHN E. WENNBERG

“It is an enduring assumption of modern life that as medical science advances and health care improves, most of us can expect to lead longer and healthier lives. More diagnostic tests, more powerful body and brain scanners, more high-tech treatments, more drugs: surely this is a recipe for longevity. Provided politicians and health insurers pump enough money into our hospitals and clinics, the benefits are bound to flow. However, things are not that simple. My colleagues and I have found that, at least for older and sicker Americans, more health care does not necessarily mean more health. Our studies consistently show that patients in areas where health care spending is high do not have longer life expectancy. At best, it remains the same as in low-spending regions.”

Wennberg JE. New Scientist. August 17, 2002:26

Note: John E. Wennberg is director of the Center for the Evaluative Clinical Sciences at the Dartmouth Medical School, Lebanon, New Hampshire.

Noted by JFL, MD
## The Maternal Lifestyle Study: Effects of Substance Exposure During Pregnancy on Neurodevelopmental Outcome in 1-Month-Old Infants


*Pediatrics* 2002;110;1182-1192

DOI: 10.1542/peds.110.6.1182

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