

# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## **The Infant Development, Environment, and Lifestyle Study: Effects of Prenatal Methamphetamine Exposure, Polydrug Exposure, and Poverty on Intrauterine Growth**

Lynne M. Smith, Linda L. LaGasse, Chris Derauf, Penny Grant, Rizwan Shah, Amelia Arria, Marilyn Huestis, William Haning, Arthur Strauss, Sheri Della Grotta, Jing Liu and Barry M. Lester

*Pediatrics* 2006;118;1149-1156

DOI: 10.1542/peds.2005-2564

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/118/3/1149>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2006 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# The Infant Development, Environment, and Lifestyle Study: Effects of Prenatal Methamphetamine Exposure, Polydrug Exposure, and Poverty on Intrauterine Growth

Lynne M. Smith, MD<sup>a</sup>, Linda L. LaGasse, PhD<sup>b</sup>, Chris Derauf, MD<sup>c</sup>, Penny Grant, MD<sup>d</sup>, Rizwan Shah, MD<sup>e</sup>, Amelia Arria, PhD<sup>f</sup>, Marilyn Huestis, PhD<sup>g</sup>, William Haning, MD<sup>h</sup>, Arthur Strauss, MD<sup>h</sup>, Sheri Della Grotta, MPH<sup>h</sup>, Jing Liu, PhD<sup>h</sup>, Barry M. Lester, PhD<sup>h</sup>

<sup>a</sup>Department of Pediatrics, David Geffen School of Medicine at UCLA and Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California;

<sup>b</sup>Brown Center for the Study of Children at Risk, Brown Medical School, Women and Infant's Hospital, Providence, Rhode Island; Departments of <sup>c</sup>Pediatrics and

<sup>h</sup>Psychiatry, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii; <sup>d</sup>Department of Pediatrics, University of Oklahoma, Norman, Oklahoma;

<sup>e</sup>Department of Pediatrics, Blank Children's Hospital-Iowa Health, Des Moines, Iowa; <sup>f</sup>Center for Substance Abuse Research, University of Maryland, College Park,

Maryland; <sup>g</sup>Section on Chemistry and Drug Metabolism, National Institute on Drug Abuse, Bethesda, Maryland; <sup>h</sup>Department of Pediatrics, Long Beach Memorial Medical Center, Long Beach, California

The authors have indicated they have no financial relationships relevant to this article to disclose.

## ABSTRACT

**OBJECTIVE.** Methamphetamine use among pregnant women is an increasing problem in the United States. Effects of methamphetamine use during pregnancy on fetal growth have not been reported in large, prospective studies. We examined the neonatal growth effects of prenatal methamphetamine exposure in the multi-center, longitudinal Infant Development, Environment and Lifestyle study.

**DESIGN/METHOD.** The Infant Development, Environment and Lifestyle study screened 13 808 subjects at 4 clinical centers: 1618 were eligible and consented, among which 84 were methamphetamine exposed, and 1534 were unexposed. Those who were methamphetamine exposed were identified by self-report and/or gas chromatography-mass spectrometry confirmation of amphetamine and metabolites in infant meconium. Those who were unexposed denied amphetamine use and had a negative meconium screen. Both groups included prenatal alcohol, tobacco, or marijuana use, but excluded use of opiates, LSD, PCP or cocaine only. Neonatal parameters included birth weight and gestational age in weeks. One-way analysis of variance and linear-regression analyses were conducted on birth weight by exposure. The relationship of methamphetamine exposure and the incidence of small for gestational age was analyzed using multivariate logistic-regression analyses.

**RESULTS.** The methamphetamine exposed group was 3.5 times more likely to be small for gestational age than the unexposed group. Mothers who used tobacco during pregnancy were nearly 2 times more likely to have small-for-gestational-age infants. In addition, less maternal weight gain during pregnancy was more likely to result in a small-for-gestational-age infant. Birthweight in the methamphetamine exposed group was lower than the unexposed group.

**CONCLUSIONS.** These findings suggest that prenatal methamphetamine use is associated with fetal growth restriction after adjusting for covariates. Continued follow-up will determine if these infants are at increased risk for growth abnormalities in the future.

[www.pediatrics.org/cgi/doi/10.1542/peds.2005-2564](http://www.pediatrics.org/cgi/doi/10.1542/peds.2005-2564)

doi:10.1542/peds.2005-2564

### Key Words

body weight, substance exposure, neonatal, prenatal, methamphetamine

### Abbreviations

SGA—small for gestational age  
SES—socioeconomic status  
IDEAL—Infant Development, Environment and Lifestyle  
GC/MS—gas chromatography-mass spectrometry

Accepted for publication Apr 17, 2006

Address correspondence to Lynne M. Smith, MD, Martin Research Center, Harbor-UCLA Medical Center, 1124 W Carson St, Torrance, CA 90502. E-mail: [smith@labiomed.org](mailto:smith@labiomed.org)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2006 by the American Academy of Pediatrics

THE RECENT INCREASE in methamphetamine use in the United States and in several regions worldwide has highlighted the need for a better understanding of the short- and long-term effects of methamphetamine use during pregnancy. Methamphetamine use during pregnancy is associated with an increased incidence of premature delivery and placental abruption.<sup>1,2</sup> Cases of cardiovascular collapse and seizures have also been reported in women using methamphetamine during pregnancy.<sup>3,4</sup> The effects of prenatal methamphetamine exposure on the developing fetus have not been well characterized. Increased rates of fetal distress have been associated with women using methamphetamine during pregnancy.<sup>1</sup> In addition, isolated cases of cardiac defects, cleft lip, and biliary atresia have been reported in infants exposed to methamphetamine in utero.<sup>5</sup> However, these reports are limited by the lack of comparison groups and small sample sizes. Despite these limitations, the available maternal and fetal data suggest that the fetus is potentially vulnerable to adverse effects secondary to prenatal methamphetamine exposure.

An important concern regarding prenatal methamphetamine use is whether in utero exposure compromises fetal growth. A retrospective review of methamphetamine-exposed neonates found an increased incidence of small-for-gestational-age (SGA) neonates relative to an unexposed group.<sup>6</sup> In addition, Oro and Dixon<sup>7</sup> found in a study of 105 mother-infant pairs with positive results of urine toxicology screens at the time of delivery that, in comparison to narcotic-exposed neonates, methamphetamine/cocaine-exposed neonates were more likely to have decreased birth weight and head circumference and to be SGA. However, these data are limited because the investigation was retrospective, included only positive urine toxicology screens at the time of delivery, and control subjects were not matched for socioeconomic status (SES). Other investigators have also reported that prenatal methamphetamine exposure is associated with decreased growth parameters.<sup>8</sup> The only study that has examined the long-term effects of prenatal amphetamine exposure is a prospectively followed sample of 65 children born to mothers in Sweden who had abused amphetamines during their pregnancy. At birth and 1 and 4 years of age, the mean weight, height, and head circumference of the amphetamine-exposed children were below the means of their peers.<sup>9</sup> Females, but not males, were significantly shorter and lighter than their peers and remained smaller at age 10.<sup>10</sup> These findings are limited, because the exposed children were compared with an unselected community sample instead of a matched comparison group and because coexposures to other drugs including opiates were prevalent in the methamphetamine group but not known in the unselected sample. In addition, all studies relied solely on maternal self-reporting for drug use.

Thus, the limited available data suggest that metham-

phetamine-exposed children are at risk for growth impairment. However, the findings are derived from retrospective analyses, samples with small numbers or inadequate control for polydrug use during pregnancy, and other confounding variables. The multisite longitudinal Infant Development, Environment and Lifestyle (IDEAL) study of prenatal methamphetamine exposure includes a prospective cohort of exposed and unexposed neonates. Here we report the preliminary growth parameter findings from the IDEAL study.

## METHODS

Because the primary goal of the research was to investigate the outcomes associated with prenatal methamphetamine exposure, clinical sites in specific geographic areas known to have methamphetamine problems were chosen to participate in the IDEAL project. The cities chosen were Los Angeles, California; Des Moines, Iowa; Tulsa, Oklahoma; and Honolulu, Hawaii. The study was approved by the institutional review boards at all participating sites. Before initiation of recruitment, personnel from all sites met for a week-long training session so that procedures could be standardized.<sup>11</sup> The planned recruitment is 2 years; the neonatal growth findings presented here are from the cohort recruited by year 1.

The exclusion criteria for the mothers are age <18, opiate use during pregnancy, institutionalization for retardation or emotional disorders, overt psychosis or a documented history of psychosis, and unable to speak English. Exclusion criteria for the children are critical illness (unlikely to survive), multiple birth, major life-threatening congenital anomaly, documented chromosomal abnormality associated with mental or neurologic deficiency, overt TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex) infection, and having a sibling previously enrolled in the IDEAL study. A National Institute on Drug Abuse certificate of confidentiality was obtained for the project, which assures confidentiality of information regarding the subjects' drug use, superseding mandatory reporting of illegal substance use. The certificate is explained to the mother during the recruitment and informed-consent process, including the condition that the certificate does not exclude reporting of evidence of child abuse or neglect.

After informed consent is obtained, a maternal interview (the Lifestyle Interview) determines drug use during pregnancy and sociodemographic information.<sup>12,13</sup> The Lifestyle Interview includes information about the course of the pregnancy, household composition, demographics (SES, education, age, race, and marital status), and services received during pregnancy. Education and occupation information is collected to calculate the 4-factor Hollingshead index of SES, which has been adapted to single-parent and nonnuclear families.<sup>14,15</sup> In addition, information about the neonate's gestation and

birth weight and questions regarding the health of the mother-neonate pair are included. Gestational age is determined by estimated date of confinement for women with good prenatal care. If there is a discrepancy between the postnatal gestation assessment and obstetrical dating, the postnatal examination is used. For women with no or inadequate prenatal care, the postnatal examination by the patient's physician is used for gestational dating.

Meconium is collected from all infants; the samples are collected in the nursery and shipped to a central laboratory (US Drug Testing Laboratory) for analysis of amphetamines, cocaine metabolites, cannabinoids, opiates, and cotinine. The specimen is screened initially with a sensitive enzyme multiplied immunoassay test (EMIT II; Dade-Behring, Cupertino, CA). If positive results are obtained, the specific drug analyte or metabolite is confirmed by gas chromatography-mass spectrometry (GC/MS).

Exposed subjects were identified by maternal report of methamphetamine use during the pregnancy on the basis of the hospital interview and/or GC/MS confirmation of amphetamine and metabolites in infant meconium. Unexposed subjects were defined as denial of methamphetamine use during this pregnancy and negative GC/MS results for amphetamine and metabolites. A history of maternal alcohol, marijuana, or tobacco use during the pregnancy was considered as a background variable in both the exposed and unexposed groups.

### Participants

From September 2002 to August 2003, 13 808 mother-infant pairs were screened. Of the 13 808 subjects

screened, 24% (3298) were not available to be approached and screened for eligibility. Of the 10 510 individuals approached, 32% (3391) were ineligible. Of the 7119 eligible subjects, 23% (1618) consented for participation in the study. Meconium tests were performed on all consented infants. Among the consented, 84 were exposed to methamphetamine. Among the exposed subjects, 82 (97.6%) were self-reporters, and 21 meconium samples were confirmed positive for methamphetamine. Two subjects denied methamphetamine use during pregnancy, but their meconium was confirmed positive for methamphetamine.

We defined SGA as <10th percentile for birth weight, as determined by Alexander's algorithm of weight for gestational age.<sup>16</sup>

### Statistical Analysis

Demographic and clinical characteristics for the groups were initially compared in unadjusted analysis by using 1-way analysis of variance for continuous variables and  $\chi^2$  tests for nonparametric variables. Significance was accepted at  $P < .05$ .

The relationship of methamphetamine exposure and growth parameters were analyzed by using multivariate linear-regression analyses. The relationship of methamphetamine exposure and the incidence of SGA was analyzed by using multivariate logistic-regression analyses. Both regression analyses adjusted for covariates. Covariates were selected on the basis of conceptual reasons, published literature, and characteristics shown in Table 1 that differed between groups if not highly correlated with other covariates. The effect of prenatal exposures to alcohol, tobacco, or marijuana on growth has been re-

**TABLE 1** Maternal and Infant Characteristics

	Exposed (N = 84)	Unexposed (N = 1534)	P
Race, n (%)			.109
White	39 (46.4)	801 (52.6)	
Hispanic	14 (16.7)	179 (11.7)	
Pacific Islander	10 (11.9)	119 (7.8)	
Asian	13 (15.5)	156 (10.2)	
Black	5 (6.0)	223 (14.6)	
American Indian	2 (2.4)	35 (2.3)	
Other	1 (1.2)	11 (0.7)	
Low SES, Hollingshead-V, n (%)	30 (35.7)	109 (7.1)	.000
SES, Hollingshead social-position index, mean (SD)	25.64 (10.02)	37.99 (12.95)	.000
Household income less than \$10 000, n (%)	25 (33.8)	170 (11.6)	.000
Public insurance, n (%)	70 (90.9)	740 (49)	.000
No partner, n (%)	48 (57.1)	442 (28.8)	.000
Education <12 y, n (%)	41 (48.8)	244 (16.0)	.000
Age, mean (SD), y	25.37 (5.38)	26.89 (5.93)	.021
Gestational age at first prenatal visit, mean (SD), wk	14.81 (8.02)	9.29 (5.28)	.000
Prenatal visits, <5, n (%)	14 (18.7)	27 (1.8)	.000
Weight gain during this pregnancy, mean (SD), lb	44.98 (19.49)	33.46 (14.73)	.000
Prenatal drug use, n (%)			
Tobacco	66 (78.6)	342 (22.3)	.000
Alcohol	36 (42.9)	331 (21.6)	.000
Marijuana	33 (39.3)	63 (4.1)	.000

ported previously.<sup>17–19</sup> In addition to observed group differences shown in Table 1, low SES, low income, single parenthood, and inadequate prenatal care are all risk factors for poor fetal growth.<sup>20–24</sup> Our study criterion for inadequate prenatal care (<5 prenatal visits) is a common clinical standard. The covariates that were used in the final analysis were prenatal alcohol exposure, prenatal tobacco exposure, prenatal marijuana exposure, gender, Hollingshead index of SES, household income less than \$10 000, prenatal care of <5 visits, mother's weight gain, maternal age, and single parenthood. All drug-exposure variables, gender, prenatal care, household income, and single parenthood were dichotomous (yes/no) variables. SES, mother's weight gain, and age were continuous variables. In addition, multiple linear regression on birth weight also adjusted for gestational age in weeks. Significance for the regression analyses was accepted at  $P < .05$ .

## RESULTS

The maternal characteristics of the 1618 mother-infant pairs (methamphetamine exposed and unexposed) are shown in Table 1. There were no differences in race between the 2 groups. Compared with the National Pregnancy and Health Survey conducted in the early 1990s,<sup>25</sup> a higher proportion of IDEAL study subjects were in a racial/ethnic category other than white, black, or Hispanic. These differences may be attributed to numerous factors including the geographic concentration for our sample instead of a wider national sample and the emphasis on targeting areas with methamphetamine problems.

The mothers in the methamphetamine-exposed group were more likely to have a lower SES and social-position index, live in a household earning less than \$10 000/year, have public insurance, be without a partner, and be educated <12 years. In addition, mothers in the methamphetamine-exposed group were younger, sought prenatal care later in gestation, had fewer prenatal care visits, and gained more weight relative to the unexposed group. We examined the apparently unexpected effect that methamphetamine-using mothers had a higher mean weight gain relative to those in the unexposed group. We compared weight gain between mothers in the exposed group who used methamphetamine during the first or second trimester only ( $N = 46$  [56%]) versus those also using in the third trimester ( $N = 36$  [44%]). Those who quit using methamphetamine earlier in gestation gained 10 lb more than those who continued to use throughout pregnancy ( $P = .019$ ), suggesting that the anorexic effects of methamphetamine are limited to continuous use, and there may be a rebound in weight gain if the mother quits.

Tobacco, alcohol, and marijuana exposures were higher in the methamphetamine-exposed group. On the basis of epidemiology at the time of recruitment, which

suggested that some methamphetamine users would also use cocaine, we enrolled subjects who were exposed to both methamphetamine and cocaine, which affected 11 (13%) of 84 in the exposed group. Preliminary analyses showed no differences in birth weight or prevalence of SGA between methamphetamine-exposed infants who were also exposed to cocaine versus those who were unexposed ( $P > .05$  in both cases). In addition, there were no differences in any maternal and infant characteristics shown in Table 1 ( $P$  values  $>.05$ ). Thus, we included subjects who were exposed to both methamphetamine and cocaine in the analyses of this study.

The gestational age at birth was lower in the methamphetamine-exposed infants relative to those in the unexposed group (mean  $\pm$  SD:  $38.7 \pm 2.4$  weeks [range: 30–43 weeks] vs  $39.2 \pm 1.9$  weeks [range: 25–44 weeks];  $P = .02$ ). The incidence of neonates born at <37 weeks' gestation was higher in the methamphetamine-exposed group than in the unexposed group (12.5% vs 6.5%;  $P = .036$ ). There was no difference in gender distribution between the groups (55% vs 51% males in the methamphetamine-exposed and unexposed groups, respectively;  $P = .478$ ).

The birth weights of those in the 2 groups are shown in Fig 1. Relative to unexposed neonates, methamphetamine-exposed neonates had lower birth weights ( $P < .05$ ). Similar findings resulted from the linear regression. When adjusted for covariates, younger gestational age, male gender, <5 prenatal care visits, annual household income less than \$10 000, prenatal tobacco exposure, low maternal weight gain, younger maternal age, and being without a partner contributed to lower birth weight (Table 2).

The incidence of SGA was higher in the methamphetamine-exposed neonates (19%) than in those in the unexposed group (8.5%) (Fig 2). Similar findings resulted from the logistic-regression analyses. Neonates in the methamphetamine-exposed group were 3.5 times

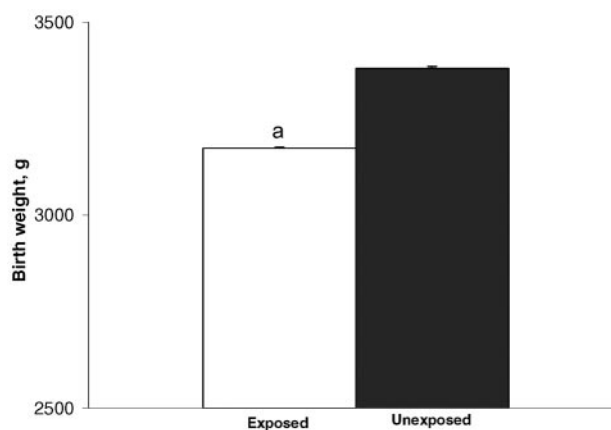
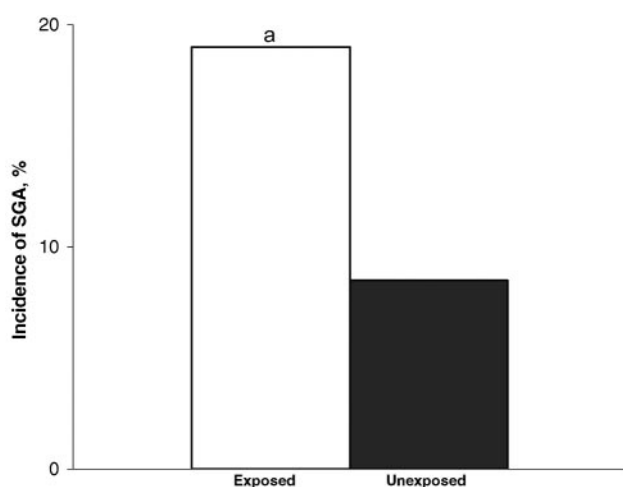


FIGURE 1  
Birth weight (mean  $\pm$  SEM) in the methamphetamine-exposed and unexposed groups.  
<sup>a</sup>  $P < .05$ .

**TABLE 2** Results of Adjusted Linear-Regression Model for the Association Between Birth Weight and Sociodemographic/Drug-Exposure Characteristics

Variables in the Model	Unstandardized Coefficients (SE)	Standardized Coefficients	P
Methamphetamine exposure status	−140.34 (58.78)	−0.05	.017
Gestational age (estimated)	171.44 (6.06)	0.57	.000
Gender, male	125.63 (21.75)	0.12	.000
Prenatal care (<5 visits)	143.87 (72.37)	0.04	.047
Household income (less than \$10 000)	−79.57 (36.39)	−0.05	.029
Prenatal marijuana exposure	−40.72 (51.44)	−0.02	.429
Prenatal tobacco exposure	−87.12 (29.24)	−0.07	.003
Prenatal alcohol exposure	−19.11 (27.32)	−0.02	.484
Mother's weight gain	6.02 (0.74)	0.17	.000
Mother's age (y)	9.40 (2.19)	0.10	.000
SES, Hollingshead index	−0.38 (1.04)	−0.01	.715
Have a partner	86.22 (27.58)	0.07	.002



**FIGURE 2** The incidence of SGA in the methamphetamine-exposed and unexposed groups. <sup>a</sup>  $P < .05$ .

more likely to be SGA than those in the unexposed group (Table 3). Consistent with birth weight findings, lower maternal weight gain and prenatal tobacco exposure were associated with a higher incidence of SGA. In contrast to the birth weight findings, male gender, having <5 prenatal care visits, annual household income less than \$10 000, younger maternal age, and being without a partner did not contribute to the increased incidence of SGA.

## DISCUSSION

Despite the rapidly emerging methamphetamine-abuse problem, data regarding the effects of prenatal methamphetamine exposure on fetal growth are limited. This is the first prospective investigation reporting the effects of prenatal methamphetamine exposure on fetal growth. We found that methamphetamine exposure in utero was associated with decreased growth parameters in newborns. After adjusting for covariates, there was an increased incidence of SGA and lower birth weight in

the exposed neonates. These findings suggest direct methamphetamine-induced growth-restrictive effects on the developing fetus.

Our findings that in utero methamphetamine exposure is associated with decreased birth weight are consistent with previous observations in children exposed to cocaine antenatally. Lower birth weight<sup>18,26–28</sup> and decreased head circumference relative to birth weight<sup>18,29,30</sup> have been reported in children exposed to cocaine prenatally. We also found an increased incidence of SGA in the methamphetamine-exposed newborns. The possible mechanisms of action for fetal growth restriction secondary to methamphetamine exposure are numerous and may arise from the direct and indirect effects of methamphetamine. In the ovine model, the vasoconstrictive effects of methamphetamine induced increases in maternal blood pressure and restriction of nutritional substrate for the developing fetus.<sup>31,32</sup> In addition, methamphetamine induced increases in fetal blood pressure and decreases in fetal oxyhemoglobin saturation and arterial pH in the ovine model.<sup>31,32</sup> Collectively, these maternal/placental effects of amphetamine could alter fetal growth and development.

Given our modest sample size, it is difficult to discern if the observed growth-restrictive effects in the methamphetamine group are related to the total dose of exposure or if certain periods of gestation are most critical for exposure to negatively impact growth. Retrospective data indicate that methamphetamine exposure throughout gestation is associated with decreased growth relative to infants exposed only for the first 2 trimesters.<sup>6</sup> Consistent with these findings, Bada et al<sup>17</sup> found that growth restriction in cocaine-exposed newborns was more pronounced as gestation approached term and remained significant even after adjusting for coexposure of opiates, tobacco, alcohol, and marijuana.

In addition to the methamphetamine-associated growth-restrictive effects, we also found that maternal weight gain was associated with greater birth weight and

**TABLE 3** Results of the Adjusted Logistic-Regression Model for the Association Between the Incidence of SGA and Sociodemographic/Drug-Coexposure Characteristics

Variables in the Model	Unstandardized Coefficients (SE)	Odds Ratio (CI)	P
Methamphetamine exposure status	1.25 (.38)	3.48 (1.65–7.33)	.001
Gender, male	−0.14 (.19)	0.87 (0.60–1.26)	.455
Prenatal care (<5 visits)	−1.00 (.65)	0.37 (0.10–1.32)	.126
Household income (less than \$10 000)	0.19 (.27)	1.21 (0.72–2.04)	.473
Prenatal marijuana exposure	−0.38 (.42)	0.68 (0.30–1.54)	.357
Prenatal tobacco exposure	0.53 (.23)	1.70 (1.09–2.66)	.019
Prenatal alcohol exposure	−0.33 (.25)	0.72 (0.44–1.19)	.199
Mother's weight gain	−0.03 (.01)	0.98 (0.96–0.99)	.000
Mother's age (y)	−0.02 (.02)	0.98 (0.94–1.02)	.283
SES, Hollingshead index	−0.01 (.01)	0.99 (0.97–1.01)	.369
Have a partner	0.29 (.22)	1.33 (0.87–2.04)	.190

negatively correlated to the incidence of SGA. These observations are consistent with previous findings that maternal weight gain is positively correlated with fetal size.<sup>33,34</sup> However, we found greater maternal weight gain in the methamphetamine-using group. These apparently paradoxical findings that growth-restrictive effects were observed in the group with greater maternal weight gain may be explained by the variability regarding when methamphetamine was discontinued during pregnancy. Amphetamine is an anorectic agent, and poor maternal nutrition can significantly contribute to low birth weight. Discontinuation of methamphetamine often leads to significant weight gain during the newly abstinent period. As a group, the methamphetamine-using mothers gained a mean of 44 lb, significantly more than the recommended 35-lb weight gain during their pregnancy.<sup>35</sup> In addition, those who quit early in pregnancy gained 10 lb more than those who continued to use throughout their pregnancy, suggesting that the anorectic effects of methamphetamine are limited to continuous use, and there may be a rebound in weight gain if the mother quits. We speculate that the overall observation of increased maternal weight gain in the exposed group reflects excessive weight gain in women who abstained from methamphetamine for the majority of gestation. Another possible explanation for the increased maternal weight gain in the methamphetamine group is that lower SES was more prevalent in the exposed group. In a review of 144 published studies, Sobal and Stunkard<sup>36</sup> found that in developed societies, there is an inverse relationship between SES and obesity among women.

The incidence of smoking during pregnancy in our exposed group is higher than most other populations of illicit drug exposures and is a possible contributor to the decreased birth weight observed. Our findings that mothers who used tobacco during pregnancy were nearly 2 times more likely to have SGA infants is consistent with previous findings that infants born to women who smoke during pregnancy have an increased

incidence of low birth weight.<sup>19,37</sup> In addition, retrospective data from neonates exposed to methamphetamine found that coexposure to smoking significantly decreased growth parameters relative to neonates exposed to methamphetamine alone.<sup>6</sup> Nicotine may cause growth impairment secondary to vasoconstriction of the fetal umbilical arteries, as demonstrated in an ovine model.<sup>38</sup> Doppler-flow studies of pregnant women who smoke have demonstrated that nicotine decreases fetal blood flow in a dose-dependent manner.<sup>39</sup> Genetic susceptibility may also contribute to the nicotine-induced fetal growth-restrictive effects. Wang et al<sup>40</sup> identified targeted metabolic genes that modify the association between cigarette smoking and infant birth weight. Our findings also support previous findings that nicotine exposure, rather than marijuana, has a more pronounced effect on fetal growth.<sup>41,42</sup> However, because the incidence of marijuana use was relatively low in our study, it is possible that we were unable to detect differences in growth parameters.

There are several limitations to this investigation; therefore, these results should be interpreted with caution. First, length and head-circumference data were not available for the majority of the unexposed neonates, which limited the ability to determine if the growth restriction was symmetric or not. Second, our sample size is not large enough to discern the importance of total dose and timing of methamphetamine exposure during gestation on fetal growth. In addition, very few infants studied were premature; therefore, the effects of methamphetamine use on growth parameters at earlier gestations were not addressed.

## CONCLUSIONS

We found that prenatal exposure to methamphetamine resulted in decreased birth weight and a 3.5-fold increase in the incidence of SGA relative to unexposed newborns. These preliminary findings suggest that methamphetamine use is associated with growth restriction in neonates born at term. The increased incidence of

SGA in the methamphetamine-exposed group has significant long-term health and neurodevelopmental implications. Low birth weight infants have an increased risk of mortality and childhood morbidity.<sup>43</sup> In addition, children born SGA have an increased risk of developing type 2 diabetes and the metabolic syndrome later in life.<sup>44</sup> These adverse health outcomes have been theorized to be secondary to accelerated postnatal growth, which stresses the limited cell mass in the growth-restricted pancreas.<sup>44</sup> In addition to the potentially serious medical complications, children with decreased head circumference relative to age have an increased incidence of developmental problems including reading and problem-solving difficulties.<sup>45</sup> Children with poor prenatal and postnatal head circumference have the worst neurodevelopmental outcomes, but even children with small head circumference at birth with good postnatal head growth fare less well developmentally than appropriate-for-gestation control children.<sup>45</sup> Long-term follow-up is needed to determine if these growth-restricted children are at increased risk for future growth and/or neurodevelopmental deficits.

#### ACKNOWLEDGMENTS

This study was supported by National Institute on Drug Abuse grant 1R01DA014918 and in part by National Center on Research Resources grants 3 M01 RR00425 and P20 RR11091.

We gratefully acknowledge Monica Paz, BA, for assistance with the manuscript.

#### REFERENCES

- Eriksson M, Larsson C, Windbladh B, Zetterstrom R. The influence of amphetamine addiction on pregnancy and the newborn infant. *Acta Paediatr Scand*. 1978;67:95-99
- Eriksson M, Larsson G, Zetterstrom R. Amphetamine addiction and pregnancy. II. Pregnancy, delivery and the neonatal period: socio-medical aspects. *Acta Obstet Gynecol Scand*. 1981; 60:253-259
- Elliott RH, Rees GB. Amphetamine ingestion presenting as eclampsia. *Can J Anaesth*. 1990;37:130-133
- Samuels SI, Maze A, Albright G. Cardiac arrest during cesarean section in a chronic amphetamine abuser. *Anesth Analg*. 1979; 58:528-530
- Plessinger MA. Prenatal exposure to amphetamines: risks and adverse outcomes in pregnancy. *Obstet Gynecol Clin North Am*. 1998;25:119-138
- Smith L, Yonekura ML, Wallace T, Berman N, Kuo J, Berkowitz C. Effects of prenatal methamphetamine exposure on fetal growth and drug withdrawal symptoms in infants born at term. *J Dev Behav Pediatr*. 2003;24:17-23
- Oro AS, Dixon SD. Perinatal cocaine and methamphetamine exposure: maternal and neonatal correlates. *J Pediatr*. 1987; 111:571-578
- Little BB, Snell LM, Gilstrap LC III. Methamphetamine abuse during pregnancy: outcome and fetal effects. *Obstet Gynecol*. 1988;72:541-544
- Eriksson M, Jonsson B, Steneroth G, Zetterstrom R. Cross-sectional growth of children whose mothers abused amphetamines during pregnancy. *Acta Paediatr*. 1994;83:612-617
- Eriksson M, Zetterstrom R. Amphetamine addiction during pregnancy: 10-year follow-up. *Acta Paediatr Suppl*. 1994;404: 27-31
- Arria AM, Derauf C, LaGasse LL, et al. Methamphetamine and other substance use during pregnancy: preliminary estimates from the Infant Development, Environment, and Lifestyle (IDEAL) Study. *Matern Child Health J*. 2006;1-10
- Bauer CR, Shankaran S, Bada HS, et al. The Maternal Lifestyle Study: drug exposure during pregnancy and short-term maternal outcomes. *Am J Obstet Gynecol*. 2002;186:487-495
- Lester B, Tronick EZ, LaGasse L, et al. The Maternal Lifestyle Study: effects of substance exposure during pregnancy on neurodevelopmental outcome in 1-month-old infants. *Pediatrics*. 2002;110:1182-1192
- Hollingshead A. *Four Factor Index of Social Status*. New Haven, CT: Department of Sociology, Yale University; 1975
- LaGasse L, Seifer R, Wright LL, et al. The Maternal Lifestyle Study (MLS): the caretaking environment of infants exposed to cocaine/opiates [abstract]. *Pediatr Res*. 1999;45:247A
- Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol*. 1996;87:163-168
- Bada HS, Das A, Bauer CR, et al. Gestational cocaine exposure and intrauterine growth: Maternal Lifestyle Study. *Obstet Gynecol*. 2002;100:916-924
- Shankaran S, Das A, Bauer CR, et al. Association between patterns of maternal substance use and infant birth weight, length, and head circumference. *Pediatrics*. 2004;114(2). Available at: [www.pediatrics.org/cgi/content/full/114/2/e226](http://www.pediatrics.org/cgi/content/full/114/2/e226)
- Jacobson JL, Jacobson SW, Sokol RJ. Effects of prenatal exposure to alcohol, smoking, and illicit drugs on postpartum somatic growth. *Alcohol Clin Exp Res*. 1994;18:317-323
- Pearl M, Braveman P, Abrams B. The relationship of neighborhood socioeconomic characteristics to birthweight among 5 ethnic groups in California. *Am J Public Health*. 2001;91: 1808-1814
- Dubay L, Joyce T, Kaestner R, Kenney GM. Changes in prenatal care timing and low birth weight by race and socioeconomic status: implications for the Medicaid expansions for pregnant women. *Health Serv Res*. 2001;36:373-398
- Kleijer ME, Dekker GA, Heard AR. Risk factors for intrauterine growth restriction in a socio-economically disadvantaged region. *J Matern Fetal Neonatal Med*. 2005;18:23-30
- Vagero D, Koupilova I, Leon DA, Lithell UB. Social determinants of birthweight, ponderal index and gestational age in Sweden in the 1920s and the 1980s. *Acta Paediatr*. 1999;88: 445-453
- Lazariu-Bauer V, Stratton H, Pruzek R, Woelfel ML. A comparative analysis of effects of early versus late prenatal WIC participation on birth weight: NYS, 1995. *Matern Child Health J*. 2004;8:77-86
- US Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse. *National Pregnancy and Health Survey: Drug Use Among Women Delivering Live Births: 1992*. Bethesda, MD: National Institutes of Health; 1996. NIH Publication No. 96-3819
- Coles CD, Platzman KA, Smith I, James ME, Falek A. Effects of cocaine and alcohol use in pregnancy on neonatal growth and neurobehavioral status. *Neurotoxicol Teratol*. 1992;14:23-33
- Hadeed AJ, Siegel SR. Maternal cocaine use during pregnancy: effect on the newborn infant. *Pediatrics*. 1989;84:205-210
- Zuckerman B, Frank DA, Hingson R, et al. Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med*. 1989;320:762-768
- Little BB, Snell LM. Brain growth among fetuses exposed to cocaine in utero: asymmetrical growth retardation. *Obstet Gynecol*. 1991;77:361-364

30. Scafidi FA, Field TM, Wheeden A, et al. Cocaine-exposed preterm neonates show behavioral and hormonal differences. *Pediatrics*. 1996;97:851–855
31. Burchfield DJ, Lucas VW, Abrams RM, Miller RL, DeVane CL. Disposition and pharmacodynamics of methamphetamine in pregnant sheep. *JAMA*. 1991;265:1968–1973
32. Stek AM, Baker RS, Fisher BK, Lang U, Clark KE. Fetal responses to maternal and fetal methamphetamine administration in sheep. *Am J Obstet Gynecol*. 1995;173:1592–1598
33. Abrams B, Carmichael S, Selvin S. Factors associated with the pattern of maternal weight gain during pregnancy. *Obstet Gynecol*. 1995;86:170–176
34. Brown JE, Murtaugh MA, Jacobs DR, Jr, Margellos HC. Variation in newborn size according to pregnancy weight change by trimester. *Am J Clin Nutr*. 2002;76:205–209
35. Committee on Nutritional Status During Pregnancy and Lactation, Institute of Medicine. *Nutrition During Pregnancy*. Washington, DC: National Academy Press; 1990
36. Sobal J, Sunkard AJ. Socioeconomic status and obesity: a review of the literature. *Psychol Bull*. 1989;105:260–275
37. Kramer MS. Intrauterine growth and gestational duration determinants. *Pediatrics*. 1987;80:502–511
38. Arbeille P, Bosc M, Vaillant MC, Tranquart F. Nicotine-induced changes in the cerebral circulation in ovine fetuses. *Am J Perinatol*. 1992;9:270–274
39. Lindblad A, Marsal K, Andersson KE. Effect of nicotine on human fetal blood flow. *Obstet Gynecol*. 1998;72:371–382
40. Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *JAMA*. 2002;287:195–202
41. Day N, Cornelius M, Goldschmidt L, Richardson G, Robles N, Taylor P. The effects of prenatal tobacco and marijuana use on offspring growth from birth through 3 years of age. *Neurotoxicol Teratol*. 1992;14:407–414
42. Fried PA, O'Connell CM. A comparison of the effects of prenatal exposure to tobacco, alcohol, cannabis and caffeine on birth size and subsequent growth. *Neurotoxicol Teratol*. 1987;9:79–85
43. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. *N Engl J Med*. 1985;312:82–90
44. Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull*. 2001;60:5–20
45. Frisk V, Amsel R, Whyte HE. The importance of head growth patterns in predicting the cognitive abilities and literacy skills of small-for-gestational-age children. *Dev Neuropsychol*. 2002;22:565–593

# The Infant Development, Environment, and Lifestyle Study: Effects of Prenatal Methamphetamine Exposure, Polydrug Exposure, and Poverty on Intrauterine Growth

Lynne M. Smith, Linda L. LaGasse, Chris Derauf, Penny Grant, Rizwan Shah, Amelia Arria, Marilyn Huestis, William Haning, Arthur Strauss, Sheri Della Grotta, Jing Liu and Barry M. Lester

*Pediatrics* 2006;118;1149-1156

DOI: 10.1542/peds.2005-2564

<b>Updated Information &amp; Services</b>	including high-resolution figures, can be found at: <a href="http://www.pediatrics.org/cgi/content/full/118/3/1149">http://www.pediatrics.org/cgi/content/full/118/3/1149</a>
<b>References</b>	This article cites 40 articles, 18 of which you can access for free at: <a href="http://www.pediatrics.org/cgi/content/full/118/3/1149#BIBL">http://www.pediatrics.org/cgi/content/full/118/3/1149#BIBL</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>Therapeutics &amp; Toxicology</b> <a href="http://www.pediatrics.org/cgi/collection/therapeutics_and_toxicology">http://www.pediatrics.org/cgi/collection/therapeutics_and_toxicology</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.pediatrics.org/misc/Permissions.shtml">http://www.pediatrics.org/misc/Permissions.shtml</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://www.pediatrics.org/misc/reprints.shtml">http://www.pediatrics.org/misc/reprints.shtml</a>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

