EXPOSURE TO MARIJUANA DURING PREGNANCY ALTERS NEUROBEHAVIOR IN THE EARLY NEONATAL PERIOD

Marina Carvalho de Moraes Barros, MD, PhD, Ruth Guinsburg, MD, PhD, Clovis de Araújo Peres, PhD, Sandro Mitsuhiro, MD, Elisa Chalem, and Ronaldo Ramos Laranjeira, MD, PhD

Objective To assess the neurobehavior of full-term neonates of adolescent mothers exposed to marijuana during pregnancy.

Study design This prospective cross-sectional study included full-term infants within 24 to 72 hours of life born to adolescent mothers at a single center in Brazil. Data on sociodemographic and obstetrical and neonatal characteristics were collected. The mothers underwent the Composite International Diagnostic Interview, and the infants were assessed with the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS). Maternal hair and neonatal meconium were analyzed. Neonates exposed in utero to tobacco, alcohol, cocaine, and/or any other drugs except marijuana were excluded.

Results Of 3685 infants born in the study hospital, 928 (25%) were born to adolescent mothers. Of these, 561 infants met the inclusion criteria and were studied. Marijuana exposure was detected in 26 infants (4.6%). Infants exposed (E) or not exposed (NE) to marijuana differed in the following NNNS variables: arousal (E, 4.05 ± 1.19 vs NE, 3.68 ± 0.70), regulation (E, 5.75 ± 0.62 vs NE, 6.04 ± 0.72), and excitability (E, 3.27 ± 1.40 vs NE, 2.40 ± 1.57). After controlling for confounding variables, the effect of marijuana exposure on these scores remained significant.

Conclusions Marijuana exposure during pregnancy alters the neurobehavioral performance of term newborn infants of adolescent mothers. *(J Pediatr 2006;149:781-7)*

Each year, approximately 900,000 teenagers become pregnant in the United States. Despite decreasing rates of teenage pregnancy, more than 4 in 10 adolescent girls will have been pregnant at least once before age 20.[1] In 1992, for every 1000 females age 15 to 19, there were 4 births in Japan, 8 in the Netherlands, 33 in the United Kingdom, 41 in Canada, and 61 in the United States.[2] Adolescent pregnancy has been associated with poverty, unmarried status, low educational levels, smoking, drug use, and inadequate prenatal care.[3] In Brazil, there were 3,059,402 live births in 2002, 23% of which involved mothers between age 10 and 19.[4]

Studies from the US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration[5] report abuse of illicit drugs during gestation in 3.3% of American women, 80% of whom use marijuana. According to the National Household Survey on Drug Abuse,[6] 2.8% of pregnant women use illicit drugs. Marijuana is used by 75% of these women during gestation, and more than 50% also use alcohol and tobacco along with marijuana. In Brazil, data regarding drug abuse during gestation are sparse and focused primarily on cocaine abuse. Magalhães et al[7] found maternal drug abuse in 1.4% of 2173 live births, and marijuana was used by 36% of the mothers in 1 maternity hospital in São Paulo in 1997.

The fetal and neonatal effects of drug abuse by pregnant women depend on several factors, including the effects of the drug(s) per se and such other variables as nutrition, risk of sexually transmitted diseases, quality of prenatal care, and other factors.[8,9] The objective of this study was to compare the neurobehavior of full-term newborn infants of adolescent mothers on the second/third day of life with regard to maternal use of marijuana during gestation.

METHODS

This cross-sectional study with prospective data collection was performed in the Mário de Moraes Altenfelder Silva Maternity Hospital, a third–level, city-owned hospital

CIDI	Composite International Diagnostic Interview	NNNS	Neonatal Intensive Care Unit Network Neurobehavioral Scale

See editorial, p 742

From the Division of Neonatal Medicine, Division of Biostatistics, and Research Unit on Alcohol and Drugs, Federal University of São Paulo, São Paulo, Brazil.

Fully funded as a thematic project by the State of São Paulo Research Support Foundation (grant 2000/10293-5).

None of the authors has any conflict of interest to declare.

Submitted for publication Dec 5, 2005; last revision received May 25, 2006; accepted Aug 19, 2006.

Reprint requests: Ruth Guinsburg, Rua Vicente Felix 77, apt 09, São Paulo, SP, Brazil, 01410-020. E-mail: ruthgbr@netpoint.com.br.

0022-3476/$ - see front matter

10.1016/j.jpeds.2006.08.046

in São Paulo, Brazil. The study was approved by the hospital and by the Federal University of São Paulo Ethical Committee and was funded by a grant from the State of São Paulo Research Support Foundation.

A neonate was included in the study after written informed consent was obtained from the mother if the following criteria were met: an adolescent mother between age 10 and 20 years[10] and a full-term infant, defined as gestational age between 37 weeks and 41 weeks, 6 days according to the best obstetric estimate or using the new Ballard method.[11] Any neonate with conditions that could potentially interfere with neurobehavioral assessment was excluded, such as a positive maternal serology for syphilis, toxoplasmosis, cytomegalovirus, or human immunodeficiency virus; maternal use of opioids, sedatives, and/or anticonvulsants during the 24 hours before delivery; use of systemic anesthesia during delivery; Apgar score < 3 at 1 minute or < 7 at 5 minutes of life; major congenital malformations; fetal exposure to tobacco (any cigarette), alcohol (more than 1 special occasion/month), cocaine, and/or other illicit drugs; and the need for monitoring vital signs, oxygen, incubators, venous infusions, phototherapy, or medications on the day of the study.

Neonates and their mothers were studied by a team of neonatologists, psychologists, and psychiatrists. A neonatologist performed a maternal interview, collecting data related to the sociodemographic and obstetrical characteristics of the adolescent mother. The psychologists administered the Composite International Diagnostic Interview (CIDI 2.1)[12] to the mother. The neonate had a clinical evaluation related to birth and clinical course. A neonatologist performed a neurobehavioral assessment of the neonate using the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS).[13] Maternal hair and neonatal meconium samples were collected for analysis of marijuana and cocaine metabolites.

The NNNS evaluates neurologic integrity, behavioral function, and the presence of stress and abstinence signs in the neonate.[13] The NNNS was administered between 24 hours and 72 hours of life by 1 of 4 trained neonatologists in a room that was warm, calm, and free of intense light. The first author was certified to perform the NNNS at Women and Infants Hospital, Brown University, and then trained the other neonatologists. After a complete NNNS evaluation, items were assessed and grouped into 13 variables according to Lester and Tronick[13]: habituation, attention, arousal, regulation, handling, quality of movement, excitability, lethargy, nonoptimal reflexes, asymmetry, hypertonicity, hypotonicity, and stress/abstinence signals.

Maternal hair and neonatal meconium were analyzed for metabolites of marijuana and cocaine. Approximately 50 hairs from each mother were cut near the scalp in the parietal-occipital region and stored in laminated packs. The 3-cm segment near the scalp was tested by semiquantitative enzymatic immunoassay, with cutoff values of 0.1 ng/mg of hair for cannabinoids and 1.0 ng/mg of hair for benzoylecgonine. All positive hair results were confirmed by gas chromatography and mass spectrometry. The sample was considered positive when both screening and confirmatory tests were positive. To avoid false-positive findings for marijuana due to environmental contamination, decontamination procedures were performed. All tests were done after initial decontamination of the samples with methanol, followed by aqueous washes.[14]

Meconium samples were collected during the first 48 hours of life to avoid decreased concentration of drugs metabolized in the gestational period[15] according to Mectest procedural guidelines (Mectest Corp) and analyzed by homogeneous semiquantitative enzymatic immunoassay (EMIT), with cutoff values of 200 ng/mL for cannabinoids and 300 ng/mL for benzoylecgonine. No further confirmatory tests were done for positive results in meconium.

During the NNNS examination, all examiners were blinded regarding infant drug exposure status during pregnancy. Results of maternal interviews and toxicology analysis of hair and meconium were known only after data collection was completed.

Mean, standard deviation, median, and 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles for each of 13 NNNS variables were determined for the entire study population. Comparison of maternal and neonatal characteristics among neonates exposed (E) and not exposed (NE) to marijuana during gestation was done using the χ^2 test for categorical variables and Student's t test for numerical variables. Comparisons of NNNS scores were done using Student's t test.

NNNS variables found to significantly differ in E and NE neonates were further analyzed by multiple linear regression. Independent variables were chosen among those with the potential to interfere in neonatal neurobehavioral performance. Therefore, for each NNNS variable that differed significantly between E and NE neonates, univariate analysis of the related scores was conducted according to anesthesia during delivery (spinal/local anesthesia vs no anesthesia), type of delivery (vaginal vs C-section), nutritional status at birth (appropriate vs small for gestational age),[16] sex (female vs male), 1- minute Apgar score, gestational age (weeks), and postnatal age (hours). Analysis of variance and correlation tests were used to verify the association between categorical and numerical variables, respectively, with the NNNS variable score. The independent variables with P value $< .20$ were analyzed by stepwise multiple linear regression models using the least squares method with the backward-elimination strategy.

The sample size was determined according to the need to include 15 neonates for each independent variable analyzed in the regression models. Because for each of the 13 NNNS variables considered dependent variables, at least 11 independent categorical variables and 5 continuous independent variables were analyzed, the minimum sample size was 240. All statistical procedures were performed using SPSS version 10.0 (SPSS Inc, Chicago, IL).

Table I. Demographic characteristics of the adolescent mothers

	Marijuana use during gestation		
	Absent (n = 534)	Present (n = 26)	*P* value
Maternal age	16.9 ± 1.5	16.5 ± 1.5	.216
White race	258 (48%)	18 (68%)	.044
Married	347 (65%)	17 (64%)	1.000
Years in school	7.3 ± 2.2	6.8 ± 2.1	.271
Per capita income (R$ per month)	198 ± 153	188 ± 103	.756
Number of gestations	1.3 ± 0.6	1.1 ± 0.3	.201
Prenatal care			
Yes	515 (96%)	26 (100%)	1.000
Number of visits	6.8 ± 2.7	6.6 ± 2.3	.640
Problems during gestation			
Urinary tract infection	153 (29%)	10 (38%)	.393
Hypertension	74 (14%)	5 (18%)	.394
Diabetes	2 (0.4%)	0	1.000
Premature onset of labor	19 (3.6%)	0	1.000
Vaginal delivery	389 (73%)	18 (69%)	.657
Spinal anesthesia	390 (73%)	22 (84%)	.256

RESULTS

Between July 2001 and November 2002, a total of 3685 infants were born at the study hospital, 928 (25%) to adolescent mothers. Of these, 367 infants met 1 or more exclusion criteria: 126 had gestational age < 37 weeks or > 42 weeks, 20 had maternal positive serology for 1 or more congenital infections, 102 had maternal tobacco use, 6 had maternal alcohol use in excess of 1 occasion/month, and 10 had maternal cocaine use during pregnancy, 28 had maternal systemic use of analgesics and/or sedatives at labor or delivery, 16 had low Apgar scores at 1 and 5 minutes, 4 had major congenital malformations, and 75 needed medical or nursing procedures in the second or third days of life. Consequently, a total 561 full-term neonates born from 560 adolescent mothers (1 twin gestation) were studied. Isolated marijuana exposure during pregnancy was detected in 26 neonates (4.6%), 23 by maternal hair analysis, 2 by neonatal meconium analysis, and 1 by maternal interview.

The general characteristics of the adolescent mothers classified according to marijuana use are listed in Table I. The mothers were typically in their first pregnancy, but 95 (17.0%) were in their second gestation, 16 (2.9%) in their third gestation, and 6 (1.1%) in their fourth gestation. Almost all mothers received prenatal care. The E and NE neonates were similar in terms of gestational age, birth weight, length, head circumference, and sex (Table II). Both groups had a mean Apgar score of 8 at 1 minute and 9−10 at 5 minutes of life. The neonates were typically discharged from hospital in the second or third day of life.

The NNNS was administered at 24 to 72 hours of life (mean, 33 hours) (Table III). Each neonatologist examined 25% of the population studied. The mean duration of the exam was 22 minutes. Rooming-in care was the standard for 488 neonates (73%). No significant differences in these variables between the E and NE neonates were found. The neurobehavioral assessment did reveal that the E neonates had higher scores for arousal and excitability and lower scores for regulation compared with the NE neonates (Table IV). That is, the E neonates were more irritable and less responsive to calming maneuvers by the examiner, cried more during the examination, and exhibited more jitteriness and startles than the NE neonates.

Univariate analysis of potential factors that could affect the NNNS arousal score showed that the following had no significant effect: anesthesia during delivery (P = .675), type of delivery (P = .874), nutritional status at birth (P = .669), sex (P = .177), and 1- minute Apgar score (r = .2%; 95% confidence interval [CI] = −8.1 to 8.5; P = .970). A correlation was observed between arousal score and gestational age (r = 13.8%; 95% CI = 5.6 to 21.8; P = .001) and hours of life (r = 14.2%; 95% CI = 6.0 to 22.2; P = .001). Therefore, a multiple linear regression model was adjusted with arousal score as the dependent variable and marijuana use during pregnancy, sex, gestational age, and hours of life as independent variables (Table V). The E neonates had higher arousal scores when adjusting for sex, gestational age, and postnatal age. This model explained 6.1% of the variability in the arousal scores (r^2 = .061).

Univariate analysis of potential factors that could affect the NNNS regulation score revealed that the following variables had no significant effect: anesthesia during delivery (P = .733), type of delivery (P = .369), nutritional status at birth (P = .201), sex (P = .340), 1-minute Apgar score (r = −1.2%; 95% CI = −9.5% to 7.1%; P = .786), gestational age (r = 0.31%; 95% CI = −5.2 to 11.3; P = .460), and hours of life (r = 3.8%; 95% CI = −4.5 to 12; P = .375). Therefore, a multiple linear regression model was adjusted with regulation score as the dependent variable and marijuana use during pregnancy and nutritional status at birth as independent variables. The final regression model showed that only marijuana

Table II. Demographic characteristics of the neonates

	Marijuana use during gestation		
	Absent (n = 535)	Present (n = 26)	*P* value
Gestational age (weeks)	39.3 ± 1.1	39.1 ± 1.1	.512
Birth weight (g)	3120 ± 409	3095 ± 405	.757
Length (cm)	48.4 ± 1.9	48.1 ± 1.9	.493
Head circumference (cm)	34.1 ± 1.3	34.1 ± 1.3	.984
Gestational age versus birth weight			
Adequate	409 (76%)	18 (71%)	.544
Small	111 (21%)	8 (29%)	.330
Large	15 (3%)	0	1.000
Female	258 (48%)	12 (46%)	1.000
Apgar at 1 minute	8.1 ± 1.3	8.5 ± 1.3	.218
Apgar at 5 minutes	9.6 ± 0.6	9.7 ± 0.6	.195
Medical problems in neonatal period			
Jaundice	150 (28%)	10 (36%)	.354
Transient respiratory distress	116 (22%)	6 (21%)	.940
Hypoglycemia	4 (0.7%)	0	1.000
Days in hospital	2.5 ± 0.9	2.4 ± 0.9	.510

Table III. Neonatal characteristics at the NNNS assessment

	Marijuana use during gestation		
	Absent (n = 535)	Present (n = 26)	*P* value
Postnatal age (hours)	33.1 ± 6.9	33.2 ± 6.1	.942
Length of assessment (minutes)	22.2 ± 5.3	25.2 ± 6.3	.005
Time after feeding (minutes)	51.2 ± 54.5	33.8 ± 28.0	.114
Time of rooming-in (hours)	25.4 ± 11.1	21.3 ± 9.6	.165

Table IV. NNNS scores in the study population

	Marijuana use during gestation		
	Absent (n = 535)	Present (n = 26)	*P* value
Habituation*	6.89 ± 1.50	6.91 ± 1.11	.962
Attention†	5.69 ± 1.31	5.30 ± 1.19	.160
Arousal	3.68 ± 0.70	4.05 ± 0.60	.009
Regulation	6.04 ± 0.72	5.75 ± 0.62	.048
Handling	0.36 ± 0.26	0.44 ± 0.28	.132
Quality of movement	5.22 ± 0.45	5.10 ± 0.64	.181
Excitability	2.40 ± 1.57	3.27 ± 1.40	.006
Lethargy	4.19 ± 1.95	4.04 ± 1.97	.691
Nonoptimal reflexes	3.71 ± 1.36	3.46 ± 1.24	.370
Asymmetry	0.72 ± 0.93	0.85 ± 0.83	.482
Hypertonicity	0.17 ± 0.38	0.08 ± 0.27	.232
Hypotonicity	0.13 ± 0.37	0.04 ± 0.20	.213
Stress/abstinence signals	0.07 ± 0.05	0.08 ± 0.06	.155

*Habituation was scored in 322 neonates in the absent group and in 18 neonates in the present group.
†Attention was scored in 490 neonates in the absent group and in 24 neonates in the present group.

exposure was significantly associated with the regulation score by the following equation: Regulation score = 6.04 − 0.287*marijuana (P = .48; r^2 = .007).

Univariate analysis of potential factors that could affect the NNNS excitability score showed that the following variables had no significant effect: anesthesia during delivery (P =

Table V. Final multiple linear regression models for NNNS arousal and excitability scores

	Coefficient	Standard error	*P* value
Arousal scores			
Marijuana use during pregnancy	0.380	0.136	.005
Sex	4.023	2.013	.046
Gestational age	0.142	0.037	<.001
Postnatal age	0.014	0.004	.001
Gestational × postnatal age	−0.104	0.051	.043
Excitability scores			
Marijuana use during pregnancy	0.886	0.313	.005
Gestational age	0.123	0.059	.037

.710), type of delivery ($P = .916$), nutritional status at birth ($P = .862$), sex ($P = .224$), and 1-minute Apgar score ($r = -.9\%$; 95% CI = −9.2 to 7.4; $P = .832$). A significant correlation was observed between excitability score and gestational age ($r = 8.4\%$; 95% CI = 0.1 to 16.6; $P = .046$), and a marginal correlation was found between excitability score and postnatal age ($r = 7.4$; 95% CI = −0.9 to 15.6; $P = .082$). Therefore, a multiple linear regression model was adjusted with excitability score as the dependent variable and marijuana use during pregnancy and gestational and postnatal age as independent variables (Table V). The E neonates had a higher excitability score, after adjusting for gestational age. This model explains 2.1% of the variability in the excitability scores ($r^2 = .0211$).

DISCUSSION

The high adolescent pregnancy rate in this study (25% of all pregnant women admitted to the hospital) was similar to Brazilian rates[4] and to the rates reported in other studies.[17-20] Marijuana use in this population of pregnant adolescents was 4.6%, almost double that seen in American teenagers.[5,6] It is noteworthy that only 1 among the 26 mothers who used marijuana during pregnancy revealed this fact during the interview, even though the interviewers were trained psychologists who applied questionnaires free of prejudicial questions about difficult issues regarding behavior of teenagers. Identification of marijuana use was determined mainly by toxicology analysis of the proximal segment of the maternal hair, meaning that marijuana was used around 3 to 5 months before delivery. Contamination of hair by environmental marijuana was avoided by vigorous methanol washing of samples before analysis.[14] Methanol decontamination procedure removes cannabinoids from untreated and permed hair.[21] Dichloromethane seems superior to methanol when applied to apparently dry hair.[21] However, dichloromethane treatment reduces the measured concentration of cannabinoid in hair, whereas methanol washes do not appear to affect the results.[22] Agreement of results between the hair and meconium tests was poor, probably because hair analysis can detect marijuana use during the months before delivery, whereas meconium analysis was performed on a single sample collected in the first 2 days of life.[23]

Prolonged fetal exposure to marijuana can result if the mother smokes the drug regularly, because tetrahydrocannabinol crosses the placenta and can be detected in fetal tissues up to 30 days after an isolated maternal use of the drug.[24] A weak negative association between marijuana use and neonatal length has been reported.[25,26] A meta-analysis of 10 studies found that maternal marijuana use at a frequency of 4 or more times per day reduced birth weight by 131 g (95% CI = 52 to 209 g).[27] Our analysis found no differences in birth weight, length, and head circumference between full-term neonates exposed or not exposed to marijuana. It is possible that excluding premature neonates from the analysis masked this effect; Gibson et al[28] observed a reduced duration of gestation of 0.8 week and a 25% incidence of premature delivery in women who smoked marijuana 6 or more times per week.

Tetrahydrocannabinol activates mesolimbic dopamine transmission in the central nervous system;[29] this activity during fetal life may be related to neurobehavioral alteration in the first days of life. Therefore, the objective of our investigation was to study such neonatal neurobehavioral alterations in the first days of life and relate them to maternal marijuana use during gestation. To accomplish this goal, we used the NNNS. This scale was developed to assess prospectively, in cohort studies, the effects of neonatal exposure to drugs during gestation.[30] The results, controlled for potential confounding variables, show that exposure to marijuana during pregnancy was associated with subtle behavioral changes, especially in terms of arousal, regulation, and excitability, which can potentially interfere with the ability of these neonates to bond with their teenage mothers. The fact that the exposed neonates required more time for testing supports the NNNS results; had they been more aroused and excitable, they may have been more difficult to test. As expected with subjective behaviors tested once in the first days of life, several factors can explain the variability of the scores. Marijuana exposure during fetal life, although significantly associated with this variability, can explain only a small part of these behaviors.

Other studies have also found poor neurobehavioral performance in neonates exposed to marijuana during gestation. Fried and Makin[31] observed jitteriness and exaggerated and prolonged startles in response to external stimuli, along with increased motor reflex response and decreased habituation capacity to visual stimuli, in the neonates exposed to marijuana during pregnancy. Coles et al[32] evaluated the effects of the maternal use of drugs during gestation in 107 full-term neonates at 2, 14, and 28 days of life using Brazelton's behavioral scale. Marijuana exposure during gestation was associated with a decreased capacity to focus and follow external stimuli at 14 days of life, as well as with increased difficulty in self-regulating the state of arousal at 28 days. Scher et al[33] showed that neonates exposed to marijuana during gestation demonstrated more disturbances in neonatal sleep cycling, with less rapid-eye-movement sleep and longer periods of indeterminate sleep.

Results related to the neurobehavioral performance of neonates exposed to marijuana during gestation are not uniform in the literature. Tennes et al[34] and Richardson et al[35] observed no behavioral consequences from fetal exposure to marijuana in neonates. A case-controlled study of neonatal effects of maternal marijuana use in Jamaica, where marijuana use has cultural, medicinal, and religious links, found no neurobehavioral abnormalities in the third day of life in infants exposed to marijuana during gestation;[36] however, at 30 days of life, these infants had better neurobehavior performance regarding autonomic stability and self-control of arousal state. The authors suggested that the improved performance at the end of the first month of life is probably related to environmental factors, because marijuana users in Jamaica have better socioeconomical and educational status. These 3 studies did not apply the NNNS, and the statistical treatment of the different confounding factors was variable.

Our results presented in this report are consistent with the action of an active metabolite of marijuana in the central nervous system during gestation with behavioral consequences documented after birth. The activity of the mesolimbic dopaminergic pathways during fetal life and early infancy could modify nervous system function in the long term. At school age, children exposed to marijuana during gestation have poorer visual-spatial ability and decreased control of impulses and attention, especially as it relates to the capacity for planning, hypothesis testing, and problem solving.[37]

The fact of being born to adolescent mothers alone may explain the neurobehavioral assessment results. Comparison of the NNNS results from our group of neonates not exposed to marijuana to those for healthy neonates of nonadolescent mothers published by Lester and Tronick[13] shows similar scores for habituation, attention, arousal, regulation, handling, excitability, lethargy, nonoptimal reflexes, asymmetry, hypertonicity, hypotonicity, and stress/abstinence signals. The NNNS scores reported in this study were distributed between the 10th and 95th percentiles of the normative data, except for quality of movements. Healthy neonates of adolescent mothers had higher quality of movement scores, meaning that they had better performance on this item. Therefore, the neurobehavioral evaluation of healthy neonates in the first days of life does not differ based on whether or not their mothers are adolescents.

The present study has several strengths regarding methodological issues, but its main limitation is the cross-sectional design, which precludes any speculation about long-term consequences of neurobehavioral findings in neonates exposed to marijuana in utero. Despite this limitation, the NNNS evaluation is an effective tool in identifying subtle changes related to marijuana abuse during pregnancy. It is necessary to counter the misconception that marijuana is a "benign drug" and to educate women regarding the risks and possible consequences related to its use during pregnancy.

We thank the Maternity Hospital Mário de Moraes Altenfelder Silva staff for their help with data collection and Adriana Sanudo for her help with the statistical analyses.

REFERENCES

1. Kirby D. Emerging answers: research findings on programs to reduce teen pregnancy (summary). Washington, DC: National Campaign to Prevent Teen Pregnancy; 2001.

2. Klein JD, Committee on Adolescence. Adolescent pregnancy: current trends and issues. Pediatrics 2005;116:281-6.

3. Fraser AM, Brockert JE, Ward RH. Association of young maternal age with adverse reproductive outcomes. N Engl J Med 1995;332:1113-7.

4. http//datasus.gov.br. Accessed November 23, 2005.

5. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration. Women and substance use, National Survey on Drug Use and Health results, 2002. Available at http://oas.samhsa.gov/NHSDA/2k2NSDUH/Sect7peTabs54to61.pdf. Accessed November 20, 2005.

6. Ebrahim SH, Gfroerer J. Pregnancy-related substance use in the United States during 1996-1998. Obstet Gynecol 2003;101:374-9.

7. Magalhães M, Beani J, Silva L. Maternal drug abuse: effects on the fetus and neonate. In proceedings of the Fourth World Congress of Perinatal Medicine, Buenos Aires, Argentina, 1999; p 821-4.

8. Funkhouser AW, Butz AM, Feng TI, McCaul ME, Rosenstein BJ. Prenatal care and drug use in pregnant women. Drug Alcohol Depend 1993;33:1-9.

9. Hawthorne JL, Maier RC. Drug abuse in an obstetric population of a mid-sized city. South Med J 1993;86:1334-8.

10. World Health Organization. Problemas de salud de la adolescencia: informe de um comitê de expertos de la OMS. Informe Técnico 308. Ginebra: OMS; 1977.

11. Ballard JL, Khoury JC, Weidig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score expanded to include extremely premature infants. J Pediatr 1991;119:417-23.

12. World Health Organization. Composite International Diagnostic Interview (CIDI 2.1). Geneva, Switzerland: World Health Organization; 1997.

13. Lester BM, Tronick EZ. The Neonatal Intensive Care Unit Network Neurobehavioral Scale. Pediatrics 2004;113:631-99.

14. Society of Hair Testing. Consensus on hair analysis. Available at http//soht.org. Accessed March 10, 2006.

15. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr 1989;15:474-7.

16. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstet Gynecol 1996;87:163-8.

17. Gama SGN, Szwarcwald CL, Leal MC. Pregnancy in adolescence, associated factors and perinatal results among low-income post-partum women. Cad Saude Publica 2002;18:153-61.

18. Sabroza AR, Leal MC, Gama SGN, Costa JV. A socioeconomic and psychosocial profile of post-partum adolescents in the City of Rio de Janeiro, Brazil, 1999–2001. Cad Saude Publica 2004;20:S112-20.

19. Simões VM, da Silva AA, Bettiol H, Lamy-Filho F, Tonial SR, Mochel EG. Characteristics of adolescent pregnancy in São Luis, Maranhão, Brazil. Rev Saude Publica 2003;37:559-65.

20. Aquino EML, Heilborn ML, Knauth D, Bozon M, Almeida MC, Araújo J, et al. Adolescence and reproduction in Brazil: the heterogeneity of social profiles. Cad Saúde Publica 2003;19:S377-88.
21. Thorspecken J, Skopp G, Potsch L: In vitro contamination of hair by marijuana smoke. Clin Chem 2004;50:596-602.
22. Chiarotti M, Costamagna L. Analysis of 11-nor-9-caboxy-delta(9)-tetrahydrocannabinol in biological samples by GC/MS-MS. Forensic Sci Int 2000;114:1-6.
23. Ostrea EM Jr, Knapp DK, Tannenbaum L, Ostrea AR, Romero A, Salari V, et al. Estimates of illicit drug use during pregnancy by maternal interview, hair analysis, and meconium analysis. J Pediatr 2001;138:344-8.
24. Kozer E, Koren G. Effects of prenatal exposure to marijuana. Can Fam Physician 2001;47:263-4.
25. Day NL, Cornelius M, Goldschmidt L, Richardson G, Robles N, Taylor P. The effects of prenatal tobacco and marijuana use on offspring growth from birth though 3 years of age. Neurotoxicol Teratol 1992;14:407-14.
26. Hurd YL, Wang X, Anderson V, Beck O, Minkoff H, Dow-Edwards D. Marijuana impairs growth in mid-gestation fetuses. Neurotoxicol Teratol 2005;27:221-9.
27. English DR, Hulse GK, Milne E, Holman CD, Bower CI. Maternal cannabis use and birth weight: a meta-analysis. Addiction 1997;92:1553-60.
28. Gibson GT, Baghurst PA, Colley DP. Maternal alcohol, tobacco and cannabis consumption and the outcome of pregnancy. Aust NZ J Obstet Gynaecol 1983;23:15-9.
29. Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. Science 1997;276:2048-50.
30. Lester BM, Tronick EZ, LaGasse LL, Seifer R, Bauer CR, Shankaran S, et al. The Maternal Lifestyles Study: effects of substance exposure during pregnancy on neurodevelopmental outcome in 1-month-old infants. Pediatrics 2002;110:1182-92.
31. Fried PA, Makin JE. Neonatal behavioral correlates of prenatal exposure to marijuana, cigarettes and alcohol in a low-risk population. Neurotoxicol Teratol 1987;9:1-7.
32. 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.
33. Scher MS, Richardson GA, Coble PA, Day NL, Stoffer DS. The effects of prenatal alcohol and marijuana exposure: disturbances in neonatal sleep cycling and arousal. Pediatr Res 1988;24:101-5.
34. Tennes K, Avitable N, Blackard C, Boyles C, Hassoun B, Holmes L, et al. Marijuana: prenatal and post-natal exposure in the human. NIDA Res Monogr 1985;59:48-60.
35. Richardson GA, Day NL, Goldschmidt L. Prenatal alcohol, marijuana, and tobacco use: infant mental and motor development. Neurotoxicol Teratol 1995;17:479-87.
36. Dreher MC, Nugent K, Hudgins R. Prenatal marijuana exposure and neonatal outcomes in Jamaica: an ethnographic study. Pediatrics 1994;93:254-60.
37. Fried PA, Watkinson B. Visuoperceptual functioning differs in 9- to 12-year-olds prenatally exposed to cigarettes and marijuana. Neurotoxicol Teratol 2000;22:11-20.
38. Goldschmidt L, Day NL, Richardson GA. Effects of prenatal marijuana exposure on child behavior problems at age 10. Neurotoxicol Teratol 2000;22:325-36.