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Impact of maternal substance use during pregnancy on childhood outcome

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Summary

The impact of maternal substance abuse is reflected in the 2002–2003 National Survey on Drug Use and Health. Among pregnant women in the 15–44 age group, 4.3%, 18% and 9.8% used illicit drugs, tobacco and alcohol, respectively. Maternal pregnancy complications following substance use include increases in sexually transmitted disorders, placental abruption and HIV-positive status. Effects on the neonate include a decrease in growth parameters and increases in central nervous system and autonomic nervous system signs and in referrals to child protective agencies. In childhood, behavioral and cognitive effects are seen after prenatal cocaine exposure; tobacco and alcohol have separate and specific effects. The ongoing use of alcohol and tobacco by the caretaker affects childhood behavior. Therefore, efforts should be made to prevent and treat behavioral problems as well as to limit the onset of drug use by adolescent children born to women who use drugs during pregnancy.

Keywords

Alcohol; Child medicine; Cocaine; Neonatal; Neurobehavioral outcome; Polydrug use; Tobacco

Introduction

Currently, about 11% of the adult population of the United States suffers from a substance-abuse problem during any one year. The cost to society of this drug use is estimated at over US$300 billion annually; this figure includes the costs of crime, heath-related problems and

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reduced work productivity. The impact of maternal substance abuse is reflected in the 2002–2003 National Survey on Drug Use and Health, which found that, of pregnant women aged 15–44, 4.3%, 18% and 9.8% used illicit drugs, tobacco and alcohol, respectively. In 2002, the approximate numbers of births complicated by maternal use of drugs were 172,934 for illicit drugs, 723,911 for tobacco and 394,129 for alcohol.[1] Thus, from the public health perspective, the impact of substance use during pregnancy in the United States extends far beyond the health of the mother and affects a large number of the unborn population.

In the 1980s, the 'war on drugs' associated with the crack-cocaine epidemic focused national attention on to the relationship between drug use and social and economic problems in society. Early reports on the effects of prenatal cocaine exposure created a public frenzy and prompted the myth about 'unfit to parent' women and their damaged 'crack babies'. This in turn had an impact on legal and policy decisions made by individual US States and affected women who use illegal drugs during pregnancy. However, studies performed since the 1980s have failed to support significant associations between prenatal cocaine exposure and the increased prevalence of serious newborn congenital malformations and medical complications at birth.

The focus of this paper is the impact of substance use on maternal, neonatal and preschool child outcome. Data from recent cohort studies, and from studies using state-of-the-art methods of documenting substance use, will be examined.

Acute maternal and neonatal effects

The risk of congenital malformations following fetal cocaine exposure was evaluated in a prospective study of 154 prenatally identified cocaine users and 154 controls matched for race, parenting and location of care.[2] It was noted that the infants who were exposed to cocaine *in utero* had a higher rate of premature birth, lower birth weights and smaller birth length and head circumference; however, no difference in the type or number of congenital abnormalities was noted between the cocaine-exposed and non-exposed infants.

The effects of cocaine exposure on neonatal cranial sonographic findings were evaluated in a prospective study (of 241 term infants) in which the level of exposure to cocaine was documented by meconium assay of metabolites.[3] After controlling for infant sex, gestational age and birth weight, and for maternal parity, ethnicity and drug use, the cranial sonographic findings in infants who received light cocaine exposure were similar to those seen in infants who were unexposed to cocaine. However, heavily cocaine-exposed infants had a higher risk of subependymal hemorrhage, with an adjusted odds ratio (OR) of 3.89 and 95% confidence interval (95% CI) of 1.45–10.35.

The impact of prenatal exposure to substance use on height, weight and head circumference at birth has been examined while controlling for multiple substance use and prenatal care. A study by Richardson et al.[4] compared women who received no prenatal care ($n = 98$) with women who had received prenatal care ($n = 295$) throughout pregnancy. The women who had not received prenatal care were interviewed at delivery. At the time of birth, it was noted that, in both groups, cocaine use in early pregnancy resulted in reduced gestational age, birth weight and head circumference after controlling for multiple covariates of cocaine use.

The impact of substance (polydrug) use was evaluated by Eyler et al.,[5] who matched 154 cocaine users with 154 non-users for race, parity, socioeconomic status and location of prenatal care. Substance use during pregnancy was evaluated by maternal history and a urine drug screen. It was noted that the amount of substance use during trimesters 2 and 3 impacted on the infant's growth measurements at birth. There was a negative relationship

between cocaine use in trimester 3 and birth length and head circumference; this effect remained after adjusting for the effects of marijuana, tobacco and alcohol.[5]

Radioimmunoassay of cocaine metabolites in maternal hair during the third trimester provides a more sensitive assessment of substance use during pregnancy than interview and urine assay. In a study of 240 infants, 136 of whom were not exposed to cocaine, 52 had low exposure and 52 had high exposure to cocaine.[6] It was noted that, after adjusting for the effects of infant birth weight, gestational age and sex, and for maternal height, weight-gain during pregnancy and other drug use, newborns with high exposure have a head circumference that is disproportionately smaller than birth weight, resulting in 'head-wasting'.

The largest study evaluating the impact of substance use on pregnancy outcome—the Maternal Lifestyle Study (MLS)—was developed in the early 1990s by the National Institutes of Child Health and Human Development (NICHD) NICU Neonatal Research Network with additional support from National Institute on Drug Abuse (NIDA). Against the backdrop of debate and controversy about the effects of prenatal cocaine exposure on child outcome, the MLS recognized that cocaine use by pregnant women is a marker variable for two critical factors that—in addition to prenatal cocaine exposure—can affect child outcome: the use of drugs other than cocaine and an inadequate caregiving environment.[7,8] The MLS was designed to address these and many other methodological issues in the field, including sample size, methods of drug detection, prematurity, other confounding variables (such as medical factors, interventions and protective services) and neurodevelopmental assessments that are sensitive to putative drug effects.

The study is ongoing and is being conducted in four sites: the University of Miami, the University of Tennessee at Memphis, Wayne State University and Brown University. Of 19,000 mothers screened between 1993 and 1995, approximately 11,800 agreed to participate. Drug exposure is determined by self-report and meconium toxicology with confirmatory analysis. The study is currently divided into four phases. The acute Phase I period extends through to hospital discharge. Phase II is a longitudinal follow-up of a subsample of 1388 exposed and comparison children between 1 month and 3 years of age. Phase III extends the follow-up to school performance at 7 years of age. Phase IV is evaluation from age 8 years to age 11.

In total, 8527 newborn meconium analyses were performed and a history of substance use by the mother taken. The prevalence of cocaine and opiate exposure was 10.7%. The confirmation of positive cocaine screens by Gas Chromatography Mass Spectrometry (GCMS) was 75.5%. It should be noted that in 38% of cases in which the meconium analysis was positive for cocaine/an opiate, the mother denied use. There was 66% agreement between positive meconium results and positive maternal report. Only 2% of the women used cocaine alone without any other drug. Polydrug use was very common and it was noted that women were 49 times more likely to use another drug if cocaine was used.[9]

The impact of both drug exposure during pregnancy and of short-term maternal outcomes was evaluated in the same study (MLS). A total of 19,079 mother–infant dyads were screened; 11,811 women agreed to participate.[10] Of these, 3184 were excluded (because of inadequate meconium samples, etc.) 1185 were cocaine exposed and 7442 were not exposed to cocaine. Cocaine exposure was found to be higher in African–American women, in those who had a history of polydrug use and in those who were older than the non-cocaine-exposed women. Cocaine-exposed women had significantly fewer prenatal care visits than non-cocaine-exposed women. Exposed women had a significantly higher risk of medical complications, including syphilis (OR 6.7; 99% CI 4.8–9.6), gonorrhea (OR 1.9; 99% CI

1.3–3.0) and hepatitis (OR 4.8; 99% CI 2.6–8.9). They also had a higher incidence of psychiatric, nervous and emotional disorders (OR 4.0; 99% CI 2.2–7.4) and of abruptio placenta (OR 2.3; 99% CI 1.4–3.9). Among those women who were tested for HIV (28% of the cohort), the risk (OR) was 8.2 (99% CI 14.3–15.4). The frequency of hospitalizations, fetal distress and cesarean section did not differ between the two groups.

The impact of substance exposure during pregnancy on neonatal outcome was evaluated in the MLS, which compared 717 cocaine-exposed infants with 7448 non-cocaine-exposed infants.[11] It was noted that infants in the cocaine-exposed group were 1 week younger in gestational age, weighed 322 g less, were 1.7 cm shorter and were 1.0 cm smaller in head circumference than the non-cocaine-exposed group. The cocaine-exposed infants also had a higher frequency of central nervous system (CNS) symptoms (adjusted OR 1.7; 99% CI 1.2–2.2), autonomic nervous system (ANS) symptoms (OR 1.5; 99% CI 1.0–2.1) and neonatal infections (OR 3.1; 99% CI 1.8–5.4). The frequency of child protective service referrals was higher in the cocaine group (OR 48.9; 99% CI 28.8–83.0) and less breast feeding was also noted in this group (OR 0.3; 99% CI 0.1–0.4) than in the non-cocaine-exposed group. No differences were detected in organ systems by ultrasound examinations.

In a subsequent publication evaluating central and autonomic system (CNS/ANS) signs within the same study sample, Bada et al. reported that the prevalence of CNS/ANS signs was low in the infants exposed to cocaine only and highest in the infants exposed to opiate and cocaine.[12] After controlling for confounders, cocaine exposure was associated with an increased risk of manifesting a constellation of CNS/ANS outcomes (OR 1.7; 95% CI 1.2–2.2) independent of opiate effect (OR 2.8; 95% CI 2.1–3.7). Opiate plus cocaine had additive effects (OR 4.8; 95% CI 2.9–7.9). Smoking also increased the risk for the constellation of CNS/ANS signs (OR 1.3; 95% CI 1.04–1.55 and OR 1.4; 95% CI 1.2–2.6, respectively, for use of less than half a pack a day and half a pack a day or more).

Neonatal size at birth and subsequent growth

Percentile estimates for birth weight, length and head circumference in MLS have revealed that growth deceleration in cocaine-exposed infants is evident after 32 weeks gestation.[13] After controlling for confounders, at 40 weeks gestation, cocaine exposure was estimated to be associated with decreases of 151 g in birth weight, 0.71 cm in length and 0.43 cm in head circumference. Smoking has a negative impact on all growth measurements, with some indication of a dose–effect relationship. Heavy alcohol use was associated with decreases in weight and length only. Opiates had a significant effect only on birth weight.

When the impact of patterns of drug use during pregnancy (consistently high, moderate, low, increasing or decreasing use across all trimesters) in full-term gestations was examined on infant growth parameters in infants born to mothers with multiple drug use, birth weight, birth length and head circumference were noted to be significantly greater in infants born to women who used no drugs than in those born to women with any history of cocaine, opiate, alcohol, tobacco or marijuana use during pregnancy.[14] Growth parameters are also greater in infants born to cocaine non-users than to cocaine users. When adjustment was made for confounders, birth weight was significantly affected by cocaine (deficit = 250 g), even with a consistently low pattern of use during the pregnancy. Birth weight was also affected by tobacco (deficit = 232 g with a consistently high pattern of use, 173 g with a consistently moderate pattern of use, 153 g with a decreasing pattern of use and 103 g with a consistently low pattern of use). Head circumference was affected by cocaine (deficit = 0.98 cm with a consistently moderate pattern of use) and by tobacco (deficit = 0.72 cm with a consistently high pattern of use and 0.89 cm with a consistently moderate pattern of use). Birth length was affected by tobacco use only (deficit = 0.82 cm with a consistently high pattern of use and 0.98 cm with decreasing use). When the factors that would increase the likelihood of

low birth weight, preterm birth and intrauterine growth restriction (IUGR) were evaluated, prenatal cocaine exposure increased the likelihood of low birth weight (OR 3.59), prematurity (OR 1.25) and IUGR (OR 2.24) after adjusting for covariates.[15] Tobacco—but not marijuana—significantly influenced these outcomes. Alcohol had an effect on low birth weight and IUGR. Etiologic fractions estimated as the percentage of population–attributable risk (PAR%) attributable to tobacco for low birth weight, prematurity and IUGR were 5.57, 3.66 and 13.7%, respectively. With additional drug exposure, including cocaine, the estimated PAR% increased to 7.20% (low birth weight), 5.68% (prematurity), and 17.9% (IUGR).

The effects of cocaine exposure during pregnancy and IUGR status at birth on longitudinal growth until 6 years of age have been evaluated.[16] At birth, cocaine-exposed infants weighed 150 g less than non-cocaine-exposed infants; however, between 1 and 6 years there were no significant differences in weight between cocaine-exposed and non-exposed children. For height, exposed children were 0.85 cm shorter than non-exposed infants at birth and were still shorter than the non-exposed children at 1–2 years of age; this difference was no longer apparent after age 3. Head circumference was 0.5 cm less in the cocaine-exposed infants at birth and was still smaller at 1 year of age; subsequently, the difference disappeared.

At birth, term IUGR infants weighed 0.5 kg less than the non-IUGR infants; this difference had increased to 2.1 kg difference by 6 years of age. At birth, children who were small for gestational age were 1.0 cm shorter and continued to be significantly impaired in height throughout childhood, compared with non-IUGR children. At 6 years, the average height of the IUGR children was 1.8 cm less than the non-IUGR children. The head circumference of IUGR children was on average 0.85 cm less than the non-IUGR children and IUGR children continue to have a smaller head circumference, with a difference of 0.9 cm at 6 years of age.

There was an interaction between cocaine exposure and IUGR status on weight at 6 years of age. The negative effect of cocaine exposure was significant in the non-IUGR children but not in the IUGR children. The negative effect of IUGR status at birth on weight at 6 years was greater in the non-cocaine-exposed than in the cocaine-exposed cohort. The negative effect of cocaine exposure on height was significant only in the non-IUGR children at 6 years. The negative effect of IUGR status on height was larger in the non-cocaine-exposed children than in the cocaine-exposed children. Thus, the effect of IUGR status at birth has a greater impact on growth in childhood than cocaine exposure status.

The association between prenatal cocaine exposure and elevated blood pressure in early childhood is unclear, with two studies producing differing results.[17,18] Nineteen percent of the MLS cohort of 891 full-term children followed for 6 years had hypertension.[19] Of the 144 children with IUGR, 25% had hypertension, as compared with the children without growth restriction. Twenty percent of cocaine-exposed children had hypertension, compared with 16% of non-exposed children ($P = 0.2$). IUGR status at birth was significantly associated with hypertension when multivariable regression analysis was performed to adjust for site, maternal race, education and tobacco, marijuana, alcohol and cocaine use during pregnancy and the child's current body mass index.

Utilization of healthcare resources following substance use during pregnancy

Data on utilization of healthcare resources by substance-abusing women are limited. Maternal hospital costs are higher among illicit drug users and neonatal hospital costs have been found to be higher due to increased length of stay.[20]

In a study that matched cocaine-exposed with non-cocaine exposed infants, those exposed to cocaine were noted to have an increased length of hospital stay, more investigations for sepsis, more admissions to the NICU and more social and family problems delaying discharge.[21] The MLS is the largest study to evaluate the utilization of health-care resources by mothers and infants following cocaine use during pregnancy. The use of medical and social services resources by 8514 mother–infant dyads was examined; 1072 of the mothers had used cocaine and 7442 had not.[22] Fewer cocaine-exposed women received prenatal care or used medication during pregnancy. Length of hospital stay for social reasons and referrals to child protective services were increased for the infants in the cocaine-exposed group. Length of stay in the neonatal intensive care unit was increased in cocaine-exposed infants weighing >1500 g, as was the need for therapies, procedures, formula feeds and intravenous fluids. The investigators noted that cocaine exposure had no deleterious or protective effects on medical resource needs of infants weighing <1500 g, or their mothers. The investigators suggest that the use of healthcare resources for surveillance and monitoring of >1500-g cocaine-exposed infants in the absence of an increase in congenital anomalies should be discouraged.

Neurobehavior in children prenatally exposed to illicit drugs

No major neurological deficits in motor development have been found after intrauterine exposure to cocaine. When motor skills were assessed in the same infants—using the NICU Network Neurobehavioral Scale (NNNS) at 1 month, the posture and fine motor assessment of infants (PFMAI) at 4 months, the Bayley Scale of Infant Development at 12 months and the Peabody Developmental Motor Scales at 18 months—it was noted that infants with exposure to cocaine showed lower motor skills at their initial status at 1 month; however, they displayed significant increases over time.[23] Both higher and lower levels of tobacco use related to poor motor performance. Compared with no use, heavy cocaine use related to poorer motor performance but there were no effects of level of cocaine use on change in motor skills.

There is now a move away from evaluating major neurological deficits towards the evaluation of neurologic ‘soft’ signs. These signs are becoming more clinically relevant because of their association with cognitive deficits and because of the increased prevalence of attention deficit hyperactive disorder and behavior problems. Neurologic soft signs are defined as deviations in motor, sensory and integrative functions that do not signify localized brain dysfunction, examples are: cranial nerve abnormalities, lateralized dysfunction and the presence of pathologic reflexes. Neurologic soft signs (non-focal signs with no localized findings) cover ten areas: speech, balance, coordination, double simultaneous stimulation (extinction), gait, sequential fingerethumb opposition, muscle tone, graphesthesia, astereognosis, and choreiform signs.[24] After scoring for each of these areas, the total score has been shown to exhibit acceptable internal consistency, as well as inter-rater and test–retest reliability.[25] Soft signs exhibit marked stability over a 1-year period in 6–9-year-old children. The symptoms of both internalizing and externalizing disorders correlate with poor performance on the soft sign examination.[26]

In 1999, Breslau et al. found that soft signs increased the risk of a subnormal intelligence quotient (IQ) and of learning disorders in children with a normal IQ.[27] Soft signs were associated with excess internalizing problems in low birth-weight (LBW) and normal birth-weight (NBW) children, and with attention and externalizing problems in LBW children at 6 years of age. Hence, soft signs are a marker of a high risk of cognitive and psychiatric problems. In the MLS evaluation of 943 children, 416 of whom were exposed to cocaine and 527 of whom were in the comparison group, more than two soft neurological signs were seen among 23.5% children, with comparable rates between children born to cocaine users and those in the comparison group.[28] When the effect of birth weight was examined, a

greater percentage of children with soft signs were noted to have a birth weight <1500 g. Of these children (n = 110), more than two soft signs were seen in 53% of cocaine-exposed and 27% of non-cocaine-exposed children (OR 3.0; 95% CI 1.4–6.7), in 71% of high-alcohol-exposed and 28% no or low-alcohol-exposed children (OR 6.4; 2.5–16.6) and in 67% of children exposed to alcohol binging and 36% who were not exposed to binging (OR 3.6; 1.0–12.8). The effect of cocaine use and alcohol use on soft neurological signs persisted after controlling for other substance use, birth weight, site, infant sex and race.

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. At 1 month of age, the NICU Network Neurobehavioral Scale demonstrated that cocaine exposure was related to lower arousal, poorer quality of movement and self-regulation, higher excitability, more hypertonia and more non-optimal reflexes, with most effects maintained after adjustment for covariates. This was also noted in the MLS study, in 658 exposed and 730 comparison infants matched for race, sex and gestational age.[29] Some of the effects were associated with heavy cocaine exposure but 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 drug exposure, including cocaine, opiates, alcohol and marijuana; they were also affected by birth weight. Fewer cry effects remained after adjustment for covariates.

Prenatal cocaine and/or opiate exposure also affects neural transmission when examined on auditory brain response at 1 month of age.[30] The MLS found that heavy prenatal cocaine exposure led to an increase in the I–III, I–V and III–V interpeak latencies and to a shorter latency to peak I. Infants with prenatal opiate exposure showed a longer latency to peak V and a longer III–V interpeak latency.

The MLS measured the direct effects of prenatal cocaine exposure and prenatal opiate exposure on infant mental motor and behavioral outcomes. Outcomes were evaluated longitudinally between 1 and 3 years of age.[31] The infants were evaluated at 1, 2 and 3 years of age by the Bayley Scales of Infant Development, which were administered to 1227 infants who had been exposed to cocaine (n = 474), opiates (n = 50), cocaine plus opiates (n = 48) and neither substance (n = 655). Overall, mental developmental index points were 1.6 below in the cocaine-exposed infants compared with infants who were not exposed to cocaine. Opiate-exposed infants scored 3.8 psychomotor developmental index points below infants who were not exposed to opiates. Neither the cocaine nor the opiate effect remained significant after controlling for covariates. Neither the cocaine nor opiate exposure was associated with the Bayley behavioral record score during the examination. Low birth weight and indices of non-optimal caregiving were associated with lower Mental Developmental Index (MDI), Psychomotor Developmental Index (PDI) and behavioral record scores among all groups of infants.

The MLS has also carried out the largest study to date evaluating the effect of prenatal cocaine exposure on childhood behavior problems. A total of 1056 children was followed using the childhood behavior checklist at ages 3, 5 and 7.[32] Longitudinal, hierarchical, linear models were used to determine the effects of prenatal cocaine exposure on behavior-problem trajectories while controlling for other prenatal exposures and for time-varying covariates (including ongoing caretaker level of use of legal and illegal substances, demographic factors, family violence and caretaker psychological distress). After controlling for confounders (including other drug use), the internalizing, externalizing and total behavior-problem scores were higher for high prenatal cocaine exposure than for some or no cocaine use during pregnancy. Significant effects persisted to age 7 years. Additional factors

(including other drug use) also had significant effects on childhood behavior problems. Prenatal tobacco and alcohol exposure were significantly associated with total behavior-problem trajectories until the age of 7, with a significant dose–response relationship, i.e. higher behavior-problem scores were associated with a greater average number of cigarettes/day and a greater average volume of alcohol/day. Moreover, ongoing tobacco and alcohol exposure significantly affected externalizing and total behavior problems. Caretaker report of physical or sexual abuse and caretaker depression were significantly associated with all behavior problems. Mediation analysis revealed that the child's living situation was a significant mediator for the relationship between prenatal cocaine exposure and behavior outcomes.

In another analysis of behavior problems, structural equation modeling was used to describe developmental pathways from birth to predict Child Behavior Check List (CBLL) scores at age 7.[33] Prenatal drug exposure was related to poor neurobehavioral scores at 1 month. The children who showed poor neurobehavioral scores had a more difficult temperament at 4 months. Children with difficult temperament had behavior problems on the CBCL at age 3 and also at age 7. This model was able to explain 52% of the variance in 7-year CBCL scores (all paths $P < 0.05$). The study of developmental pathways might be particularly useful for identifying ‘touch-points’ for intervention.

When evaluated up to 36 months in MLS, the attachment status in children exposed prenatally to cocaine and other substances showed that those children exposed to cocaine and opiates were more likely to be insecurely attached. The type of insecurity was more likely to be ambivalent than avoidant.[34] Continued postnatal alcohol use was associated with higher rates of insecurity and disorganization at 18—but not 36—months of age. Stability of attachment across the 18-month period was barely above chance expectation. Attachment status at 18 months was associated with child temperament and caregiver child interaction; at 36 months attachment was associated with child temperament, child behavioral problems and the caregiver's parenting and self-esteem.

In a longitudinal analysis of the trajectory of mental development at ages 1, 2, 3, 4.5 and 7 years, the MLS looked at 1270 subjects. After adjustment for covariates, the effects of cocaine on IQ were 1.45 points up to age 3; this increased to 4.4 points between 4.5 and 7 years of age ($P = 0.003$).[35] In addition, cocaine-exposed children were more likely (OR = 1.56; $P = 0.03$) to be referred for special education services in school than unexposed children. It was estimated that the additional cost to society for this cocaine effect alone is US$25,248,384 per year. The fact that cocaine effects increased as children grew older could reflect latent effects of the drug, which affect later-emerging prefrontal cortical areas of the brain.

Opiates

In comparison with cocaine, marijuana, alcohol and tobacco abuse, opiate addiction during pregnancy is rare.[1] However, the introduction into the drug market of a smokeable form of cheap heroin that is more potent than crack cocaine has led to a recent resurgence in use. The effects of acute withdrawal to opiates by the fetus are well demonstrated in the newborn infant. Physiological and neurobehavioral signs and symptoms are frequent and well described by ‘the opiate abstinence syndrome’.[36–38] Heroin and methadone are the most common opiates abused but many new synthetic narcotics are becoming available to the substance-abusing population.

Infants who acutely withdraw from narcotics exhibit signs of dysregulation, such as sweating, hyperirritability, posturing, hypertonity, jitteriness, exaggerated startle response, tachycardia and—occasionally—seizures. These infants often have extended stays in

hospital due to poor feeding, slow weight gain, electrolyte disturbances, diarrhea and dehydration. Reports to child protective services often result in the infants being removed from parental care and placed in foster or adoptive care. No obvious teratogenic impact has been consistently demonstrated in infants of mothers who abused opiates during their pregnancy.[36–38] Long-term outcome studies are rare and, as in most follow-up reports on substance-exposed infants, outcome is confounded by multiple medical and psychosocial factors that make the identification of a single drug effect difficult. Effects such as low birth weight, prematurity, growth retardation and perinatal depression have all been reported in opiate-exposed newborns. However, low socioeconomic status, multiple drug use, lack of adequate and early prenatal care and sexually transmitted diseases confound the potential opiate effects. Studies on the long-term outcome of opiate exposure are relatively uncommon.

The MLS, which identified and enrolled over 11,000 pregnant women at delivery, identified drug exposure as the confirmed use of cocaine and/or opiates during pregnancy. Of the 8600 with documented exposure—either by admission of use or by meconium analysis confirming drug metabolites—approximately 100 were identified as isolated users of opiates, with an equal number having used both cocaine and opiates. This very large, prospective, multisite study confirmed the findings of previous reports.[11] No clear teratogenic effects were demonstrated in any opiate-exposed infant. Transient, but dramatic, neurobehavioral signs were present in the first week of life, primarily related to the ANS and including increased irritability, jitteriness, sweating, hiccupping, sneezing, poor suck and exaggerated irritability. These infants required longer hospital stays due to their withdrawal symptomatology, which often required sedation medication, and also because of sociolegal involvement in determining their placement.

The MLS has followed the majority of these exposed infants and compared them with a matched control group of non-drug-exposed infants. At 3 years of age, although opiate-exposed infants ($n = 50$) had lower psychomotor developmental scores than those who were not exposed to either cocaine or opiates ($n = 655$), the effect was no longer significant after controlling for covariates.[31] Cognitive outcomes at age 10 show little difference between opiate-exposed and non-exposed infants.[39] However, scores on calculation subtest evaluation lagged behind those in non-exposed children, even when adjusted for site, sex, race and socioeconomic status. Of interest, the opiate-exposed infants ranked higher in resilience, an important social skill. There were no significant differences in growth parameters; in fact, the opiate-exposed children had a slightly higher height and slightly greater head circumference than non-opiate-exposed children. There were also no differences in medical diagnoses, blood pressure, hospitalizations, motor development or overall health status. Although assessments of language processing and phonological processing at age 9 similarly showed no consistent significant effects, there was a trend for the opiate-exposed children to score consistently—but not statistically significantly—lower than controls in all domains except their understanding of complex sentences (paragraph comprehension), which was significantly lower. This finding could have implications for future learning capacity as tasks become more complex and difficult. This weakness might reflect reduced short-term memory and attention skills.

In summary, there were no dramatic findings in children in their pre-adolescent years who were exposed *in utero* to opiates; no medical, teratogenic or growth differences were seen. A non-significant trend toward lower cognitive performance and complex learning skills might reflect the complex interaction of exposure and psychosocial environmental factors. Follow-up into high school, college and work might better reflect potential disparities that are not yet obvious. It is encouraging that, despite their dramatic presentations in the immediate

newborn period, these children grow into pre-adolescence as healthy, capable children not obviously different from their non-drug-exposed peers.

Statistical implications

The MLS is a prospective, observational study examining long-term effects of prenatal cocaine exposure in a predominantly minority and low-socioeconomic-status population. Analysis and interpretation of the MLS data therefore present several statistical challenges, some of which are briefly outlined below.

Covariate selection

The MLS collects a vast amount of information, over time, from multiple sources (child, parent/caregiver, medical charts, school records, etc.). The statistical challenge is to tease apart the independent effect of prenatal cocaine exposure in the presence of all the other factors that need to be accounted for. As there are usually too many variables to adjust for in this observational cohort study (where covariate imbalances are expected), methodologically sound *a priori* covariate selection strategies[32,40] are essential.

A related complexity is the issue of factors that might be considered to be in the causal pathway from prenatal cocaine exposure to long-term outcomes. This problem is especially acute for ongoing changes in the home environment because of near-complete confounding between prenatal cocaine exposure and out-of-home placement for children in the MLS. In recent articles,[32] the MLS investigators have used the mediation framework to account for such factors in analyses.

Inter-related outcomes

At each assessment, the MLS collects information on several outcomes from each child in the study. Frequently, such outcomes are correlated and might purport to measure the same underlying condition or construct. To boost statistical efficiency, statistical analyses should reflect these aspects and also allow for the outcome-specific cocaine-exposure effects that are of interest. Individual analyses for each outcome ignore correlations among multiple outcomes, thus producing imprecise effect estimates. Multiple comparisons are another problem with individual analyses, because performing several tests on the data inflates the type I error to unacceptable levels. Thus, MLS investigators have adopted a multivariate modeling approach to analyze multiple outcomes by borrowing from statistical methods for longitudinal and repeated measures data to simultaneously model all the outcomes assessed on an individual.[40,41]

Missing data

Missing data are the challenge of longitudinal studies and the MLS is no exception. Ordinary analyses, which simply ignore the missing information, can give biased results. Statistical methods for missing data (under certain assumptions) include imputations (where the missing data are estimated) and analytic methods, such as maximum likelihood estimation, which do not require complete outcome data to produce valid inferences. Thus, MLS investigators have utilized likelihood-based methods (as opposed to generalized estimating equations) such as Hierarchical Linear Modeling (HLM) for longitudinal analyses. However, although this affords protection against missing outcomes, missing covariates still pose a problem. In certain analyses,[32] MLS investigators used multiple imputation, in which a set of values drawn from the predictive distribution of the missing values is imputed for each missing value, as implemented in the sequential regression imputation method (SRIM)[42] to impute missing values for selected covariates.

Conclusions

Maternal substance use has been demonstrated to be related to an increase in maternal pregnancy complications, more sexually transmitted disorders and increases in abruptio placenta and in HIV-positive status. Effects on the infant include decreased birth weight, birth length and head circumference; increased neonatal CNS and ANS signs and an increase in referrals to child protective agencies. Patterns of substance use during pregnancy impact on fetal growth. Healthcare resource utilization is increased among infants weighing >1500 g at birth. In childhood, behavioral and cognitive effects are seen after prenatal cocaine exposure; prenatal tobacco and alcohol have separate and specific effects. Ongoing caretaker use of alcohol and tobacco affects childhood behavior. IUGR status at birth impacts on the risk of hypertension in childhood. It is also clear that substance use during pregnancy has physical and mental health implications beyond childhood. Although the behavioral and cognitive effects are subtle and not as large as expected, they are likely to impact on how the adolescent will function in society. Treatment for mental health and special education needs poses a financial burden, hence it is imperative that efforts are made for the prevention and early treatment of behavioral problems of drug use by adolescent children born to women who used drugs during pregnancy.

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