Is exposure to cocaine or cigarette smoke during pregnancy associated with infant visual abnormalities?

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The aim of this study was to assess the association between cocaine or cigarette smoke exposure in utero and visual outcome. A total of 153 healthy infants (89 males, 64 females; gestational age range 34 to 42 weeks) were prospectively enrolled in a masked, race-matched study. Quantitative analyses of urine and meconium were used to document exposure to cigarette smoke and cocaine. Infants with exposure to other illicit drugs, excepting marijuana, were excluded. At 6 weeks of age, grating acuity and visual system abnormalities (VSA; eyelid oedema, gaze abnormalities, and visual inattention) of 96 infants from the original study sample were assessed with the Teller acuity card procedure and a detailed neurological examination. Neither cocaine nor cigarette smoke exposure was associated with acuity or VSA. However, VSAs were associated with abnormal neurological examination, independent of drug exposure and other risk factors (odds ratio 7.9; 95% confidence interval 2.0 to 31.5; p=0.004). This unexpected finding could prove a helpful clinical marker for the infant at risk for neurological abnormalities.

Substance abuse in pregnant women continues to be a major public health problem in the USA (Anon. 2002, Weber et al. 2002). Substances of abuse include illicit drugs, ethanol, and tobacco. Fetuses exposed to cocaine or cigarette smoke are at risk for neurodevelopmental impairment (Dempsey et al. 2000, Fried and Watkinson 2000, Frank et al. 2001, Singer et al. 2002, Walstab et al. 2002, Fried et al. 2003). The potential adverse effects of substance abuse on the developing visual system are unknown, despite some early studies indicating adverse effects of cocaine or other illicit drugs (Good et al. 1992, Struthers and Hansen 1992, Jan et al. 1996, Tsay et al. 1996).

The visual system could be ideal for assessing neurological risk, because some standardized measures already exist to determine function. Optic radiations lie in close proximity to motor tracts, so both systems might be affected by insults that involve the germinal matrix and occur during gestation. For example, children with cortical visual impairment show a range of neurological problems, including motor and cognitive deficits, and language delay (Dutton et al. 1996, Houliston et al. 1999).

One particular measure of vision called 'forced preferential looking', of which the Teller acuity card procedure is an example, allows the assessment of visual function in infants. Forced preferential looking can be measured in awake, preverbal children, is simple to perform, and is reliable in infants without disabilities (Teller et al. 1986, Salomao and Ventura 1995). The Teller acuity card procedure has been validated for children with severe disabilities and learning disabilities* (Hertz and Rosenberg 1992). Cioni et al. (1996) and Ipata et al. (1994) validated the Teller acuity card procedure with magnetic resonance imaging studies in children with neonatal encephalopathy and with cerebral palsy. In preterm infants, reliability and predictive validity of the Teller acuity card procedure has been demonstrated (Mash and Dobson 1998).

The aim of this study was to determine the effect of cocaine or cigarette smoke exposure in utero on the visual system of infants who seem healthy at birth. At 6 weeks of age, infants' visual acuity was measured with the Teller acuity card procedure and a neurological examination was carried out which included a clinical examination of the visual system with the assessment of eyelid oedema, visual attention, and gaze ability. This analysis was part of a study investigating neurological outcomes in infants prenatally exposed to cocaine (Dempsey et al. 2000).

Method

PATIENTS

This study was approved by the University of California Committee on Human Research. The cohort of infants reported in this study has been described previously, and a detailed description of the participants and study is given in that publication (Dempsey et al. 2000). In brief, this was a prospective masked study comparing cocaine exposed to cocaine unexposed infants, matched for infant age and race of mother. The race-matching took place in blocks in order to ensure similar cohorts with regard to ethnicity; for details see Dempsey et al. (2000). All infants were born at San Francisco General Hospital, which is a county hospital serving a patient population of low socioeconomic status. Enrolment consent was given by parents for the infants within 24 hours of birth. The exclusion

*US usage: mental retardation.

criteria were: birth weight less than 2000g; illness requiring admission to the intensive care nursery or the special care nursery; maternal age less than 18 years; non-English-speaking mother, and exposure to illicit drugs other than cocaine, marijuana, and ethanol. All neonates at San Francisco General Hospital who are considered at risk for maternal illicit drug use undergo a qualitative urine toxicology screen that tests for alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, benzoylecgonine, opiates, and phencyclidine. The definition for neonates 'at risk' includes the following factors: no prenatal care, history of substance abuse, obstetrical suspicion (e.g. placental abruption), intrauterine growth retardation, history of prostitution, history of incarceration, major psychiatric diagnosis, and family violence. These criteria have been validated previously by the hospital with universal toxicology testing of neonates.

The San Francisco General Hospital toxicology screen does not include cannabinoids. Infants were not excluded for maternal marijuana use. Alcohol is rapidly eliminated and has no long-lived metabolite, so abstinence cannot be documented with a biomarker. Infants of mothers who were known alcoholics were excluded. Infants were considered 'cocaine exposed' if any research or hospital sample was positive for cocaine metabolites, or if the mother stated that she had used cocaine during this pregnancy. Infants were considered 'cocaine unexposed' if the mother had no history of cocaine use during pregnancy, and all biological samples were negative for drugs of abuse except marijuana. Of 80 neonates who were considered cocaine unexposed, 47 had a negative meconium sample. Of the remaining 33 children, 27 had a urine sample from either the mother, the infant, or both that tested negative for cocaine or its metabolites. Of the remaining six children without any biological marker, five had no follow-up examination. Mothers were defined as cigarette smokers if they admitted smoking status or if the maternal or neonate urine sample had a cotinine concentration of at least 30ng/ml. Cotinine, a metabolite of nicotine with a long half-life, is used as a biomarker for cigarette smoking (Jarvis 1989, Benowitz 1996).

SAMPLE COLLECTION

The hospital collected urine from all at-risk neonates and tested the urine for alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, benzoylecgonine, opiates, and phencyclidine. The hospital screened for the cocaine metabolite benzoylecgonine using the Kinetic Interaction of Microparticles in a Solution assay (KIMS assay; Roche Diagnostic Systems, Nutley, New Jersey, USA), with confirmation using the enzyme multiplication immunoassay technique (Syva Co, San Jose, California, USA). The threshold for detection of benzoylecgonine was 300ng/ml. In addition to the hospital screening, research personnel collected the following samples from all maternal infant pairs: maternal urine, infant urine, and meconium (milk stools excluded). Meconium was assayed using the Abbott fluorescence polarization immunoassay for cocaine, cocaine metabolites (cocaethylene, benzoylecgonine, *m*-hydroxy-benzoylecgonine), amphetamines, cannabinoids, morphine, codeine, benzodiazepines, and barbiturates (US Drug Testing Laboratories, Chicago, IL, USA). Quantitative drug levels in meconium were determined by gas chromatography–mass spectrometry, and the threshold for detection of cocaine and metabolites was 25ng/g (US Patent numbers 5,532,131 [2 July 1996], and 5,587,323 [24 December 1996]). Research urine samples were acidified with sodium bisulphate and frozen until gas chromatography–mass spectrometry analysis was carried out using the methods of Jacob et al. (1981, 1987). The levels of quantification were cocaine 5ng/ml, benzoylecgonine 10ng/ml, nicotine 1ng/ml, and cotinine 10ng/ml.

EXAMINATION AT 6 WEEKS

At 6 weeks of age, infants were brought to the General Clinical Research Centre at San Francisco General Hospital. Some children were born preterm (below 37 weeks' gestation) and because acuity increases rapidly within the first few months of age, age at examination was corrected for prematurity. Infants were examined by a pediatric neurologist; infants' histories, previous examinations, and exposure status were masked. The neurological examination was standardized and included the items listed in Table I. Visual system abnormalities (VSA) were assessed at the beginning of the neurological examination as part of the cranial nerve examination and were defined as eyelid oedema, gaze abnormalities, or visual inattention. Gaze abnormalities included poor visual tracking, downward gaze, a unilateral gaze preference (right or left), roving eye movements, and sunsetting. Bilateral ptosis caused by oedema was also considered to be an abnormality of the visual system. Visual inattention was also assessed during the visual acuity examination. An overall assignment of normal or abnormal neurological assessment result was given at the end of the examination. To avoid assessment bias, infants were examined without the presence of caregivers; the presence of caregivers might have provided information as to whether or not infants had been exposed to cocaine. We encountered no difficulties examining the children. They were fed before the examination

Table I: Neurological examination at 6 weeks

Examination	*Signs*	*Score*
Inspection	Dysmorphism, neurocutaneous signs	Yes, no
Adaptive capacities	Appropriate response to light, sound, and touch	Yes, no
Mental status	Alertness, vocalization, curiosity, and consolability	Normal, abnormal (hypo, hyper)
Cranial nerves	Function by examination	Normal, abnormal
Motor system	Tone (active, passive), truncal, and extremities	Increased, decreased, normal
	Power, truncal, and extremities	Increased, decreased, normal
	Stretch reflexes	Increased, decreased, normal
	Primitive reflexes	Present, absent

and, from a developmental point of view, stranger anxiety was not an issue.

Visual acuity and attention were assessed with the Teller acuity card procedure (McDonald et al. 1985). This standardized procedure is based on the infant's preference for a pattern stimulus compared with a plain, luminance-matched field. Acuity was expressed as cycles/cm and could range from 0.32 to 38.0 cycles/cm. To describe the reliability of the examination, confidence levels indicate the compliance of the child and range from 5 (high) to 1 (low). Acuity assessed with confidence levels 5 and 4 were used for the analysis. Of the 96 children examined, one was lethargic and two had poor visual attention. One of the latter two reached an acuity of 0.23 cycles/cm. The other inattentive child and the lethargic child were given a value of 0 to express poor attention. Both children with poor visual attention were included in the group with VSA.

STATISTICAL ANALYSIS

Differences between exposed and unexposed infants were analyzed with a two-tailed *t*-test for continuous, normally distributed data, with χ^2 or Fisher's Exact Probability test for dichotomous data, and with the Mann–Whitney *U* test for ordinal data or non-normally distributed data. Correlation between cocaine and nicotine levels in infant and maternal urine with acuity scores at 6 weeks was evaluated by Spearman's rank correlation. As acuity scores at 6 weeks of age were correlated with gestational age ($r=0.26$, $p=0.01$) and with age at examination ($r=0.60$, $p<0.001$), the association between drug exposure and acuity scores included both variables in the multiple regression analysis.

The association between acuity or VSA and abnormal neurological examination was assessed by logistic regression and expressed as an odds ratio (OR) with the 95% confidence interval (95% CI). Variables included in the multiple logistic regression model were associated with VSA in the simple logistic regression analysis at a $p<0.3$ (cigarette smoke exposure, abnormal neurological examination, gestational age, head circumference at examination, and corrected age at examination). To test for an interaction between cigarette smoke exposure and neurological abnormalities (association between visual and neurological abnormalities might depend on cigarette smoke exposure), an interaction term was added into the model.

Results

One hundred and fifty-three infants were enrolled after birth, and 96 (63%) returned for neurological and visual system examinations at 6 weeks of age. Thirty-one of the 40 cocaine exposed infants had mothers who smoked cigarettes, whereas 10 of the 56 cocaine unexposed infants had mothers who smoked. Infants were seen at a mean age of 38 days corrected age (range 0 to 103 days, standard deviation [SD] 2.1 days). Cocaine exposed infants who returned had a higher mean birthweight (mean 2999g [SD502] versus 2780g [SD435]; $p=0.05$) and gestational age (mean 38.5 weeks [SD1.5] versus 37.5 [SD1.8]; $p=0.008$) than those who did not return at 6 weeks of age. Cocaine exposed mother–infant pairs were less likely to return for follow-up than those who were unexposed (χ^2 test, $p=0.052$). However, we did not find differences in the levels of cocaine, nicotine, and their metabolites between those who returned and those who did not. There was no statistically significant difference between the cocaine exposed infants who returned and those who did not return at 6 weeks of age with regard to race, sex, urine benzoylecgonine level, urine cotinine level, prenatal care, maternal alcohol use, head circumference and length at birth, entry into foster care, or homelessness (for details see Dempsey et al. 2000). Because infants with cocaine exposure were born at an earlier gestational age, they were also seen at an earlier corrected age for their visual examination (32.5 days, SD 19.0 days, versus 41.6 days, SD 21.4 days; $p=0.04$). For the cohort of infants examined at the 6-week examination, we confirmed the commonly reported demographic characteristics associated with cocaine exposure (Dempsey et al. 2000).

COCAINE AND CIGARETTE SMOKE EXPOSURE AND VISUAL OUTCOME

Overall, the median acuity score was 0.86 cycles/cm, ranging from 0 to 6.5 cycles/cm, with the 25th centile at 0.64 cycles/cm and the 10th centile at 0.43 cycles/cm. Median acuity scores did not differ between cocaine exposed and cocaine unexposed infants. They also did not differ between infants exposed to cigarette smoke and those who were unexposed (Table II). In a multiple regression, corrected for age at examination and gestational age, no association was found between cocaine exposure and acuity ($p=0.38$) or between cigarette smoke exposure and acuity ($p=0.93$). Logistic regression revealed no association between cocaine or cigarette smoke exposure and acuity scores below the 25th centile or below the 10th centile. Levels of maternal and infant urine cocaine, benzylecgonine, and cotinine as well as levels of meconium cocaine, benzylecgonine, and cotinine were not correlated with visual acuity.

At the 6-week examination, 18 (19.6%) infants had VSA. They included significant eyelid oedema ($n=6$), eyelid oedema with visual inattention ($n=3$) or with esotropia ($n=1$), gaze abnormalities ($n=5$), poor visual tracking and strabismus ($n=1$), bilateral ptosis ($n=1$), and occasional sunsetting ($n=1$).

Table II: Prenatal drug exposure and visual examination at 6 weeks of age

Exposure	*n*	*Eyelid oedema*			*Acuity*	
		Yes, n (%)	*No, n (%)*	*p*	*Median (range)*	*p*
Cocaine exposed	40	5 (12.5)	35 (87.5)	0.21	0.86 (0–3.2)	0.28[a]
Cocaine unexposed	56	3 (5.4)	53 (94.6)	–	0.86 (0–6.5)	–
Cigarette-smoke exposed	47	7 (14.9)	40 (85.1)	0.05	0.86 (0–6.5)	0.69[a]
Cigarette-smoke unexposed	49	1 (2.0)	48 (98.0)	–	0.86 (0–4.8)	–
Total	96	8 (8.3)	88 (91.7)	–	0.86 (0–6.5)	–

[a]Mann–Whitney *U*-test.

Gestational age was associated with VSA: the lower the gestational age at birth, the greater the likelihood of VSA (Table III). Exposure to cocaine or cigarette smoke was not associated with overall VSA. However, eyelid oedema alone was associated with cigarette smoke exposure during pregnancy (OR 12.2; 95% CI 1.2 to 123.8; $p=0.04$) but not with cocaine exposure (OR 2.0; 95% CI 0.4 to 10.7; $p=0.43$) after adjustment for gestational age and head circumference. Maternal and infant urine levels of cocaine, benzylecgonine, and cotinine as well as meconium levels of cocaine, benzylecgonine, and cotinine were not correlated with VSA or with eyelid oedema alone. One infant with eyelid oedema also had microphthalmia, hypotelorism, and malpositioned ears (lowset and rotated), suggesting an underlying genetic disorder not diagnosed at birth. His mother was a cigarette smoker; in other respects his chart review did not reveal exposure to alcohol or other potentially harmful substances.

VISUAL OUTCOME AND NEUROLOGICAL EXAMINATION

Infants with acuity scores below the 10th centile ($n=8$) were more likely to exhibit generalized hypertonia at 6 weeks than infants with acuity scores above the 10th centile (OR 3.5; 95% CI 0.8 to 15.2; $p=0.08$). After adjustment for cocaine exposure, cigarette smoke exposure, gestational age, and head circumference at examination, the OR decreased significantly (OR 1.2; 95% CI 0.2 to 7.2; $p=0.77$). Infants who had an acuity score below the 25th centile ($n=15$) were not more likely to have neurological abnormalities than infants above the 25th centile (OR 1.2; 95% CI 0.4 to 3.5; $p=0.79$).

Of the 18 infants with VSA at 6 weeks, 14 had an abnormal neurological examination, whereas 30 of the 76 infants without VSA had an abnormal neurological examination (χ^2 test, $p=0.002$). The neurological abnormalities in infants with VSA consisted of hypotonia ($n=3$), generalized hypertonia ($n=9$), and appendicular (extremities only) hypertonia ($n=2$). Several predictors or confounding factors were associated with VSA (Table III), namely cigarette smoke exposure, gestational age, head circumference at examination, and corrected age at examination. After adjustment for these confounding variables (Table IV), infants with VSA were almost eight times more likely to have an abnormal neurological examination than infants without VSA. There was no interaction between cigarette smoke exposure and neurological abnormalities.

Discussion

In this masked prospective case-control study we found that grating acuity and VSA at 6 weeks of age were not affected by exposure to cocaine or cigarette smoke during pregnancy.

Cigarette smoke exposure was associated with eyelid oedema at 6 weeks of age, but not with poor visual acuity. The significance of this association is not clear. As a small number of infants ($n=8$) had eyelid oedema at 6 weeks, the finding should be viewed with caution with regard to clinical significance. These findings contradict previous research that showed eyelid oedema and impaired visual attention linked to cocaine exposure, albeit in symptomatic neonates (Tsay et al. 1996).

A new finding from this study was that VSA, including eyelid oedema, gaze abnormalities, and visual inattention, were associated with neurological abnormalities at 6 weeks of age. This finding occurred independently of exposure to drugs,

Table III: Simple logistic regression of variables associated with visual system abnormalities (eyelid oedema, gaze abnormalities, and visual inattention)

Variables	*OR*	*Lower CI*	*Upper CI*	*p*
Cocaine exposure	1.11	0.39	3.13	0.85
Cigarette smoke exposure	1.75	0.61	5.03	0.29
Ethanol exposure	0.67	0.21	2.12	0.50
Abnormal neurological examination	5.75	1.72	19.21	0.005
Gestational age	0.65	0.46	0.92	0.02
Head circumference at examination	0.76	0.56	1.02	0.07
Ethnicity (African American)	1.50	0.54	4.15	0.44
Corrected age at examination	0.97	0.94	1.00	0.05

OR, odds ratio; CI, confidence interval (lower and upper for 95th centile).

Table IV: Multiple logistic regression of variables associated with visual system abnormalities (eyelid oedema, gaze abnormalities, and visual inattention)

Variables	*OR*	*Lower CI*	*Upper CI*	*p*
Cigarette smoke exposure	0.94	0.26	3.32	0.92
Abnormal neurological examination	7.93	1.99	31.47	0.004
Gestational age	0.86	0.49	1.50	0.59
Head circumference at examination	0.84	0.55	1.26	0.40
Corrected age at examination	0.98	0.93	1.03	0.45

Variables were included if $p<0.3$ in a simple logistic regression analysis. OR, odds ratio; CI, confidence interval (lower and upper for 95th centile).

and seems to be a good marker for early neurological morbidity. If cigarette smoke exposure during pregnancy is associated with neurological abnormalities and neurological abnormalities are associated with VSA, why did we not find an association between cigarette smoke exposure during pregnancy and VSA? Our findings indicate that the association between neurological abnormalities and VSA also occurs in unexposed children, and that cigarette smoke exposure during pregnancy does not have an additional or independent effect on the visual system. 'Neurological abnormalities' can also be seen as an intermediate variable, mediating the effect of prenatal exposure to cigarette smoke.

The present study included only a population characterized by an uneventful neonatal clinical course. The abnormalities previously described by us and others in association with prenatal exposure to cocaine were seen in a select sample of high-risk cocaine exposed infants who had complicated neonatal courses and often had been born very preterm (Good et al. 1992, Fries et al. 1993, Tsay et al. 1996). In this current study, two infants showed delayed visual attention at 6 weeks of age; they were both awake but visually inattentive. One had been exposed to cocaine, cigarette smoke, and alcohol; his neurological examination was normal. The other infant had not been exposed to any substances. However, he had generalized hypertonia on neurological evaluation. Although frank delayed visual attention was seen in one cocaine exposed infant in this study, delayed visual attention was not more common in infants exposed to cocaine or cigarette smoke; otherwise, the acuity scores would have been significantly different between infants exposed to cocaine or cigarette smoke and those who had been unexposed.

Interestingly, low acuity scores were not correlated with an abnormal neurological examination. This finding demonstrates that visual acuity measures in this cohort were not significantly influenced by the underlying neurological status of the infants, and that acuity was probably unaffected in these infants. A study by Struthers and Hansen (1992), using the Fagan Test of Intelligence, found abnormalities of visual attention and habituation in cocaine exposed infants. The test relies on the fact that infants habituate to familiar stimuli and prefer novelty, but it is not a measure of visual acuity per se. The investigators found that cocaine exposed term infants had lower scores than unexposed infants at 6 and 12 months of age. The study population of Struthers and Hanson (1992) was comparable to the population in this study because all infants were born at term and were excluded if they were admitted to the special care nursery. However, over half of the participants had been exposed to amphetamines alone or in combination with cocaine (cigarette smoke exposure was not quantified).

The large sample size of our study makes it unlikely that we did not find any differences in ophthalmologic abnormalities as a result of lack of statistical power. This does not exclude the possibility that cocaine or cigarette smoke exposure has an effect on the developing eye, but suggests that these abnormalities may occur later in life or very rarely, thus necessitating a longer follow-up time or a population that is already unwell in the neonatal period. The lack of association was not the result of our examination of less heavily exposed infants because drug levels were similar in cocaine exposed infants who attended and in those who did not attend.

What is the significance of the finding that VSAs, such as eyelid oedema, gaze abnormalities, and visual inattention, are correlated with abnormal neurological findings at 6 weeks of age? Recent work in infants with neonatal encephalopathy demonstrates that abnormalities at a neurological examination at the age of 3 months predict an abnormal examination when the infant reaches 1 year of age (Hajnal et al. 1999). Thus, an early clinical examination is a helpful and significant tool for identifying infants at risk for subsequent neurological problems.

One of the VSAs seen in these infants was gaze disturbance. They are caused by supranuclear disturbances or factors. Previous research on infants in the first days of life have indicated that such gaze findings are common and insignificant (Hoyt et al. 1980). The finding in this cohort at a later age (6 weeks), suggests that the significance of this finding should be reconsidered, at least for persistent gaze disturbances. This is the first study to assess neurological risk in infants with gaze disturbances; our findings suggest that gaze abnormalities might be a marker for neurological morbidity. Therefore, we suggest that all at-risk infants, regardless of exposure to cigarette smoke or cocaine, should be examined for VSA at about 2 months of life. The examination should assess the presence of eyelid oedema, gaze abnormalities, and visual inattention. These findings can be assessed with a standardized neurological examination as presented in Table I and with the Teller acuity card procedure, which can be easily learned and is inexpensive.

In summary, we have shown that neither cocaine nor cigarette smoke exposure in utero is associated with poor acuity or visual abnormalities early in infancy. However, independent of drug exposure, VSAs are associated with an abnormal neurological examination. This unexpected finding could prove a helpful clinical marker for the infant at risk for neurological abnormalities.

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