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Maternal Cocaine Abuse: The Spectrum of Radiologic Abnormalities in the Neonatal CNS

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The purpose of this study was to determine the pattern and frequency of CNS abnormalities in the offspring of cocaine-abusing mothers. The study group consisted of a retrospective review of all neonates born or admitted to our neonatal intensive care unit over a 1-year period who met criteria for maternal cocaine abuse (43 patients). A control group (62 patients) was obtained from patients seen during the same interval and the cases were matched for gestational age and race. The radiologic studies were analyzed by two independent reviewers, and CNS abnormalities were assessed by means of sonography, CT, or MR. By matching the study and control groups for gestational age, we eliminated the higher frequency of prematurity. This allowed us to determine if maternal cocaine use was associated with any intracranial abnormalities other than those seen with prematurity. The frequency of intracranial hemorrhage, ventricular enlargement, and periventricular leukomalacia was not significantly different between the study and control groups. The frequency of cortical infarction was 17% in the study group and 2% in the control group. The frequency of major congenital malformations was 12% in the study group and 0% in the control group. All five of the congenital malformations seen were midline CNS abnormalities, particularly neural tube defects.

It is postulated that the higher statistically significant frequency of stroke and congenital malformations in the babies of maternal cocaine abusers is related to vasospasm caused by cocaine when used in the third and first trimesters, respectively.

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In the last year, an unusual constellation of midline CNS malformations were noted in neonates born or admitted to our institution. Maternal cocaine abuse was found to be a common denominator among these cases. The unusual irritability of babies born to cocaine-abusing mothers also prompted further radiologic investigation of the infants' CNS. The purpose of our study was to determine the pattern and frequency of CNS abnormalities in the offspring of maternal cocaine abusers.

Materials and Methods

The study group consisted of a retrospective review of all neonates born or admitted to our neonatal intensive care unit from January 1, 1988, to January 31, 1989, who met one of the following criteria for maternal cocaine abuse: (1) the mother confessed to cocaine use during the pregnancy, (2) the mother had a positive cocaine screen at delivery, or (3) the baby had a positive cocaine screen at birth. A control group was obtained from the same admission interval and the cases were matched for gestational age and race. An attempt was also made to match the urban geographic area from which the cases originated. There were 43 babies in the study group and 62 babies in the control group.

The entry criteria are summarized in Table 1. All the mothers in our study group used crack (i.e., cocaine free-based). All the mothers confessed to first trimester use and the majority continued drug use throughout the pregnancy. The maternal population consisted mainly of indigent crack addicts with a history of regular use (e.g., three patients were found

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using crack in the delivery room). Actual dosages were not available. Mothers who admitted to or were found to have physical evidence of IV drug abuse were excluded from the study. The frequency of recreational marijuana and alcohol use as well as cigarette smoking was not significantly different between the study and control groups. The cocaine screen was a urine assay performed according to the enzyme-mediated immunoassay technique (Syva EMIT d.a.u. kits) for benzoylecgonine, the major metabolite of cocaine. Any sample that was initially tested positive was confirmed with gas chromatography–mass spectrometry (GC-MS). Unfortunately, all the urine samples were tested for phenobarbital first, and the specimen volume was often insufficient for confirmation by GC-MS. Thus, even if the initial screen was positive on the first 3 ml of urine, if there was not a further 5 ml to confirm with GC-MS the assay would be called negative. Cocaine metabolites persist for only approximately 3 days, so occasionally it was a problem to obtain enough urine from a premature infant within such a short time.

Table 2 illustrates the demographic data and the match obtained between the study and control groups. The gestational age was matched between the study group and control group to within 1 week of both the mean and median gestational age. Since the study and control groups consisted of neonatal intensive care unit admissions, most (see Table 3) had sonography on a routine basis. Irritability, seizures, and structural abnormalities were other indications for study. Suspected cortical/subcortical infarctions on sonography were confirmed with CT. All congenital malformations were confirmed with CT and/or MR.

The radiologic CNS examinations of the study and control groups were collected and analyzed by two blinded independent reviewers. The following specific abnormalities were assessed whether they were found on sonograms, CT scans, or MR images: subependymal and intraventricular hemorrhage (SEH, IVH); intraparenchymal hemorrhage (IPH); ventricular dilatation; periventricular leukomalacia (PVL); porencephaly; infarcts; and congenital anomalies.

The cerebral sonograms were obtained on a real-time scanner with a 5-MHz transducer (Acuson, Mountain View, CA). CT studies were done on a third-generation scanner with 7-mm-thick axial images through the entire brain. MR imaging was performed on a 0.6-T Technicare unit using standard spin-echo pulse sequences, including short TR/short TE sequences in both the axial and sagittal planes and long TR/double-echo TE sequences in the axial plane or, alternatively, in the sagittal plane when a spine examination was being performed. A 7.5-mm slice thickness, a 2.5-mm interslice gap, a 256 × 128 matrix size, a 25-cm field of view, and two excitations were used. The effective pixel size was 1.9 × 1.0 mm.

A Fischer exact test was performed on the data obtained from the study and control groups for each type of abnormality to determine if cocaine abuse was associated with a higher frequency of these abnormalities. All results were reported as statistically significant if $p < .05$.

TABLE 1: Entry Criteria

	Study Group	Control Group
Maternal history of cocaine use	(n = 42, 1 set twins)	(n = 61, 1 set twins)
Yes	90% (38)	0% (0)
No	10% (4)	100% (61)
Urine cocaine screen maternal	(n = 42)	(n = 61)
Positive	21% (9)	0% (0)
Negative	5% (2)	8% (5)
Insufficient quantity/not done	74% (31)	92% (56)
Urine cocaine screen neonate	(n = 43)	(n = 62)
Positive	58% (25)	0% (0)
Negative	35% (15)	24% (15)
Insufficient quantity/not done	7% (3)	76% (47)

TABLE 2: Demographic Data

	Study Group (n = 43)	Control Group (n = 62)
Race		
Black	84% (36)	76% (47)
Hispanic	5% (2)	6% (4)
White	11% (5)	15% (9)
Other	0% (0)	3% (2)
Sex		
Male	44% (19)	47% (29)
Female	56% (24)	53% (33)
Gestational age (weeks)		
Mean	31.4 (24–41)	30.4 (24–41)
Median	31	31

TABLE 3: Imaging Data

Type of Examination	Study Group (n = 43)	Control Group (n = 62)
Sonography	93% (40)	87% (54)
CT	57% (23)	10% (6)
MR	16% (7)	6% (4)

TABLE 4: Radiologic Abnormalities

Abnormality	Study Group (n = 43)	Control Group (n = 62)	p Value
Subependymal hemorrhage	35% (15)	34% (21)	NS
Intraventricular hemorrhage	22% (10)	21% (13)	NS
Intraparenchymal hemorrhage	12% (5)	3% (2)	NS
Ventricular dilatation	14% (6)	16% (10)	NS
Periventricular leukomalacia	14% (6)	6% (4)	NS
Porencephaly	19% (8)	8% (5)	NS
Infarction	17% (7)	2% (1)	$p < .05$ ($p = .02$)
Congenital abnormalities	12% (5)	0% (0)	$p < .05$ ($p = .01$)

Note.—NS = not significant.

Results

The radiologic data are summarized in Table 3. Cerebral sonography was performed in 93% of the study group and 87% of the control group. By matching the study and control groups for gestational age, we eliminated the higher rate of occurrence of prematurity. This allowed us to determine if maternal cocaine use is associated with intracranial abnormalities other than those seen with prematurity (e.g., germinal matrix hemorrhage).

The frequency of the various forms of intracranial hemorrhage, PVL, porencephaly, and ventricular enlargement was not significantly different between the study and control groups although the frequency of IPH, PVL, and porencephaly was higher in the study group (Table 4). The frequency of infarctions and congenital abnormalities was clearly higher than in the control group and statistically significant (Table 4). Sonography identified seven cortical infarctions in the study group within 72 hr of birth compared with one in the control group. All seven infarcts were confirmed on CT (four bland, Fig. 1; three hemorrhagic, Fig. 2) and two also had MR. Neonatal and/or maternal cocaine screens were positive in six of the seven cases of infarction. Maternal use within 48

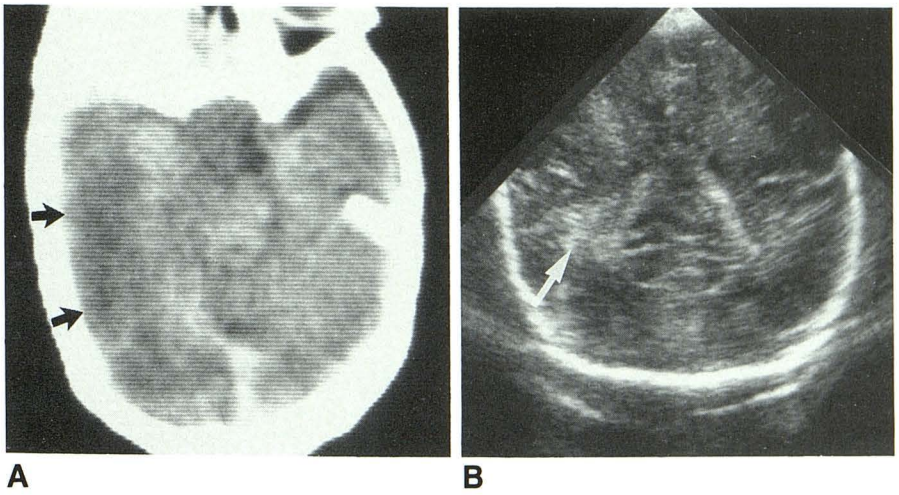

Fig. 1.—32-week gestational age male infant with a right temporoparietal infarct.

***A*, Axial unenhanced CT scan. Note lucency of right temporoparietal lobe (*arrows*), which involves the cortical mantle.**

***B*, Real-time sonogram in coronal plane. *Arrow* marks hyperechoic area of ischemia in right temporoparietal lobe.**

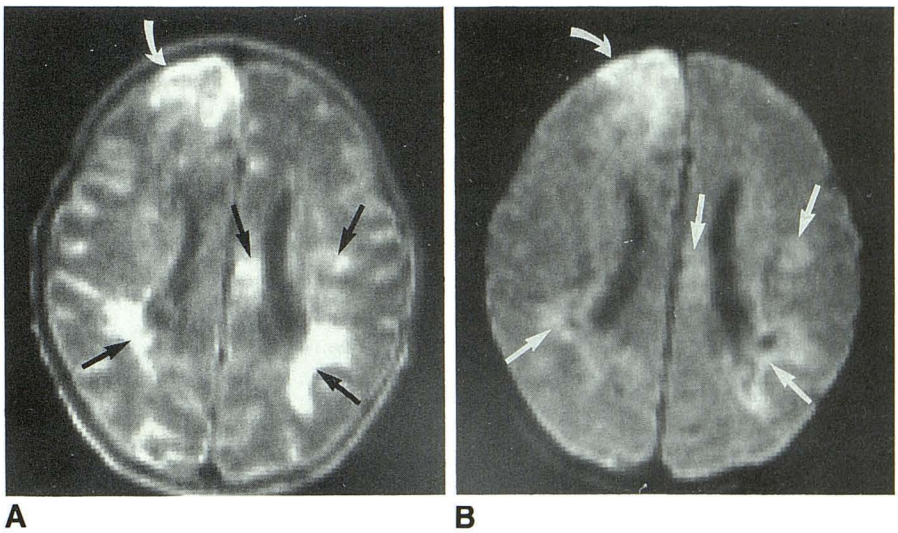

Fig. 2.—37-week gestational age female infant with a hemorrhagic right frontal infarct.

***A* and *B*, Axial spin-echo T1-weighted, 500/20 (*A*), and T2-weighted, 2000/60 (*B*), MR images. *Curved arrows* show hemorrhagic right frontal cortical infarct. *Straight arrows* indicate bilateral hemorrhagic periventricular leukomalacia (which was bland on the initial CT scan done 4 days before). The cortical mantle of gray matter is particularly bright on this sequence owing to the window settings.**

hr of delivery was confirmed by history in all cases. No major congenital malformations (only one case of syndactyly) were found in the control group. Five major congenital malformations confined to the CNS were found in the study group. The most unique was a form of towering encephalocele (Fig. 3). A more conventional posterior encephalocele (Fig. 4) as well as a case of holoprosencephaly also occurred. Another unusual midline CNS malformation consisted of an intraspinal lipoma that communicated with a cutaneous ectopic penis at the level of the lower thoracic spine (Fig. 5). The last anomaly was a hypoplastic cerebellum. A nasofacial hemangioma (Fig. 6) developed after birth in one case.

Discussion

Many authors have reported on the apparent deleterious effects of maternal cocaine use on the fetus. The abnormalities have included increased rates of spontaneous abortion, abruptio placenta, prematurity, intrauterine growth retardation, low birth weight, and decreased length and head circumference [1–9]. A higher frequency of congenital malformations was also reported by several authors [1, 3–5, 10].

Conflicting reports of the teratogenicity of cocaine has been found in experimental animal studies. Mahalik et al. [11] found nontoxic doses of cocaine to be teratogenic in mice who exhibited midline skull defects such as exencephaly, split supraoccipital bones, anophthalmia, and malformed lenses as well as non-CNS defects such as cryptorchidism. The work of Fantel and Macphail [12], also with mice, did not support the hypothesis that cocaine possesses teratogenic potential. Church et al. [13] found both cephalic hemorrhages and CNS anomalies (unilateral anophthalmia and microcephaly) in cocaine-exposed rat fetuses that did not occur in the nonexposed group.

Bingol et al. [10] noted that cocaine abuse in humans significantly reduced the weight of the fetus, increased the

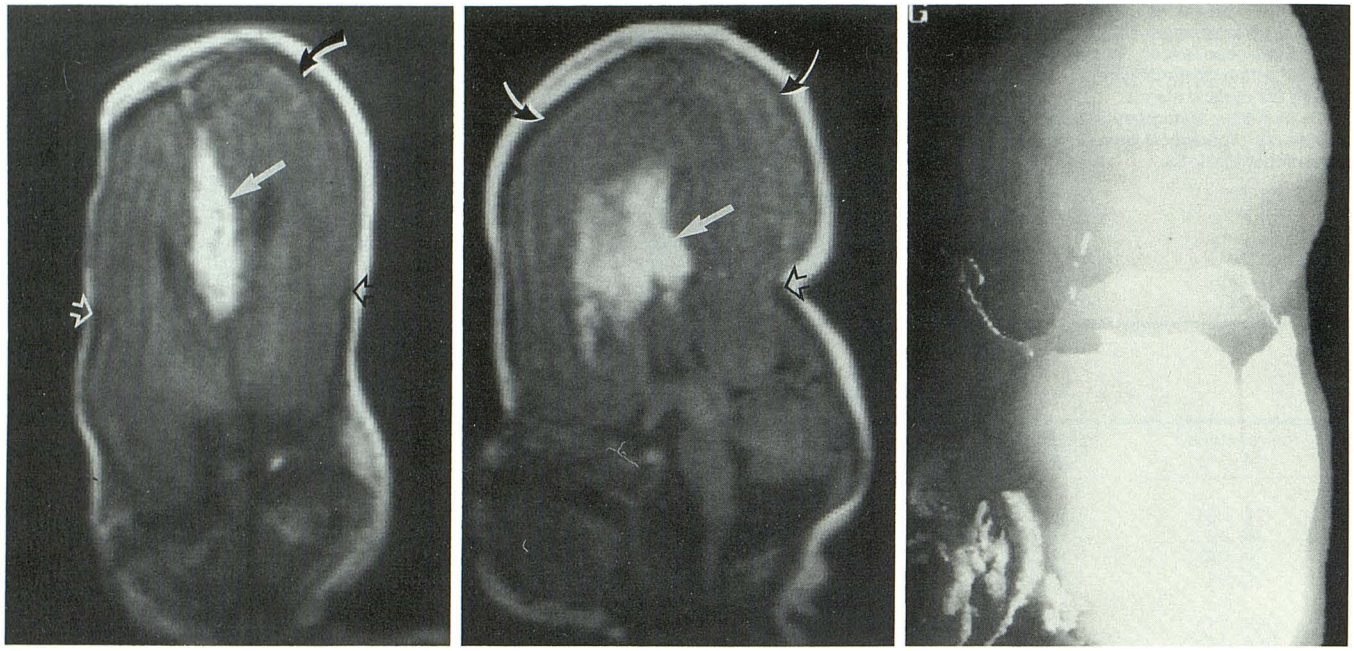

Fig. 3.—36-week gestational age female infant with a towering encephalocele, agenesis of the corpus callosum, and a midline lipoma.

***A* and *B*, Coronal (*A*) and sagittal (*B*) T1-weighted (500/20) spin-echo MR images. *Large white arrows* indicate hyperintense lipoma, which occupies the space of the absent corpus callosum. Note elevation of contents of posterior fossa as most of the supratentorial brain has herniated out through the skull defect. *Open arrows* indicate the hypointense edge of the termination of the skull. The hypointense rim about the herniated brain (*curved arrows*) is caused by CSF.**

***C*, 3-D CT reconstruction image shows large skull defect from a posterior aspect.**

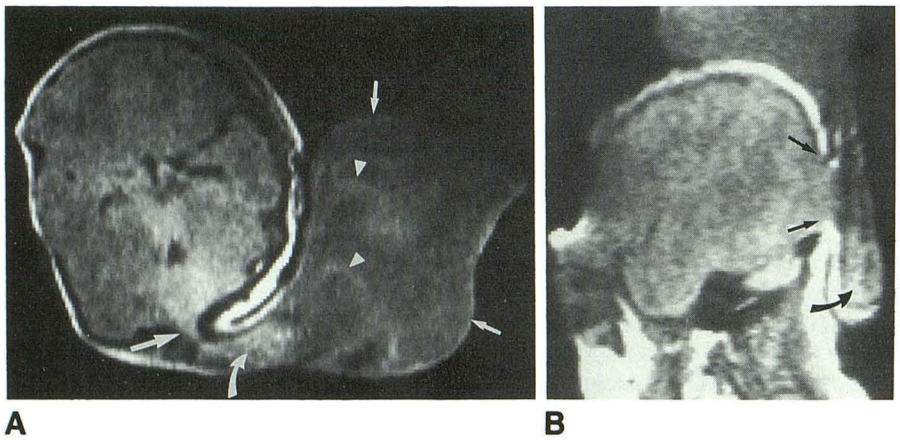

Fig. 4.—40-week gestational age female infant with a large posterior encephalocele.

***A* and *B*, Axial T1-weighted, 950/35 (*A*), and sagittal T1-weighted, 750/35 (*B*), spin-echo MR images. *Large straight arrow* indicates dehiscence in skull. *Curved arrows* indicate herniated cerebellum. The sac (*small straight arrows*) contains CSF and meninges (*arrowheads*).**

still-birth rate related to abruptio placenta, and was associated with a higher frequency of congenital malformations (10% versus 2% for the control group). The malformations were all midline CNS abnormalities, specifically, one case of exencephaly, one parietal encephalocele, and one case of skull dysraphism with parietal bone defects. Our findings were similar, with five congenital malformations (12% versus 0% for the control group, $p = .01$) confined to the CNS, including an unusual towering encephalocele (Fig. 3), a posterior encephalocele (Fig. 4), holoprosencephaly, a hypoplastic cerebellum, and a spinal teratoma (Fig. 5). Other authors who compared cocaine-exposed and nonexposed control groups found the rate of congenital malformations to be 5% versus 1.4% [1], 12.3% versus 0.8% [3], and 14% versus 0% [4, 5]. Many of these malformations involved the genitourinary tract.

Cerebrovascular events have been well documented in cocaine abusers [14–17] but have rarely been identified in the neonate after maternal use. A perinatal cerebral infarction was seen in a term infant after maternal cocaine use in the 72 hr before delivery [18], and an intracranial hemorrhage was identified by sonography in a term infant with a positive urine cocaine screen [19]. Seven cortical infarctions (four

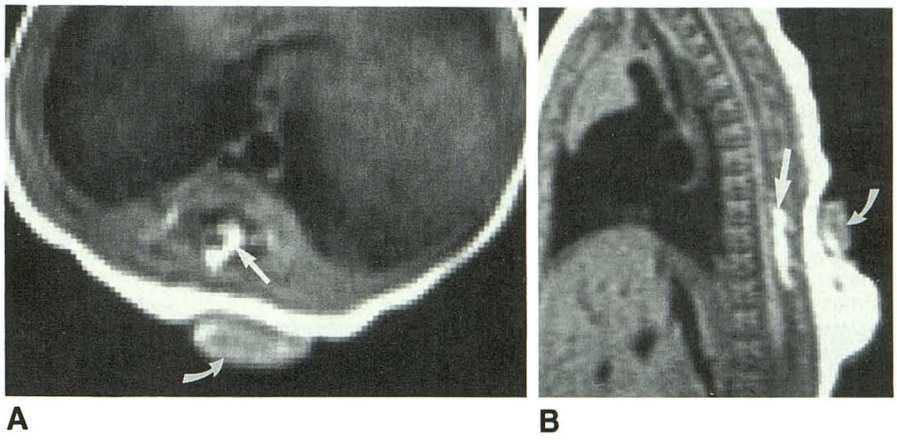

Fig. 5.—39-week gestational age male infant born with an ectopic penis protruding from lower thoracic spine.

***A* and *B*, Axial T1-weighted, 750/35 (*A*), and sagittal T1-weighted, 500/35 (*B*), spin-echo MR images. *Curved arrows* indicate ectopic penis. *Straight arrows* indicate associated intraspinal lipoma. The extra- and intracanalicular components were removed in toto and the pathology was consistent with a teratoma.**

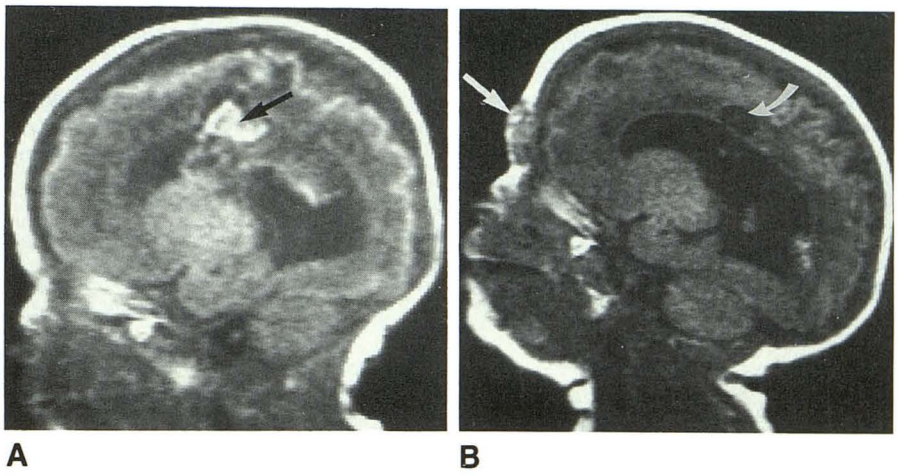

Fig. 6.—30-week gestational age female infant with subependymal, intraventricular, and intraparenchymal hemorrhages.

***A*, Sagittal T1-weighted (750/35) spin-echo MR image shows subependymal hemorrhage (*arrow*).**

***B*, Sagittal T1-weighted (600/35) spin-echo MR image obtained 2 months later shows nasal hemangioma, which has developed in the interim (*straight arrow*). *Curved arrow* points to cystic area, which has resulted from prior hemorrhage.**

bland, three hemorrhagic) were found in our study group (Figs. 1 and 2) compared with one in the control group ($p = .02$). Six of these cases had positive neonatal and/or maternal cocaine screens, and in each case the mother had a history of cocaine use in the 48 hr before delivery.

Cocaine raises catecholamine levels by inhibiting the reuptake of catecholaminergic neurotransmitters at the synaptic junction [11]. The excess catecholamines can cause vasospasm either in the placenta or the neonatal brain itself. Studies in pregnant ewes found that maternally administered cocaine produced dose-dependent increases in maternal blood pressure and decreases in uterine blood flow, reflecting uterine vasoconstriction. This resulted in fetal hypoxemia, hypertension, and tachycardia [20]. Cocaine has been shown to cause vasoconstriction of cerebral arteries in cats [21]. Hypoxia resulting from vascular constriction has been implicated in the pathogenesis of congenital malformations [22–25], usually causing an area of hemorrhage that involutes leaving behind a focal defect. This appears to be a likely cause of the anomalies seen with fetal cocaine exposure [26]. All the mothers in the study group were using cocaine at the time of conception through the first trimester. The neural tube develops during the third and fourth weeks of gestation so the potential for its involvement existed. It is postulated that placental or cerebral artery vasoconstriction from cocaine use in the first trimester resulted in the congenital malformations while vasospasm of the cerebral vessels at or near the time of birth accounted for the higher occurrence of ischemic events.

Although this study is retrospective and urine cocaine screens were not universally obtained, the findings support the work of other authors. Cocaine has a teratogenic potential and a tendency to cause cerebral vascular events in the neonate. In view of the current crack epidemic, the investigation of neonatal stroke and neural tube defects should include a history of drug use and urine screening.

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