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REVIEW ARTICLE

Prenatal exposure to cocaine: review of the neurobehavioral effects

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Abstract

Objective: to study prenatal cocaine exposure, emphasizing its behavioral effects.

Methods: literature review of the last 15 years, through Medline and direct search.

Results and conclusions: according to the literature, the incidence of prenatal cocaine exposure is up to 15.5%, and its effects on the newborn are particularly on the development of the nervous system. Pediatricians and sub-specialists must know the consequences of such exposure in order to diagnose and affect the prognosis of these children.

J Pediatr (Rio J) 2000; 76(3): 179-84: cocaine, maternal exposure, child behavior, child development.

Introduction

Prenatal exposure to drugs may potentially lead newborns to present symptoms related to intoxication or abstinence; this has been a significant public health problem since the 1970s and 1980s. From a historical point of view, the incidence of prenatal exposure to drugs has been decreasing. The literature shows a significant decrease in the prenatal exposure to cocaine, from 15%, in 1985, to 3%, in 1996. However, this decrease was observed only in populations that are not at risk.[1]

Even considering that the current rate of intrauterine exposure is 3%, the social and economical costs associated with this situation are extremely high, and deserve attention from professionals providing maternal and infant health care. In addition to the various negative effects of prenatal drug exposure on the health of pregnant women and of the newborn, studies show that neonatal costs increase up to 10 times in case of exposure. Psychosocial, medical and chronic learning problems are probably much costlier and more incapacitating among exposed children.[2,3]

Pharmacology

Cocaine – benzomethylecgonine, or cocaine hydrochloride – is an alkaloid derived from the leaves of the genus Erythroxylum. It is available as cocaine hydrochloride or as a highly purified alkaloid, or free-base cocaine, commonly known as crack. Cocaine hydrochloride may be taken orally, intravenously, or through aspiration; the free base is inhaled.

Cocaine crosses the hematoencephalic and placental barriers. In the brain, it reaches concentrations up to four times higher than the plasma concentrations.[4]

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The activities of hepatic and plasma cholinesterase enzymes, which metabolize cocaine, and as a consequence, the elimination rates, are lower in pregnant women, in fetuses and in newborn guinea pigs observed in experimental research. There are no reports of studies with human beings concerning this aspect. Newborns of mothers who used cocaine up to 2 days before their birth excrete cocaine metabolites for up to 7 days.[5] For the investigation of prenatal exposure, urine dosages detect such exposure within 72 hours; meconium analysis (during the last 2 trimesters of pregnancy), and more recently, hair testing in newborns, are able to detect prenatal exposure occurring as early as the 1st trimester of pregnancy.[6-11]

Cocaine acts through four basic mechanisms. First, it prevents adrenaline and noradrenaline uptake in the presynaptic nerve endings, triggering adrenergic effects and causing the main symptoms of intoxication (hypertension, tachycardia and vasoconstriction). The second mechanism prevents dopamine uptake through the presence of binding sites on the carrier, followed by dopamine accumulation in the synaptic vesicles; as a result, the dopaminergic system is activated, causing euphoria through the involvement of both the mesolimbic and the mesocortical ducts. In the case of chronic use, however, there is a decrease of dopamine in the nerve endings, causing dysphoria and constant craving for the drug. Cocaine also prevents the homeostasis of serotonine through the obstruction of the serotonine precursor tryptophan and of serotonine itself, causing sleep alterations such as decreased need and overlapping the excitatory effects of dopamine. Finally, the fourth mechanism acts on the peripheral nervous system, blocking the increase of sodium permeability and thus the propagation of nervous impulses. This has an anesthetic effect and probably determines some of the cerebral vascular effects of the drug.[5]

Mirochnick, in 1991, showed an increase in the activity of catecholamines in newborns exposed to cocaine, and Needlman, in 1993, found a significant reduction of dopamine metabolites in the liquor of newborns exposed to cocaine.[12,13]

Prenatal effects

The use of cocaine has deleterious effects on both the pregnant woman and the fetus. Usually, the consequences are multifactorial.

Hypertension, tachycardia, and maternal and fetal hyperthermia may occur as consequences or as direct effects of the drug. There may also be a decrease in the uterine blood flow, fetal hypoxemia, malformations, abortion, fetal death, premature separation of the placenta, prematurity, retarded intrauterine growth, decrease in the average length of the newborns, microcephaly, electrocardiographic disorders in the newborns, increased risk for necrotic enterocolitis, and sudden infant death syndrome. Still, cocaine use determines an increase in the rate of admission to neonatal intensive care units.[14-21]

Incidental factors such as poverty, absence of prenatal care, poor nutrition, congenital infections, concomitant use of other drugs, and mental disorders act synergistically, increasing morbimortality.[22-24]

Concerning the fetus, the development of each part of the brain occurs in eight stages, some of which continue after the birth. They are: induction of neural plaque, cellular proliferation (neurons and glia), cellular migration, cellular aggregation, neuronal maturation, synaptogenesis, cellular reduction or death and elimination process.[4] The brain itself develops in three stages, according to Volpe.[5] The first stage, named proliferative, occurs between the 2nd and 4th months of pregnancy for neurons and between the 5th month of pregnancy and the 1st year after birth for glial cells. In the second phase, cellular migration happens between the 3rd and the 5th months of gestation; and the third phase involves organization and remodeling. During this third stage, progressive events, such as synaptogenesis, are counterbalanced by regressive or remodeling events, and some unused cerebral processes are eliminated. This phase begins approximately at the 6th month of gestation and lasts for many years. It is critical for the final development of cerebral circuits. Most of the postnatal cerebral growth occurs during the first 3 or 4 years of life, but changes in myelination and in the cortical area continue throughout life.

Modifications resulting from traumatic interventions, due to either exposure to toxic substances or life events, are intimately associated with the central nervous system development stage during the period of exposure. Thus, exposure during the first half of gestation affects cytogenesis and histogenesis, and exposure after this period acts on cell differentiation and on the growth of specific cerebral areas.[4,25]

Cocaine may affect the formation and remodeling of the brain through an effect on the monoamine metabolism. It also acts on the ontogenesis of the neurotransmitter system. In human beings, at the end of the 2nd month of gestation, norepinephrine and serotonine may be detected. Monoaminergic neurons influence proliferation and cellular differentiation in the cerulean locus, in the raphe nucleus, and in the substantia nigra both in human fetuses and in animals. The treatment of pregnant guinea pigs with cocaine results in an increased density of catecholaminergic fibers in cerebral areas, such as the parietal cortex, the hippocampus, and the cingular cortex, although the clinical significance of this observation is not yet clear.[4,25]

Serotonine also influences neuronal development. The inhibition of serotonine synthesis is related to delays in cellular differentiation. Cellular cultures and in vivo studies have shown a reduction in the density of serotominergic fibers in the cortex and in the hippocampus in association with cocaine.[4]

Several behavioral disorders occur among exposed human beings and animals, which suggests a probable effect on the activity of dopamine, which has an important role in the modulation of activity levels.[4]

Research has demonstrated the existence of teratogenic effects on fetuses who were exposed to cocaine. The most frequent cerebral abnormality is microcephaly, caused by an alteration in cellular proliferation, reported in up to 16% of the newborns compared with 6% of the control group, even after statistical control of confusion factors. Symmetric intrauterine growth retardation occurs, even in an unusual form, in which the cephalic perimeter is proportionally smaller than the somatic growth. Exposure during neural tube formation, between the 3rd and 4th gestational weeks, may lead to the formation of myelomeningocele and encephalocele. Disorders in neuronal migration (3 to 5 months of gestation) and in prosencephalic development (2 to 3 months of gestation), such as corpus callosum agenesis, absence of septum pellucidum, septo-optic dysplasia, schizencephaly, optic nerve hypoplasia, dysgenesis and retinal coloboma have been reported. Dysgenesis and retina coloboma may be more frequent than suspected, since routine funduscopy is not performed in newborns, and the available imaging techniques do not detect these abnormalities. Still, disorders in nervous system differentiation (starting at the 5th gestational month), causing permanent disorders, such as problems in speech acquisition and memory, are shown in neurobehavioral, neuropharmacological, neurochemical, and physiological studies with guinea pigs and human beings. Until this moment, the basic mechanisms causing these teratogenic effects are not known, but it is supposed that hypoxemia, alterations in DNA synthesis in some cerebral regions, as well as alterations in neurotransmitters may be involved.[5]

Destructive lesions may also affect the nervous system of exposed newborns. Cerebral infarctions, mainly in the medium cerebral artery region, occurring in variable periods of the prenatal period, have been reported in many studies.[5]. Dixon & Bejar, in 1989, studied a group of 32 newborns. Those authors performed cerebral ultrasonography during the first 3 days of the child's life, and observed cerebral infarctions in 6% of the patients, 16% with cavitary lesions, 12% with ventricular dilatations, 12% with subarachnoid hemorrhage, 12% with subependymary hemorrhage, and 12% with intraventricular hemorrhage.[26] In one study performed with very low-weight newborns, a higher risk for development of intraventricular hemorrhage was observed.[27] McLenan et al., in 1994, as well as King et al., in 1995, obtained contradictory results - they did not find any increase in the prevalence or gravity of intraventricular hemorrhages and of abnormalities in cerebral ultrasonography. The mechanism of these destructive lesions is multifactorial.[28,29] Hypoxemia, vasospasm, alterations in the sodium channels, and direct effects leading to neuronal death act concurrently.[5,30]

Postnatal effects

The existence of a cocaine abstinence syndrome has not been demonstrated yet. Therefore, it is believed that the effects observed among exposed newborns are related to the direct effect of the drug. Among adults, it is known that abstinence is mediated by neurotransmitters such as dopamine and serotonine, but no study aiming to characterize cocaine abstinence syndrome among newborns was published until the present moment .[1,31]

Electroencephalographic alterations were found in two studies.[32,33]

The study of neurobehavioral effects is very recent, and many contradictory questions persist, for example concerning effects related to each phase of the gestation, and also concerning the persistence of alterations and its relation with neurotransmitters. Exposure may have early effects, due to alterations in the development of the central nervous system. These early effects may be temporarily minimized through compensatory mechanisms or alterations; however, they become more evident as time goes by, since the central nervous system is unable to develop and sustain new capacities that have to be acquired.[4]

Concerning neurobehavioral effects, no differences between male and female newborns were observed. Characteristically, these infants are not very responsive, and when alert, they are easily irritable and have difficulty in interacting. They may present a neurological syndrome characterized by sleep alterations, tremors, feeding difficulties, irritability, and, eventually, convulsive crises; the syndrome is usually more accentuated on the 2nd day of life and it is autolimited.[4,5] Studies using the Brazelton Neonatal Behavioral Assessment Scale (NBAS) show altered states of consciousness, an increase in abrupt motor responses (startles), orientation and habituation difficulties; however, these results were variable and were not confirmed.[4,31,34]

The acoustic characteristics of the exposed newborn cry were studied by Lester et al., in 1991.[35] That study confirmed two behavioral patterns, one characterized by an increase in excitability as a direct effect of the drug, and the other characterized by depressed functioning, related to poor nutrition and to intrauterine growth retardation, to which these newborns were submitted. The excitable pattern presents longer cries, with a higher fundamental frequency; the depressed pattern is characterized by higher latency, lower amplitude, and more dysphonic characteristics.

In 1998, Lester et al.[24] reviewed 76 studies about the development of children exposed to cocaine during the prenatal period. All the studies reviewed were reports of original research including a control group, with adequate statistical analysis, published in indexed journals. Several measures were used to evaluate the infants,[24] such as NBAS, Neonatal Abstinence Score (NAS), Finnegan's Abstinence Scale, Bayley's Scale, Fenegan's Intelligence Test for Infants, development quotient, affection, ludic

activities, temper, Stanford Binet, mother/child interaction, sleep, care environment, McCarthy, habituation, Denver Development Screen, feeding, Movement Assessment Inventory, cry, glabella, and sucking. Among these, only NBAS and the measurements of abstinence were used in more than 10 studies, and both were applied in the neonatal period. NBAS showed significant results in 10 out of 12 studies. However, the results were not confirmed among different studies; in addition, only 51% of the examiners were blind to the newborns' exposure status. Concerning abstinence rates, they were considered in 10 out of 18 studies, but they were probably related to the effects of the opioids to which the newborns had been exposed. Bayley's Scale did not show alterations in 5 out of 8 studies; and 7 out of 9 studies assessing temperament reported the presence of an effect associated with exposure to cocaine.

In 1993, a scale aiming to detect the particular characteristics of newborns exposed to intrauterine substances was created. This scale, called Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS), was based on other instruments, such as NBAS, Neurobehavioral Assessment of the Preterm Infant (NAPI), Assessment of Preterm Infant Behavior (APIB), Amiel-Tison's Neurological Examination of the Maturity of Newborn Infants (1968), and Prechtl's Neurological Examination of the Full-Term Newborn Infant (1977). The NNNS can be used to assess babies between 34 and 44 gestational weeks, and it was specially adapted to infants at risk. It is currently used in the Maternal Lifestyles Study, coordinated by the National Institute of Child Health and Human Development, in the United States. Napiorkowski et al., in 1996, used the scale to describe alterations in muscular tonus and motor capacity, stress signs, as well as the excitability and lethargy patterns described above.[36]

Alterations in the respiratory pattern and in the excitability of the exposed newborns have shown an association with the incidence of sudden infant death syndrome. Five studies reported an incidence of 15%, 0.9%, 0.8%, 0.5%, and 0.4%.[5]

Long-term effects

Very little is known about the effects of prenatal exposure to cocaine during child development. The few studies published so far are inconclusive and present methodological flaws.

The main topics analyzed in follow-up studies concerning these infants involve the concomitant use of various drugs, confusion and intensifying factors, as well as protective factors.

Family problems, violence, and the quality of maternal responses (which is intimately associated with the mother's educational level) have been shown to be the main factors that modify the effects of exposure to the drug.

Lester et al. report that out of 9 studies in which exposed infants were followed until age 3 to 6 years with the usual cognitive development tests, only one showed a significant effect, with lower scores.[24,37,38] In 7 of them, a subscale was applied to evaluate speech, and a significant difference was found in 5 cases. Differences in speech increased until the age of 4 and a half.

Higher levels of anxiety, depression, abstinence and stress symptoms were reported by the mothers, as well as difficulty in concentration, cooperation activities, and auto-regulation.

A confused attitude was observed during the play session, as well as less representational play. Bayley's Scale applied at 2 years of age did not show significant differences. The Psychomotor Development Index (PDI) applied at 30 months of age did not show differences between exposed and non-exposed infants.

The study of protective factors started in 1990, and the first results were published in 1996.[39] The main factors resilience that were found are summarized below:

- adequate diagnosis of the problems faced by the family and the child;
- non-judgmental attitude on the part of the professionals providing care in each specific case;
- realistic expectations within the personal possibilities of the child and his/her parents;
- decreased prenatal exposure, adequate treatment of the parents and recovery of the parents;
- early success in the improvement of autoregulation and mutual regulation activities between the infant and the caregiver;
- secure attachment and adequate responses to the infant's needs;
- non-exposure to home violence;
- specialized support to parents and to professionals who work with these families;
- child care provided by an individual pediatrician or professional who has a positive relationship and access to the child, instead of care provided by a team.

Conclusion

The data available until the present moment result from studies involving infants, and follow-up studies are rare. Cocaine exposure is a risk marker, and it reflects environmental factors that affect child development. The available studies are not able to differentiate drug effects from environmental effects. In addition, some consequences of cocaine exposure, such as low birth weight, may affect behavior.

Despite the methodological flaws, research has shown an association between cocaine exposure and neurobehavioral effects, although these tend to disappear with time.

The newborns' brain is able to adapt and to counterbalance at least some biological insults. Together, cerebral plasticity and adequate care may counterbalance some or all the consequences of exposure.

Future perspectives

Currently, follow-up studies with exposed newborns are being performed. The main emphasis of these studies is on the identification of resilience factors and of the actual effects of the drug, eliminating confusion factors.

In Brazil, these data motivated investigators from the Graduate Program in Pediatrics at Universidade Federal do Rio Grande do Sul to develop a research protocol to 1) study the epidemiology of prenatal exposure to cocaine, and 2) describe the specific neurobehavioral characteristics of exposed newborns in their setting. This study is being performed by the authors of this review and is on the final stages of data collection.

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