Developmental Consequences of Maternal Drug Use During Pregnancy

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The consumption of psychoactive substances during pregnancy has a negative impact on fetal growth. Heroin, methadone, and heavy alcohol consumption during pregnancy are associated with lower birth weight and central nervous system (C NS) dysfunction. Recent evidence suggests that marijuana use also may be associated with lower birth weight No information documents the impact of cocaine use on fetal outcome.

This paper will primarily present information pertaining to the identification of the major independent variables associated with developmental outcome for infants exposed prenatally to a variety of drugs Information regarding developmental assessment will also be presented.

STRUCTURAL TERATOGENICITY-FEATURES COMPATIBLE WITH FETAL ALCOHOL SYNDROME

In addition to lower birth weight, infants of mothers who consume large amounts of alcohol during pregnancy may exhibit a pattern of physical anomalies referred to as the Fetal Alcohol Syndrome (FAS). Because the reported incidence of the syndrome is rare (between 1 and 2 per 1000 live births), criteria developed by Hansen et al (1978) are used to classify infants as having features compatible with the fetal alcohol syndrome (CFAS). This classification is an attempt to identify an association between lower levels of drinking and less extensive fetal involvement. Each infant is rated according to the following criteria: 1) small size for gestational age (weight, length, or both, less than the third percentile); 2) microcephaly (head circumferences less than the third percentile); 3) short palpebral fissures Class than 1.8 cm wide in infants >36 weeks' gestational age); and 4) multiple dysmorphic features, judged by clinical observation, including: broad low nasal bridge, epicanthic folds, thin upper lip, hypoplastic philtrum, small nails, limitation of joint movement, large hemangiomas, altered palmar crease patterns, cardiac murmurs, and ear anomalies. Infants are classified as having features compatible with the fetal alcohol syndrome if rated abnormal on at least two of the four criteria. One of the two criteria must be either short palpebral fissures or multiple dysmorphic features.

CFAS features may not be specific to alcohol. Of 1,384 infants examined in a study (Hingson et al. 1982) of the effect of alcohol on fetal development, conducted at Boston City Hospita1 (BCH), 31 (2.3%) had features compatible with the fetal alcohol syndrome. Women who smoked marijuana during pregnancy were five times more likely than nonusers to deliver a child with CFAS features (p<.00l). Women who gained less than 5 pounds during pregnancy were 2.6 tines more likely to deliver a CFAS child than women who exhibited the mean weight gain in the sample (p<.00l). The relative risk for women who were expc8ed to roentgenograms was 2.8 compared with women who were not exposed (p<.02). In contrast, the relative risk for women who averaged two or more drinks daily compared with nondrinkers was 0.6 and not significant. This is the only study that the author is aware of that attempts to identify a possible association between factors other than alcohol and CFAS.

Features compatible with FAS may reflect a final common pathway of numerous agents or combination of agents rather than a specific teratogenic effect of alcohol. This may be more true with fetal alcohol effects, which are identified when two of three areas (growth, dysmorphology, and C NS related development) demonstrate abnormality. while some investigators consider the facial dysmorphology the most unique aspect of FAS, a recent report demonstrates the similarity between the facial appearance in FAS and the face of children born to mothers with phenylketonuria (Lipson et a]. 1981). In reviewing her work and other studies regarding craniofacial dysmorphogenosis, Sulik (1984) also concludes that the creation of the FAS phenotype may not be unique to alcohol. Animal studies suggest that teratogen exposure, such as might be seen with high levels of alcohol during the gastrulation (primitive streak) stage of development, results in the interference with the formation of the prechordal mesoderm. At this stage of development, teratogens must get to the embryo by diffusion, since the placenta is not yet formed. A teratogenic process at this stage of development will result in the craniofacial, brain, and eye defects noted in severe forms of FAS which is on the mild end of the spectrum of malformations which extends to holoprosencephaly (failure of cleavage of the prosencephalon, a primary brain vesicle in the embryo, with a deficit in midline facial development). Other agents, such as other drugs or radiation, or a combination of agents, may also interfere with embryogenosis at this stage. The commonly accepted association between alcohol and this constellation of dysmorphic features known as FAS may be because alcohol is the teratogen to which humans expose themselves most frequently. In summary, there is epidemiologic and animal data to suggest that alcohol may not be specific to either end of the spectrum of malformations associated with FAS.

VALIDITY OF SELF-REPORTED DRUG USE

The unreliability of self-reported drug use may explain the inconsistent association of the use of some drugs and fetal growth in the research literature to date. The association between low birth weight and certain substances, such as cigarettes, heroin, and methadone, is fairly consistent across studies. The association of low birth weight and other substances, however, such as the moderate use of alcohol and marijuana, differs from investigation to investigation.

A pilot study conducted at Boston City Hospita1 (Zuckerman et al, in press) raises questions about the validity of self-reported drug use. Seventy-five pregnant women were interviewed about their consumption of marijuana and other drugs. In addition, a urine sample was analyzed for the presence of marijuana metabolites. The urine assay technique used detects marijuana metabolites 5 to 7 days after smoking one marijuana cigarette. Eighteen women (24%) had urine samples positive for the presence of marijuana metabolites. Eight of these women (12.5%) reported not having smoked marijuana in the previous week. While all eight women reported having used marijuana at some point, four of them reported using marijuana prior to, but not during, their pregnancy. The other four acknowledged using marijuana during their pregnancy, but not during the week before the interview. Had we relied on self-reporting alone, we would have missed 15% (4 of 27) of the women who used marijuana during pregnancy. The misclassification of 15% of women who did consume marijuana during pregnancy might result in an underestimation of an association between marijuana use and neonatal growth.

This B C H study also found a greater percentage of pregnant women reporting marijuana use, smoking cigarettes, and drinking alcohol during pregnancy than did a 1977-79 study (Hingson et al. 1982) at BCH (table
1). There are four possible, not necessarily mutually exclusive, explanations for the discrepancy between these findings 1) Awareness that their self-report might be confirmed by urine assay may have prompted more women to report their substance use accurately in the 1983 sample, compared to the earlier study: 2) Demographic differences between the two study populations may account for the different patterns of substance use identified; 3) Health habits during pregnancy may be determined more accurately by prenatal rather than postpartum interview, because there is less risk of recall bias; and 4) True changes in drug use during pregnancy from the late 1970s to the early 1980s may be reflected in this data.

The first explanation is consistent with the bogus pipeline paradigm (Jones and Sigall 1971) that involves connecting subjects to a fictitious lie detector type device. Subjects are then asked to report their feelings and attitudes toward topics likely to alicit highly socially desirable responses. Various studies demonstrate that participants in the bogus pipeline condition give more truthful responses to questions subject to high social desirability bias than those asked to answer without a lie detection type device (Quigley-Fernandez and Tedeschi 1978). The higher rate of reported drug use in our recent study may be due to women’s knowledge that their urine was to be assayed. Correspondingly, the lower rate of drug use in our previous study may be due to underreporting because of social stigma attached to the illegal status of some of the drugs. Pregnant women, particularly, may feel pressure to underreport certain health habits if they believe thc6e habits will damage their unborn infant.

One could speculate that in the absence of urine samples, people might systematically underreport drug use. The effects of underreported factors may be underestimated or incorrectly attributed to other habits. Specifically, if Illicit substances such as marijuana or cocaine are more

TABLE 1

Self-Reported Substance Use Any Time During Pregnancy

	Boston City Hospital Pilot Project Study	June 1983+
Substance Use During Pregnancy Feb. 1977-Oct. 1979*		
	N=1690	N=75
Marijuana	14%	31%
Cigarettes	48%	60%
Psychoactive Drugs	1%	11%
Alcohol	38%	64%

* Hingson et aLl982
\+ Zuckerman ~ al, in press

often underreported than legal substances, such as alcohol or cigarettes, researchers may misattribute the effects of illicit psychoactive substances to alcohol and cigarettes. This may help explain the reported consistency in the association between cigarette smoking and lower birth weight. and the lack of consistency in findings concerning the effects of other either illicit or socially undesirable substances upon birth weight The accurate determination of such substance use is critical to the interpretation of our ongoing study and all previous work in the field. We are conducting a methodological trial to assess the impact of urine testing upon the reporting of cigarette, marijuana, alcohol, cocaine, and other psychoactive drug use during pregnancy. Our hypotheses are 1) More pregnant women will report drug use when they know their urine will be tented; and 2) the impact of the urine assay will be greater for drugs that are illegal or considered l~ socially desirable. Use of illicit drugs, such as marijuana and cocaine, will be underreported more often than alcohol consumption or cigarette smoking when urine tests are not obtained.

BEHAVIORAL TERATOGENICITY-NEUROBEHAVIORAL ASSESSMENT OF THE NEONATE

The Neonatal Behavioral Assessment Scale (NBAS) developed by Brazelton (1973) is the most commonly used assessment of neonatal neurobehavioral functioning. The scale assess 20 reflexes and 26 behavioral items, such as the ability of the neonate to habituate to stimuli; to orient to social and nonsocial stimuli to regulate states of arousal, vasomotor functioning, and activity level4 and to exhibit social behaviors, such as smiling or cuddling. A newborn’s neurobehavioral

functioning is a reflection of genetic endowment coupled with intrauterine exposures and experiences. The scale has been extensively used in the fo1lo wing types of studies: 1) to evaluate the effect of prenatal and intrapartum effects on newborn behavior; 2) to relate newborn behavior to maternal responsivity; 3) to compare different clinical populations of infants; and 4) to determine the predictive validity of the scale to later developmental outcome. An important consideration in the use of the scale is the magnitude of decrements in performance. Behaviors are assessed on a nine-point scale. Differences in performance of l~ than one point may not be clinically significant. This is a special problem when large numbers of subjects are assessed, and statistically significant differences in behavioral functioning may not be clinically significant.

The behavioral teratogenicity of prenatal opiate ingestion is described in terms of a withdrawal syndrome. Specific behavioral characteristics of opiate addicted newborns identified by the NBAS include numerous state changes, tremors, motor in maturity, decreased alertness, decreased ability to habituate to stimuli, and decreased auditory and visual orientation. (Soule et al. 1974; Strauss et al 1976; Chasnoff et al. 1982).

Alcohol consumption during pregnancy is associated with infants who have poorer ability to habituate and have a lowered level of arousal (Streissguth et al 1983). Using a special pressurized mattress, neonates of mothers who were heavy alcohol users during pregnancy demonstrate poorer state regulation as manifested by a decrease in total amount of sleep and an increase in the fragmentation of sleep periods (Rosette et al 1979). Fried (1980) demonstrated that infants of mothers who used marijuana during pregnancy were less likely to respond to and habituate to repeated visual stimuli than infants of mothers who did not use marijuana during pregnancy. The infants exposed to marijuana in utero also demonstrated more tremors and startles. Finally, in a study of the effects of prenatal exposure to smoking, caffeine, and small amounts of alcohol, Jacoteen (in press) demonstrated independent effects on behavior by alcohol and caffeine, but not cigarette smoking. The obvious withdrawal symptoms of opiate-exposed newborns and these studies which control for confounding variables suggest a behavioral teratogenetic effect of prenatal drug exposure of the specified agents. The independent effect of marijuana remains to be conclusively demonstrated.

It cannot be ascertained from these findings whether the observed behavioral differences reflect permanent CNS damage, or a transient drug or withdrawal effect on CNS functioning. Even if the behavioral dysfunction is transient. it may have an indirect effect on later childhood functioning via mother-infant interaction. For example, a decreased ability for an infant to habituate may result in a more irritable infant. Excessive crying is reported as the reason for battering by 80% of the abusing parents whose infants are less than 1 year old (Weston 1968). Infants with poor arousal may not elicit sufficient care-taking (stimulation and nutrition) from their mothers, which may contribute to a cycle of failure to thrive. This cycle may be compounded when a mother is less sensitive to her infant’s signals because of her own drug use.

CONSEDERATIONS REGARDING DEVELOPMENTAL ASSESSMENTS

Developmental outcome studies should include repeated assessments over time. An assessment at any one point in time can only demonstrate a dysfunction at that time; one cannot assume that a particular symptom, delay, or dysfunction will endure over time. For example, the Bayley Test of Infant Development only becomes modestly predictive of early school age LQ. at 18 months. The study of children asphyxiated at birth demonstrates this point (Corah et al 1965). Compared to nonasphyxiated children, children suffering from asphyxia had more neurobehavioral signs at birth, and, at 3 years of age, scored lower on all tests of cognitive function and had more positive neurologic findings. However, when reassessed at age 7, significant LQ. differences had disappeared between the anoxic group and control population. Similar findings are reported between children with neonatal hyperbilirubinemia compared to controls. Children with hyperbilirubinemia had decreased motor development at 8 months and increased evidence of neurologic abnormalities at 1 year. However, there was no difference in LQ. scores and neurologic examination between groups at age 4 and 7 years (Ruben et al. 1979). These findings emphasize the value of repeated assessments and suggest plasticity of the central nervous system.

In addition to repeated assessments, numerous skills should be assessed to best understand a child's central nervous system functioning. A false conclusion about an adverse effect of an in utero exposure might be made if only I. Q. scores are used. I. Q. scores reflect a summation of numerous skills. Children with learning disabilities may have significant deficits in their perceptual or language functioning, but have an average LQ.. In utero exposure to a drug may result in a significant CNS deficit in one area of functioning, which is balanced by a strength in another area. Multiple areas of functioning should be assessed. Developmental assessment should include age appropriate assessment of perceptual$_1$ cognitive, and motor skills; speech and language abilities; and behavior (especially attentional abilities). Laboratory assessments of attention in young children may be a more sensitive indicator of future cognitive or memory functioning than developmental testing.

In addition to these clinical assessments, newer physiologic techniques such as evoked responses (somatosensory, visual, and train stem auditory), Electroencephalogram (EEG), Brain Electrical Activity Mapping (BEAM), Positron Emission Tomography (PET Scanner), and Nuclear Magnetic Resonance (NM R), may prove to be important adjuncts in assessing central nervous system functioning more objectively and with greater sensitivity in both neonates and older children. Neonatal assessments are especially important because postnatal. factors are less likely to confound the results. These electrophysiologic techniques have an added advantage of being able to be used in the neonatal period.

MULTIFACTORIAL MODEL FOR DEVELOPMENTAL OUTCOME

Outcomes measured in the neonatal period can be ascribed best to intrauterine events. Low birth weight is the major adverse outcome described for numerous substances, such as cigarettes, alcohol, heroin,

and marijuana, used during pregnancy. The significance of low birth weight is its association with increased infant mortality and morbidity. The Select Panel for the Promotion of Child Health (1981) reported that very low birth weight is among the most significant predictors of later developmental deficits. However, correlations between birth weight and developmental outcome demonstrate conflicting findings due in part to methodologic differences among studies (Kiely and Paneth 1981).

Few studies have assessed the relationship between substance use during pregnancy and developmental outcome. At 18 months of age, children born to methadone-maintained mothers had more neuralgic signs and significantly lower scores on the Bayley Test of Infant Development (Rosen and Johnson 1982). Retrospective studies have associated alcohol consumption during pregnancy with lower LQ. scores (Streissguth et al 1978) and learning disorders or hyperactivity (Shaywitz et al 1980). A prospective study of children exposed to alcohol in utero demonstrates a small but statistically significant decrease in their scores at 8 months on the Bayley Scales of Infant Development (Streissguth et al 1980).

Research in the past 20 years on the outcome of newborns with perinatal complications and low birth weight provides an important source of information to understand better the developmental consequences of drug exposure during pregnancy. Pasamanick and Knobloch (1966) coined the term “continuum of reproductive causality’ to describe the relationship between perinatal factors, such as anoxia, low birth weight. and delivery complications, to deviant development, such as cerebral palsy, epilepsy, mental retardation, and learning disorder. They demonstrated in a retrospective study that children having more serious conditions, such as cerebral palsy, had more obstetrical complications than children who had mild disorders, such as a learning problem. They proposed that the greater the perinatal insult$_1$ the greater the brain damage, and the worse the clinical condition. Subsequent prospective studies on anoxia and low birth weight do not completely support this entirely biologic explanation of outcome. For instance, infants with low Apgars (<5) at 5 minutes, demonstrate a four-fold increase in neurologic abnormalities at 1 year compared to infants with higher Apgar scores. However, 96% of the infants with low Apgars did not demonstrate any gross neurologic abnormality (Drage et al 1968). While hypoxic insult contributes to poor outcome for some children, the vast majority of children appear to do well$_1$ and individual prediction is limited. Other studies of low birth weight (Drillien 1964) and perinatal complications (Werner et al 1971) suggest that poor outcome is most likely to occur when the adverse condition is associated with low socioeconomic status of the family.

Perinatal complications can be considered somewhat analogous to prenatal drug exposure because both of these events can result in C NS damage. Perinatal asphyxia is associated with hypoxic-ischemic injury of the brain. Animal research has clearly documented an adverse impact of methadone (Zagon and McLaughlin 1978) and alcohol (Abel et al. 1983) on the developing brain. Animal research has also directly assessed the plasticity of the developing brain. When experimental lesions are induced in selected areas of adult monkey’s brain, the associated function is permanently lost. However, when these same lesions are

experimentally induced prenatally, the monkeys perform as well as normal animals (Goldman-Rakic and Galkin 1978). By injecting tritiated amino acids, Goldman-Rakic (1978) demonstrated the reorganization of CNS connections following a specific experimentally induced brain lesion. The process of C NS reorganization and four other possible pathways for recovery of function in infants with known CNS insult are reviewed by Saint James-Roberts (1979).

Sameroff and Chandler (1975) propose a transactional model of development to explain the perinatal risk research findings. This model states that developmental and behavioral outcome are due to ongoing reciprocal interactions between the organism and the environment. This model goes beyond a unitary model, which explains outcome either entirely by biologic or environmental factors. Research in the past 10 years has furthered the understanding of the developmental process by defining characteristics of the child, such as temperament and behavior, and the child's environment. including maternal depression, social supports, surrogate child care, and quality of the home environment. A recent study demonstrates that responsive caregiving is the most important factor associated with developmental competence at 5 years of age for low birth weight infants (Cohen et al 1982). Neonatal problems per se did not contribute to the developmental vulnerability of these infants.

One study directly controlled for the caretaking environment of drug using mothers by comparing four groups of children: a heroin-exposed group, a drug environment comparison group (children who lived with addicts or whose parents used heroin after the birth of the child), and two groups matched for perinatal complications and socioeconomic status. There were few differences between the in utero exposed children compared to the children exposed to the social environment of drug using caretakers (Wilson et a]. 1979).

To best understand the developmental consequences of prenatal drug exposure, one must understand both the in utero environmental effect (teratogenic effect on the brain) and the postnatal environmental effect (drug using caretakers). The effect of the social environment in research models must go beyond the measurement of socioeconomic status. More specific aspects of the caretaking environment. such as mother-infant interaction, social supports, etc., need to be included. Characteristics such as depression may be very important because there is a known association between depression and heroin-methadone, and marijuana use. Children of drug users may be subject to a double jeopardy. They may suffer in utero effects on their central nervous system associated with drug abuse and then suffer from poor environmental circumstances due to non-optimal parenting associated with a drug user's lifestyle. From a public health perspective, injuries are the leading cause of childhood morbidity and mortality. It has never been adequately studied whether children of drug-using mothers sustain more injuries. Do drug—using mothers provide the same level of supervision and compliance with safety guidelines as nondrug using mothers?

In summary, developmental outcome is the result of a complex interaction of a variety of factors. In utero exposure to certain

substances, best documented by studies using excessive amounts of heroin, methadone, and alcohol, represents a significant source of biological vulnerability. The valid identification of specific drugs associated with a behavioral or structural teratogenic effect on the fetus remain a source of methodologic concern. These drugs may interact synergistically, as well as with poor nutrition or health, to further impair optimal in utero growth. Many conditions associated with poor developmental outcome are more prevalent among people living in poverty, which further confounds the effect of prenatal drug exposure. These conditions include drug exposure, increased perinatal complications, congenital infections, and postnatal health factors such as lead exposure and malnutrition; social factors like maternal depression; lower maternal education; and less optimal caretaking environments. Studies that assess the developmental consequences of in utero drug exposure need to assess the variables that are associated with childhood outcomes, especially those variables that are more likely to be found among mothers whose lifestyles involve excessive drug use.

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