Exposure to Opiates: Behavioral Outcomes in Preschool and School-Age Children

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HISTORICAL OVERVIEW

The purpose of this chapter is to review current literature on the developmental outcomes of preschool and school-aged children prenatally exposed to opiates, and in so doing to provide a sense of where the field has been and directions for the future. Clearly, this is a challenging task; the literature is relatively sparse and was primarily generated in the seventies and early eighties. The majority of data for children between 3 and 6 years of age are from the work of a few groups of investigators: Kaltenbach and Finnegan of Philadelphia, Rosen and Johnson of New York, Strauss and colleagues of Detroit, Hans and colleagues of Chicago, and Wilson and colleagues of Houston. This work consists primarily of longitudinal studies that began in the mid to late 1970s and culminated in the mid-1980s. At present there are no prospective data available for school-age children. While it may appear reasonable to assume that the paucity of recent literature reflects a decline in opiate use among pregnant women, the reality is that the incidence of prenatal opiate exposure continues to be significant. In recent years, however, the focus has been on investigating the effects of cocaine exposure, often to the exclusion of differentiating whether a woman uses opiates in addition to cocaine. A review of the literature on prenatal cocaine exposure yielded fewer than five studies that identified whether opiates were used in addition to cocaine. Such an approach to the delineation of drug exposure is not unique to current investigations, but reflects a typical lack of specificity that is evident throughout the literature on prenatal exposure to illicit drugs.

Although the occurrence of newborn drug withdrawal associated with maternal opiate dependency has been known for over a century, the reemergence of heroin use in the late 1950s and early 1960s among women of childbearing age led to concern regarding the effects of opiates on the developing fetus. The advent of methadone maintenance

for pregnant opiate-dependent women in the early 1970s provided the impetus for investigations to determine both short- and long-term neurobehavioral effects of prenatal opiate exposure. The impetus was twofold: there was concern regarding potential risks to the progeny of methadone-maintained women, and women in methadone treatment programs provided accessible study populations. It is important to note, however, that methadone exposure does not preclude exposure to other psychoactive agents. Research investigating prenatal opiate exposure includes exposure to heroin, methadone, or both, and may also include exposure to amphetamines, barbiturates, benzodiazepines, cocaine, alcohol, nicotine, and propoxyphenes. For example, a study by Rosen and Johnson (1988) included three groups of pregnant women: women on methadone maintenance, nonmethadone-maintained polysubstance abusers, and those who used no drugs. However, within the methadone maintenance group, 12 percent used only methadone.

Prenatal Opiate Exposure and Perinatal Outcome

In a review of outcome data for preschool and school-age children exposed to opiates in utero, it is necessary to consider relevant neonatal and infant outcomes. Studies that have compared infants born to heroin-dependent women not maintained on methadone with infants born to heroin-dependent women receiving methadone have found higher birthweights in infants born to methadone-maintained women (Connaughton et al. 1975, 1977; Kandall et al. 1976, 1977; Zelson 1973). Kandall and colleagues (1976) reported a significant relationship between the first trimester maternal methadone dose and birthweight. This study suggests that methadone may promote fetal growth in a dose-related fashion even after maternal heroin use, whereas heroin itself is associated with fetal growth retardation. Stimmel and colleagues (1982) analyzed the birth records of 239 infants born to narcotic-dependent women on supervised methadone maintenance, women on unsupervised methadone maintenance, women on street heroin, and women who were polydrug users. They found that perinatal outcome was significantly improved in those infants born to women on supervised methadone maintenance as compared with all other groups.

In general, studies that have compared methadone-exposed infants and nondrug-exposed infants have yielded consistent findings. Studies that compared methadone-exposed infants with nondrug-exposed infants found that methadone-exposed infants had lower birthweights than comparison infants. Remarkably, the mean birthweights for methadone-

exposed infants across these studies were relatively the same, with a range of 2,830 to 2,882 grams (gms) (Chasnoff et al. 1982; Hans 1989; Kaltenbach and Finnegan 1987; Lifshitz et al. 1983), although two studies reported somewhat higher birthweights. Strauss and colleagues (1975) found no difference in birthweight between methadone-exposed (X = 3,005 gm) and nondrug-exposed (X = 3,203 gm) infants. In a study by Rosen and Johnson (1982) in which methadone-exposed infants and a drug-free comparison group were matched for weight (±250 gm), the mean birthweight for methadone-exposed infants was over 3,100 gms.

Neonatal Abstinence

Infants born to heroin- or methadone-dependent mothers have a high incidence of neonatal abstinence. Neonatal abstinence is described as a generalized disorder characterized by signs and symptoms of central nervous system (CNS) hyperirritability; gastrointestinal dysfunction; respiratory distress; and vague autonomic symptoms that include yawning, sneezing, mottling, and fever. Neonates undergoing abstinence often suck frantically on their fists or thumbs, yet they may have extreme difficulty feeding because they have an uncoordinated and ineffectual sucking reflex. Infants who undergo abstinence generally develop tremors that are initially mild and occur only when the infant is disturbed, but which progress to the point where they occur spontaneously without stimulation. High-pitched crying, increased muscle tone, and irritability develop (Finnegan and Kaltenbach 1992).

With appropriate pharmacotherapy, neonatal abstinence can be satisfactorily treated without any untoward neonatal effects. It has been recommended that an abstinence scoring system be used to monitor the passively addicted neonate in a comprehensive and objective way to assess the onset, progression, and diminution of symptoms of abstinence (Finnegan 1986; Finnegan and Ehrlich 1990; Finnegan and Kaltenbach 1992). However, the initiation, type, and duration of pharmacotherapy for the treatment of neonatal abstinence varies across studies. In addition, the relationship between maternal methadone dose and severity of withdrawal symptoms has not been clearly established. Wilson and colleagues (1981) reported that although the incidence of severity of neonatal abstinence was similar for heroin- and methadone-exposed infants, neonatal abstinence was of longer duration in the methadone-exposed infants. Ostrea and colleagues (1976) and Madden and colleagues (1977) reported a significant relationship between severity of neonatal withdrawal and maternal methadone dose. Kaltenbach and

colleagues (1990) examined maternal methadone dose during pregnancy and neonatal outcome and found no relationship between methadone dose and severity of withdrawal.

Few studies have examined the relationship between severity of withdrawal and developmental outcome. Kaltenbach and Finnegan (1986*a*) found no relationship between severity of withdrawal and developmental scores on the Bayley Scale of Infant Development. Similarly, Lifschitz and colleagues (1983) reported no relationship between severity of withdrawal and cognitive outcome at 3 years of age. It is important to note that in both these studies infants were objectively assessed for abstinence and received pharmacotherapy when indicated.

Infant Studies

There have been a number of studies investigating the neurobehavioral and developmental outcome of infants exposed to opiates in utero. Procedures used in infant followup studies are quite similar. Children are evaluated throughout infancy, typically at 6-month intervals, with the Bayley Scales of Infant Development (Bayley 1969). Children born to nondrug-dependent women from comparable socioeconomic and racial backgrounds are used as comparison groups.

Overall, most studies suggest that infants through 2 years of age function within the normal range of development. Strauss and colleagues (1976) found both methadone-exposed infants and comparison infants scored well within the normal range on the Bayley Mental Development Index (MDI) and the Motor Development Index (PDI) at 3, 6, and 12 months of age. PDI scores for the methadone-exposed infants, however, declined with age and differed from comparison infants at 12 months of age. Wilson and colleagues (1981) also found no difference in MDI scores at 9 months of age, but found lower PDI scores for the methadone-exposed infants. Although Rosen and Johnson (1982) found no difference between groups on MDI and PDI scores at 6 months of age, they found methadone-exposed infants to have lower MDI and PDI scores at 12 and 18 months of age. In a sample of 2-year-olds, Hans (1989) found no difference in MDI scores, but methadone-exposed infants had lower PDI scores and poorer gross and fine motor coordination as measured by the Bayley Infant Behavior Record (IBR). In comparison, Hans and Marcus (1983) reported no differences between groups in MDI or PDI scores at 4 and 12 months of age; Chasnoff and colleagues (1984) reported no difference in MDI or PDI scores at 3, 6, 12, and 24 months of age; and

Kaltenbach and Finnegan (1986*b*) found no difference in MDI scores at 6, 12, and 24 months of age.

Such diverse findings often reflect the numerous confounding variables that exist within these studies. Mothers differed on amounts of daily methadone dose, length of methadone maintenance during pregnancy, type and quantity of polysubstance abuse, amount of prenatal care, and obstetrical complications. The use of pharmacological intervention for neonatal abstinence was not consistent with variations in initiation, type, and duration of treatment. The effect of the caretaking environment on children in substance-abusing families has also been identified as a critical factor that must be taken into account.

Additionally, some of the diverse findings may be explained by differences in the sample populations within studies. Although the infant studies are presented as longitudinal in design, the difficulties inherent in subject retention for this population often result in different sample compositions at different age points. The Rosen and Johnson (1982) study reported data gathered at 6, 12 and 18 months of age. Although all of the subjects were enrolled in the study at birth, data for the age points did not necessarily include repeated assessments of the same infants. Conversely, the length of time required to obtain longitudinal data may result in initial publications having smaller samples. The outcome data for 2-year-old infants reported in the Hans (1989) study was obtained from a larger sample (N = 74) that included infants (N = 39) from the Hans and Marcus study (1983) that reported on outcome at 4 and 12 months of age.

Studies of Preschool Children

The preceding discussion presents the context in which the review of the available preschool data should be considered. Wilson and colleagues (1979) reported differences between opiate-exposed children and three different comparison groups that included drug-naive subjects in drug-using households, a high-risk group, and a socioeconomic comparison group. This cross-sectional study assessed subjects between approximately 3 to 6 n years of age during a 5-month period. Maternal drug use was based on self-report, and hospital records were abstracted to obtain perinatal data.

The drug-exposed group (N = 22) was comprised primarily of infants born to women who used heroin continuously during their pregnancy,

with one-third of the women reporting concomitant abuse of other drugs. The drug environment comparison group (N = 20) consisted of infants born to women involved in the drug culture, either through their partner or their own heroin use subsequent to the birth of the child, but who reportedly used no drugs during their pregnancy. The high-risk comparison group (N = 15) consisted of nondrug-exposed infants who had medical risk factors similar to the heroin-exposed infants such as dysmaturity, intrauterine growth retardation, and fetal distress. The socioeconomic comparison group (N = 20) lived in the geographic area near the city hospital where they were born. Pregnancy and delivery were uneventful and mothers reported no history of drug abuse.

This study (Wilson et al. 1979) used an extensive battery of assessments, including the Illinois Test of Psycholinguistic Abilities (ITPA) (Kirk et al. 1968), the Columbia Mental Maturity Scale (Bergemeister et al. 1972), the McCarthy Scales of Children's Abilities (McCarthey 1972), and the Minnesota Child Development Inventory (Ireton and Thuirg 1974). Differences on the ITPA were found between the three risk groups and the socioeconomic comparison group but were within normal range. No difference between groups was found on the Columbia Mental Maturity Scale or Minnesota Child Development Inventory. However, the heroin-exposed children performed more poorly than the comparison groups on the general cognitive index (GCI) and on the perceptual, quantitative, and memory subscales. This study also included a videotaped 5-minute free play and structured doll-play situation in which no difference among groups was found in activity level or speech and language function.

Strauss and colleagues (1979) evaluated children from the original (Strauss et al. 1976) sample studied when the children were 5 years of age. These children were part of the original sample of newborns but were not neces-sarily in the sample assessed at 3, 6, and 12 months of age. Moreover, there had been no contact with the subjects for 4 years. Children in the drug-exposed group were born to methadone-treated heroin-addicted women participating in the Methadone Maintenance-Obstetric Care pro-gram; no other maternal drug use information was provided. Children were assessed with the McCarthy Scales of Children's Ability and a 15-minute videotape of behavior in the waiting room. No differences were found between methadone-exposed children (N = 33) and nondrug-exposed comparison children (N = 30) on the McCarthy GCI or any of the sub-scales. Scores for both groups were well below the standardization means (methadone-exposed children X =

87; comparison children X = 26). Videotapes of waiting room behavior were coded for children's playing and talking; interaction with caregiver and other children; wandering; and for mother's playing with child, positive/negative responses, initiation of interaction, and reprimands. No difference was found between the two groups of children or their mothers during the waiting room observation. However, the drug-exposed children were found to be more active, ener-getic, and immature, and displayed more task-irrelevant activity during the structured testing situation, as measured by a modified version of the IBR.

Other studies include longitudinal investigations in which the sample was enrolled at birth and assessed repeatedly throughout development. All of the studies reflect significant subject attrition from their original samples. Lifschitz and colleagues (1985) evaluated 92 children between the ages of 3 to 6 drawn from a previous (Wilson et al. 1981) sample. The study sample was comprised of a methadone-exposed group (N = 26), a heroin-exposed group (N = 25), and a drug-free comparison group (N = 41). The methadone-exposed infants were born to women enrolled in a methadone maintenance treatment program, and the heroin-exposed infants were born to heroin-addicted women who were not in a treatment program. Maternal drug use history included program records of daily methadone dose and results of qualitative urine screenings. Cigarette smoking and alcohol consumption were also assessed. Almost all (95 percent) of the women receiving methadone continued to use illicit and/or prescription psychoactive drugs. Cognitive development during the preschool years was assessed with the McCarthy Scale of Children's Abilities. Physical and psychosocial characteristics of the child's home were measured by the Home Observation for Measurement of the Environment (HOME) inventory (Caldwell 1972). Performance on the McCarthy GCI was comparable for all three groups (methadone-exposed children X = 90; heroin-exposed children X = 85; comparison children X = 89). Variables identified as predictive for cognitive performance were amount of prenatal care, prenatal risk, and the HOME inventory; the degree of maternal opiate use was not a factor.

Kaltenbach and Finnegan (1989) evaluated 47 children (27 methadone-exposed and 17 nondrug-exposed comparison children) from their longitudinal sample at 4 n years of age. The mean daily maternal methadone dose during pregnancy was 38.42 milligrams (mg), and 72 percent of the children required pharmacotherapy for neonatal abstinence. No difference was found between groups on the McCarthy

GCI or any of the subscales (methadone-exposed children X = 107, comparison children X = 106). These scores were higher than those reported in other studies, and are higher than one would expect for both groups considering that children from low socioeconomic backgrounds usually score lower than average on cognitive tests (Ramey et al. 1985). It may have been that mothers who continued to participate throughout the 5-year study were a self-selected sample of motivated mothers especially interested in their children's development and/or their ongoing participation provided an informal intervention.

Rosen and Johnson (1985) evaluated their longitudinal sample at 3 years of age. They were able to assess 62 children from their original cohort of 94. The methadone-exposed children (N = 39) and comparison children (N = 23) were assessed at 36 months with a 30-minute videotaped free play and structured-task situation and with the Merrill-Palmer Scale of Mental Tests (Stutsman 1931). They found no difference between groups on the Merrill-Palmer scores and percentiles. The videotapes were used to assess spontaneous language production. No differences were found between groups but the mean length of utterances (MLU) for both groups were lower than those reported for middle-class samples.

In general, by the late 1970's to mid-1980's, investigators began to move from a bivariate approach to a recognition that research needed to address the multiple factors that may have a direct or indirect effect on the out-come of children born to substance-abusing mothers.

A review article by Kaltenbach and Finnegan (1984) recommended that outcome studies investigating the effects of prenatal drug exposure should also take into account maternal characteristics, maternal psychiatric morbidity, degrees of life stress, patterns and stability of child care, and mother-child interaction. The later work of Lifschitz and colleagues (1985) was able to show that the outcomes of drug-exposed children do not differ from a high-risk comparison group when sociodemographic, biological, and health factors that are frequently altered by the narcotic user's lifestyle are taken into account. In a study by Johnson and colleagues (1987), path analysis was used to determine the impact of multiple variables such as maternal medical history, drug abuse, neonatal outcome, and family functioning characteristics on developmental outcome. Neonatal complications and social disorganization were found to have direct effects on outcomes at 36 months. This study suggested that in assessing outcomes of children born to substance abusers,

maternal drug use is not necessarily the most important factor; family characteristics and functioning play a significant role.

Future Directions

Before the potential of a multifactorial approach could be fully realized, research investigating the effects of prenatal opiate exposure basically ceased as concern shifted to maternal cocaine use. However, the data on the effects of prenatal opiate exposure indicate, overall, that opiate-exposed infants through 2 years of age function well within the normal range of development and that children between 2 and 5 years of age do not differ in cognitive function from a high-risk population. Moreover, the data consistently suggest that psychosocial demographic factors may have as much, or more, effect on development as maternal opiate use. Clearly this finding has provided a foundation for future research. Although the drug of choice (and hence the focus of investigations) may change, the effects of maternal substance abuse must be examined within an interactive context of biological, psychosocial, and environmental factors in order to fully understand the etiology of developmental effects.

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