Long-Term Effects of Prenatal Methadone Maintenance

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Methadone maintenance has been the treatment of choice for heroin addiction for several years. The prenatal and early neonatal effects have been described in several reports (Kandall et al. 1979; Finnegan 1983). However, there have been few reports on the long-term effects of methadone maintenance during pregnancy on the child's somatic and neurobehavioral development. Some investigators have described mild neurobehavioral abnormalities, while others have found none (Finnegan 1983: Wilson et al. 1981; Lifschitz et al. 1983; Strauss et al. 1979).

Since 1977, we have followed a group of children born to mothers on methadone maintenance during pregnancy and a matched group of children born to drug-free mothers. The children are now between 3j and 7 years old. This report covers in some detail our findings from the neonatal period through 36 months. The trends in the data that have been collected thus far on the children who have reached ages 4, 5, 6, and 7 years will then be discussed.

METHODS

Fifty-seven mothers on methadone maintenance were enrolled in the study during pregnancy. After delivery, their children were enrolled in the follow-up study. The 31 comparison mothers and their neonates were enrolled within 24 hours after birth and were matched to the methadone subjects for maternal race, socioeconomic status (SES), sex, birth weight, and gestational age. A total of 61 infants (30 females and 31 males) of methadone maintained mothers and 32 infants (15 females and 17 males) of comparison mothers were enrolled in the follow-up study. There were 4 sibling pairs in the methadone group and 1 sibling pair in the comparison group. By the time the child reached
36 months of age, the attrition rate was 36% in the methadone group and 28% in the comparison group. At the present time, in the 7th year of the study, the attrition rate is 43% for both groups. Comparisons were made between the lost and continuing subjects, and no significant differences were found in the prenatal and neonatal characteristics. Table 1 is a summary of the maternal and neonatal data at intake. Although the comparison mothers are significantly younger than the methadone mothers, both groups are well within optimal childbearing age. Another significant finding is that

methadone mothers smoke more than one pack of cigarettes/day with higher frequency than the comparison mothers. In the methadone group, maternal urines were analyzed during pregnancy for drugs of abuse, using the homogeneous enzyme immunoassay procedure (EMIT) (SYVA Palo Alto, Calif) and thin-layer chromatography. Multidrug abuse of such drugs as diazepines, opiates, cocaine, barbiturates, and tricyclics was evident in 56% of the methadone mothers. Fifteen percent were also moderate to severe alcohol abusers, as evaluated by frequent history taking. By 36 months, 10% of the mothers on methadone maintenance had discontinued their methadone use. Also, significantly more comparison mothers than methadone mothers were working and off welfare by 36 months (p<.O2).

TABLE 1

Maternal and Neonatal Data at Intake

Maternal Data	Methadone	Comparison
Age	26.8+5*	22+.9*
Race (%)		
White	7.3	3.6
Black	78.2	78.6
Hispanic	14.5	17.9
Obstetrical complications (%)	22.2	14.3
Methadone dose (mg/day)	42+3	
Months on methadone	43+3	—-
Multidrug abuse (%)	56	0
Tobacco (1 pack/day)	90*	28.6*
Neonatal Data		
Birth weight (gin)	3129+192	3037+101
Premature rate (%)	15.4	11
SGA (%)	13	3
Apgar score 1	7.4+.3	8.1+.l
Apgar score 5	8.5+.2	9.0+.1
Sex (n)		
Males	31	17
Females	30	15
Withdrawal syndrome (%)	75.1	—-
Severe (%)	23.3	
Moderate (%)	51.8	——
Mild (%)	24.9	——

* $p < .^{05}$

NEONATAL PERIOD

Procedures

All neonates had a physical and neurological evaluation within 48 hours of birth. Gestational age was determined by the estimated date of conception (EDC) when known and/or using Dubowitz criteria (1970). Severity of narcotic abstinence syndrome was evaluated using a withdrawal scoring system modified from one used by Finnegan et al. (1975) daily until discharge. In addition, Brazelton's Neonatal Behavioral Assessment Scale was administered to each infant between 48 and 96 hours after birth (Brazelton 1973).

Results

As illustrated in table 1, there was a higher incidence of small for gestational age infants and head circumferences below the third percentile in the methadone group ($p < .05$). These findings were not associated with alcohol intake or tobacco smoking. The incidence of narcotic withdrawal was 75%, with 75% of these cases exhibiting moderate to severe symptoms. In early infancy, at approximately 2 weeks of age, 20 infants of mothers on methadone maintenance developed elevated systolic blood pressure as measured using the Doppler. The mean systolic blood pressure was 95, with a range of 59 to 132 mm/Hg. This occurred irrespective of the severity of narcotic abstinence syndrome, and lasted for about 12 weeks. This systolic hypertension may be secondary to autonomic nervous system dysfunction as a result of in utero narcotic drug exposure (Rosen and Johnson 1982).

Correlations were run between prenatal and neonatal variables. Methadone dose and length of methadone maintenance correlated positively with the presence of obstetrical complications and the severity of narcotic abstinence syndrome ($p < .01$). Maternal methadone dose also correlated positively with birth weight ($p < .05$). The Brazelton Behavioral Assessments, done at 48 to 72 hours of life, revealed several differences between the methadone group and comparison group infants. The methadone neonates were less responsive to rattle decrement, less responsive to inanimate visual orientation, less alert, less cuddly, and less consolable. They also demonstrated increased tone, less motor maturity, increased pull-to-sit, and more tremulousness. Many of these findings were most likely related to the infants' experiencing narcotic abstinence syndrome. FOLLOWUP: 2 TO 36 MONTHS

Procedures

After birth, the infants were seen at the follow-up clinic at 2, 4, 6, 8, 10, and 12 months of age and then every 6 months. Each follow-up visit included physical, neurological, and behavioral evaluations, as well as routine well baby care. Emergency medical care and social service assistance also were provided when necessary.

In general, the physical and neurological examination covered growth parameters, cranial nerves, tone, gross and fine motor coordination, normal and abnormal reflexes, and developmental milestones. In addition, hospital and clinical charts were reviewed for emergency room/clinic visits and number and type of infections and referrals. The behavioral evaluation included the Bayley Scales of Infant Development, which was given at 6, 12, 18, and 24 months of age, and the Merrill-Palmer Scale of mental tests at 36 months. At 30 and 36 months, a 30-minute mother—infant interaction session, including both free play and structured task situation, was videotaped. Spontaneous language production in these tapes was analyzed, using Brown's (1973) procedures for computing length of utterance.

Results

During the first 36 months follow-up there were no significant differences in somatic growth among the two groups. There was a consistently higher incidence of head circumferences below the third percentile in the methadone group of children. Many of these children demonstrated eye disorders, such as strabismus and/or nystagmus. With respect to the rate of infections during the first 24 months of life, the methadone children had significantly more episodes of acute and chronic otitis media ($p < .OOl$). These episodes may have been due either to therapeutic noncompliance or to an early immune deficit. The neurological evaluations, summarized in table 2, showed a significantly higher incidence of abnormalities in the methadone children. These abnormalities included hypotonia or hypertonia, poor fine motor coordination, delays in attaining developmental milestones, and poor language development. The Bayley Scales scores are summarized in table 3. All mean scores were within the range for normal performance. However, the methadone group scored significantly lower on both the Mental Development Index (MDI) and Psychomotor Development Index (PDI) at 12 and 18 months, and on the PDI at 24 months ($p < .05$). To determine if there were differences in score distribution, the frequency of Bayley scores below 85 was examined in each group at both 12 and 24 months. Methadone children had disproportionately more low scores at 12 months in both MDI and PDI scales ($p < .O5$). Further analysis of the components of the Bayley Scales revealed that responsiveness to verbal requests from others by 12 months of age was only present in 18% of the methadone children as compared to 50% of the comparison children. The ability to express wants, usually present by 18 months, was evident in only 28% of methadone versus 47% of comparison children at this age (Rosen and Johnson 1982).

To evaluate consistency of neurobehavioral performance across measures and across time, correlations between Bayley MDI and PDI scores and neurological assessments were run for each subject group. In the methadone group, there were strong correlations between Bayley scores at different time points, as well as between the neurological evaluations and Bayley scores at both 12 and 24 months ($p < .05$ for all correlations).

TABLE 2 Neurological Evaluations (6-36 months)

| Age (mo.) | Suspect to Abnormal (%) | |
	Methadone	Comparison
6	(n~45)	(n=25)
	44.3	36
12	(n~46)	(n=22)
	22*	4.5
18	(n=38)	(n~23)
	18.3*	4.3
24	(n=39)	(n=21)
	20.6*	43*
36	(n=39)	(n=23)
	32	13

TABLE 3
Developmental Evaluations

I. Bayley Scales of Infant Development

	Methadone	Comparison
6 months	(n=41)	(n=23)
MDI	95+2.5	100.7+4.2
PDI	lOT.0+2.8	105.1+2.9
12 months	(n=41)	(n=22)
MDI	98.4+2.7	107.0+2.8*
PDI	94.9+2.5	102.8+2.3*
85 (MDI)	20%	
(PDI)	20%	
18 months	(n=38)	(n=23)
MDI	96+2.3	.106.4+3.6*
PDI	92.6+2.4	105.3+2.2*
24 months	(n=34)	(n=22)
MDI	90.4+2.6	96.9+3.1
PDI	99.1+2.7	108.is2.7*
85 (MDI)	39	15*
(PDI)	17	5

II. Merrill-Palmer Scale

36 months	(n=39)	(n=21)
NIPS	44.6+2.1	46.3+2.3
SPP	55.7+4.4	63.1+5.1
25%	18%	4%

*   p ~•.05

The relationship between various prenatal and neonatal characteristics and developmental outcome was further examined at 18 and 24 months. Perinatal variables included maternal age, length of methadone maintenance, methadone dose, multidrug abuse, obstetrical complications, Apgar score at 5 minutes, and severity of narcotic abstinence syndrome. There were no significant correlations between these perinatal variables and developmental outcome (Rosen and Johnson 1982; Johnson et al. 1984). An analysis of covariance in a regression mode indicated that treatment group (methadone vs. comparison) and sex (male vs. female) were the only factors related to poor developmental outcome (Rosen and Johnson 1982; Johnson et al. 1984). The scores of the Brazelton Neonatal Assessment Scale did not correlate with the 18 months neurodevelopmental outcome.

At 36 months there were no differences in the mean Merrill—Palmer scores and percentiles, although lower scores were more prevalent in the methadone group. Measurement of head circumference and the neurological evaluation correlated with the Merrill—Palmer scores.

Using the videotapes, an analysis of spontaneous language production with mean lengths of utterances (MLU) was performed at 36 months. The MLU was based on 50, rather than 100, utterances due to only 30 minutes of videotaping. However, even with this lower utterance requirement it was necessary to drop 5 methadone and 6 comparison children from the analysis. The mean MLU for the methadone children was $2.71 \pm .66$ and $3.14 \pm .66$ (p<.O7) for the comparison children. These MLU samples are lower than those reported for middle-class samples (Brown 1973).

Cluster analysis was used to determine whether the study population was comprised of homogeneous groups having distinct patterns of developmental outcome (Hartigan 1975). In this analysis, developmental outcome was defined by four variables: percentile head circumference, neurological examination, Merrill—Palmer Scales scores, and number of referrals for educational and/or developmental problems. The mean scores are illustrated in table 4. Cluster III, the group showing the weakest developmental status, consisted overwhelmingly of methadone children (85%) 5:1 ratio. This suggests that some children born to mothers on methadone maintenance demonstrate no long-term effects, while for others, their outcome is guarded. The factors that distinguish one group from the other are not yet known. We found no differences in Clusters I and Ill as far as prenatal and neonatal factors were concerned. At present, we are further examining the environmental and early experiences of these infants.
FOLLOWUP: 37 TO 84 MONTHS

Procedures

Children are seen for routine follow-up evaluations every 6 months, although the project continues to provide emergency medical care and social service assistance when needed. The focus of the physical and neurological evaluations remains on growth parameters, tone, motor coordination, and developmental milestones.

TABLE 4

Summary of Variable Means for 3-Cluster Analysis of

Continuing Subjects at 36 Months

Cluster	I	II	III
Head circumference (%)	61.5+13.7	32.5+7.1	6.0+5.2
Neurological evaluation @	1.4+.6	1.2+.5	1.4+.?
Merrill-Palmer score ~	52.1+14.7	45.1±9.4	41.0+9.7
Referral for Special Services @	0		
Number of methadone subjects (n=36)	9	10	17
Number of comparison subjects (n=18)	4	11	3

@   M±SD

The behavioral evaluations have concentrated on language and perceptual development. Between 42 and 60 months, children receive verbal and comprehension tests and the Perceptual Integration Test. At 66 and 78 months, the children receive three standardized measures of emerging skills. The first, the Boehm Test of basic concepts. measures mastering of basic relational concepts. The Boehm Test is widely used and has been standardized for inner-city children. The second measure is the Motor—Free Visual Perception Test (MVPT), which yields a perceptual quotient relating the child's perceptual development to his age. The third measure is the Northwestern Syntax Screening Test, which yields separate scores for receptive and expressive language skills. In addition, children receive the McCarthy Scales of Children's Abilities at 72 months, and the Wechsler Intelligence Scale for Children-Revised at 84 months.

Results

Because not all of the children have reached 84 months, results are preliminary. Again, there are no differences in height and weight between the methadone and comparison children. These children are generally healthy. There are three children with generalized lymphadenopathy of unknown etiology which, thus far, have yielded negative workups. Neurological evaluations, summarized in table 5, show a higher prevalence of abnormalities of fine and gross motor coordination, poor balance, hyperactivity, decreased attention span, and speech and language delays in the methadone children. Significance

was not determined as the numbers are still incomplete in each group. Table 6 is a summary of the behavioral evaluations. As the children approach school age, it appears that the differences between the two groups are diminishing. There is a trend toward lower scores in the Northwestern receptive language evaluations among the methadone children. There is also a higher incidence of referrals among the methadone children for behavioral and academic problems. Those children who showed poor neurological development at 18 to 36 months continue to do poorly at 37 to 84 months. As the comparison group children approach school age they have begun to show poor performance in testing. This has been reported by others in children from low socioeconomic class. There is no significant difference in the McCarthy Scales between the two groups. Further preliminary analysis of the McCarthy scores, in relation to the three clusters created, reveal the following: Cluster I means the GCI score was 100.7+4; Cluster II score was 83.6+3; and Cluster III score was 85.4+3. Those children in Cluster III continued to perform poorly. The children in Cluster II showed poor performance on the McCarthy Scales. This most likely reflects the deteriorating performance of the comparison children..

TABLE 5

Neurological Evaluations (48-72 months)

| Age (mo.) | Suspect to Abnormal (%) | |
	Methadone	Comparison
48	(n=36)	(n=19)
	44	32
60	(n=31)	(n=15)
	42	33
72	(n=20)	(n=9)
	50	11.1

DISCUSSION

The data from our study reveal no uniform long-term effects of prenatal methadone maintenance. In the first 36 months of life, however, children in the methadone group do exhibit a higher incidence of minor neurological abnormalities and lower scores on developmental evaluations. While the comparison children seem to do better during the first 36 months of age, their performance deteriorates as they approach school age. The methadone children show very little flexibility in developmental course. Children in the methadone group seem to continue early patterns of performance and developmental status without a change. Thus, despite exposure to similar prenatal as well as postnatal environmental stresses, some methadone children do well initially and throughout early childhood, while others do poorly

initially, and then continue to show poorer development. At the same time, however, various prenatal variables (e.g., use of other drugs, obstetrical history, and neonatal course) did not correlate with neurodevelopmental outcome. The methadone-exposed babies, born at high risk, have special needs which place extra demands on their mothers. However, many of these mothers themselves have many special needs and problems which make it very difficult for them to adjust to their infants' needs. Consequently, inconsistent mothering and unstable environments may further accentuate the effects of early infant characteristics (Thomas and Chess 1977). In examining further the characteristics of the children who did well on the Merrill-Palmer at 36 months, two factors emerged: maternal education and family stability. Other researchers have also reported on children who were born at risk, but who were able to overcome their handicaps because they were reared in stable environments with parents responsive to their needs (Sameroff 1975; Werner et al. 1968).

TABLE 6

Developmental Evaluations (66-78 months)

	Methadone		Comparison
MVPT PQ 66 mo. (n=13)	85.08+3.72	(n=6)	96.8+ 3.9
78 mo. (n=12)	95.8+ 3.7	(n=7)	98.4+ 7.3
Boehm % 66 mo. (n=12)	62.9+ 8.3	(n=6)	82.5+10.6
78 mo. (n=12)	31.5+ 6.9	(n=7)	39.3+10.4
NW Rec % 66 mo.(n=l0)	40.2+10.9	(n=5)	58.0+14.8
78 mo. (n=12)	41.9+ 7.2	(n=7)	28.4+ 7.9
NW exp % 66 mo. (n=10)	25.9+ 7.9	(n=5)	31.6+15.2
78 mo.			
MGCI 72 mo. (n=18)	89.22+3.4	(n=l0)	88.9+ 3.2

(M± SE)

In our study, as the children got older, the differences in mean scores between the groups have become smaller. This phenomenon has already been noted at 36 months on the Merrill-Palmer Scales and at 72 months on the McCarthy scores. This type of decline in scores has been shown in low SES children by others after 24 months (Bradley and Caldwell 1976). In analyzing individual tasks, however, the methadone children seem to have particular difficulty with tasks which are highly structured or involve verbal instruction. In summary, a child born to a mother on methadone maintenance is not only exposed to a drug or drugs in utero, but is also exposed to the continued emotional, familial, and environmental instability associated with the drug culture. This places the child at even greater risk for long—term developmental difficulties.

An examination of the interaction between prenatal factors, early experience, and environment should be used to plan intervention and treatment programs to enhance the subsequent development of these children.

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