Effects of Maternal Narcotic vs. Nonnarcotic Addiction on Neonatal Neurobehavior and Infant Development

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There is no question that the number of women using and abusing nonnarcotic drugs far exceeds the number who are addicted to narcotics (Chambers and Hart 1977). Current data show that 63% to 93.5% of women use analgesics during pregnancy and that sedative drug use ranges from 22% to 28% (Doering and Stewart 1978; Forfar and Nelson 1973; Hill 1973). However, until recently, little attention has been given to pregnancies complicated by the maternal use of drugs other than heroin and methadone.

At the Perinatal Addiction Project of Northwestern Memorial Hospital, the last 5 years have seen a rapid increase in the proportion of women enrolling in our program who are using and abusing non-narcotic substances during pregnancy. Screening of all women presenting to Prentice Women's Hospital and Maternity Center for prenatal care during a 6-month period in 1982 revealed that 3% of these women had evidence of sedative-hypnotics in their urine at the time of admission to the general maternity clinic (Chasnoff et al., in press). Reflecting the increasing popularity of phencyclidine hydrochloride (PCP) in the United States (Showalter and Thorton 1977), a number of pregnant women who abuse PCP have entered the Perinatal Addiction Project. The present report will review the intrauterine growth, neonatal behavior, and growth and development of infants whose mothers used nonnarcotic substances during pregnancy. These infants will be compared to infants born to mothers who used narcotics during pregnancy and to infants delivered to women with no history or evidence of substance abuse.

SUBJECTS AND METHODS

Data are available on 95 infants born to mothers enrolled in the Perinatal Addiction Project between December 1976 and December 1982. All of the women were enrolled in the first or early second trimester of pregnancy and completed a course of intensive prenatal care. Maternal urine samples were obtained regularly to screen for illicit drug use. For neonatal assessment, the 95 infants were divided according to the type of primary maternal addiction:
heroin/methadone (N=5l), Group I; mixed sedative/stimulant (N=22),

Group II; pentazocine/tripelennamine (N=13), Group III; and PCP (N=9), Group IV.

Mothers in Group I conceived while on heroin. Forty-seven of these women were abusing heroin only. Four women abused an additional one or two nonnarcotic drugs. Upon admission to the program, each woman was placed on a variable initial daily dose of methadone. This dosage was steadily decreased to the lowest level which would prevent craving or withdrawal in the mother. By the beginning of the third trimester, each woman was on a maintenance dose of methadone, ranging from 5 to 40 mg daily (mean=15.9, S.D.=1O.4). This dose was held at the same level for the rest of the pregnancy, and no woman was completely withdrawn during pregnancy. Daily urine screens indicated that all but three of the women remained clean of narcotic and non narcotic drugs, other than the prescribed methadone.

Mothers in Group II were addicted to multiple licit and/or illicit nonnarcotic drugs. Each woman used two to five of the following drugs in various combinations before and during pregnancy: phenobarbital, diazepam, marijuana, alcohol, and cocaine. These women received the same regimen of prenatal care as Group I except that they did not receive methadone. Although abstinence was the objective for this group, only five of the women remained clean of drug use throughout the third trimester of pregnancy.

Thirteen infants were delivered to women who abused a combination of pentazocine and tripelennamine (T's and blues, respectively) during pregnancy (Group III). All of the women in this group sporadically used other, nonnarcotic drugs, but T's and blues were the only drugs consistently used throughout pregnancy. Although abstinence was the objective of the program, none remained clean of T's and blues during the third trimester of pregnancy.

Group IV infants were delivered to nine women whose primary drug of abuse throughout pregnancy was PCP. All of the women had positive urine screens which demonstrated sporadic use of other nonnarcotic drugs in addition to the PCP, which was the only substance used heavily (at least 5 days per week) throughout the third trimester.

Three of the Group II women sporadically used T's and blues or PCP during pregnancy, but this use was very limited and did not occur in the third trimester. Hence, these three women were included in Group II based on their primary abuse of various sedatives and stimulants throughout pregnancy.

For comparison, infants of a group of drug-free mothers (Group V, N27) were selected for neonatal assessment in the order the women presented for prenatal care to the clinic of Prentice Women's Hospital and Maternity Center. These women had no history or evidence of drug or alcohol abuse, and management of prenatal care and nutrition was similar to the four drug-abusing groups of women.

All groups were evaluated for maternal factors which might affect neonatal outcome: race, maternal age, education, gravidity, prenatal care, nutrition, cigarette smoking, and drug use. Analysis of variance and chi—square analysis were utilized for statistical analysis of these parameters. All neonates were examined at birth, and weight, crown-to-heel length, and fronto—occipital head circumference were recorded. The Brazelton Neonatal Behavioral Assessment Scale (BNBAS) (Brazelton 1976) was administered at 2 days of age by trained examiners who were blind to the infants' prenatal history. Results of neonatal data were analyzed utilizing analysis of variance. For those items which reached statistical significance ((.05), the Fischer's LSD (Kirk 1968) was utilized to identify homogenous subsets.

For long-term follow-up, the opiate-exposed infants (Groups I and III) were combined into Group A, and nonopiate-exposed infants (Groups II and IV) were combined into Group B. The previous group of control infants (Group V) was expanded to include a total of 35 infants to serve as controls for long-term assessment (Group C). The Bayley Scales of Infant Development (Bayley 1969) were administered to all infants at 3, 6, 12, and 24 months of age. The infants were examined at these same time intervals, and weight, fronto-occipital head circumference, and crown—to—heel length were recorded. Differences between control and each drug—exposed group of infants at each interval for all parameters of growth and development were analyzed through use of the two—tailed t test.

RESULTS

Neonatal Assessment

Demographic data (age, gravidity, education) for the women in Groups I through V were similar, as was the frequency of cigarette smoking in each of the groups. However, racial distribution varied between the groups (table 1). Thus, for analysis of neonatal data, race was controlled through covariate analysis when each drug-using group was compared to the Group V mothers and infants.

All infants were delivered at term gestation as determined by the criteria of Ballard et al. (1977). There was an even distribution of infants by sex in each group. Apgar scores in the five groups were similar, and no significant perinatal complications occurred in any group. Twelve infants in Group I required therapy for significant withdrawal, based on clinical criteria of marked irritability, poor feeding, and/or excessive weight loss. No infants in the other drug groups required therapy for withdrawal.

Somatic Measures

Infants delivered to mothers in Group I and in Group III had a significantly lower weight and length than control (Group V) infants (table 2). In addition, these Group I and Group III infants had significantly smaller head circumference than both the control infants and those in Groups II and IV. These differences remained when

TABLE 1

Racial Distribution of Neonates

	I Heroin/ Methadone		II Sedative/ Stimulant		III T & B		IV PCP		V Drug-free	
	N	%	N	%	N	%	N	%	N	%
White	33	65	10	45	1	8	8	89	7	26
Black	16	32	11	50	12	92	1	11	12	44
Hispanic	2	3	1	5	0	-	0	-	7	26
Oriental	0	-	0	-	0	-	0	-	1	4

TABLE 2

Neonatal Growth Parameters

	I Heroin/ Methadone		II Sedative Stimulant		III T & B		IV PCP		V Drug free	
	$\bar{X}$	S.D.	$\bar{X}$	S.D.	$\bar{X}$	S.D.	$\bar{X}$	S.D.	$\bar{X}$	S.D.
Weight (gm)	2840*	600	3165	560	2799*	430	3201	440	3479	623
Length (cm)	48.2*	3.5	50.0	3.1	48.1*	1.8	49.3	2.6	51.1	2.8
Head circumference (cm)	32.2*†	2.4	33.9	1.5	32.9*†	1.2	33.7	2.0	34.7	1.7

*ANOVA (Specific Drug Group x Group V), $p<.01$

†Significant difference from Groups II and IV (Multiple Range Test)

race was statistically controlled. The birth weights, lengths, and head circumferences of the sedative/stimulant- and PCP-exposed infants were not significantly different from those of the control infants.

Neonatal Behavior

Means and standard deviations for those BNBAS items for which statistically significant differences were obtained are listed in table
3. Significant differences were obtained in items related to interactive ability, motor maturity, and state control. Items related to visual and auditory orientation and motor maturity differentiated the methadone-dependent group from both the control and all other drug groups (Fischer's LSD). All four groups of drug-exposed neonates showed deficits in state control with an abnormal predominant state, an increased lability of state, and poor consolability. In addition, PCP-exposed infants (Group IV) showed significantly increased lability of states and poor consolability when compared to all other drug groups (Fischer's LSD).

Infant Assessment: Two-Year Follow-up

In this portion of the study, demographic data for the two drug-exposed groups of infants and the control group of infants were again similar. In addition, upon combining Groups I and III (opiate-exposed infants) into Group A and Groups II and IV (nonopiate—exposed infants) into Group B, racial distribution was similar for the two study groups and the control group (C): 53% white, 43% black, 4% Hispanic in Group A; 58% white, 39% black, 3% Hispanic in Group B; 52% white, 40% black, 6% Hispanic, 2% Oriental in Group C.

Somatic Growth

Infants in Group A had significantly lower weight and length than the Group C drug-free infants at both 3 and 6 months (t test) (table 4). By 12 months of age, Group A infants had caught up in weight and length to the control infants. [lead circumference measurements for the opiate-exposed Group A infants did not exhibit such catch—up growth, however, and head circumference for these infants remained significantly smaller than that of the control infants throughout the 2-year follow-up. Polydrug-exposed infants in Group B exhibited normal growth patterns throughout the 2-year period for all parameters, except that head growth had slowed by 18 months, and mean head circumferences at 18 and 24 months were significantly smaller than those of the control infants. Growth parameters for PCP-exposed infants were almost identical to those of the polydrug-exposed infants, so that separate analysis was not performed.

Infant Development

Mean scores of the three groups of infants on the Bayley Scales of Infant Development are shown in table 5. Group A infants had significantly lower Mental Developmental Index (MDI) scores from

TABLE 3

BNBAS Items Which Discriminated Between The Neonatal Groups

	I Heroin/ Methadone		II Sedative/ Stimulant		III T & B		IV PCP		V Drug-free	
	$\bar{X}$	S.D.	$\bar{X}$	S.D.	$\bar{X}$	S.D.	$\bar{X}$	S.D.	$\bar{X}$	S.D.
Interactive										
Inanimate Visual Orientation	3.3*	2.2	5.7	2.1	5.2	2.7	6.0	2.0	5.6	1.9
Inanimate Auditory Orientation	3.4*	1.2	5.6	1.4	5.4	1.7	4.3	2.0	5.3	2.3
Animate Visual Orientation	3.9*	1.7	4.9	2.1	4.5	1.9	4.5	1.3	5.7	1.9
Animate Auditory Orientation	3.9*	1.6	5.2	1.6	4.3	.5	4.5	1.0	5.2	2.4
Consolability	4.4*	2.4	3.7*	2.2	4.2*	2.2	2.5*	1.0	6.3	1.5
Motoric										
Motor Maturity	3.3*	1.4	4.5	1.4	4.7	2.4	5.0	2.2	4.8	1.6
Organization, State										
Predominant State	4.1*	1.4	4.8*	.4	4.5*	1.9	4.8*	.5	3.9	1.0
Lability of State	3.2*	1.6	3.7*	1.9	3.3*	1.5	5.0*	1.9	1.6	1.1

*ANOVA (Specific Drug Group x Group V), $p<.01$

TABLE 4

Mean Growth Parameters, Ages 3 Months to 2 Years

Age (mos.)	A Narcotic $\bar{X}$	A Narcotic S.D.	A Narcotic N	B Nonnarcotic $\bar{X}$	B Nonnarcotic S.D.	B Nonnarcotic N	C Controls $\bar{X}$	C Controls S.D.	C Controls N
				Weight (gm)					
3	5,485*	854	40	5,865	931	24	5,904	708	35
6	7,261*	922	37	7,753	904	18	7,579	807	35
12	9,588	1102	25	9,541	1250	13	9,729	1036	35
18	11,247	1266	20	11,092	1557	11	11,133	1201	35
24	12,341	1833	16	12,544	1852	9	12,199	1275	35
				Length					
3	59.5*	3.0	40	61.4	3.0	24	62.3	2.6	35
6	67.0*	3.5	37	68.7	2.7	18	69.3	2.6	35
12	76.1	2.6	25	74.3	4.9	13	77.5	2.9	35
18	83.7	3.0	20	82.8	5.0	11	84.5	3.2	35
24	89.0	3.1	16	89.1	4.2	9	90.2	4.3	35
				Head Circumference					
3	39.1*	1.2	40	39.6	1.4	24	40.6	1.6	35
6	42.0*	1.6	37	42.9	1.9	18	43.3	1.7	35
12	45.3*	1.7	25	45.9	3.2	13	46.8	1.7	35
18	46.7*	1.3	20	46.9*	1.5	11	47.8	1.6	35
24	47.7*	1.6	16	47.2*	2.0	9	48.8	1.6	35

*$p < .05$

TABLE 5

Mean Scores on the Bayley Scales of Infant Development

Age (mos.)		A Narcotic			B Nonnarcotic			C Controls		
		$\bar{X}$	S.D.	N	$\bar{X}$	S.D.	N	$\bar{X}$	S.D.	N
3	MDI	104.2	11.1	36	99.0	13.6	22	99.2	9.0	34
	PDI	104.3	11.8	36	97.6*	9.8	22	102.8	7.0	34
6	MDI	103.6*	13.5	26	99.9	12.7	17	111.0	12.3	29
	PDI	102.2	11.9	26	103.2	8.8	17	107.6	15.1	29
12	MDI	99.6*	10.6	20	103.5	8.1	12	105.8	8.1	27
	PDI	104.4	11.9	20	98.1	12.3	12	103.8	12.5	27
24	MDI	98.7	16.0	16	104.8	15.1	9	96.2	15.9	14
	PDI	100.3	14.2	16	97.9	10.1	9	98.2	8.9	14

Controls at 6 and 12 months (t test). Group B infants had a significantly lower MDI at 6 months and Psychomotor Developmental Index (PDI) at 3 months. If PCP infants were considered separately, their scores were almost identical to the polydrug-exposed infants. In general, scores for both Groups A and B and for the control group of infants were in the normal range, but exhibited a downward trend by 24 months of age.

DISCUSSION

The extensive literature devoted to the effects of intrauterine exposure to heroin and methadone on the fetus and neonate has recently been reviewed (Householder et al. 1982). However, information regarding the outcome of nonnarcotic-exposed neonates is sparse. In the present study, newborns delivered to women whose primary substance of abuse was sedative/stimulants or PCP were found to demonstrate marked deficits in neonatal behavior. These two groups of infants showed significantly poorer state organization and consolability than the drug-free controls. In addition, when internal comparisons were made, the PCP-exposed neonates were found to demonstrate more lability of state and poorer consolability than all other groups of drug-exposed neonates. The unique neurobehavioral changes of the PCP-exposed infants during the neonatal period clearly differentiated them from the other drug-exposed newborns (Chasnoff et al. 1983). The low threshold of stimulation and rapid changes in state are similar to behavior reported in children and adults intoxicated with PCP (Showalter and Thorton 1977; Welch and Correa 1980).

Sedative/stimulant- and PCP-exposed neonates did not manifest significant differences from normals in somatic growth measures at birth, orientation, or motor maturity responses. Deficits in intrauterine growth appeared mainly in narcotic-exposed infants, especially in relation to head growth. Similar to methadone-exposed neonates, neonates exposed to T's and blues showed significantly lower somatic growth rates and poorer state control than the drug-free controls, although the methadone-addicted neonates could be further differentiated by poorer visual and auditory orientation responses and poorer motor control. The similarities between the methadone-exposed and the T's and blues-exposed neonates may be related to the mixed opiate agonist-antagonist properties of pentazocine (Chasnoff et al. 1983).

There are no previous studies evaluating long-term patterns of growth and development in nonnarcotic-exposed infants, although preliminary developmental data have been examined (Chasnoff et al. • in press). The nonnarcotic-exposed infants in the present study demonstrated normal growth patterns in weight and length throughout the 2-year follow-up period. The narcotic-exposed infants, on the other hand, demonstrated early deficits in growth at 3 and 6 months and subsequently caught up to normals by 12 months of age. This same early stunting of growth during the period of subacute withdrawal for the narcotic-exposed infants is similar to the early growth patterns of methadone—addicted infants reported by our group in 1982 (Chasnoff et al.).

The early depression of growth could be due to the direct effect of methadone on the hypothalamic-hypophyseal axis of the newborn (Friedler and Cochin 1972). With the slow excretion of the methadone by the newborn, plasma and tissue drug levels fall, the endocrinological effect of the drug subsides, and growth recovers.

The mean head circumference of the narcotic-addicted newborns was significantly smaller than controls at birth and remained so throughout the 2-year follow-up period. The inhibitory effects of heroin on fetal growth include effects on brain growth (Chasnoff et al. 1982; Naeye et al. 1973). The mean head circumference of the nonnarcotic-exposed infants was normal at birth and continued so until 12 months. By 18 months of age, however, head growth had slowed and the mean head circumference for these infants had fallen to a significantly lower level. Small head size in young infants has been reported to be predictive of poor developmental outcome (Gross et al. 1983) and may be another indicator of the high-risk status of all drug-exposed infants.

Two-year developmental follow-up showed that the drug-exposed infants' development, as measured on the Bayley Scales of Infant Development, was comparable to that of the drug-free infants. The isolated instances in which mean MDI or mean PDI fell to a low level are probably not clinically significant in that all scores were within the normal range, as defined for the Bayley Scales (100±S.D. 10). Of greater concern is the fact that all three groups of infants, including controls, demonstrated a downward trend in mean developmental scores by 2 years of age. From the present data, it appears that the infants' environment and subsequent lack of stimulation had a more direct influence on 2-year development than maternal drug use during pregnancy.

The problems involved in evaluating the effects of maternal substance abuse on the developing fetus and infant are multiple, not the least of which are the difficulties involved in following these infants over a long period of time. The chaotic and transient nature of the drug-seeking environment impairs the early intervention and intensive follow-up necessary to insure each infant's maximum development. In addition, most women from substance-abusing backgrounds lack a proper model for parenting. These factors, compounded by the early neurobehavioral deficits of the drug-exposed newborns, earmark these infants to be at high risk for developmental and school problems. Maternal and perinatal addiction programs should be aimed at not only helping the mothers to deal with their addiction but teaching them the parenting skills necessary for proper infant stimulation and subsequent development. Future programs must develop methods to ensure adequate follow-up of all infants born to substance-abusing women.

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