

Marijuana: Prenatal and Postnatal Exposure in the Human

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Recent studies of prenatal exposure to marijuana have produced presumptive evidence that marijuana has an adverse effect on growth and development of the fetus. Two investigators (Linn et al. 1983; Gibson et al. 1983) reported a decrease in birth weight and an increase in malformations in marijuana—exposed infants, but differences between marijuana users and nonusers were not statistically significant when confounding factors were taken into account. Hingson et al. (1982) reported that woman who used marijuana during pregnancy delivered infants with a mean birth weight 105 grams lighter than infants of nonusers, and the infants were five times more likely than infants of nonusers to have features compatible with Fetal Alcohol Syndrome. Although confounding factors were controlled statistically, the investigators cautioned that marijuana use might identify a group of women at higher pregnancy risk due to unexplored maternal factors, rather than identifying a specific agent causing abnormal fetal development. In a preliminary report from an ongoing prospective study in Canada, Fried (1980, 1982) found no difference in birth weight between marijuana users and nonusers, but infants of heavy users had shorter gestations and signs of neurobehavioral immaturity as compared with matched controls.

Some protection from potentially harmful effects of cannabis on fetal development may be due to the partial restriction of cannabis compounds by the placenta. In a recent study of placental transfer of Δ^9 -THC and the principal metabolite, 9-carboxy-THC (Blackard and Tennes 1984), levels of the cannabinoids were found to be two-and-a-half to seven times higher in maternal plasma than in fetal cord plasma at delivery in 10 women who used marijuana daily. Although these results may not apply to placental transfer at periods of gestation other than delivery, or to peak plasma concentrations immediately after smoking, the findings are in agreement with animal studies that have indicated that the fetus is exposed to appreciably less cannabis than is ingested by the mother (Reviews: Bloch et al. 1978; Abel 1980).

Because of the limited number of studies and the complexity of factors that need to be controlled in human clinical research of illicit drug use, it has been difficult to estimate the seriousness of risks associated with marijuana use during pregnancy.

This paper reports our study of the effects of marijuana in a population of pregnant women known to include a relatively high proportion of marijuana users (Tennes and Blackard 1980). The purpose of the study was to investigate effects of exposure to marijuana on fetal growth and development at birth and at 1 year of age.

Method

Population and Data Collection

During a 12—month period beginning in November 1981, 1,032 pregnant women were approached at the prenatal—care clinics of Denver General and University Hospitals during the women’s regular clinic visits. The population served by these clinics is predominantly of lower-middle to lower—class socioeconomic status. The subjects selected were at least 24 weeks pregnant. Vietnamese and Hispanic women who did not speak English were excluded.

Of those approached, 865 women gave informed consent and were interviewed by one of three experienced interviewers. A structured questionnaire developed in a previous study (Tennes and Blackard 1980) was used to obtain information on demographics, illnesses, and medications, as well as use of caffeine, nicotine, alcohol, marijuana, and other illicit drugs. Specific details about kind, potency, and physiologic effects of marijuana, as well as use by the child's father, were obtained. After delivery, the women were interviewed a second time to cover drug use in the interval between the initial interview and delivery. An attrition rate of 16% between the initial approach and delivery was due to 8% who refused to participate and 8% who moved away or delivered at a different hospital.

Infants of the 756 participating women were scheduled between 24 and 72 hours of age for an examination by one of four examiners who were blind to all information about the mother. We developed a systematic examination procedure which included measurement of length, head circumference, and palpebral fissures; the Brazelton Neonatal Behavioral Assessment Scale (Brazelton 1973), a scale of muscle tone derived from Parmalee (Howard 1976); and a checklist of 34 minor physical anomalies prepared by Blackard and Tennes (1981). All examiners had been certified for administration of the Brazelton prior to this research.

Birth weight, the Dubowitz score for gestational age (Dubowitz et al. 1970), Apgar scores and neonatal clinical data were obtained from the infants' hospital charts. Antepartum and intrapartum clinical data on the women were obtained from their medical records. Women with diabetes, renal, or collagen disease were excluded.

At 1 year of age, infants of a selected sample of marijuana users and controls were seen for measurements and examination with the Bayley Infant Scale of Mental and Motor Development and Behavior Checklist (1969). After the examination, the mothers were interviewed regarding the child's health, routine care, behavioral traits, and special problem during the first year. Women who had breastfed completed a questionnaire regarding drug use during breastfeeding. Two investigators were present at all examinations, one acting as examiner and the other as observer, and all scales were scored independently by each. Correlation coefficients between examiners' and observers' scores of mental and motor development were .95 and .97.

RESULTS

Thirty—four percent of the 756 women in the sample reported using marijuana during pregnancy. Marijuana users were significantly different from nonusers ($p < .001$) in age, marital status, number of prior live births, and frequency of induced abortions (table 1). No significant differences were found between users and nonusers in race, socioeconomic status, spontaneous abortions, or previous stillbirths. Alcohol, nicotine, and other illicit drugs (hash, cocaine, amphetamines, LSD, barbiturates, PCP, or psilocybin) were more frequently used by marijuana smokers than by nonsmokers.

TABLE 1

Significant Differences ($p < .001$) in Demographics
Between Marijuana Users and Nonusers.

<u>Demographics</u>	<u>Nonusers</u>	<u>Users</u>
	N=498	N=258
Mean age (mean years)	23.0 years	21.8 years
Marital status: Married	58%	42%
Single or Cohabiting	32%	51%
Prior live births	57%	37%
Elective abortions	20%	32%
Nicotine use	30%	40%
Alcohol use	30%	70%
Other illicit drugs	4%	31%

Levels of Exposure

To estimate the dose—response relationships between drugs and outcome variables, the number of times the women used the drug was totaled for each week of the pregnancy, and the weekly amounts were summed to estimate the exposure for the entire pregnancy or for each trimester separately. The unit of measure for alcohol was number of drinks of beer, wine, or liquor; for nicotine, packs per day; for marijuana, the number of joints; for the other illicit drugs, the number of occasions the drug was used.

There was a significant linear dose—relationship between the women’s use of marijuana and alcohol ($r=.45$, $p<.01$), but not between marijuana and nicotine ($r=.07$, n.s.).

There was a high correlation between amounts of marijuana smoked by trimesters ($r = .71$ and $.73$), but the amounts smoked decreased during pregnancy. To examine change in marijuana use during pregnancy, estimates of marijuana were converted to an approximate weekly average and the women were categorized as nonusers, light (one time only to once a week), moderate (more than one a week but less than daily), and heavy (once or more daily). The categories were established for each trimester.

The proportion of women in each category shifted during the course of pregnancy (table 2). Nonusers increased from 68% in the first trimester to 84% in the third, and the number of daily users declined from 10% in the first trimester to 2% in the third. The women who continued to smoke daily throughout pregnancy decreased from a mean of 4.5 (S.D.=4.5) per day in the first trimester to a mean of one a day (S.D.=1.1) in the third.

TABLE 2

Changes in Reported Marijuana Use During Pregnancy

	<u>First</u> <u>Trimester</u>	<u>Second</u> <u>Trimester</u>	<u>Third</u> <u>Trimester</u>
<u>Level of Use</u>			
Nonuser	519 (68%)	601 (79%)	633 (84%)
Light	87 (12%)	73 (10%)	67 (9%)
Moderate	89 (10%)	49 (6%)	42 (5%)
Heavy	72 (10%)	33 (4%)	14 (2%)

Pregnancy and Delivery Complications

We compared the frequency of medical complications among nonusers and marijuana groups. No dose—response relationship was found for a specific complication nor for the total number of complications incurred by each woman. The only differences found in medical histories was that marijuana users gained significantly more weight during pregnancy than nonusers (mean gain by users 36.25 lbs., nonusers 32.0 lbs.).

We compared marijuana users and nonusers on 12 indices of complications at delivery, namely: precipitous labor, prolonged labor, need for oxytocin, chorioamnionitis, abnormal presentation, fetal distress, meconium staining, placental abruption, assisted vaginal delivery, cesarean section, pain relief requirements, and narcotics used in labor. The only significant difference between users and nonusers was an increased requirement for pain—relieving medication during labor (users 67%, nonusers 57%, $p < .01$). In multiple—variant analysis of factors contributing to narcotic dose and to administration of analgesics, only parity and delivery complications were significant determinants. Since more marijuana users than nonusers were primiparous, the difference in pain—relieving medication may be attributed to parity rather than marijuana.

Infant Outcomes

Heavy marijuana use was found to be associated with an increase in male over female offspring, a finding previously reported by Fried (1982). Women who reported smoking marijuana three times a week or more throughout pregnancy ($N = 31$) gave birth to 61% males and 38% females as compared with 50% males and 49% females among nonusers ($N = 498$). Among fathers who were reported to be chronic smokers of more than one ‘joint’ a day, the ratio was 67% males to 33% females (table 3).

Table 3

Ratio of Male to Female Births for Fathers Using Marijuana

	Frequency of Marijuana Use			
	<u>No Data</u>	<u>Nonuser</u>	<u>One A Day Or Less</u>	<u>More Than One A Day</u>
Females	96 (52%)	158 (47%)	71 (55%)	35 (33%)
Males	87 (48%)	181 (53%)	58 (45%)	70 (67%)

Chi square = 13.29, $p = .004$

Intrauterine Growth

Multivariate analyses of the impact of marijuana on three measures of fetal growth—birth weight, length and head circumference—did not yield uniform results.

Infant length was the only measure influenced by marijuana when confounding variables were taken into account. Of eight variables, accounting for 22% of the variance in length, marijuana (total amount used during the first trimester) entered the regression on the fourth step (table 4). Other confounding variables considered in the regression that did not reach significance were: mother's age, parity, Hispanic race, socioeconomic status, caffeine, alcohol, hash, amphetamines, and cocaine. As calculated from the unstandardized β -coefficients, the reduction of .55 centimeters in length, attributable to smoking an average of three joints a day during the first trimester, was roughly comparable to the reduction of .48 centimeters attributable to smoking one—and—a-half packs per day of cigarettes.

When the analysis was repeated for second and third trimester use of drugs, or for the total amount smoked during pregnancy, marijuana did not have a significant impact on infant length.

TABLE 4

Step—wise Multiple Regressions on Infant Length at Birth

Dependent Variable: Length Mean = 49.8 cm., S.D. = 2.23

<u>Variables</u>	<u>Significance r^2 change</u>		<u>Beta</u>
Gestational age (weeks)	.000	.100	.29
Infant Sex	.000	.035	.19
Nicotine (packs per day)	.000	.019	— .13
Marijuana, first trimester	.001	.015	— .07
Weight gain during pregnancy	.001	.014	.13
Ponderal Index	.001	.015	.12
Mother's Height	.007	.009	.11
Black Race	.009	.008	— .09
N=659	R=.47	R ² =.22	

In contrast to the findings on length, no independent effect of marijuana on birth weight or head circumference was found when marijuana was considered either by trimesters or by the total amount smoked.

We also analyzed multiple drug use, not as an assessment of the synergistic effect of several drugs, but rather as a surrogate variable representing lifestyle attributes of women who used one or more illicit drugs other than marijuana. This measure of the

number of different kinds of other illicit drugs, regardless of frequency, was found to have a significant but marginal impact on the regression on birth weight ($p < .01$, r^2 change = .006, $p = .07$). The calculated reduction in birth weight associated with exposure to four different illicit drugs other than marijuana was 199 grams. Thus, infants of women who use multiple illicit drugs, regardless of kind or amount, appear to be at an increased risk for a significant reduction in birth weight.

Gestational Age

The total amount of marijuana used during pregnancy was positively correlated with the infant's gestational age at birth ($r = .10$). Three indices of gestational age that had been recorded were the woman's reported last menstrual period, the Dobowitz examination of the infant, and the obstetrician's estimate given in the medical record. The mean or mode of the three was used as the estimate. In a multiple regression analysis, five variables accounted for 4 percent of the variance in gestational age (table 5). Two of the significant variables, pregnancy complications and black race, are known to be associated with preterm deliveries (Berkowitz et al. 1982). The three other significant variables, weight gain, ponderal index, and marijuana, were associated with prolongation of gestation. Additional noncontributing variables entered in the regression were Hispanic race, mother's age and height, infant sex, socioeconomic status, parity, and abortions (yes and no). None of 31 women who smoked an average of three times or more a week throughout pregnancy gave birth preterm (before 37 weeks), as compared with 7% of nonusers.

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TABLE 5

Step-wise Multiple Regression of Gestational Age Dependent Variable:
Gestational Age Mean=39.88 weeks,

<u>Variables</u>	<u>Significance</u>	<u>r^2 change</u>	<u>β-coefficient</u>
Ponderal Index	.01	.01	.14
Pregnancy complications	.01	.009	— .09
Weight gain	.01	.009	.11
Marijuana	.03	.006	.09
Black race	.04	.005	— .08
N=719	MultipleR= .23	R^2 .04	

Postnatal Outcomes

No associations were observed between exposure to marijuana and assessments of the infants' postnatal course in the nursery period. Apgar scores of less than seven were not more frequent among nonusers (23%) than users (light 13%, moderate 13%, heavy 22%). Nursery complications as measured by time in high—risk nursery, time in isolette, jaundice, peripheral hematocrit, Dextrostex, weight change, presence of hypothermia, or feeding problems were no different in exposed than in nonexposed infants.

We found no evidence of a teratogenic effect associated with marijuana nor with the other illicit drugs. Of 39 infants with major malformations recorded in the infants' medical records, 12 (31%) were children of marijuana users, which is the expected percentage for the population. Likewise, no disproportionate increase in any of 34 minor anomalies observed by the investigators, or pattern of these anomalies, was evident in either dose—response relationships to the drugs or time during gestation of the exposure. Furthermore, there was no increase in the total number of anomalies per infant in the exposed subjects.

None of the variance in infants' responses to individual items on the Brazelton scale, nor to scores on clusters of the Brazelton items (adopted from factor analysis of the scale by Lester' et al. 1982) was accounted for by exposure to marijuana, alcohol, nicotine, or other illicit drugs.

Three variables—black race, nicotine, and gestational age—made significant contributions to the prediction of variance in muscle tone (Multiple R = .16, $p < .01$). However, exposure to marijuana was not associated with either hyper— or hypotonicity.

Fried (1980) reported that infants of heavy marijuana users, as compared with matched controls, had heightened tremulousness and startles. To examine this relationship, in addition to the assessment of these behaviors on the Brazelton, 46 infants whose mothers reported using marijuana within 48 hours of delivery were compared with nonexposed infants. No increase in startles, tremors, or other neurobehavioral measures was apparent in these infants.

Evaluation of One—Year-Old Infants

Seventy—nine women who had reported smoking marijuana an average of seven times a week or more for one or more trimesters of pregnancy were selected for the follow-up study when the children were 1 year of age. Eighty women who had reported smoking less

than an average of seven times a week, and 80 women who were nonusers were selected randomly from each of these groups as controls.

Sixty percent of those selected were located and agreed to participate in the examination. Although 10% fewer users than nonusers were located, the difference in attrition was not statistically different among groups ($X^2 = 2.42$, $p < .10$). Additional cases were lost from the analysis by delays beyond 2 weeks from the child's birthday in arranging the appointments. The final data base consisted of infants of 38 heavy users, 44 light or moderate users, and 47 nonusers. There were significantly more first—born infants among the marijuana users (73%) than nonusers (32%), ($X^2 = 19.2$, $p < .001$) and also a higher percentage of males (table 6).

TABLE 6

Growth and Development of One—Year-Old Infants Selected for Level of Prenatal Exposure to Marijuana

Marijuana Category	N	Means				
		Males%	Weight (kgs)	Height (cms)	Mental Score	Motor Score
Nonusers	47	55	8.9	72.3	104.6	98.3
Light and Moderate	44	50	9.3	73.0	101.8	103.3
Heavy	38	63	9.1	72.8	104.8	98.2

No significant differences in infant outcome measures were observed among the groups (table 6). Multiple regression analysis on total amount of marijuana use reported during pregnancy, controlling for sex and parity, revealed no independent association of prenatal exposure to marijuana on growth or development scores. No significant differences attributable to marijuana were found in infant temperament, as assessed by the Bayley Behavior Checklist, or by the mothers' reports of illnesses, eating or sleeping problems, or personality characteristics during the first year.

Exposure to Marijuana During Breastfeeding

Sixty—two of the infants seen at 1 year of age had been breast— fed. Of these, 27 of the mothers reported using marijuana during breastfeeding; 12 of them smoked once a month or less, 9 weekly, and 6 daily.

No significant difference was found between users and nonusers in the age infants were weaned, suggesting that marijuana did not interfere with lactation.

Comparison of infant outcomes on growth, or on mental and motor development, revealed no apparent effects of postnatal marijuana exposure. Since statistical analyses were limited due to the small numbers and lack of comparability among cases for duration or dose, raw data for growth and development of the infants of six women who reported using marijuana daily during breast—feeding are given in table 7.

TABLE 7

Individual Data for Six One—Year-Old Infants Exposed
Daily to Marijuana Prenatally and Through Breastfeeding

<u>Infant Characteristics</u>	<u>Subjects</u>					
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Number of weeks breastfed	52	52	28	12	12	12
Prenatal exposure (av. per day)	1	2	1	3.6	2	2
Infantsex	M	M	F	N	F	M
Height (cns)	76	72	69	74	73	75
Weight (kgs)		9.0	10.9	7.7	9.0	9.0
	12.1					
Mental Score		109	122	84	89	93
	112					
Motor Score	105	98	63	98	98	111

DISCUSSION

The findings in this investigation are consistent with other studies that have reported a trend toward or a significant reduction in fetal growth associated with exposure to marijuana during gestation (Hingson et al. 1982; Linn et al. 1983; Gibson et al. 1983). The previous studies found an impact on birth weight, whereas in the present study the impact was on length. This discrepancy may be related to different smoking habits in the populations sampled. In the present study an effect on birth weight may have been prevented by the marked reduction in number of women smoking and in amounts of marijuana consumed in the third trimester, which is the crucial period for fetal weight gain, and by the better—than—average weight gain during pregnancy by the marijuana users. Similarly, the effect on length may have been detected because of the high proportion of women ingesting relatively large doses of marijuana in the first trimester, when growth of cells may be affected (Miller and Merritt 1979; Redmond 1979). Further research comparing different populations and habit patterns is needed to clarify these discrepancies.

The finding of a positive correlation between length of gestation and marijuana exposure is in conflict with reports of an inverse relationship between gestation and marijuana by two investigators (Fried 1982; Gibson et al. 1983). In one animal study, gestation was found to be prolonged by 1 to 2 days in

rats exposed to A—9—TSC throughout pregnancy (Borgen et al. 1971). The evidence of prolonged gestation in the human from the present study is weak in terms of the magnitude of the effect calculated from the equation, which was an average of two days delay associated with daily marijuana exposure throughout pregnancy. Research using animal models to investigate marijuana effects on maintenance of pregnancy or initiation of delivery may be required to resolve this controversy.

To our knowledge, no other study of humans has reported a significant increase in male births associated with father's marijuana use. In two animal studies, an increase in male offspring was observed in rats and in chimpanzees sired by males exposed to marijuana prior to mating (Fried and Charlebois 1979; Grilley et al. 1974). - In the present study, the assumption that marijuana is the sole determinant of the altered ratio is subject to question, since no information about the father's use of other drugs was obtained. If the finding is confirmed in other human studies, it would be of interest to determine the mechanisms involved in the reduction of female births.

Although there was no apparent increase in malformations among marijuana—exposed infants, the results of this study cannot be considered as providing firm evidence that marijuana or the other illicit drugs used by the women are not teratogens. Since the subjects in the study were selected after 6 months gestation, we could not investigate the possibility that exposure to marijuana early in gestation is associated with lethality for severely malformed fetuses. Our examination included inspection for minor physical anomalies compatible with Fetal Alcohol Syndrome which Hingson et al. (1982) had reported to be increased among marijuana users. Failure to replicate Hingson's findings may have been due to differences in criteria used to make the subtle clinical judgments required to discriminate a unique pattern of anomalies. Nonetheless, the findings from this study are compatible with experimental animal studies that report an absence of malformations associated with —9—THC administered orally in doses equivalent to heavy human use (Wright et al. 1976).

The results of examinations of development and behavior in the neonate and at 1 year of age do not suggest that fetal or postnatal exposure to marijuana is associated with marked deficits in central nervous system functioning. Discrepancies between the present study and Fried's observation of poor habituation to a visual stimulus, increased tremors, and a peculiar cry as characteristics of marijuana—exposed neonates (1980) may be due to unknown differences in the two samples or differences in methodology.

Fried (1982), in agreement with the present study, reported no negative effects associated with prenatal marijuana use in a small number of infants examined at one year of age. In the present study, the evaluation of effects at 1 year of age may

have been biased by the self-selection of women who participated in the 1-year follow-up. However, there were no differences in refusal rates between marijuana users and controls to suggest that more marijuana users than controls failed to participate if the infant was developing poorly.

Although evidence of effects on central nervous system functioning in the neonate are inconclusive and no convincing evidence of effects lasting until 1 year of age have been produced, the possibility of effects on more complex cognitive functioning which develops after infancy, particularly the acquisition of verbal learning, have not been addressed to date.

In conclusion, several additional areas of research are needed to estimate the health risk associated with prenatal exposure to marijuana. Investigations of pregnant women are appropriate to establish the dose level of cannabis that may be related to adverse effects on fetal growth. Comparative studies with different species might clarify the effects of cannabis on duration of pregnancy. Additional longitudinal studies of children are needed to determine if there are long-term health risks associated with prenatal exposure.

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