Postnatal Consequences of Maternal Marijuana Use

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Interest in marijuana's effects on various aspects of reproduction has a surprisingly long history. In his absorbing account of cannabis, Abel (1980) describes how Eastern European folk medicine has proclaimed for several centuries that marijuana could be used to hasten delivery. Reports from India that circulated widely in Europe discussed marijuana as both a sexual stimulant and a sexual inhibitor and, in the mid 1800s, the U.S. Dispensory (the widely read pharmacopea of the time) reiterated what the Arabs had been saying in the 16th century--that marijuana possessed aphrodisiac properties.

More contemporary reports that link marijuana with increased sexual pleasure have been plagued by the difficulty of separating the drug's effect from the drug user's overall lifestyle and the value placed on sexual activity (Abel 1981).

Moving from the realm of anecdotal reports to more objective reproductive measurements, one comes across a number of studies that have explored the relationship between maternal marijuana ingestion and fetal outcome in a variety of nonhuman species. A review of the data and an interpretation of these works is described by Abel (this volume). With respect to the human fetus, however, we are still very much at the frontier of knowledge.

Cannabis constituents can cross the placenta and be stored in the amniotic fluid (Harbison and Mantilla-Plata 1972; ldanpaun-Heikkila et al. 1969). Transfer of marijuana constituents from mother to infant can also occur via the milk as animal studies have shown (Jakubovic et al. 1974). This method of potential exposure of the neonate takes on considerable importance in the human as central nervous system (particularly glial and myelin growth) develops extensively postnatally.

The combination of the absence of information with respect to humans, the animal work from our own laboratory as well as others, the prevalence of marijuana use by women of reproductive age, and the cooperation of a number of hospitals in the Ottawa area led to what

we have called the Ottawa Prenatal Prospective Study. Since 1978, data has been collected from approximately 700 pregnant women in the Ottawa area for this study. Mothers-to-be are informed of the study by their obstetricians or by notices in waiting rooms of prenatal clinics in the four largest area hospitals. Upon volunteering to participate, each subject is interviewed once during each of the trimesters remaining in her pregnancy. The volunteer method of subject recruitment, dictated mainly by ethical considerations, serves to increase the reliability of self-report (discussed below) and to increase the likelihood of a long-term commitment to the study by the participants. Aside from the subjects who have moved from the Ottawa region (29%), we have maintained a retention rate of over 98% during the past 4 years.

During each of the interviews, typically conducted in the home of the mother-to-be, information is collected concerning socio-demographic status, mother's health (both currently and prior to the pregnancy), father's health history, obstetrical history of previous pregnancies, a 24-hour dietary recall, and past and present drug use, with particular emphasis on marijuana, alcohol, and cigarette use. For the drug histories, information is gathered pertaining to the year before pregnancy and each trimester of pregnancy.

The details of the interview and the categorization of the various drugs have been described earlier (Fried et al. 1980). Because the range of marijuana use in the sample was quite broad and bimodal in distribution, the drug data were usually not treated as a continuous variable, but rather as an interval variable. Four levels of use have been developed (Fried et al. 1980; Fried 1982): nonuser; irregular user (one joint or less per week or exposure to the exhaled smoke of others); moderate user (two to five joints per week); and heavy user (more than five joints per week). If hashish use was reported, the number of joints was multiplied by five to take into account the estimated greater concentration of tetrahydrocannabinol (THC) in hashish (the major psychoactive ingredient in cannabis) (Lerner and Zeffert 1968).

The method of using interviews to assess such variables as nutrition and drug habits raises critical issues of both validity and reliability. Several factors are relevant. Despite the potential shortcomings of self-reporting questionnaires, there is no practical alternative method of establishing the information needed for this type of investigation. A number of procedures to enhance the probability of an accurate self-report have been utilized in the present research. First, in order to develop a relaxed rapport, the same female interviewer "followed" the mother-to-be during her entire pregnancy. Second, the questionnaire was administered once during each trimester and, during each of these interviews, the questions pertaining to drug use for each trimester were repeated, permitting a test-retest reliability measure. With marijuana, the consistency of self-report was very high, with fewer than 7% of the women inconsistently reporting their marijuana usage. When an inconsistency was reported, the higher figure was utilized.

The demographic details and the extent of drug use during pregnancy among the first 407 subjects in the study have recently been published (Fried et al. 1984), as has a comparison of drug use before, during, and after pregnancy (Fried et al., in press). In the present sample, 80% stated that they did not use any marijuana in the year before pregnancy, 12% used it irregularly, 3% smoked 2 to *5* joints per week, and *5%* smoked 6 or more joints per week. Upon becoming pregnant, usage declined significantly, but during each of the trimesters the percentages remained relatively constant with 90% reporting no use, 6% reporting irregular use, 1% smoking 2 to *5* joints, and 3% reporting 6 or more joints per week.

Many, but not all, of the women who smoked marijuana regularly during pregnancy differed from the remainder of the sample on a number of factors that could be associated with adverse effects on the course of pregnancy and on the development of the offspring. These potential confounding factors included lower socioeconomic level, less formal education, and increased cigarette smoking. Increased alcohol consumption was also associated with heavy marijuana use, although not as strongly as was cigarette smoking. With respect to age, the heavy marijuana users were a significant 3.2 years younger than the remainder of the sample. However, no differences in parity were noted. Further, nutritional adequacy did not differ among the four categories of marijuana use.

A variety of variables have been examined during the course of the ongoing Ottawa Prenatal Prospective Study. The work that has been carried out and the work that is presently underway are described in table I.

One aspect that we have considered is the course of pregnancy (Fried et al. 1983). In our work, no differences have been found between the marijuana users and their matched controls (matched in terms of alcohol use, cigarette use, and family income) in terms of rate of miscarriage, type of presentation at birth, Apgar status, and the frequency of complications or major anomalies at birth.

In a recent report, Greenland et al. (1982) described the results of the effects of marijuana use in 35 pregnancies. The women included in the investigation reported not using other illicit drugs and were recruited from two California prenatal clinics. Compared to control subjects, significant differences in duration of labor (both protracted and prolonged) were observed, as well as an increased incidence of meconium staining among the infants born to marijuana users. A subsequent study (Greenland et al. 1983), which was designed to replicate the first, did not find that these adverse outcomes reached statistical significance. One of the principal differences in the two studies was a general higher level of health and living conditions among the women who participated in the second study. The sample in the latter report was more similar in terms of ethnicity, education, and general health to the Ottawa subjects than were the women in Greenland’s first report.

TABLE 1

Protocol of the Ottawa Prenatal Prospective Study

Birth

Labour-anaesthetics and analgesics
General birth measurements
Cord blood assay
Apgar
Postpartum medications
Birth Anomalies

Neonatal Perception Inventory
(Day 2 and 30)

Mother's perception of how her child compares to the "average" child with respect to crying, feeding etc.

Visual and Auditory Sensory Assessment
(one test at 3 - 5 years)

Ophthalmological examination
Visual and auditory cortical evoked potentials

Pegboard fine motor coordination test
(48,60 months)

Fine motor

Physical Anomaly Assessment
(one examination between 18 months and 4 years)

Anomalies of the face, head, hands and feet

Brazelton Neonatal Assessment Scale
(Day 4)

Visual and auditory responsiveness and habituation
Temperament
Tremors
Startles
Reflexes
Gross motor
Physical assessment

Bayley Scales of Infant Development
(6,12,18,24 months)

Temperament
Physical Assessment
Fine motor
Gross motor
Cognitive skills
Language comprehension and expression

Reynell Expressive Language and Verbal Comprehension Scale
(18,24,36,48,60 months)

Language comprehension and expression

Tactile Form Recognition Test
(48,60 months)

Fine motor
Sensory interaction

Postnatal Questionnaire
(one after child's first birthday)

General health of child
Age of walking
Onset of speech
Mother's use of alcohol nicotine, cannabis and caffeine during first year postpartum
Feeding decisions and pattern during first year postpartum
Socio-economic status
Family make-up
Childcare arrangements

Prechtl Neurolological Test
(Day 9 and 30)

Motor activity
Physical state and facial configuration
Reflexes
Visual and Auditory responsiveness and habituation
Physical assessment
Temperament
Nervous System symmetry

HOME Inventory
(24 months)

Assesses child's environment - both animate and inanimate

McCarthy Scales of Children's Abilities
(48,60,72 months)

Fine and gross motor
Cognitive skills
Language comprehension and expression

Peabody Picture Vocabulary Test
(48, 60 months)

Language comprehension

Neuropsychological Battery
(60,72,84,96 months)

Fine and gross motor
Sensory
Visual-motor
Spatial
Language and abstract reasoning abilities
Behavioural Rating Scale

In one animal study (Charlebois and Fried 1980), the interaction of marijuana with other pregnancy risk factors has been demonstrated and is consistent with Greenland's observations. In Charlebois and Fried's study, rats were exposed to either cannabis smoke, placebo smoke, or no smoke while concurrently consuming one of three diets differing in protein concentration. Both the diet and drug treatments were administered 20 days prior to and throughout gestation. A number of dependent variables, including stillbirths, litter destruction, and postnatal deaths, were potentiated by a combination of a low protein diet and cannabis smoke. Interestingly, some physiological and developmental milestones that were delayed in the normal-protein-diet/cannabis-smoke condition were attenuated in the high-protein-diet/cannabis-smoke condition.

An additional pregnancy variable that was noted in the Ottawa study was an inverse dose-response relationship between marijuana use and the length of gestation (Fried et al. 1984). An average use of marijuana six or more times per week during pregnancy was associated with a significant reduction in length of gestation of 1.1 weeks after statistically adjusting for nicotine, alcohol, parity, mother's prepregnancy weight, and the child's sex. With similar adjustments, no reduction in birth weight was noted once gestational age was taken into account. The association between marijuana use and shortened gestation is consistent with historical anecdotes that have, over the past centuries, described how cannabis has been used as a method to increase the vigor of contractions and shorten labor (Abel 1980).

Animal work has indicated that cannabis constituents can alter a wide range of pituitary-ovarian and adrenal hormones (Dalterio and Bartke 1979; Harclerode 1980; Smith 1980). Harclerode's study provides indirect evidence that THC can affect steroid production by the placenta. Although the underlying physiological nature of the shortened gestation length associated with heavy marijuana use can only be speculated upon at this stage of research, a likely candidate for the mechanism of action is marijuana's influence upon the reproductive hormonal system.

As part of the Ottawa Prenatal Prospective Study, we have examined the relationship between marijuana and minor physical anomalies (MPA) (O'Connell and Fried, in press). The offspring of 25 cannabis using women and the offspring of 25 matched controls were examined for the presence of a large number of anomalies. None of the anomalies noted occurred more frequently among the offspring of cannabis users, nor were the number of anomalies present in an individual correlated with maternal cannabis use. Although a pattern of anomalies was not detected among the offspring of cannabis users, two anomalies--true ocular hypertelorism and severe epicanthus--were found only among children of heavy users of cannabis.

The lack of a definite relationship between minor physical anomalies and prenatal cannabis exposure is compatible with several other reports in the recent literature (Linn et al. 1983; Rosett et al. 1983). Apparent exceptions are one large generally prospective study (Hingson

et al. 1982) and two reports based on five Individual cases (Qazi et al. 1982; Qazi et al. 1983). All of these studies examined neonatal outcome in relation to maternal alcohol or marijuana consumption in large, racially mixed, inner-city samples.

Rosett et al. (1983) found that the risk of congenital anomaly was greater among offspring of women who drank heavily throughout pregnancy as compared to those of women who stopped drinking, but the risk was not increased by the use of cigarettes or marijuana.

Linn et al. (1983) found crude associations between marijuana use and lowered birth weight, prematurity, and major malformations, which disappeared when demographic characteristics, other drug use, and medical history were controlled for.

The reports of congenital anomalies related to maternal cannabis use have dealt with those anomalies which are part of the diagnostic criteria of the fetal alcohol syndrome (FAS). Flingson et al. (1982) found that women who smoked marijuana during pregnancy were five times more likely than nonusers to deliver a child with features considered compatible with the fetal alcohol syndrome (CFAS).

In the case reports, Qazi et al. (1982; 1983) suggested a link between prenatal cannabis exposure and FAS-type features because, in four of the five cases reported, the mothers were regular users of cannabis, but denied use of alcohol or any other psychoactive drugs during pregnancy. However, little demographic information or medical history was given in the reports, and no matching to control potentially confounding variables was undertaken.

The lack of statistically significant CFAS features in the Ottawa sample may be due to at least three factors: sample size, age of the subjects, and the relative “risk status” of the women in the Study.

First, the sample size in the Ottawa Prenatal Prospective Study hindered the finding of significant relations among the variables studied. This difficulty has been encountered by other researchers in similar studies (Greenland et al. 1982). If the 2% rate of occurrence of CFAS found in Hingson’s study could be considered accurate and was applied to the present sample, only one child would be expected to meet the diagnosis.

The subject of the Hingson et al. (1982) study were all examined during the first week of extra-uterine life. The mean age of the subjects in the present study was 28.8 months. This difference is an important one considering that some MPA’s are transient, being seen only in the neonatal period, or gradually changing as development proceeds through infancy, e.g., epicanthal folds (Smith 1974). Evidence suggests that features indicative of fetal alcohol effects may normalize with age, thus suggesting a delay, rather than a deficit, in development (Majewski 1981).

As maternal nutrition interacts with cannabis consumption during pregnancy to influence fetal outcome (Charlebois and Fried 1980), it is not surprising that definite physical effects have been reported only in a sample where poor nutrition (as evidenced by low weight gain) and poor prenatal care are common. The influence of cannabis may be one of potentiation of the maternal factors which have a direct effect on fetal outcome. This interaction was not evident in the sample, which appeared, overall, to be better nourished than those of Hingson et al. (1982). The mean weight gain of the present sample was 16.02 kilograms compared to 13.64 kilograms in the Hingson sample. Several maternal factors combined to place the children of the Ottawa Prenatal Prospective Study at a low risk for environmentally induced congenital anomalies. The mothers lacked any chronic or debilitating diseases; received prenatal care; had an improved nutritional status; and had a higher socioeconomic status (i.e., 18% of the Hingson sample had a yearly income of less than $6,000, but only 2% of the present sample did).

Published data pertaining to the issue of the potential behavioral teratological effects of in utero marijuana exposure are limited to the work arising from the Ottawa Prenatal Prospective Study. The widely used Brazelton Neonatal Behavioral Assessment Scale (NBAS) (Brazelton 1973) is utilized in an effort to quantify the newborn's response to external stimuli, motor organization, and ability to regulate alertness (table 1). In the Ottawa Prenatal Prospective Study, the examination is conducted at 60 to 80 hours postpartum, midway between feedings in a warm quiet room free from sudden extraneous noises, and located close to the hospital nursery. Observed behaviors include consolability, self—quieting, irritability, tremulousness, startles, alertness, orientation to animate and inanimate visual and auditory stimuli, habituation to stimuli in various modalities, hand-to-mouth movements, pull-to-sit muscle tone, Moro reflex, and liability of states. Assessment is carried out by two trained raters who are not aware of the mother's drug history.

A number of group differences have emerged using the Brazelton Scale (Fried 1980; Fried 1982). Smoking marijuana regularly during pregnancy was correlated with a marked decrease in the likelihood of the offspring responding to a light repeatedly directed at their eyes. Among infants born to women categorized as heavy users, 46% did not respond to the light in contrast to 16% of the babies born to matched nonusers ($X^2 = 4.282$, $p < .04$). Among the babies of the heavy users that did respond to the light, 33% failed to habituate compared to 7% of the matched controls. In the auditory modality, there were no differences between the marijuana offspring and the matched controls.

The apparent association between in utero marijuana exposure and visual functioning has been reported in previously published nonhuman primate work. Golub et al. (1981) examined the behavior of offspring of monkeys who had received daily treatment of tetrahydrocannabinol prior to and during pregnancy and throughout lactation. The types of behavior that were examined at I and 2 years of age included regulation of activity level, environmental responsiveness, problem solving, and social interaction. The category of behavior that

distinguished cannabis offspring from control offspring was visual attentiveness. In comparison to the offspring of untreated animals, the experimental babies failed to habituate visually to novel visual stimuli. It may also be noteworthy that Lodge (1977) and Finnegan (1981) observed that babies born to methadone-using mothers also responded poorly to visual stimuli, but were not abnormal in their responsiveness to auditory stimulation.

The most consistent and visible consequences of regular heavy marijuana consumption were significantly heightened tremors and startles. Among those offspring born to heavy marijuana users, 73% displayed marked tremors (a score of 7 or higher on the Brazelton Scale) contrasted to 30% of matched controls ($X^2 = 6.744$, $p < .009$). Startles (spontaneous and elicited) were also more pronounced among the offspring of heavy marijuana users ($X^2 = 5.287$, $p < .03$). These, together with the altered visual responsiveness, may reflect neurological dysfunction, possibly in the form of nervous system immaturity or a manifestation of drug withdrawal. However, unlike infants going through narcotic withdrawal, the marijuana babies were not more irritable than controls and were readily consolable. Finally, at this age, in our study, no association was observed between the degree of activity or of alertness and maternal marijuana use.

The Prechtl and Beintema neurological examination (1969) is given at 9 and 30 days of age (table 1). By using standardized techniques to elicit a comprehensive selection of reflexes and responses, this neurological inventory is designed to measure subtle qualitative and quantitative differences in behavior. Results from this test indicate that the altered responsiveness of the visual system noted above persisted in those infants whose mothers smoked marijuana six or more times per week during their pregnancy. The consistency was rather striking. Of the offspring of the heavy marijuana users who failed to respond to the visual stimuli at 3 days of age, 71% were not responsive at 9 days and *50%* continued to be unresponsive at 30 days. In contrast, all of the babies of heavy users that did respond to the visual stimulus during the Brazelton test continued to respond on the Prechtl test at 9 days of age. Among the matched controls who did not respond on the Brazelton, all did respond at 9 days, and all but one at 30 days when tested on the Prechtl.

As part of the Prechtl test, various extraocular movements were also examined, and some abnormalities among the marijuana infants were noted. In order to pursue these “soft” visual signs of the potential effect of intrauterine exposure to marijuana, a series of neuro-ophthalmological and electrophysiological tests are presently being conducted jointly with Drs. B. W. Tansley (sensory psychologist) and H.
T. J. Mount (neuro-ophthalmologist). Included in this neuro-ophthalmological battery are pupillary responses, gaze preponderance, tracking capability, optokinetic reflexes, and visual-evoked potentials to a patterned stimuli.

The preliminary results are quite striking. The dimension of interest in the pattern-evoked cortical response are the latencies of various

components of the waveform, with particular emphasis on the major positive component, P100, which occurs at approximately 100 milliseconds after the stimulus onset in adults. This component tends to be later in children and begins to approximate the adult waveform by 10 years of age.

Twenty children born to mothers who used marijuana prenatally were matched with 15 control children on the basis of child's age (3 to 6 years) and mothers' prenatal use of alcohol and nicotine. Findings showed that the P100 latency is consistently delayed in both left and right eye monocular condition. This is consistent with the notion that prenatal exposure to marijuana may delay the maturation of the visual system.

The ophthalmological examination has also demonstrated differences among the marijuana subjects and their controls in terms of myopia, strabismus, abnormal oculomotor functioning, and unusual discs. The neuro-ophthalmologist, examining the children without knowledge of their prenatal history, noted that *35%* of the marijuana subjects had more than one of the above problems, as compared to only 6% of the controls ($z = 2.43$, $p < .008$).

The Prechtl examinations also revealed some motor differences among the babies born to the heavy marijuana users. Most prominent were the marked tremors which at 9 days were observed in 43% of the babies contrasted with 12% of the matched controls ($X^2 = 9.362$, p (.003), and at 30 days were still present in 25% of the heavy marijuana offspring and only 8% of the controls ($X^2 = 3.806$, $p < .06$). The tremors among the babies born to the heavy marijuana users were significantly more likely to be low frequency, high amplitude in nature compared to the controls. Other motor differences observed among the infants of heavy marijuana users included an exaggerated Moro reflex, increased occurrence of athetoid movements and disinhibition in a number of motor tests. Like some of the observations made soon after birth, many of these behaviors are similar to those observed in infants undergoing narcotic withdrawal (Finnegan 1981).

In the Ottawa study, children are administered the Bayley Scale of Infant Development (Bayley 1969) at 6, 12, 18, and 24 months of age (table 1). The mental portion of this test assesses sensory perceptual abilities, early acquisition of object constancy, problem solving, and the onset of vocalization. The motor portion is directed at assessing both gross and fine motor abilities. A temperament portion measures more clinical aspects of behavior, evaluating various general aspects of the child's functioning rather than assessing particular skills. At 18, 24, 36, and 48 months of age, the Reynell Expressive Language and Verbal Comprehension Scale (Reynell 1969) is administered and, at 36 and 48 months, the McCarthy Scales of Children's Abilities (McCarthy 1972) is given. Table I outlines the tests administered to the infants and children at the various ages.

Group data collected from the tests administered at 6 and 12 months of age failed to discriminate between those babies born to heavy

marijuana users and either those born to matched controls or normative scores based on the general population. However, among the offspring of the heavy marijuana users, two subgroups were identified. Although the number of subjects that fulfill the criteria for inclusion within the subgroups is small, the results are quite pronounced. Among those babies who demonstrated a consistent decrease in visual responsiveness on all three neonatal tests and for whom the two Bayley scores are available (N = 6), the mean Mental Developmental Index (MDI) was 82 (range 60 - 92) at 6 months, and 96 (range *75* - ill) at 12 months. Among the few children who did not show the neonatal decreased visual responsivity, but who were born to mothers with similar heavy marijuana habits (N = 7), the mean MDI at 6 months was 118 (range 106 - 129), and at 12 months was 106 (range 98 - 120). Among the matched controls, the mean MDI at 6 months was 102 and at 12 months, 101. At 18 and 24 months, no differences were noted on the MDI between the offspring of the heavy marijuana users who were consistently visually less responsive as neonates and those who had normal visual responses.

An examination of both the overall motor portion of the Bayley Psychomotor Developmental Index (PDI) and the fine and gross motor clusters at 6, 12, 18, and 24 months failed to reveal any differences between the offspring of marijuana users and matched controls. Further, subdividing the babies born to mothers who used marijuana heavily into those who showed marked tremors on the neonatal tests and those who did not failed to distinguish the babies on the Bayley motor tests.

The picture that has emerged to date is that there are a number of neonatal neurobehavioral variables that are correlated with in utero marijuana exposure that persist after controlling for nonmarijuana drug habits, the history of previous pregnancies, socioeconomic status, and nutritional (including caffeine) intake.

Finally, the general observation that the neonatal nervous system alterations seen in the offspring of regular maternal marijuana users seemingly does not express itself in poorer performance on cognitive and motor tests at U and 2 years of age must be interpreted cautiously. It is not at all clear whether this is the true state of affairs arising because neurological disturbances present at birth are truly transient and are overcome, or compensated for with maturity, or whether the tests used at the Ii and 2 year ages might have a decreased discriminatory sensitivity to subtle cognitive differences that actually may exist.

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