Rakhee Bowker, MD/PGY-2
IRC Rotation
March 28, 2011

Neurodevelopmental Sequelae of Perinatal Exposure to Cannabis:
A prospective randomized controlled trial assessing whether intensive prenatal marijuana cessation counseling improves neurodevelopmental outcomes in children of marijuana-using mothers

1. Study Purpose and Rationale
Approximately 4.6% of women in the United States report illegal drug use during pregnancy, according to the 2004 National Survey on Drug Use and Health [12]. Cannabis is the most commonly abused illicit substance during pregnancy, representing almost 75% of perinatal drug use, with 3% of pregnant women reporting marijuana use during their first trimester of pregnancy [1, 2]. In Europe, the prevalence of prenatal cannabis exposure is between 2-5%, with an increased prevalence of up to 13% in high-risk populations including individuals of low socioeconomic status (SES) and pregnant adolescents [3]. Pregnant marijuana users are a vulnerable population, as these women are more likely to be African American, unmarried, uneducated, and of lower SES; these women also frequently use other illicit drugs and generally receive less prenatal care than non drug users, putting these women at increased risk for poor pregnancy outcomes [12, 13].

Marijuana use during pregnancy is often perceived, incorrectly, to be harmless. However, existing evidence clearly suggests that exposure to cannabis during fetal development is not benign, via longitudinal human cohort studies and animal models which demonstrate the negative influence of prenatal cannabinoid exposure on behavior and mental health. 33% of delta-9-tetrahydrocannabinol (the major psychoactive component of marijuana) undergoes cross-placental transfer when marijuana is smoked. Frezza and colleagues found that prenatal exposure to delta-9-THC was associated with increased emotional reactivity, inhibited social interaction and play behavior, and increased anxiety in rats [14]. Several studies in adults and adolescents demonstrate an association between in-utero marijuana exposure and cognitive impairment, poor impulse control, increased substance abuse and psychiatric disorders including anxiety, depression and schizophrenia [7,8,9,10]. Studies have also shown increased rates of fetal distress, growth retardation, and adverse neurodevelopmental outcomes in infants with prenatal cannabis exposure [4, 5, 6]. Although cohort studies have been published looking at how prenatal cannabis exposure impacts development in the first few years of life, a lack of consistency in these studies has yielded conflicting results [8].

Despite documentation of adverse outcomes, there is limited information regarding the neurobiological consequences of cannabis exposure during human fetal brain development. A growing body of evidence supports that the endocannabinoid system (ECS) is involved in central nervous system (CNS) patterning of the mesocorticolimbic system, thereby regulating structures responsible for cognition, motivation, and emotional processes [7]. Endocannabinoids affect maturation of the dopamine signaling system, whose dysfunction has been implicated in the pathophysiology of schizophrenia; and those individuals with a genetic susceptibility for schizophrenia appear to be vulnerable to developing psychological symptoms such as disorganization and hyperactivity/inattention with cannabis use [11]. The ECS also has a strong interaction with opioid systems involved in addictive behaviors and reward pathways.

Although studies have shown that prenatal exposure to cannabis is associated with cognitive and neurobehavioral deficits, it is unclear whether marijuana cessation early in pregnancy will ameliorate these effects, or whether there is something about expectant women who choose to smoke marijuana that results in poorer neurodevelopmental outcomes in their offspring. In this study, we propose to identify women who are currently using or have used marijuana within 3-6 months of becoming pregnant, and assess whether intensive marijuana cessation counseling early in pregnancy results in improved neurodevelopmental outcomes in their children, secondary to decreased cannabis exposure during fetal development.

The results of this study will clarify the impact of prenatal cannabis exposure on the developing fetus, and will thereby help obstetricians to counsel patients more effectively on the risks of fetal exposure to cannabis. If intensive cessation counseling early in pregnancy is found to improve neurodevelopmental outcomes in the children of marijuana-using mothers, the clinical implications are significant and the results will support development of targeted initiatives to discourage use of marijuana during pregnancy. If no difference in outcomes is shown, the data may indicate that our targeted intervention does not decrease maternal marijuana use. Alternately, if intensive counseling is found to decrease maternal marijuana use but has no effect on clinical outcomes, such results may indicate that the impact of maternal marijuana use on fetal development occurs prior to conception, or is tied to the multitude of socioeconomic, cognitive, behavioral and psychological factors that drove these mothers to abuse marijuana in the first place. If so, further study will be required to identify strategies for prevention and early intervention.

2. Study Design and Statistical Procedures
This will be a single-center prospective randomized controlled trial assessing whether intensive prenatal marijuana cessation counseling early in pregnancy improves neurodevelopmental outcomes in infants of marijuana-using mothers as compared with standard prenatal care. The primary outcome will be neurodevelopmental outcomes as measured by the Bayley Scale of Infant Development - Third Edition (BSID-III). Secondary outcomes will include: decrease in maternal marijuana use during and after pregnancy, gestational age at birth, newborn growth parameters (height, weight and head circumference), and children's scores on the Vineland Adaptive Behavior Scale.

PRIMARY OUTCOME	METHOD OF MEASUREMENT
Child's **neurodevelopment** as measured by cognitive, motor and language scores on the Bayley Scale of Infant Development - 3rd Edition (BSID-III)	BSID-III will be administered by trained research assistants who are blinded to child's marijuana exposure status, at 12, 18, 24, 30 and 36 months
SECONDARY OUTCOMES	**METHOD OF MEASUREMENT**
Maternal **marijuana use** during and after pregnancy	Drug risk score calculated at the first prenatal visit and monthly throughout pregnancy, then every 6 months after delivery
	Urine toxicology screens monthly during pregnancy and every 6 months after delivery reflecting marijuana use in the last 4 weeks
Infant's **gestational age** at birth	Estimated by prenatal ultrasonography in the first trimester and mother's last menstrual period

Growth parameters: recumbent length, weight, head circumference	Recumbent length: measured at birth, expressed in centimeters
	Birthweight: measured on an infant scale in the delivery room, expressed in kilograms
	Head circumference: measured at birth, expressed in centimeters
Child's adaptive behavior: ability to cope with environmental changes, as indicated by scores on the Vineland Adaptive Behavior Scale (VABS)	The VABS is a neurodevelopmental evaluation looking at developmental delays, behavior problems such as aggression and temper tantrums, and hyperactivity, as reported by the primary caregiver.
	4 behavior domains: Communication, Daily Living Skills, Socialization, and Motor Skills
	Administered at 18, 24, 30 and 36 months, by trained research assistant obtaining primary caregiver's report

In this study, we propose to identify women who are currently using or have used marijuana within 3-6 months of becoming pregnant. We will recruit and enroll women at their first prenatal visit. We will randomize women to the treatment arm, which involves intensive marijuana cessation counseling beginning at the first prenatal visit and continuing throughout pregnancy on a monthly basis, or the control arm, in which mothers will receive standard prenatal care and a pamphlet outlining the risks of smoking marijuana during pregnancy. We will aim to enroll 65 women in each group.

We will obtain information on maternal IQ and calculate a psychosocial risk score for each mother which may be used for further analysis. We will obtain measures of prenatal drug exposure, obstetrical complications, gestational age at delivery, newborn growth parameters and neurological functioning in the neonates. We will perform neurodevelopmental assessments in all newborns at an average of 6-month intervals beginning at 12 months until the age of 3 years and determine whether intensive marijuana cessation counseling early in pregnancy results in improved neurodevelopmental outcomes in the children secondary to decreased cannabis exposure during fetal development.

We will use t tests to compare mean values of the subjects in the treatment arm with mean values of the control subjects with regard to our primary outcome, performance on the BSID-III at 12, 18, 24, 30 and 36 months. We will not adjust Type I error for the number of behavior outcomes analyzed because these variables are not independent of each other and dividing alpha by the number of outcome variables would be too conservative.

With regard to the secondary outcome of decreased marijuana use, each mother will be assigned a total drug abuse score per trimester of pregnancy and post delivery and t tests will be used to compare the means of both groups. The t test will also be used to compare the remaining secondary outcomes including newborn growth parameters, gestational age at delivery, and children's scores on the Vineland Adaptive Behavior Scale.

A sample size of 65 patients in each group was calculated using the t test to achieve 80% power with an alpha-error rate of 0.05 to detect a difference of 0.5 standard deviations (SD) on the BSID-III, assuming a SD of 15 with a mean of 100.

3. Study Procedures

Pregnant mothers with a history of marijuana use within the preceding 3-6 months will be recruited at their first prenatal visit and will be randomized to intensive counseling versus standard prenatal care. For the treatment arm, intensive marijuana cessation counseling will begin at the first prenatal visit and will be provided by a master's level psychologist. Further counseling will occur on a monthly basis in conjunction with scheduled prenatal visits through delivery. At each counseling session, the known risks of marijuana exposure during fetal development will be emphasized and the subject's marijuana use in the preceding month will be documented and discussed. A drug risk score will be issued at each visit. Positive reinforcement and encouragement will be provided as well as gift certificates for purchase of infant clothing or supplies if the mother is able to remain drug free between visits. For the control arm, mothers will receive standard prenatal care from their OB-GYN along with a pamphlet outlining the dangers of prenatal marijuana exposure.

During the initial prenatal visit, a psychosocial risk score will be calculated for each mother-newborn dyad derived from 6 items from a psychosocial questionnaire, which includes living situation and marital status, education, occupation, employment status, language spoken at home, and maternal age at birth. The Wechsler Abbreviated Scale of Intelligence (WASI) will be administered to the mothers to control for maternal IQ and its impact on the infants' cognitive outcomes. Because the study subjects are randomized, these measures should be approximately equal across groups; however, we will obtain the information for further analysis.

At each visit from birth thru 36 months, a physician will perform a physical and neurological exam on the infant. Developmental assessments will be administered by trained practitioners who have been certified in scoring and interpretation of the assessment tools and are blinded with regard to the subject's cannabis exposure status. Motor, language and cognitive development will be measured using the BSID-III, which provides a language score, motor score, and cognitive score, beginning at 12 months and re-administering the assessment every six months through 36 months. To assess behavioral outcomes, the Vineland Adaptive Behavior Scale will be administered. The Vineland provides a measure of the child's ability to cope with environmental changes and skills as reported by the mother, and is a neurodevelopmental evaluation looking at developmental delays, behavior problems such as aggression and temper tantrums, and hyperactivity.

4. Study Drugs or Devices
N/A

5. Study Questionnaires
Screening questionnaire: The screening questionnaire will be used to determine eligibility of participants for enrollment in the study. It will ask about the type and amount of previous drug use during pregnancy as well as information on general health and age of the mother and gestational age of the baby if known.

Psychosocial questionnaire: During the initial prenatal visit, a psychosocial risk score will be calculated for each mother-newborn pair derived from 6 items from a psychosocial questionnaire, which includes living situation and marital status, education, occupation, employment status, language spoken at home, and maternal age at birth.

6. Study Subjects
N = 130 pregnant women of age range 18-40 years

The study participants will be representative of the continuum of marijuana use within the Washington Heights clinic population. All participants will be pregnant women 18-40 years of age who are either currently using marijuana or have used marijuana within the past 3-6 months. Based on the demographics of the catchment area served by our institution, and the increased prevalence of marijuana use among pregnant minorities, the racial distribution will likely be predominantly African American and Hispanic.

Inclusion Criteria:
- Pregnant or trying to become pregnant (in which case patients would be instructed to contact the study coordinator when they became pregnant)
- Maternal age 18-40 years
- Maternal use of marijuana either currently or within the past 3-6 months, either by report or via urine toxicology screen positive for marijuana

Exclusion Criteria:
- Maternal heavy alcohol use defined as >2 ounces per day and episodes of binge drinking
- Maternal use of barbiturates, psychotropic medications, cocaine, heroin or methadone
- Severe maternal medical problems such as >class II diabetes, AIDS, seizure disorder

7. Recruitment
Pregnant women will be recruited from the clinics at New York Presbyterian Medical Centers, Morgan Stanley Children's Hospital, and from various treatment centers, adult psychiatry clinics and hospitals in the NYC area.

Initial contact with pregnant women will be made by clinic staff and with advertisement leaflets summarizing the study. Women will be enrolled in the study as early as possible during their pregnancies. A psychologist or a physician involved with the study will conduct screening and recruitment. We will screen 1000 pregnant women at their first prenatal visit with the goal of obtaining 130 study subjects. A screening survey will be used to determine whether individuals are eligible for enrollment. This survey will not contain identifying information, but rather will ask about type and amount of current and prior drug use, as well as information on the general health and age of the expectant woman and gestational age of the fetus if known. The subject's responses will be reviewed to determine her eligibility for the study. If the potential participant meets eligibility requirements for the study, the study will be described to her in detail, and she will be given opportunity to ask questions about the study. If she is willing to participate, she will be asked to read and sign a consent form (in English or Spanish), which will include permission to review her medical records.

8. Confidentiality of Study Data

All the information obtained from the participants will be coded by number and kept in locked, confidential files. Information will not be accessible to anyone but the study investigators. All the electronic data will be stored behind firewalls and de-identified.

9. Potential risks

There are no clear risks associated with this study. Specifically, no risks are associated with neuropsychological tests, diagnostic interviews, or marijuana cessation counseling. A mother may feel guilty for continuing to use marijuana if she is unable to quit. If the study participant does not wish to continue counseling, she may stop at any time. All diagnostic tests will be performed by a trained member of the research staff, and any issues that warrant clinical attention will be reported to a supervising physician so that appropriate referrals can be made.

10. Potential benefits

Direct Benefit to Mothers and Infants in the Treatment Arm:
For those individuals randomized to the treatment arm, intensive counseling will be provided which will help the mothers stop using marijuana, and if the intervention is effective, may result in improved neurodevelopmental outcomes for their infants. The marijuana cessation counselor will become involved in the lives of the mother and her child through monthly prenatal visits, providing empathetic listening and information, marijuana cessation counseling, as well as assisting mothers in gaining access to resources. Counselors will also contact study participants at home on a regular basis to offer support as necessary and to obtain updates of contact information. After the babies are born, any infants who are identified on developmental screening as having special needs (such as speech delay, motor delay, and/or cognitive delays) will be referred appropriately to speech therapy, occupational therapy and/or physical therapy.

Direct Benefit to Mothers and Infants in the Control Arm:
For those individuals randomized to the control arm, a research assistant will contact study participants on a monthly basis to offer support as necessary and to obtain updates of contact information. As with the subjects in the treatment arm, any children who are identified on developmental screening as having special needs will be referred to appropriate therapy.

Indirect Benefit: Children of marijuana-abusing mothers will benefit indirectly by the possibility of improvement in the understanding of neurodevelopmental sequelae of intrauterine exposure to cannabis and possible improvements in medical and psychiatric treatment of these conditions.

Compensation: Mothers will receive gift certificates for baby clothes/supplies at the initial prenatal visit and will receive additional gift certificates on a monthly basis if they remain drug-free between study visits. Following birth of the babies, all mother-infant dyads will receive gift certificates at each study visit to help purchase clothing and baby supplies. Age-appropriate educational toys and books will be provided for the infants/toddlers at each study visit, and cards at holidays and birthdays.

11. Alternatives

The alternative option available to expectant mothers is to decline to participate in this study. All pregnant women approached regarding the study will be reassured that the decision to participate is strictly voluntary and that their prenatal care and the care of their newborn children will not be compromised if they decline.

REFERENCES

[1] SAMHSA. Results from the 2005 National Survey on Drug Use and Health: National Findings. In: SAMHSA Office of Applied Studies, Rockville, MD. Cited in: Jutras-Aswad D, DiNieri JA, Harkany T, Hurd YL. Neurobiological consequences of maternal cannabis on human fetal development and its neuropsychiatric outcomes. *Eur Arch Psychiatry Clin Neurosci* 2009; 259: 395-412

[2] Goldschmidt L, Day NL, Richardson GA. Effects of prenatal marijuana exposure on child behavior problems at age 10. *Neurotoxicology and Teratology* 2000;22:325-36

[3] Williamson S, Jackson L, Skeoch C, Azzim G, Anderson R. Determination of the prevalence of drug misuse by meconium analysis. *Arch Dis Child Fetal Neonatal Ed* 2006; 91:F291-F292

[4] Hurd YL, Wang X, Anderson V, Beck O, Minkoff H, Dow-Edwards D. Marijuana impairs growth in mid-gestation fetuses. *Neurotoxicol Teratol* 2005;27:221-229

[5] Day NL, Richardson GA, Geva D, Robles N. Alcohol, marijuana and tobacco: effects of prenatal exposure on offspring growth and morphology at age six. *Alcohol Clin Exp Res* 1994;18:786-794

[6] Day NL, Richardson GA, Goldschmidt L, Robles N, Taylor PM, Stoffer DS, Cornelius MD, Geva D. Effect of prenatal marijuana exposure on the cognitive development of offspring at age three. *Neurotoxicol Teratol* 1994;16:169-175

[7] Jutras-Aswad D, DiNieri JA, Harkany T, Hurd YL. Neurobiological consequences of maternal cannabis on human fetal development and its neuropsychiatric outcomes. *Eur Arch Psychiatry Clin Neurosci* 2009;259:395-412

[8] Fried PA, Watkinson B. 12- and 24-month neurobehavioral follow-up of children prenatally exposed to marihuana, cigarettes and alcohol. *Neurotoxicol Teratol* 1988;10:305-313

[9] Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol* 1998;20:293-306

[10] Fried PA, Watkinson B. Differential effects on facets of attention in adolescents prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol* 2001;23:421-430

[11] Hollis C, Groom MJ, Das D, Calton T, Bates AT, Andrews HK, Jackson GM, Liddle PF. Different psychological effects of cannabis use in adolescents at genetic high risk for schizophrenia and with attention deficit/hyperactivity disorder (ADHD). *Schizophr Res* 2008;105:216-223

[12] Van Gelder, MMHJ, Reefhuis J, Caton AR, Werler MM, Druschel CM, Roeleveld N. Characteristics of pregnant illicit drug users and associations between cannabis use and perinatal outcome in a population-based study. *Drug and Alcohol Dependence* 2010;109:243-47

[13] Day NL, Cottreau CM, Richardson GA. The epidemiology of alcohol, marijuana, and cocaine use among women of childbearing age and pregnant women. *Clin Obstet Gynecol* 1993;36:232-45

[14] Trezza V, Camplongo P, Cassano T, Macheda T, Dipasquale P, Carrutu MR, Gaetami S, Cuomo V. Effects of perinatal exposure to delta-9-tetrahydrocannabinol on the emotional reactivity of the offspring: a longitudinal behavioral study in Wistar rats. *Psychopharmacology* 2008; 198:529-537

[15] Fride E, Gobshtis N, Dahan H, Weller A, Giuffrida A, Ben-Shabat S. The endocannabinoid system during development: Emphasis on perinatal events and delayed effects. Chapter Six in *Vitamins and Hormones*, Elsevier Inc. 2009; 81: 139-158

[16] Campolongo P, Trezza V, Casano T, Gaetani S, Morgese MG, Ubaldi M, Soverchia L, Antonelli T, Ferraro L, Massi M, Ciccocioppo R, Cuomo V. Perinatal exposure to delta-9-tetrahydrocannabinol causes enduring cognitive deficits associated with alteration of cortical gene expression and neurotransmission in rats. *Addict Biol.* 2007; 12(3-4): 485-95