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Risk of neonatal and childhood morbidity among preterm infants exposed to marijuana

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Abstract

Background—Limited data exist regarding the neonatal and neurodevelopmental outcomes of infants exposed to marijuana (MJ) in-utero, particularly among preterm infants. We hypothesized that MJ-exposed preterm infants would have worse neonatal and childhood developmental outcomes compared to MJ-unexposed infants.

Methods—Secondary analysis of multicenter randomized-controlled trial of antenatal magnesium sulfate for prevention of cerebral palsy was conducted. Singleton non-anomalous infants delivered <35 weeks exposed to MJ in-utero were compared to MJ-unexposed. Primary neonatal outcome was death, grade 3/4 intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and/or stage II/III necrotizing enterocolitis before discharge. Primary childhood outcome was death, moderate/severe cerebral palsy, or/and Bayley II Scales <70 at age 2. Backwards-stepwise regression used to estimate odds of primary outcomes.

Results—1,867 infants met inclusion criteria; 135(7.2%) were MJ-exposed. There were no differences in neonatal (20%vs26%, p=0.14) or childhood (26%vs21%, p=0.21) outcomes in MJ-exposed infants compared to MJ-unexposed infants. In adjusted models, MJ-exposure was not associated with adverse neonatal outcomes (aOR 0.83 95%CI 0.47,1.44) or early childhood outcomes (aOR 1.47, 95%CI 0.97, 2.23).

Conclusions—Among infants born <35 weeks of gestation, MJ-exposure was not associated with adverse neonatal or childhood outcomes. Long-term follow up studies are needed to assess later childhood neurodevelopmental outcomes following MJ-exposure.

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Keywords

marijuana; neonatal morbidity; prematurity; developmental outcomes

Introduction

Marijuana (MJ) is one of the most commonly used recreational substances in the United States,(1) and use is currently on the rise particularly among young Hispanic and Black women.(2, 3) Recent studies estimate that more than 10% of pregnant women use MJ during pregnancy.(4) Among pregnant teenage women (15–17 years), MJ use may be as high as 17–29%.(5, 6)

Although the prevalence of MJ among pregnant women is high, there is limited information on the effects of MJ use on pregnancy and neonatal outcomes. MJ use in pregnancy and its association with adverse neonatal outcomes including lower Apgar scores, low birth weight in term infants and NICU admission in term infants is conflicting.(7–10) Results of these studies are difficult to interpret given the high frequency of associated tobacco and drug use and confounding by race and age of mothers. MJ-exposure in-utero may have neurodevelopmental implications, including an increase in behavioral problems, poor performance on visual tasks, and decreased language comprehension above the age of 4 among a cohort of babies born at term.(11, 12) However, follow-up of this same cohort of children between ages 9–12 showed a resolution of these differences.(13) Another large cohort suggested differences in verbal reasoning at age 6 in children exposed in the first trimester.(14) Studies of perinatal outcomes and MJ use in pregnancy are challenging given the multiple confounding aspects, however these reports of potential long term effects of in-utero MJ-exposure are concerning.(15)

Since it is highly lipophilic, MJ may remain in adipose and other tissue for a prolonged period after a single exposure; delta 9 tetrahydrocannabinol (THC) readily crosses the placenta.(16) Theoretically, even single or intermittent exposures continue to affect the fetus long after initial exposure. Cannabinoid receptors are present in the fetal brain and the uterine decidua, and binding to these receptors may have undesired downstream effects. Effects of the increased carbon monoxide related to MJ inhalation on the fetus are unknown. Furthermore, both short- and long-term effects of MJ-exposure may be more pronounced in infants born prematurely, due to an increased susceptibility of their immature organ systems to perturbations.

The objective of this study was to investigate if prenatal MJ-exposure is associated with adverse neonatal and early childhood outcomes among preterm infants delivered <35 weeks gestation.

Materials / subjects, and Methods

This study is a secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) randomized placebo-controlled, double-masked

multicenter trial of antenatal magnesium sulfate for the prevention of cerebral palsy. In this study, women at risk of imminent delivery between 23 5/7 and 31 6/7 weeks were recruited from 20 centers between 1997 and 2004, and randomized to receive placebo or magnesium. The details of this study were previously published.(17) This study was reviewed and deemed exempt from oversight by the University of North Carolina at Chapel Hill Institutional Review Board. We included singleton, non-anomalous live born infants who delivered <35 weeks and 0 days gestation. The gestational age of 35 weeks was selected in order to minimize exclusion of women with PPROM who were induced starting at 34 weeks as the majority of the study population was women with PPROM. From the original BEAM cohort (n=2,444), we excluded twin gestations (n=406), infants with major congenital anomalies (n=65) and those infants who delivered after 34 weeks and 6 days of gestation (n=106), leaving 1,867 infants for the analysis. Our primary exposure was prenatal MJ use. We used the same definition for MJ-exposure as was used in the original trial which included self-reported use at study enrollment or a positive drug screening test for delta-9-tetrahydrocannabinol (THC). There are issues with self-reporting (i.e. under reporting, recall bias, etc). The primary neonatal outcome of this study was a composite neonatal morbidity including one or more of the following prior to initial hospital discharge: death prior to hospital discharge, grade 3 or 4 intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD), and grade II or III necrotizing enterocolitis. The primary childhood outcome was a composite of adverse childhood morbidity including one or more of the following: death before age 2, moderate or severe cerebral palsy (CP), or a Bayley Scales of Infant Development II Mental or Psychomotor Developmental Indices (MDI and PDI respectively) <70 (2 standard deviations below the mean) assessed at age 2. CP diagnosis was made by a board-certified pediatrician or pediatric neurologist blinded to the treatment allocation of magnesium. All infants included in the analysis of the primary study were evaluated (for CP, and given a Bayley Scales of Infant Development II Mental or Psychomotor Developmental Indices) by the above providers at the age of 2. Neonatal birthweight was classified as AGA (10–90%tile), LGA (≥90%tile), or SGA (<10%tile) based upon gender- and gestational-age specific contemporary national norms.(18) Secondary outcomes included the components of the composite, any CP, and MDI < 85 (one standard deviation below the mean) and PDI <85. We also performed a planned subgroup analysis for infants delivered <28 weeks and zero days gestation.

Bivariate analyses were performed using chi-square or Fisher's exact test as appropriate. The multivariable analysis was conducted using a stepwise backward-elimination approach for all infants, then again in a separate model for those who delivered at <28 weeks and 0 days. Covariates were selected for the model based on known associations with the primary outcome and those significant in the bivariate analysis. A p- value of <0.05 was considered statistically significant. Decision to include magnesium exposure and antenatal corticosteroids in the models was made *a priori*. Covariates with p<0.20 were retained in final models. Because of the high concomitant use of MJ and other drugs and tobacco, interaction terms were assessed in the final regression model to determine if any of these factors were effect modifiers on neonatal or childhood outcomes. A p-value ≤ 0.1 was

considered statistically significant. STATA 13.0 (StataCorp, College Station, TX USA) was used to perform all analyses.

Results

Of 1867 singleton, non-anomalous preterm infants, 138 (7.2%) were exposed to MJ. MJ-exposed infants were more likely to be born to mothers who were Black and unmarried (Table 1). Compared to those who did not use MJ in pregnancy, those women who used MJ during pregnancy were less likely to have received prenatal care and to have graduated high school, and were more likely to have used other drugs and smoked cigarettes during pregnancy. However, other baseline characteristics (including exposure to antenatal corticosteroids or magnesium), did not vary by MJ-exposure.

There were no differences in the frequencies of the composite major neonatal morbidity or major childhood morbidity between MJ exposed and non-exposed infants (Table 2). There were also no differences in the components of the composite outcomes or other secondary outcomes between MJ exposed and non-exposed infants. MJ exposed infants were more likely to have a MDI<85 compared to non-exposed infants (p=0.03). When only considering infants born at <28 weeks, there was no difference in neonatal or childhood outcomes (Table 3).

In a multivariable analysis, tobacco and other drugs were not associated with either neonatal or childhood outcomes, thus were not retained in the models. For both adverse neonatal and early childhood composite outcomes, there was also neither a significant interaction between tobacco and MJ use (p=0.64 & 0.68 respectively), nor other drugs and MJ use (p=0.72 & p=0.74 respectively). There was a trend toward worse early child outcomes among women who used MJ when controlling for covariates (aOR 1.47, 95% CI 0.097, 2.23, p=0.073) (Table 4). Interaction was similarly assessed for the subgroup analysis of infants born before 28 weeks, but once again, no significant interactions were found (all p<0.95). For infants born at <28 weeks, MJ use was not associated with increased odds of adverse neonatal or early childhood outcomes (Table 5).

Discussion

Among singleton preterm infants born prior to 35 weeks, MJ-exposure in-utero was not associated with adverse neonatal or early childhood outcomes, including neonatal death. In 2015, recreational MJ use was legal in four states, decriminalized and medicinal MJ is permitted in several other states and the District of Columbia. Increasingly states are moving towards legalization and decriminalization of MJ. In response to any anticipated increase in MJ by reproductive age women, publications on MJ-exposure in pregnancy are becoming more abundant, though there is still a relative paucity of data on this subject, specifically among preterm infants.

Data on neonatal outcomes are limited, and almost entirely relegated to term infants. Most recently, Conner et al looked retrospectively at a cohort of approximately 8000 term neonates, including 680 who were exposed to MJ.(8) In that cohort, there was no difference in adverse neonatal outcomes (including NICU admission, 5 minute Apgar<7, umbilical

artery pH<7.1, and birth weight <2500g) among infants exposed to MJ. The same group also recently published a meta-analysis to evaluate the effects of MJ-exposure on neonatal outcomes, and did not find an association between MJ use and short-term outcomes after adjusting for confounding factors.(19)

Day et al studied childhood neurodevelopmental outcomes based on in-utero MJ-exposure at three, six, and ten years of age in a high-risk low income population and identified no difference at age three in intelligence testing, some decreased verbal reasoning at age 6, and worse reading and spelling testing scores at age ten in MJ exposed children compared to non-exposed children.(14, 20) In another cohort of children, Fried and colleagues found a negative effect of prenatal MJ-exposure on cognition and executive function at age 3, 4, and 6.(11, 12) Both of these studies had no or very small numbers of preterm infants. Our study suggests that neonatal outcomes of preterm infants exposed to MJ prenatally are not different than unexposed infants. However, there is a trend in both of our multivariable models to an association with adverse childhood outcomes. It may be that follow-up limited to two years of age is not long enough to see deficits in higher cognitive functioning observed in other longitudinal studies, or simply that we need a larger sample size.

This study has several strengths. First, the data were from a large prospective randomized controlled trial, in which data on patients and outcomes were collected using standardized protocols by trained research staff. Specifically, childhood neurodevelopmental outcomes were collected by trained pediatricians or pediatric neurologists. Of the 1,867 infants in our study, 96% were assessed for CP, however only 81% had MDI and PDI testing completed. Additionally, data from this study were collected at 20 centers across the United States and represent an ethnic makeup similar to the general population, thus making these findings more generalizable.

A limitation of this study includes inability to assess the frequency or timing of MJ use during pregnancy. Because this is a dichotomous variable in our study, women who used daily are categorized the same as those who used once during pregnancy. Though data does not exist on MJ specifically regarding quantity of exposure, there is evidence that quantity of tobacco or cocaine used is proportionally related to adverse outcomes.(21, 22) At this time, there are no human data regarding the fetal effects of MJ based on trimester of exposure. Further, we did not have urine drug screen results on all women, and use may be under-reported. Finally, the majority of babies in this study were delivered following PPROM, an obstetric complication traditionally associated with high rates of neonatal and childhood morbidity and mortality due to an increased likelihood of infectious morbidity. It is unclear whether a similar null-effect of MJ on neonatal and childhood outcomes would be observed in a cohort of babies delivered preterm for maternal indications such as preeclampsia, for example. In addition, our cohort may have been too small to detect a smaller but potentially clinically meaningful difference in neonatal and childhood outcomes between groups. In order to detect the observed difference in adverse childhood outcomes of 4.6%, we would need over 6500 women, of which 604 used MJ.

In conclusion, among preterm neonates born at <35 weeks largely due to PPROM, in-utero exposure to MJ was not associated with an increased risk of adverse neonatal or early

childhood developmental outcomes. However the potential trend towards an association with adverse childhood outcomes warrants further investigation in a larger cohort with quantification of the timing and duration of exposure.

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Table 1

Maternal, delivery, and neonatal characteristics by prenatal marijuana exposure

	No Marijuana n=1732	Marijuana n= 135	*p* value
Maternal characteristics			
Age (median, IQR)	26 (21,30)	26 (22,31)	0.33
Race/ethnicity, n (%)			<0.001
Black	741 (42.8)	91 (67.4)	
White	629 (36.3)	38 (28.2)	
Other	362 (20.9)	6 (4.4)	
High school or less	1231 (71.1)	111 (82.2)	0.006
Missing	4 (0.2)	0 (0)	
Married	849 (49.2)	32 (23.7)	<0.0001
Missing	5 (0.3)	0 (0)	
Obese (BMI>30)	387 (22.3)	23 (17.0)	0.07
Missing	197 (11.4)	8 (5.9)	
Multiparous	1115 (64.5)	89 (65.9)	0.72
Prior PTB	484 (27.9)	36 (26.7)	0.75
Smoking	431 (24.9)	104 (77.0)	<0.0001
Other drugs	58 (3.4)	43 (31.9)	<0.0001
Diabetes	91 (5.3)	5 (3.7)	0.43
Chronic medical conditions (HTN)	304 (17.6)	17 (12.6)	0.14
Delivery characteristics			
No prenatal care	123 (7.1)	23 (17.4)	<0.0001
Any magnesium exposure	1010 (58.4)	86 (63.7)	0.22
Corticosteroids	1683 (97.2)	131 (97.0)	0.93
PPROM	1519 (87.7)	123 (91.1)	0.24
Cesarean delivery	647 (37.4)	39 (28.9)	0.05
Neonatal characteristics			
Gestational age (wks)	29 (27, 32)	30 (28, 31)	0.41
Preterm < 28 wks	534 (30.8)	35 (25.9)	0.23
Birth weight (grams)	1355 (981,1722)	1360 (1075,1640)	0.88
Male infant	931 (53.8)	68 (50.4)	0.45
Five-minute Apgar < 7	318 (18.4)	22 (16.3)	0.54
Missing	3 (0.2)	0 (0)	

Abbreviations: IQR, interquartile range; BMI, body mass index; PTB, preterm birth; HTN, hypertension; PPROM, preterm premature rupture of membranes

Values are n(%),median (interquartile range)

Table 2

Neonatal outcomes by prenatal marijuana exposure

	No Marijuana n=1732	Marijuana n= 135	*p* value
Adverse neonatal outcome *	477 (25.8)	27 (20.0)	0.14
Death before hospital discharge	92 (5.3)	5 (3.7)	0.43
Missing	9 (0.5)	2 (1.5)	
Severe NEC	82 (4.7)	7 (5.2)	0.79
Missing	9 (0.5)	2 (1.5)	
Grade 3 or 4 IVH	35 (2.0)	1 (0.8)	0.28
Missing	78 (4.5)	1 (0.7)	
Bronchopulmonary dysplasia	313 (18.1)	16 (11.8)	0.07
Missing	9 (0.5)	2 (1.5)	
Periventricular leukomalacia	35 (2.0)	2 (1.5)	0.63
Missing	78 (4.5)	1 (0.7)	
Adverse early childhood outcome **	369 (21.3)	35 (25.9)	0.21
Death prior to age 2	28 (1.6)	3 (2.2)	0.60
Moderate or severe cerebral palsy	38 (2.2)	0 (0)	0.08
Missing	77 (4.5)	3 (2.2)	
MDI<70	235 (13.6)	25 (18.5)	0.12
Missing	339 (19.6)	25 (18.5)	
PDI <70	209 (12.1)	20 (14.8)	0.35
Missing	326 (18.8)	25 (18.5)	
Other outcomes			
Intrauterine growth restriction	69 (4.0)	4 (3.0)	0.56
Small for gestational age ^ (<10th percentile)	41 (2.4)	4 (3.0)	0.66
Large for gestational age ^ (≥90th percentile)	215 (12.4)	12 (8.9)	0.23
Any cerebral palsy	77 (4.5)	3 (2.2)	0.20
Missing	77 (4.5)	3 (2.2)	
MDI<85	610 (35.2)	60 (44.4)	0.03
Missing	339 (19.6)	25 (18.5)	
PDI <85	464 (33.5	39 (28.9)	0.60
Missing	326 (18.8)	25 (18.5)	

P value denotes association between marijuana exposure and variable using chi-square or Kruskal Wallis test, as appropriate.

Abbreviations: NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage, PVL, periventricular leukomalacia; BPD, bronchopulmonary dysplasia; MDI, mental developmental indices; PDI, psychomotor developmental indices

* Composite Primary Short term outcome: Death, Grade 3 or 4 IVH, PVL, NEC, BPD

** Composite Primary Long term Outcome: Death before age 2, moderate or severe cerebral palsy, PDI or MDI <70

^ by sex and gestational age at delivery for US population

Table 3

Neonatal outcomes by prenatal marijuana exposure for women who delivered at <28 weeks (n=569)

	No Marijuana n=534	Marijuana n=35	*p*-value
Adverse neonatal outcome *	336 (62.8)	19 (54.3)	0.37
Death before hospital discharge	73 (13.7)	4 (11.4)	>0.99
Missing	6 (1.1)	0	
Severe NEC	43 (8.0)	4 (11.1)	0.52
Missing	6 (1.1)	0	
Grade 3 or 4 IVH	27 (4.9)	1 (3.6)	>0.99
Missing	33 (6.2)	0	
BPD	260 (48.7)	13 (37.1)	>0.99
Missing	6 (1.1)	0	
PVL	18 (3.5)	1 (2.8)	>0.99
Missing	38 (6.9)	0	
Adverse early childhood outcome **	167 (31.3)	15 (42.9)	0.19
Death prior to age 2	14 (2.6)	1 (2.8)	>0.99
Moderate or severe cerebral palsy	23 (4.3)	0	0.39
Missing	17 (3.2)	1 (2.9)	
MDI <70	107 (20.0)	10 (28.6)	0.25
Missing	147 (27.5)	10 (28.6)	
PDI <70	99 (18.6)	9 (25.7)	0.24
Missing	138 (25.8)	10 (28.6)	
Other outcomes			
Intrauterine growth restriction	34 (6.4)	1 (2.9)	0.72
Small for gestational age ^ (<10th percentile)	10 (1.9)	0	>0.99
Large for gestational age ^ (≥90th percentile)	51 (9.6)	1 (2.9)	0.24
Any cerebral palsy	54 (9.8)	1 (1.8)	0.24
Missing	19 (3.5)	1 (2.8)	
MDI<85	219 (41.0)	18 (51.4)	0.15
Missing	147 (27.5)	10 (28.6)	
PDI <85	182 (34.1)	15 (42.9)	0.22
Missing	138 (25.8)	10 (228.6)	

Abbreviations: NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage, PVL, periventricular leukomalacia; BPD, bronchopulmonary dysplasia; MDI, mental developmental indices; PDI, psychomotor developmental indices

P value denotes association between marijuana exposure and variable using Fisher's exact test

* Composite Primary Short term outcome: Death, Grade 3 or 4 IVH, PVL, NEC, BPD

** Composite Primary Long term Outcome: Death before age 2, moderate or severe cerebral palsy, PDI or MDI <70

^ by sex and gestational age at delivery for US population

Table 4

Multivariable logistic regression model. Shown are factors associated with neonatal morbidity[a] (n=1866) and childhood morbidity[b] (n=1862).

Characteristics associated with neonatal morbidity	**OR**	**95% CI**	**p-value**
Marijuana use	0.83	0.47, 1.44	0.50
Race (African American = referent)	–	–	–
Caucasian	1.34	0.98, 1.81	0.064
Other	0.62	0.42, 0.92	0.018
No prenatal care	0.51	0.29, 0.89	0.018
Received magnesium sulfate	1.04	0.79, 1.38	0.76
Male infant	1.68	1.27, 2.21	<0.01
PPROM	0.59	0.40, 0.88	0.010
Received steroids	1.04	0.46, 2.38	0.92
Gestational age at delivery (additional week)	0.48	0.45, 0.52	<0.01
Delivery route – Cesarean	1.48	1.12, 1.95	<0.01
Characteristics associated with childhood morbidity	**OR**	**95% CI**	**p-value**
Marijuana use	1.47	0.97, 2.23	0.073
Race (African American = referent)	–	–	–
Caucasian	0.90	0.69, 1.17	0.42
Other	1.27	0.94, 1.72	0.12
No prenatal care	0.73	0.47, 1.15	0.17
Received magnesium sulfate	0.96	0.76, 1.21	0.75
High school education or less	1.23	0.94, 1.60	0.13
Male infant	1.50	1.19, 1.88	<0.01
Received steroids	0.96	0.49, 1.88	0.90
Gestational age at delivery (each additional week)	0.85	0.81, 0.89	<0.01
Delivery route – Cesarean	1.21	0.97, 1.54	0.094

[a]Additional factors considered in the model: Recreational drug use, tobacco use, marital status, high school education or less

[b]Additional factors considered in the model: Recreational drug use, tobacco use, marital status, and preterm premature rupture of membranes

Abbreviations: PPROM, preterm premature rupture of membranes;

Table 5

Multivariable logistic regression model. Shown are factors associated with neonatal morbidity[a] (n=567) and childhood morbidity[b] (n=569) in infants born at <28 weeks

Characteristics associated with neonatal morbidity	**OR**	**95% CI**	**p-value**
Marijuana use	0.84	0.39, 1.85	0.67
Race (African American = referent)	–	–	–
Caucasian	1.17	0.75, 1.81	0.49
Other	0.58	0.35, 0.97	0.036
No prenatal care	0.58	0.28, 1.20	0.14
High school education or less	0.58	0.37, 0.90	0.016
Received magnesium sulfate	1.00	0.68, 1.47	<0.99
Male infant	1.68	1.15, 2.46	0.007
PPROM	0.55	0.30, 1.00	0.051
Received steroids	0.51	0.17, 1.51	0.23
Gestational age at delivery (each additional week)	0.44	0.36, 0.54	<0.01
Delivery route – Cesarean	1.40	0.95, 2.06	0.085
Characteristics associated with childhood morbidity	**OR**	**95% CI**	**p-value**
Marijuana use	1.73	0.86, 3.50	0.13
Received magnesium sulfate	0.92	0.64,1.32	0.67
Male infant	1.34	0.94, 1.92	0.11
Received steroids	2.22	0.63, 7.83	0.22
Gestational age at delivery (each additional week)	0.81	0.68, 0.96	0.014

[a]Additional factors considered in the model: Recreational drug use, tobacco use, marital status, no prenatal care

[b]Additional factors considered in the model: Race, recreational drug use, tobacco use, marital status, no prenatal care, high school education or less, preterm premature rupture of membranes, and mode of delivery

Abbreviations: PPROM, preterm premature rupture of membranes