Title

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Prenatal cannabis use and infant birth outcomes in the Pregnancy Risk Assessment Monitoring System

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Abstract

Objectives: To examine the association of prenatal cannabis use and adverse infant outcomes in a nationally representative cohort, and consider the impact of concurrent cigarette exposure.

Study design: We conducted a retrospective cohort study on 32,583 new mothers from the 2017–2019 Pregnancy Risk Assessment Monitoring System (PRAMS). Cannabis use was evaluated as a binary variable (use or no use) as well as ordinal categories (no, light, moderate, heavy use). We used multivariable logistic regression to examine the relationship between prenatal cannabis exposure and low birthweight (LBW), preterm birth, and small for gestational age (SGA).

Results: Prenatal cannabis use was associated with significantly greater odds of LBW (adjusted odds ratio [OR] 1.27, 95% confidence interval [CI] 1.05, 1.54) and SGA (adjusted OR 1.35, 95% CI 1.09, 1.68) but not preterm birth. Compared to nonusers, heavy users (weekly or more) were twice as likely to deliver a LBW (adjusted OR 2.07, 95% CI 1.46, 2.94) or SGA infant (adjusted OR 2.14, 95% CI 1.38, 3.30). When examining combined cannabis and cigarette use, prenatal exposure to both substances increased the likelihood of LBW (adjusted OR 2.27, 95% CI 1.71, 3.01), preterm birth (adjusted OR 1.61, 95% CI 1.12, 2.31), and SGA (adjusted OR 3.29, 95% CI 2.39, 4.55) compared with no use, and the increased odds were larger than for either substance alone.

Conclusions: Our results suggest that cannabis use during pregnancy may harm fetal development, and recommendations to improve birth outcomes should address co-use of cannabis and tobacco.

Introduction

An estimated 3-5% of pregnant women use cannabis,[1–3] making it the most commonly used illicit drug during pregnancy.[4,5] With increased medical and recreational legalization in more than 30 states and a lack of updated information about potency and risks,[6] cannabis is often perceived to be harmless and acceptable for use during pregnancy, including as treatment for first trimester nausea.[7]

The main psychoactive chemical in cannabis, Δ-9-tetrahydrocannabinol (THC), is known to cross the placental barrier and thought to be associated with poor neonatal health outcomes. A number of observational studies have examined the association between prenatal cannabis use and birth outcomes. While some studies have found significant associations of prenatal cannabis use and reduced fetal growth,[2] low birthweight (LBW) or smaller mean birthweight,[8–13] and decreased gestational period,[14,15] other studies have not found any associations with birth outcomes.[16–21] These inconsistent findings are potentially explained by low statistical power and sample sizes, insufficient assessment of co-use of cannabis with cigarette smoking during pregnancy, and discrepancies between self-reported use and objective blood or urinary biomarkers of exposure. Notably, the majority of epidemiologic studies of prenatal cannabis use were conducted in the 1980s through early 2000s, when attitudes, trends, and legality of cannabis use were different than they are today.[22] THC has become increasingly potent in cannabis products in recent decades and use has increased substantially among young people.[23] A recent study used data from the Pregnancy Risk Assessment Monitoring System (PRAMS) but only analyzed information through 2017 and in eight U.S. states.[24] More updated information on

fetal and neonatal health outcomes is needed to reflect current changes in social attitudes and chemical composition of cannabis.

Our investigation accounts for some of these methodological limitations, including examining the independent and co-exposure risks of cannabis and tobacco during pregnancy. Information was collected from a large, representative sample of women across 20 U.S. states and territories. The purpose of this study is to evaluate the association between prenatal cannabis and LBW, preterm birth, and small for gestational age (SGA) in infants using a recent dataset that reflects current cannabis usage patterns and formulations. We hypothesized that prenatal cannabis use is associated with greater risk of poor infant birth outcomes after controlling for important confounding variables and that heavier use increases the risk.

Methods

PRAMS is an ongoing, population-based surveillance system that collects information on maternal characteristics, behaviors, and experiences that occur during the pre-conception period, during pregnancy, and immediately following delivery. PRAMS is conducted by the Centers for Disease Control and Prevention (CDC) in collaboration with 51 state, territorial, and tribal health departments in the United States.[25] A stratified random sample of mothers who have delivered an infant in the preceding two to four months are selected from each state's birth certificate records to participate in a mail or telephone questionnaire. Women are contacted up to five times via mail or 15 times via telephone to participate. In addition to the self-reported responses from the questionnaire, birth certificate information on the infant is linked to each participant. Survey

weights are applied to ensure that the sample is representative of the state's population of new mothers. Each state or territory had a weighted response rate between 55% and 81%.

The initial sample size was 72,116 women who completed the PRAMS Phase 8 questionnaire between 2017 and 2019. The PRAMS questionnaire comprises Core questions asked in every state and optional questions that states may opt to ask, including questions about cannabis use. We first excluded women who lived in states that did not collect data on prenatal cannabis use (N = 32,437). We then excluded multiple gestation pregnancies (N = 3,077) and mothers with incomplete information on cannabis use during pregnancy (N = 4,019), leaving a final sample size of 32,583 women who delivered live, singleton infants between 2017 and 2019 in the following 20 states and territory: Alaska, Colorado, Illinois, Kansas, Kentucky, Maine, Michigan, Missouri, Montana, New Hampshire, New Jersey, New Mexico, New York, North Dakota, Pennsylvania, Puerto Rico, South Dakota, Washington, West Virginia, and Wisconsin. During the study period, both recreational and medical cannabis use were legal in Alaska, Colorado, Maine, and Washington.[6] Medical cannabis was legal in Illinois, Michigan, Missouri, Montana, New Hampshire, New Jersey, New Mexico, New York, North Dakota, Pennsylvania, Puerto Rico, and West Virginia.[6] Non-respondents were older (30.2 ± 0.1 years) than women with information on cannabis use (29.5 ± 0.04 years), more likely to be non-White (43.4% versus 35.7%), unmarried (39.0% versus 37.0%), have a Bachelors degree or higher (39.3% versus 36.1%), and not have health insurance during their pregnancy (6.3% versus 4.9%). However, there were no significant differences in tobacco use during pregnancy (7.8% versus 9.0%) or in adverse birth outcomes of their infants (17.5% versus 17.5%).

The states that chose to assess cannabis use during pregnancy used one of three similar but not identical questions: “During any of the following time periods, did you use marijuana or hash in any form: during my most recent pregnancy,” “During your most recent pregnancy, did you take or use any of the following drugs for any reason: marijuana or hash,” and “At any time during the 3 months before you got pregnant *or* during your most recent pregnancy, did you use marijuana or hash in any form?” For the last question, an affirmative answer was followed by a question asking specifically about the frequency of cannabis intake during pregnancy. We operationalized cannabis use during pregnancy as a binary variable (any versus no use), based on a positive response to one of these questions.

Of the 20 states that asked about any cannabis use during pregnancy, nine states additionally opted to ask about the frequency of use with the following question: “During your most recent pregnancy, how often did you use marijuana products in an average week?” The states that collected data on frequency of use during pregnancy were Alaska, Illinois, Maine, New Jersey, New Mexico, New York, North Dakota, Pennsylvania, and West Virginia. To examine a dose-response relationship with birth outcomes, we grouped respondents into nonusers, light users (once a month or less), moderate users (2-3 times per month), and heavy users (once a week or more). These cutoff points were chosen in order to remain consistent with the literature and improve reporting accuracy.[26] Data on frequency of use was available on 30% of the study sample.

Finally, we assessed cigarette smoking to separate the effects of cannabis from cigarette use during pregnancy. Information on cigarette smoking was defined as a dichotomous variable on

the birth certificate (any versus none). We categorized women as: using neither substance, using cannabis only, using cigarettes only, and using both substances during their pregnancy.

The main outcomes were infant LBW (birthweight less than 2,500 grams), preterm birth (delivery before 37 weeks), and SGA (birthweight less than tenth percentile of all national singleton births adjusted for gestation length, race/ethnicity, and infant sex) as ascertained from birth certificate information.

Statistical weights were incorporated into the analysis to account for complex survey sampling design, allowing estimates from the selected groups to reflect the actual proportion of births in subpopulations. Analyses were weighted for sampling design, nonresponse, and noncoverage (i.e., omission from the sampling frame).

We conducted multivariable logistic regression to obtain odds ratios (OR) of cannabis use and LBW, preterm birth, and SGA. Covariates were selected *a priori* based on the literature and a directed acyclic graph and were: maternal age, maternal race/ethnicity, parity, maternal education, marital status, tobacco use during pregnancy, any prenatal care utilization, health insurance status, state/territory of residence, and year of interview. These covariates were categorized as shown in Table 1. Household income information was missing for a large number of women, and so we controlled for health insurance status as a measure of socioeconomic status instead. All analyses were conducted in R version 3.6.1.

The general PRAMS methodology and protocol is approved by the CDC Institutional Review Board. Our analysis was exempt from human subjects research by the University of California, Berkeley Committee for Protection of Human Subjects.

Results

Our sample was representative of pregnant women from 20 states between the years 2017 and 2019. We found that 4.9% of respondents used cannabis during pregnancy. Among those with additional data on frequency of use, 0.9% reported light use, 0.6% reported moderate use, and 2.5% reported heavy use of cannabis. The prevalence of preterm deliveries was 7.6%, of LBW was 6.2%, and of SGA was 9.7%.

Table 1 presents the prevalence of cannabis use during pregnancy by demographic characteristics. Those who reported cannabis use tended to be younger (mean age: 27.1 ± 0.2 years for users vs. 29.5 ± 0.05 years for non-users) with 9.5% of those 19 years old and younger reporting use during pregnancy. Use varied by race, with 11.5% of American Indian and Alaskan Native women and 9.4% mixed or other race women reporting prenatal cannabis use. Cigarette smoking during the pregnancy was more than six times as likely among those who reported cannabis use. Additionally, unmarried women, women with less than high school education, women without prenatal care, with public or no insurance, and with lower household incomes were also significantly more likely to use cannabis. Maine had the highest proportion of respondents reporting prenatal cannabis use (12%), followed by Alaska (9.3%) and Colorado (7.7%). There were no associations between cannabis use and parity or the year of interview.

In crude analyses, cannabis exposure during pregnancy was associated with a significantly increased risk of LBW (OR 1.89, 95% confidence interval [CI] 1.59, 2.24), preterm birth (OR 1.40, 95% CI 1.14, 1.73), and SGA (OR 1.96, 95% CI 1.61, 2.39) (Table 2). However, associations were attenuated after controlling for confounders. In adjusted logistic regression models, prenatal cannabis exposure was associated with an increased risk of delivering an infant with LBW (adjusted OR 1.27; 95% CI 1.05, 1.54) and with SGA (adjusted OR 1.35, 95% CI 1.09, 1.68). No significant association was observed for preterm birth (adjusted OR 1.16, 95% CI 0.92, 1.45).

Table 3 shows the relationship of cigarette smoking and cannabis use on birth outcomes. As expected, women who used cigarettes were at significantly increased risk of LBW (adjusted OR 2.15, 95% CI 1.84, 2.53), preterm birth (adjusted OR 1.38, 95% CI 1.14, 1.68), and SGA (adjusted OR 2.33, 95% CI 1.94, 2.80) compared to women who did not use either substance during pregnancy. However, women who used cannabis but not cigarettes were also more likely to have a child with LBW, although the associations were not as strong as for cigarette smoking only (adjusted OR 1.46, 95% CI 1.15, 1.86). Women with both cigarette and cannabis exposure had the greatest risk of LBW (adjusted OR 2.27, 95% CI 1.71, 3.01), preterm birth (adjusted OR 1.61, 95% CI 1.12, 2.31), and SGA (adjusted OR 3.29, 95% CI 2.39, 4.55).

Table 4 shows that, for the subset of women in which information about frequency of use was gathered, prenatal cannabis use was associated with an increased risk of LBW among those reporting heavy use compared to those reporting no use (adjusted OR 2.07, 95% CI 1.46, 2.94).

Both light (adjusted OR 2.62, 95% CI 1.27, 5.38) and heavy use (adjusted OR 2.14, 95% CI 1.38, 3.30) were associated with SGA compared to no cannabis use during pregnancy.

Discussion

This study found that cannabis use during pregnancy was associated with increased odds of LBW and SGA in infants but was not associated with preterm birth. This cohort also had partial data on mothers who reported their frequency of intake. Heavy prenatal cannabis use, defined as use of cannabis once a week or more, was associated with a higher risk of LBW and SGA than no cannabis use.

The findings from the four-level analysis of substance use (neither cigarette smoking or cannabis, cigarette use only, cannabis only, and both cigarette smoking and cannabis) confirmed that cannabis use on its own was associated with an increased risk of LBW, but the magnitude was not as large as the relationship seen in cigarette smoking only. Furthermore, prenatal cannabis use in addition to cigarette smoking confers greater risk than prenatal tobacco use alone. Women who used both cannabis and cigarettes had the highest odds of delivering an infant with LBW, preterm birth, and particularly SGA.

A strength of our study is the use of large and representative surveillance data at a national scale. PRAMS has one of the most robust protocols to survey maternal behaviors, and birth outcome data are collected from objective state birth certificates, which may be more accurate than surveyed responses. Since PRAMS interviews new mothers after their delivery by telephone or

by mail, we are able to generalize our findings beyond other studies that only use hospital-based sampling frames, which by design restrict to those who receive prenatal care or have health insurance. Additionally, while most studies have controlled for confounding by cigarette smoking, we examined the effects of cannabis only use during pregnancy independent of cigarette only and concurrent use of cannabis and cigarettes, highlighting the potential relationship between cannabis and adverse health outcomes in infants. This is an important addition to the existing literature since cannabis and cigarettes are commonly used together during pregnancy.[18] Lastly, the dataset uses survey responses from the past four years, which captures current trends in substance use.

Although we had information on frequency of use in more than 9,000 women, most of the states in our dataset did not collect frequency information, only any cannabis use. Thus, women who reported cannabis use in pregnancy may have used widely different amounts of cannabis or used at different times during pregnancy. Additionally, the method of cannabis consumption, such as vaporizing, ingesting, or smoking, was asked only in a few states' questionnaires and could not be examined in our study. Although PRAMS is one of the largest datasets to collect information on prenatal cannabis use, it would be helpful to have more granularity on the timing, frequency, and mode of use.

An additional limitation of our study is the reliance on self-reported drug use. Around 5% of women in this study admitted to using cannabis during pregnancy, which is consistent with the self-reported use in other observational studies.[17] However, these numbers could underreport the true proportion that use cannabis in the population if participants are reluctant to disclose

substance use. We found large geographical differences in the prevalence of cannabis use, ranging from 0.4% in Puerto Rico to 12% in Maine. Although these rates may reflect real geographical differences, they may also be affected by state-level differences in wording of questions or respondents' willingness to admit cannabis use. Recall bias could have differentially influenced our findings, since information about exposure was collected retrospectively to the birth.

Although we did not find a strong dose-response relationship with frequency of use, the wide confidence intervals suggest that our power was hampered by small sample sizes. Despite our large population, only 82 women reported moderate use (i.e., 2-3 times per month) of cannabis among a total of 9,923 respondents (0.8%). Similarly, the small sample sizes may explain why light and heavy use of cannabis were associated with an increased risk of SGA, but moderate use was not.

Our findings corroborate with previous research studies, which point towards a relationship with LBW or smaller infants, but not preterm birth or a decreased gestational period.[12,27] This suggests that prenatal cannabis use may restrict fetal growth. One explanation for how cannabis may restrict intrauterine growth is by depriving the fetus of oxygen in the blood, similar to cigarette smoking.[28] Cannabis is composed of nearly 500 compounds,[29] and its smoke may contain toxicants that can stunt growth. It is difficult to ascertain if there is a threshold exposure associated with these adverse birth outcomes or if there are critical windows of exposure during pregnancy without large studies with detailed information on frequency and timing of use. Furthermore, the combined effect of cannabis and cigarette use during pregnancy has not been

thoroughly studied, but our analysis suggests an additive risk of experiencing one of the adverse birth outcomes when women use cannabis concomitant with smoking cigarettes.

Our findings are especially timely in the shifting landscape of the acceptance and perceived safety of cannabis. This study has important regulatory and clinical implications. Although the American College of Obstetricians and Gynecologists recommends discontinuation of cannabis products during pregnancy,[4] many women still use them, influenced by legality in different jurisdictions, ease of accessibility, and claims of medicinal properties as a treatment for nausea.[7] Our study shows higher cannabis use among women who do not receive prenatal care or lack private health insurance, suggesting that health messaging should be directed toward federal and state programs, such as the Supplemental Nutrition Program for Women, Infants, and Children (WIC) and Medicaid. Finally, it is especially pressing to examine mandatory reporting laws that may criminalize prenatal substance use since this may lead to underreporting in research, hinder honest conversations about cannabis use between patients and providers, and discourage seeking prenatal care among users for fear of punishment.[30] Future studies should focus on how different modes of cannabis use, timing in relation to sensitive developmental stages, and dosage may impact fetal growth.

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Table 1. Weighted percentages of self-reported cannabis use in pregnancy by characteristic from the Pregnancy Risk Assessment Monitoring System (PRAMS), 2017-2019 (*N* = 32,583)

Characteristic	Overall Population (weighted %)	Percentage Using Cannabis (weighted %)	Percentage Not Using Cannabis (weighted %)	*P*-value[a]
Maternal age				
≤19	4.5	9.5	90.5	< 0.001
20-24	18.7	7.8	92.2	
25-29	30.1	5.4	94.6	
30-34	29.4	3.1	96.9	
≥35	17.3	2.5	97.5	
Race/ethnicity				
Non-Hispanic White	64.1	5.0	95.0	< 0.001
Non-Hispanic Black	9.9	7.1	92.9	
American Indian or Alaskan Native	1.2	11.5	88.5	
Asian or Pacific Islander	4.7	1.0	99.0	
Hispanic	16.6	2.9	97.1	
Mixed race, Other	3.5	9.4	90.6	
Tobacco use during prenatal period				
No	91.0	3.3	96.7	< 0.001
Yes	9.0	20.9	79.1	
Marital status				
Not married	37.0	9.6	90.4	< 0.001
Married	63.0	2.0	98.0	
Maternal education				
Less than high school	11.0	9.2	90.8	< 0.001
High school graduate	24.8	7.8	92.2	
Some college, associate degree	28.2	5.2	94.8	
≥Bachelor's degree	35.9	1.2	98.8	
Received prenatal care				
No	2.5	11.4	88.6	< 0.001
Yes	97.5	4.7	95.3	
Insurance status				
No insurance	4.9	7.1	92.9	< 0.001
Public insurance	38.5	8.2	91.8	
Private insurance	56.5	2.4	97.6	

Household income				
≤$20,000	26.9	10.5	89.5	< 0.001
$20,001–40,000	21.2	5.8	94.2	
$40,001–60,000	13.8	3.2	96.8	
>$60,000	38.1	1.3	98.7	
State of residence				< 0.001
Michigan	13.4	4.3	95.7	
Illinois	11.4	4.4	95.6	
Washington	10.6	5.0	95.0	
Missouri	8.6	6.6	93.4	
Pennsylvania	8.2	3.9	96.1	
Colorado	7.9	7.7	92.3	
Wisconsin	7.6	5.3	94.7	
Kentucky	6.2	4.3	95.7	
New Jersey	5.3	1.0	99.0	
Kansas	4.3	4.3	95.7	
New York	3.4	2.8	97.2	
New Mexico	2.6	5.6	94.4	
Puerto Rico	2.4	0.4	99.6	
West Virginia	1.7	7.5	92.5	
Maine	1.5	12.0	88.0	
South Dakota	1.4	3.9	96.1	
North Dakota	1.3	4.6	95.4	
Alaska	1.2	9.3	90.7	
Montana	0.5	6.5	93.5	
New Hampshire	0.5	4.1	95.9	
Previous live births				
0	38.4	4.9	95.1	0.79
≥1	61.6	4.8	95.2	
Year of interview				0.73
2017	34.6	4.7	95.3	
2018	49.6	4.9	95.1	
2019	15.7	5.1	94.9	

[a] *P*-values comparing cannabis users and non-users, based on chi-square tests.

Table 2. Crude and adjusted[a] ORs of birth outcomes and prenatal cannabis use, PRAMS 2017–2019

	Low Birthweight (N^b = 30,735)			Preterm Birth (N^b = 30,727)			Small for Gestational Age (N^b = 30,676)		
Cannabis use during pregnancy	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value
Crude model									
Nonusers	Ref			Ref			Ref		
Users	1.89	(1.59, 2.24)	< 0.001	1.40	(1.14, 1.73)	< 0.01	1.96	(1.61, 2.39)	< 0.001
Adjusted model									
Nonusers	Ref			Ref			Ref		
Users	1.27	(1.05, 1.54)	0.02	1.16	(0.92, 1.45)	0.20	1.35	(1.09, 1.68)	< 0.01

[a] Adjusted for maternal age, marital status, parity, maternal race/ethnicity, maternal education, prenatal care, health insurance, cigarette smoking during pregnancy, state/territory of residence, and year of interview.
[b] Unweighted N.

Table 3. Adjusted[a] ORs of birth outcomes and cigarette and cannabis use during pregnancy, PRAMS 2017–2019

		Low Birthweight (N^b = 30,735)			Preterm Birth (N^b = 30,727)			Small for Gestational Age (N^b = 30,676)		
Cigarette and cannabis use during pregnancy	N^b	Adjusted OR	(95% CI)	*P*-value	Adjusted OR	(95% CI)	*P*-value	Adjusted OR	(95% CI)	*P*-value
Did not use either	27,720	Ref			Ref			Ref		
Cannabis only	1,228	1.46	(1.15, 1.86)	< 0.01	1.15	(0.88, 1.52)	0.30	1.30	(0.99, 1.70)	0.06
Cigarettes only	2,644	2.15	(1.84, 2.53)	< 0.001	1.38	(1.14, 1.68)	< 0.01	2.33	(1.94, 2.80)	< 0.001
Both cigarettes and cannabis	783	2.27	(1.71, 3.01)	< 0.001	1.61	(1.12, 2.31)	0.01	3.29	(2.39, 4.55)	< 0.001

[a] Adjusted for maternal age, marital status, parity, maternal race/ethnicity, maternal education, prenatal care, health insurance, state/territory of residence, and year of interview.
[b] Unweighted N

Table 4. Adjusted[a] ORs of birth outcomes and frequency of prenatal cannabis use in Alaska, Illinois, Maine, North Dakota, New Jersey, New Mexico, New York, Pennsylvania, and West Virginia, PRAMS 2017–2019

		Low Birthweight (N^b = 9,401)			Preterm Birth (N^b = 9,400)			Small for Gestational Age (N^b = 9,377)		
Frequency of cannabis use during pregnancy[b]	N^c	Adjusted OR	(95% CI)	*P*-value	Adjusted OR	(95% CI)	*P*-value	Adjusted OR	(95% CI)	*P*-value
Nonusers	9,286	Ref			Ref			Ref		
Light users	137	1.43	(0.67, 3.04)	0.349	1.49	(0.65, 3.41)	0.347	2.62	(1.27, 5.38)	0.009
Moderate users	82	1.17	(0.55, 2.48)	0.678	2.12	(0.77, 5.85)	0.145	1.12	(0.35, 3.57)	0.854
Heavy users	418	2.07	(1.46, 2.94)	< 0.001	1.12	(0.68, 1.82)	0.664	2.14	(1.38, 3.30)	0.001

[a] Adjusted for maternal age, marital status, previous live births, maternal race/ethnicity, maternal education, prenatal care, health insurance, cigarette smoking during pregnancy, state/territory of residence, and year of interview.
[b] Nonusers, no use during pregnancy; Light users, monthly or less; Moderate users, 2-3 times per month; Heavy users, once per week or more.
[c] Unweighted N.