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Association Between Self-reported Prenatal Cannabis Use and Maternal, Perinatal, and Neonatal Outcomes

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IMPORTANCE Recent evidence suggests that cannabis use during pregnancy is increasing, although population-based data about perinatal outcomes following in utero exposure remain limited.

OBJECTIVE To assess whether there are associations between self-reported prenatal cannabis use and adverse maternal and perinatal outcomes.

DESIGN, SETTING, AND PARTICIPANTS Population-based retrospective cohort study covering live births and stillbirths among women aged 15 years and older in Ontario, Canada, between April 2012 and December 2017.

EXPOSURES Self-reported cannabis exposure in pregnancy was ascertained through routine perinatal care.

MAIN OUTCOMES AND MEASURES The primary outcome was preterm birth before 37 weeks' gestation. Indicators were defined for birth occurring at 34 to 36 6/7 weeks' gestation (late preterm), 32 to 33 6/7 weeks' gestation, 28 to 31 6/7 weeks' gestation, and less than 28 weeks' gestation (very preterm birth). Ten secondary outcomes were examined including small for gestational age, placental abruption, transfer to neonatal intensive care, and 5-minute Apgar score. Coarsened exact matching techniques and Poisson regression models were used to estimate the risk difference (RD) and relative risk (RR) of outcomes associated with cannabis exposure and control for confounding.

RESULTS In a cohort of 661 617 women, the mean gestational age was 39.3 weeks and 51% of infants were male. Mothers had a mean age of 30.4 years and 9427 (1.4%) reported cannabis use during pregnancy. Imbalance in measured maternal obstetrical and sociodemographic characteristics between reported cannabis users and nonusers was attenuated using matching, yielding a sample of 5639 reported users and 92 873 nonusers. The crude rate of preterm birth less than 37 weeks' gestation was 6.1% among women who did not report cannabis use and 12.0% among those reporting use in the unmatched cohort (RD, 5.88% [95% CI, 5.22%-6.54%]). In the matched cohort, reported cannabis exposure was significantly associated with an RD of 2.98% (95% CI, 2.63%-3.34%) and an RR of 1.41 (95% CI, 1.36-1.47) for preterm birth. Compared with no reported use, cannabis exposure was significantly associated with greater frequency of small for gestational age (third percentile, 6.1% vs 4.0%; RR, 1.53 [95% CI, 1.45-1.61]), placental abruption (1.6% vs 0.9%; RR, 1.72 [95% CI, 1.54-1.92]), transfer to neonatal intensive care (19.3% vs 13.8%; RR, 1.40 [95% CI, 1.36-1.44]), and 5-minute Apgar score less than 4 (1.1% vs 0.9%; RR, 1.28 [95% CI, 1.13-1.45]).

CONCLUSIONS AND RELEVANCE Among pregnant women in Ontario, Canada, reported cannabis use was significantly associated with an increased risk of preterm birth. Findings may be limited by residual confounding.

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Cannabis is commonly used during pregnancy, and in the United States, the prevalence was 7% in 2016 based on self-reports and toxicology.[1] In Canada, data suggest that the prevalence of cannabis use has increased among young men and women aged 15 to 24 years from 21.6% to 26.9% between 2011 and 2017,[2] and among pregnant women aged 15 to 24 years from 4.9% to 6.5% between 2012 and 2017.[3] Overall, cannabis use during pregnancy was reported by about 2% among mothers in Ontario, Canada, in 2017.[3] With recent legalization in Canada and the United States, coupled with evidence of the potential medical benefits of the cannabinoids cannabidiol and tetrahydrocannabinol (THC), it is anticipated that cannabis use may further increase including among pregnant women.[4,5]

Cannabinoids can readily cross the placenta and enter the fetal bloodstream.[6] Animal studies suggest that THC exposure during pregnancy can disrupt the complex fetal endogenous cannabinoid signaling system and may be associated with adverse pregnancy outcomes.[7] Clinical studies have shown associations between prenatal cannabis consumption and incidence of stillbirth, lower birth weight, small for gestational age (SGA), and increased admission to neonatal intensive care compared with infants whose mothers did not use cannabis.[8-10] Previous studies have varied in methodology and treatment of confounding factors, limiting the ability to identify an independent association of cannabis on pregnancy outcomes.[11] A systematic review did not find maternal cannabis use to be independently associated with low birth weight or preterm delivery after adjusting for tobacco use.[12]

Using a comprehensive perinatal registry in the province of Ontario, the aim was to assess whether there are associations between reported prenatal cannabis use and maternal, perinatal, and neonatal outcomes.

Key Points

Question Is there an association between prenatal cannabis exposure and maternal, perinatal, and neonatal outcomes?

Findings In this retrospective cohort study that included 661 617 pregnancies and 9427 reported cannabis users, the rate of preterm birth among reported cannabis users was 12% vs 6% in nonusers, a statistically significant difference.

Meaning Reported cannabis use in pregnancy was associated with significant increases in the rate of preterm birth following adjustment for confounding.

Methods

Research ethics board approval for this study was obtained from the Ottawa Health Science Network Research Ethics Board and the Children's Hospital of Eastern Ontario. Under the Personal Health Information Protection Act, 2004, Ontario's Better Outcomes Registry & Network (BORN) can collect and use personal health information without consent for facilitating or improving health care.

Study Population and Data Source

BORN Ontario captures all births occurring in the province, representing about 40% of births in Canada.[13] The routine data collection includes information on maternal demographics and health behaviors including substance use, preexisting health problems, obstetric complications, intrapartum events, birth outcomes, and admission to neonatal intensive care. Data are collected from perinatal records, clinical forms, and patient interviews when a woman is admitted to hospital to give birth. Data quality audits have indicated high levels of completeness (<10% missing) and high levels of accuracy (85% with $\kappa > 0.6$) in selected data fields.[13]

We conducted a retrospective cohort analysis including women of at least 15 years of age who delivered a singleton infant at a gestational age of 20 weeks or more in an Ontario hospital between April 1, 2012, and December 31, 2017.

Exposure

Maternal exposure to cannabis in pregnancy was recorded during routine prenatal care for mothers. A standardized perinatal record is completed for all pregnant women with their obstetrician, family physician, or midwife. At the first prenatal visit, women are explicitly asked about substance use in pregnancy. The question is recorded as "yes, use of cannabis" or "no" for the current pregnancy. Data from the perinatal record are abstracted into the registry. In addition, cannabis exposure can be captured from clinical histories obtained from patients at admission to hospital for labor and delivery.

Maternal, Obstetrical, Perinatal, and Neonatal Outcomes

The primary outcome was preterm birth at less than 37 weeks' gestation. Preterm birth is one of the most important indicators of perinatal health,[14] and a major risk factor for infant morbidity and mortality.[15] Prespecified binary indicators were defined for births at less than 37 weeks' gestation (all preterm births), 34 to 36 6/7 weeks' gestation (late preterm), 32 to 33 6/7 weeks' gestation, 28 to 31 6/7 weeks' gestation, and less than 28 weeks' gestation (very preterm birth).

Secondary perinatal outcomes were SGA at birth (<10th percentile, <third percentile), placental abruption, and incidence of stillbirth. Maternal outcomes were incidence of preeclampsia, gestational diabetes, and mode of delivery (cesarean, operative vaginal vs spontaneous vaginal). Neonatal outcomes included transfer to neonatal intensive care unit and 5-minute Apgar score (<4).[16]

Covariates

Maternal age was derived from maternal birth date and date of delivery. Area-level median family income quintiles were extracted from the Canadian Census using patient postal codes and the Postal Code Conversion File, an electronic program providing correspondence between 6-digit postal codes and standard geographical units for census tracts and dissemination areas (SAS Institute).[17] Prepregnancy body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) was obtained from the BORN registry and/or the prenatal screening database and was based on recorded first-trimester weight and maternal

height. Gestational weight gain was derived as the difference between maternal weight at delivery and prepregnancy weight and categorized using Institute of Medicine guidelines based on prepregnancy BMI category.[18]

Because the amount of missing data was small (5% for cannabis exposure information and 7% for other covariates or outcomes), no imputation was conducted. Rather than excluding additional observations due to missing BMI (11.8% of the cohort), these observations were retained in the matching procedure as a separate category. Parity; antenatal care by family physician, obstetrician, or midwife; year of birth; tobacco smoking; alcohol use; use of selective serotonin reuptake inhibitors; opioid use; use of other drugs (including cocaine, methamphetamines); and maternal mental health conditions were included as potential confounders. Substance use is captured as "yes, use of substance" or "no" for the current pregnancy. Opioid use included opioid antagonist therapy.

Statistical Analyses

Women who self-reported use of cannabis during pregnancy were compared with those who did not report use across all baseline characteristics using standardized mean differences (SMDs). SMDs are a comparison of means of the covariates across reported cannabis users and nonusers, presented in units of the pooled standard deviation.[19] Unlike conventional statistical tests, the standardized difference is not influenced by sample size; standardized differences of greater than 10% were considered indicative of a meaningful difference across groups.

We used matching methods to reduce imbalance and account for potential confounding across maternal obstetrical and sociodemographic characteristics between reported cannabis users and nonusers.[20] Specifically, we used coarsened exact matching methods to match between reported users and nonusers within defined categories of covariates.[21] Coarsened exact matching involves 2 steps prior to running statistical analyses. First, age, parity, area-level income quintile, smoking status, alcohol use, opioid use, selective serotonin reuptake inhibitor use, other drug use, maternal mental health conditions, antenatal care, and year of birth were categorized as presented in **Table 1**. Next, reported users and nonusers were matched within strata representing unique combinations of covariate categories. Any stratum with no reported cannabis users or no nonusers was excluded. All available controls were selected for matching and weights were generated so that the covariate distribution for nonusers was normalized to match the distribution in the users. The L_1 statistic was used as a global measure of imbalance in the data set.[22] The matched cohort was used to fit unconditional Poisson regression models with robust sandwich variance estimators[23,24] to estimate risk differences (RDs) and relative risks (RRs) for pregnancy outcomes associated with prenatal cannabis exposure. Models accounted for repeated pregnancies that occurred for the same mother during the study period. Poisson models with robust variance estimation have been shown to provide a better alternative than logistic regression for the analyses of binary outcomes with the advantage of directly estimating the RR or RD.[25] Associations were reported with 95% CIs. We used 2-sided tests of statistical significance with a threshold of $P < .05$. Crude analyses were conducted in the unmatched cohort for each outcome.

Subgroup analyses were conducted in the matched cohort to examine the association of reported cannabis use on preterm birth among a priori–identified groups of women who reported smoking tobacco, using alcohol, or using opioids in pregnancy. Each category of exposure was treated independently and interaction terms were included in the adjusted Poisson regression models. The self-reported cannabis-preterm birth association was also examined in a subgroup of women who reported no use of tobacco, alcohol, or opioids.

We tested the accuracy of cannabis exposure coding in the electronic registry by reviewing the antenatal and delivery records of a sample of 577 patients, selected randomly by year, maternal age, and exposure status. Substance use history was abstracted from birth, obstetrical assessment, and labor and delivery records by trained medical record abstractors who were blinded to the cannabis coding in BORN. Sensitivity, specificity, and positive and negative predictive values were calculated. All statistical analyses were conducted in R (version 3.5.2; The R Foundation).

Results

The initial study cohort was composed of 759 281 pregnancy records resulting in a singleton birth (eFigure in the Supplement). Exclusions included 42 586 women (5.6%) who were missing cannabis exposure information. An additional 55 078 observations (7.3%) were missing data on covariates and were excluded, yielding a final analytical sample of 661 617. The mean gestational age of the infant sample was 39.3 weeks, and 51.4% were male. Mothers had a mean age of 30.4 years, and 9427 (1.4%) reported cannabis use. An analysis of the excluded data indicated some moderate differences by age, area-level income, antenatal care, and year of birth (SMD > 10%; eTable 1 in the Supplement).

Significant imbalance was identified across covariates between reported cannabis users and nonusers. SMDs greater than 10% existed for maternal age (1.03), parity (0.34), area-level income (0.58), prepregnancy BMI (0.32), maternal smoking (1.31), alcohol use (0.58), opioid use (0.43), psychiatric disorders (0.97), antenatal care (0.45), and year of birth (0.14), indicating association between reported cannabis use and covariates. The matched cohort was composed of 98 512 records, of which 5639 were reported cannabis users and 92 873 were nonusers. Imbalance in measured baseline covariates between reported cannabis users and nonusers was removed in the matched cohort (all SMD < 0.001) (Table 1). The L_1 statistic was 0.97 in the unmatched cohort and this was reduced to 0.79 following matching.

Association Between Reported Prenatal Cannabis Use and Preterm Birth

The crude rate of preterm birth at less than 37 weeks' gestation was 6.1% among women who did not report use of cannabis and 12.0% among reported cannabis users in the unmatched cohort (RD, 5.88% [95% CI, 5.22%-6.54%]) (**Table 2**).

Table 1. Characteristics of Cannabis Users and Nonusers in the Unmatched and Matched Cohorts, BORN Ontario, 2012-2017

Characteristic	Unmatched Cohort, No. (%)			Matched Cohort, No. (%)		
	Nonusers (n = 652 190)	Cannabis Users (n = 9427)	SMD	Nonusers (N = 92 873)	Cannabis Users (n = 5639)	SMD
Age, y						
15-19	22 784 (3.5)	2272 (24.1)	1.03	7490 (23.4)	1317 (23.4)	<0.001
20-24	88 722 (13.6)	3233 (34.3)		25 736 (37.1)	2093 (37.1)	
25-29	207 418 (31.8)	2290 (24.3)		37 829 (24.9)	1405 (24.9)	
30-34	223 058 (34.2)	1197 (12.7)		18 592 (11.5)	647 (11.5)	
≥35	110 208 (16.9)	435 (4.6)		3226 (3.1)	177 (3.1)	
Parity (not including index pregnancy)						
0	279 420 (42.8)	5486 (58.2)	0.34	68 650 (64.1)	3615 (64.1)	<0.001
1	229 885 (35.2)	2091 (22.2)		17 811 (22.0)	1239 (22.0)	
2	93 735 (14.4)	1061 (11.3)		5171 (8.8)	497 (8.8)	
>2	49 150 (7.5)	789 (8.4)		1241 (5.1)	288 (5.1)	
Area-level income quintile						
1	99 436 (15.2)	3060 (32.5)	0.58	19 313 (32.9)	1858 (32.9)	<0.001
2	101 843 (15.6)	2111 (22.4)		16 158 (21.7)	1226 (21.7)	
3	135 695 (20.8)	1841 (19.5)		21 131 (20.3)	1143 (20.3)	
4	154 329 (23.7)	1486 (15.8)		18 680 (15.4)	868 (15.4)	
5	160 887 (24.7)	929 (9.9)		17 591 (9.6)	544 (9.6)	
Prepregnancy body mass index[a]						
<18.5	30 825 (4.7)	1233 (13.1)	0.32	2073 (9.7)	549 (9.7)	<0.001
18.5-24.9	288 992 (44.3)	4219 (44.8)		50 881 (48.1)	2712 (48.1)	
25.0-29.9	145 337 (22.3)	1616 (17.1)		18 406 (17.1)	963 (17.1)	
≥30.0	109 625 (16.8)	1398 (14.8)		11 837 (15.5)	874 (15.5)	
Missing	77 411 (11.9)	961 (10.2)		9676 (9.6)	541 (9.6)	
Gestational weight gain[b]						
Inadequate	168 158 (25.8)	2550 (27.0)	0.14	15 408 (23.9)	1348 (23.9)	<0.001
Recommended	117 150 (18.0)	1290 (13.7)		10 050 (11.7)	661 (11.7)	
Excessive	289 471 (44.4)	4626 (49.1)		57 739 (54.8)	3089 (54.8)	
Missing	77 411 (11.9)	961 (10.2)		9676 (9.6)	541 (9.6)	
Self-reported substance use during current pregnancy[c]						
Tobacco smoking	48 260 (7.4)	5554 (58.9)	1.31	7743 (47.5)	2679 (47.5)	<0.001
Alcohol use	13 185 (2.0)	1787 (19.0)	0.58	611 (6.0)	341 (6.0)	<0.001
Opioid use	6538 (1.0)	1047 (11.1)	0.43	134 (1.8)	103 (1.8)	<0.001
SSRI use	8745 (1.3)	439 (4.7)	0.20	101 (1.2)	67 (1.2)	<0.001
Other drug use	1844 (0.3)	436 (4.6)	0.28	6 (0.1)	5 (0.1)	<0.001
Mental health conditions[d]	97 779 (15.0)	5348 (56.7)	0.97	11 343 (46.0)	2595 (46.0)	<0.001
Antenatal care						
Family physician	166 102 (25.5)	3790 (40.2)	0.45	23 397 (41.6)	2347 (41.6)	<0.001
Obstetrician	378 368 (58.0)	4100 (43.5)		62 452 (47.7)	2689 (47.7)	
Midwife	95 014 (14.6)	860 (9.1)		6721 (8.1)	458 (8.1)	
Other/none	12 706 (1.9)	677 (7.2)		303 (2.6)	145 (2.6)	
Year of birth						
2012	109 489 (16.8)	1273 (13.5)	0.14	12 774 (13.8)	778 (13.8)	<0.001
2013	110 567 (17.0)	1394 (14.8)		14 749 (14.8)	832 (14.8)	
2014	108 593 (16.7)	1577 (16.7)		15 301 (16.9)	954 (16.9)	
2015	116 681 (17.9)	1683 (17.9)		16 470 (17.6)	993 (17.6)	
2016	117 635 (18.0)	1948 (20.7)		19 276 (20.5)	1154 (20.5)	
2017	89 225 (13.7)	1552 (16.5)		14 303 (16.5)	928 (16.5)	

Abbreviations: SMD, standardized mean difference; SSRI, selective serotonin reuptake inhibitor.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Institute of Medicine guidelines.[18]

[c] Reported use of substances in current pregnancy. Tobacco use is any reported use at admission to labor/delivery. Alcohol use is any reported use during current pregnancy.

[d] Includes addiction, anxiety, bipolar disorder, depression, postpartum depression, or schizophrenia diagnosed or self-reported in current pregnancy.

Table 2. Pregnancy Outcomes in Users and Nonusers of Cannabis During Pregnancy in the Unmatched Cohort, BORN Ontario, 2012-2017

Outcome	No. of Events (% Risk)		Risk Difference, % (95% CI)[a]	Relative Risk (95% CI)[a]
	Nonusers (n = 652 190)	Cannabis Users (n = 9427)		
Preterm birth, weeks' gestation				
<37	39 955 (6.1)	1134 (12.0)	5.88 (5.22 to 6.54)	1.96 (1.86 to 2.07)
34-36 6/7	30 085 (4.7)	791 (8.7)	4.00 (3.41 to 4.58)	1.86 (1.74 to 1.99)
32-33 6/7	4026 (0.7)	132 (1.6)	0.90 (0.63 to 1.17)	2.40 (2.01 to 2.86)
28-31 6/7	2936 (0.5)	124 (1.5)	1.00 (0.73 to 1.27)	3.09 (2.57 to 3.71)
<28	2908 (0.5)	87 (1.0)	0.57 (0.34 to 0.80)	2.20 (1.77 to 2.73)
Maternal Outcomes				
Preeclampsia	31 884 (4.9)	393 (4.2)	−0.70 (−1.11 to −0.29)	0.86 (0.78 to 0.94)
Gestational diabetes	48 159 (7.4)	398 (4.2)	−3.16 (−3.58 to −2.74)	0.58 (0.52 to 0.63)
Delivery Type				
Cesarean	179 472 (27.5)	2213 (23.5)	−4.04 (−4.90 to −3.18)	0.85 (0.82 to 0.88)
Assisted vaginal	57 880 (8.9)	828 (8.8)	−0.11 (−0.68 to 0.47)	0.99 (0.93 to 1.06)
Perinatal Outcomes				
SGA (third percentile)	15 856 (2.4)	596 (6.3)	3.91 (3.42 to 4.41)	2.60 (2.40 to 2.82)
SGA (10th percentile)	60 360 (9.3)	1712 (18.2)	8.96 (8.17 to 9.74)	1.96 (1.88 to 2.05)
Placental abruption	5359 (0.8)	172 (1.8)	1.02 (0.75 to 1.30)	2.24 (1.92 to 2.60)
Stillbirth	2500 (0.4)	58 (0.6)	0.23 (0.07 to 0.39)	1.60 (1.24 to 2.08)
Neonatal Outcomes				
Transfer to NICU	77 611 (11.9)	2368 (25.1)	13.19 (12.31 to 14.07)	2.11 (2.04 to 2.19)
Apgar score <4 (5 min)[b]	4615 (0.7)	130 (1.4)	0.68 (0.44 to 0.92)	1.95 (1.64 to 2.32)

Abbreviations: NICU, neonatal intensive care unit; SGA, small for gestational age.

[a] Risk difference and relative risk adjusted for infant sex; standard errors account for repeated pregnancies within mothers.

[b] Apgar scores from 0 to 10 assigned at 5 minutes after birth based on measures of heart rate, respiratory effort, skin color, muscle tone, and reflex irritability; lower scores indicate depressed vitality.[16]

The risk of preterm birth was greater among reported cannabis users for all categories of gestational age, although absolute risks of early preterm birth at less than 32 weeks were lower among reported users and nonusers due to fewer events. Reported cannabis exposure was also associated with statistically significant increases in secondary perinatal and neonatal outcomes including SGA (third percentile and 10th percentile), placental abruption, admission to neonatal intensive care unit, and 5-minute Apgar score less than 4 in the unmatched cohort. Rates of perinatal and neonatal outcomes were generally higher among reported cannabis users compared with nonusers in crude analyses. For instance, SGA (third percentile) was 6.3% in infants of reported cannabis users compared with 2.4% among nonusers (RD, 3.91% [95% CI, 3.42%-4.41%]).

In the matched cohort, reported cannabis exposure was significantly associated with an RD of 2.98% (95% CI, 2.63%-3.34%) and an RR of 1.41 (95% CI, 1.36-1.47) for preterm birth at less than 37 weeks' gestation, an RD of 1.75% (95% CI, 1.43%-2.07%) and an RR of 1.31 (95% CI, 1.25-1.38) for preterm birth between 34 and 36 6/7 weeks' gestation, an RD of 0.38% (95% CI, 0.24%-0.52%) and an RR of 1.46 (95% CI, 1.28-1.66) for preterm birth between 32 and 33 6/7 weeks' gestation, an RD of 0.68% (95% CI, 0.55%-0.80%) and an RR of 2.42 (95% CI, 2.10-2.80) for preterm birth between 28 and 31 6/7 weeks' gestation, and an RD of 0.51% (95% CI, 0.39%-0.63%) and an RR of 1.97 (95% CI, 1.70-2.28) for preterm birth at less than 28 weeks' gestation (**Table 3**). The RR increased from 1.31 to 2.42 for categories of preterm birth between 34 to 36 6/7 weeks' gestation and 28 to 31 6/7 weeks' gestation and reduced to 1.97 for less than 28 weeks' gestation. Compared with the crude estimates from the unmatched cohort, the RDs and RRs were attenuated for all categories of preterm birth after accounting for the matching.

Association Between Reported Prenatal Cannabis Use and Maternal and Obstetrical Outcomes

There was a small statistically significant protective association between reported cannabis exposure and preeclampsia (RR, 0.90 [95% CI, 0.86-0.95]) and gestational diabetes (RR, 0.91 [95% CI, 0.86-0.96]), which remained statistically significant at the 5% level in the matched cohort, although the magnitude of the RDs were less than 0.5% (Table 3). In addition, reported cannabis exposure was inversely associated with cesarean vs spontaneous vaginal delivery in the matched cohort (RR, 0.98 [95% CI, 0.96-1.00]) but the RD was not statistically significant (RD, −0.33% [95% CI, −0.85 to 0.18]). Reported use of cannabis was not associated with assisted vaginal delivery in either cohort.

Subgroup Analyses

A comparison of the RDs and RRs of cannabis exposure on preterm birth at less than 37 weeks' gestation was conducted by subgroups of women who reported use of tobacco, alcohol, opioids, or no other substances in pregnancy (eTable 2 in the Supplement). Among women who reported use of cannabis but no other substances, the crude rate of preterm birth was 9.1% compared with 5.9% among women who reported no use of substances. In the matched cohort, the RD for this comparison was 2.2% (95% CI, 1.73%-2.67%) and the RR was

Table 3. Pregnancy Outcomes in Users and Nonusers of Cannabis During Pregnancy in the Matched Cohort, BORN Ontario, 2012-2017[a]

Outcome	No. of Events (% Risk)		Risk Difference, % (95% CI)[b]	Relative Risk (95% CI)[b]
	Nonusers (n = 92 873)	Cannabis Users (n = 5639)		
Preterm birth, weeks' gestation				
<37	5396 (7.2)	573 (10.2)	2.98 (2.63 to 3.34)	1.41 (1.36 to 1.47)
34-36 6/7	4068 (5.6)	401 (7.3)	1.75 (1.43 to 2.07)	1.31 (1.25 to 1.38)
32-33 6/7	552 (0.8)	63 (1.2)	0.38 (0.24 to 0.52)	1.46 (1.28 to 1.66)
28-31 6/7	402 (0.5)	56 (1.1)	0.68 (0.55 to 0.80)	2.42 (2.10 to 2.80)
<28	374 (0.5)	53 (1.0)	0.51 (0.39 to 0.63)	1.97 (1.70 to 2.28)
Maternal Outcomes				
Preeclampsia	4869 (4.9)	248 (4.4)	−0.46 (−0.71 to −0.22)	0.90 (0.86 to 0.95)
Gestational diabetes	5131 (4.7)	240 (4.3)	−0.41 (−0.66 to −0.17)	0.91 (0.86 to 0.96)
Delivery Type				
Cesarean	24 166 (24.1)	1337 (23.7)	−0.33 (−0.85 to 0.18)	0.98 (0.96 to 1.00)
Assisted vaginal	11 546 (9.3)	538 (9.5)	0.27 (−0.08 to 0.62)	1.02 (0.99 to 1.06)
Perinatal Outcomes				
SGA (third percentile)	2564 (4.0)	346 (6.1)	2.13 (1.84 to 2.41)	1.53 (1.45 to 1.61)
SGA (10th percentile)	9434 (12.1)	958 (17.0)	4.93 (4.48 to 5.38)	1.41 (1.36 to 1.45)
Placental abruption	685 (0.9)	88 (1.6)	0.68 (0.53 to 0.82)	1.72 (1.54 to 1.92)
Stillbirth	319 (0.5)	33 (0.6)	0.13 (0.03 to 0.22)	1.25 (1.05 to 1.48)
Neonatal Outcomes				
Transfer to NICU	11 553 (13.8)	1089 (19.3)	5.50 (5.04 to 5.97)	1.40 (1.36 to 1.44)
Apgar score <4 (5 min)[c]	638 (0.9)	62 (1.1)	0.24 (0.12 to 0.37)	1.28 (1.13 to 1.45)

Abbreviations: NICU, neonatal intensive care unit; SGA, small for gestational age.

[a] Cohort matched on all Table 1 variables using coarsened exact matching.

[b] Risk difference and relative risk adjusted for infant sex; standard errors account for repeated pregnancies within mothers.

[c] Apgar scores from 0 to 10 assigned at 5 minutes after birth based on measures of heart rate, respiratory effort, skin color, muscle tone, and reflex irritability; lower scores indicate depressed vitality.[16]

1.34 (95% CI, 1.27-1.42). Among women reporting tobacco use, the magnitude of the RD between reported cannabis exposure and preterm birth was higher (3.73% [95% CI, 1.41%-6.05%] vs 2.28% [95% CI, 1.84%-2.73%]; *P* for interaction < .001). The RR was 1.46 (95% CI, 1.16-1.83) vs 1.36 (95% CI, 1.29-1.44) (*P* for interaction = .08), although the test of interaction was not statistically significant. Tests of interaction in the association of reported cannabis use on preterm birth were not statistically significant in subgroups of women reporting alcohol (*P* for interaction = .69 for RD; *P* for interaction = .25 for RR) or opioid (*P* for interaction = .24 for RD; *P* for interaction = .99 for RR) use in pregnancy.

In a sample of 577 patients randomly selected across year of birth and maternal age, and with 236 (41%) having reported cannabis exposure documented in BORN, 213 (37%) had cannabis exposure recorded in medical, antenatal, or delivery records and the remainder had no recorded use. This reabstraction study found that reported cannabis use defined in BORN had a sensitivity of 97% (95% CI, 93%-99%) and a specificity of 94% (95% CI, 91%-96%) compared with clinical records and the positive predictive value was 90% (95% CI, 85%-94%).

Discussion

In this study using a large, population-based pregnancy cohort, a significant association was observed between reported prenatal cannabis use and preterm birth. Although an association between prenatal cannabis use and adverse perinatal outcomes has been previously reported,[23] studies in this field experience a high likelihood of residual confounding due to misclassification of cannabis exposure and other confounders including tobacco use and substance use. Although there are limits to determining the underlying effect of prenatal exposure to cannabis using observational epidemiology, and randomized trials are unlikely, this study attempted to address a set of known confounders using a matched design to improve the estimate of the prenatal cannabis use and preterm birth association using the currently available data.

A monotonic increase in the magnitude of the RR of preterm birth from cannabis exposure was observed between 34 to 36 6/7 weeks' and 28 to 31 6/7 weeks' gestation, although no further increases were observed for very preterm birth at less than 28 weeks' gestation. It may be that cannabis exposure is associated more strongly with early and moderate preterm births as opposed to very preterm births, which may have different risk factors including infection, pregnancy-induced hypertension, or incompetent cervix.[26] The risk of preterm birth associated with cannabis exposure was statistically significant in subgroups of women who only used cannabis and no other substances, and among women using tobacco. There was evidence to suggest that the association between reported cannabis use and preterm birth may be stronger within the subgroup of tobacco users, which is a known risk factor for preterm birth.

The findings related to associations between cannabis use and maternal outcomes merit consideration. Cannabis use was associated with a 0.5% reduction in the incidence of preeclampsia and gestational diabetes, and similar findings have been observed in a recent study from the United States.[27] However, the modest reduction in RD may not be clinically important. The association with preeclampsia may be related to cannabis use by smoking. Decreased rates of preeclampsia and hypertensive disorders in pregnancy have been associated with maternal cigarette smoking and the mechanism is possibly related to combustible carbon monoxide.[28,29] In addition, some studies and animal models have suggested a potential role for cannabinoids in reducing oxidative stress and diabetic complications[30-32]; further studies investigating gestational diabetes may be warranted.

Limitations

This study has several limitations. First, in BORN and other administrative data, there is likely misclassification of cannabis exposure in pregnancy.[33] Although no data exist on the degree of underreporting, survey data suggest that 9% of reproductive age women in Canada were regular users of cannabis.[2] The data presented here on the use of cannabis in pregnancy come from self-reports, routine care records, and physician disclosure. These sources may be influenced by social stigma, desirability bias, and fear of intervention by child protection or social services.[34-36] Second, information about frequency, trimester, and duration of use of cannabis in pregnancy was not available in the current study. However, data from the ALSPAC birth cohort in the United Kingdom indicated that 2.5% of the cohort used cannabis in the first trimester and 2.1% continued in the second trimester, suggesting that use may be relatively stable in pregnancy.[9]

Third, although analyses indicated that capture of cannabis exposure in BORN was accurate compared with medical records, both sources may have similar biases. Fourth, urine toxicology screening for cannabis exposure in pregnancy was not available in BORN and is not routinely performed in this population. A moderate correlation has been demonstrated between self-reports of cannabis use and urine testing.[37,38] Due to variation in the rate of excretion and half-life time, urine screening for THC metabolites may be accurate for assessing exposure within 3 to 10 days.[37,39] Ideally, multiple urine screens throughout pregnancy would provide better exposure assessment. Despite these limitations, self-report does seem to be a reliable method for determining cannabis use during pregnancy in epidemiological studies. The effects of underreporting and exposure misclassification would likely attenuate the observed association toward the null; therefore, the associations observed are potentially smaller in magnitude compared with the underlying associations without error.

Fifth, observational studies on behavioral exposures, such as cannabis smoking, are not readily testable in randomized trials and are at risk of confounding. This limitation was addressed in the present study through matching methods on the available covariates. Although the matched cohort was balanced across covariates, including maternal age, socioeconomic status, tobacco smoking, and other correlates of cannabis exposure, it is likely that residual confounding from unmeasured and unknown confounders remains and this limitation cannot be addressed through matching. Sixth, 5% of the cohort was missing cannabis exposure information and an additional 7% was missing data on other covariates and/or outcomes. Although these exclusions may have introduced some bias, only moderate differences were noted between the excluded and analytical samples. Missing data in the registry generally arise through data capture issues for covariates that are unrelated to study outcomes and, therefore, complete case analysis may be appropriate.[40]

Conclusions

Among pregnant women in Ontario, Canada, reported cannabis use was significantly associated with an increased risk of preterm birth. Findings may be limited by residual confounding.

ARTICLE INFORMATION

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