Cannabis Use in Pregnancy in British Columbia and Selected Birth Outcomes

Sabrina Luke, PhD;[1] Jennifer Hutcheon, PhD;[1,2] Tamil Kendall, PhD[1,3]

[1]Perinatal Services British Columbia, Vancouver, BC

[2]Department of Obstetrics and Gynaecology, Faculty of Medicine, University of British Columbia, Vancouver, BC

[3]School of Population and Public Health, Faculty of Medicine, University of British Columbia, Vancouver, BC

S. Luke

Abstract

Objective: This study sought to determine the association between cannabis use in pregnancy and stillbirth, small for gestational age (SGA) (<10th percentile), and spontaneous preterm birth (<37 weeks).

Methods: The study used abstracted obstetrical and neonatal medical records for deliveries in British Columbia from April 1, 2008 to March 31, 2016 that were contained in the Perinatal Data Registry of Perinatal Services British Columbia. Chi-square tests were conducted to compare maternal sociodemographic characteristics by cannabis use. Logistic regression was conducted to determine the association between cannabis use and SGA and spontaneous preterm births. Cox proportional hazards regression modelling was used to identify the association between cannabis use and stillbirth. Secondary analyses were conducted to ascertain differences by timing of stillbirth (Canadian Task Force Classification II-2).

Results: Maternal cannabis use has increased in British Columbia over the past decade. Pregnant women who use cannabis are younger and more likely to use alcohol, tobacco, and illicit substances and to have a history of mental illness. Using cannabis in pregnancy was associated with a 47% increased risk of SGA (adjusted OR 1.47; 95% CI 1.33−1.61), a 27% increased risk of spontaneous preterm birth (adjusted OR 1.27; 95% CI 1.14−1.42), and a 184% increased risk of intrapartum stillbirth (adjusted HR [aHR] 2.84; 95% CI 1.18−6.82). The association between cannabis use in pregnancy and overall stillbirth and antepartum stillbirth did not reach statistical significance, but it had comparable point estimates to other outcomes (aHR 1.38; 95% CI 0.95−1.99 and aHR 1.34; 95% CI 0.88−2.06, respectively).

Conclusion: Cannabis use in pregnancy is associated with SGA, spontaneous preterm birth, and intrapartum stillbirth.

Résumé

Objectif : Cette étude visait à déterminer s'il y a une association entre la consommation de cannabis pendant la grossesse et la mortinaissance, la petite taille pour l'âge gestationnel (< 10e centile) et la naissance prématurée spontanée (< 37 semaines).

Méthodologie : Nous nous sommes servis de données obstétricales et néonatales extraites des dossiers médicaux de femmes ayant accouché en Colombie-Britannique entre le 1er avril 2008 et le 31 mars 2016. Les données sont tirées du Perinatal Data Registry des services périnataux de la Colombie-Britannique. Un test du chi carré a été effectué pour comparer les caractéristiques sociodémographiques des mères selon leur consommation de cannabis, et une régression logistique a servi à déterminer s'il y avait une association entre la consommation de cannabis et la petite taille pour l'âge gestationnel ou la naissance prématurée spontanée. Un modèle de régression de Cox a été utilisé pour établir une association entre la consommation de cannabis et la mortinaissance. Des analyses secondaires ont été effectuées pour évaluer les différences en fonction du moment de la mortinaissance (classification II-2 du Groupe d'étude canadien).

Résultats : Au cours des 10 dernières années, la consommation de cannabis pendant la grossesse a augmenté en Colombie-Britannique. Les femmes enceintes qui consomment du cannabis sont plus jeunes qu'avant et sont plus susceptibles de consommer de l'alcool, du tabac et des substances illicites ou d'avoir des antécédents de troubles de santé mentale. La consommation de cannabis pendant la grossesse a été associée à un risque accru de petite taille pour l'âge gestationnel de l'ordre de 47 % (RC ajusté : 1,47; IC à 95 % : 1,33–1,61), à un risque accru de naissance prématurée spontanée de l'ordre de 27 % (RC ajusté : 1,27; IC à 95 % : 1,14–1,42) et à un risque accru de mortinaissance intrapartum de l'ordre de 184 % (RR ajusté [RRA] : 2,84; IC à 95 % : 1,18–6,82). Ni l'association entre la consommation de cannabis pendant la grossesse et le taux global de mortinaissances, ni celle entre la consommation pendant la grossesse et la mortinaissance antepartum n'étaient significatives, mais leurs estimations ponctuelles étaient comparables à celles des autres issues (RRA : 1,38; IC à 95 % : 0,95–1,99; et RRA : 1,34; IC à 95 % : 0,88–2,06, respectivement).

Conclusion : La consommation de cannabis pendant la grossesse est associée à une petite taille pour l'âge gestationnel, à la naissance prématurée spontanée et à la mortinaissance intrapartum.

INTRODUCTION

On June 21, 2018, the Canadian government passed the Cannabis Act (Bill C-45), which creates a legal framework for the possession, distribution, sale, and production of cannabis in Canada for both recreational and medicinal purposes.[1] Canada has one of the highest rates of cannabis use in the world, particularly among youth.[2] Rates of use have been increasing among Canadian women in recent years.[1] Cannabis is reported as the most commonly used illicit substance in pregnancy.[1,3,4] This is concerning given that nearly half of all pregnancies in Canada are unplanned and that cannabinoids readily cross the human placenta with greater transfer in early pregnancy.[5,6]

Previous research has shown that cannabis use in pregnancy may affect fetal growth and development.[6−9] Although results are mixed, cannabis use has been associated with lower birth weight, reduced head circumference, visual and behavioural developmental abnormalities, and restricted fetal growth.[6,7] Previous research has also shown an independent effect of early pregnancy cannabis use on spontaneous preterm birth after adjusting for tobacco use and socioeconomic status. However, other studies have not corroborated this association.[8] Research on the association between cannabis use and stillbirth is sparse. A recent systematic review identified only two out of 28 studies that specifically studied cannabis use and stillbirth.[9] Potential mechanisms of action suspected in the pathophysiology of cannabinoid-induced fetal outcomes include changes to the placental vasculature that restrict blood flow and nutrients to the fetus, changes to insulin growth factors that control fetal growth, and the binding of cannabinoids to receptors in the pancreas.[7,10−15] Additional research, including a population-based study that draws on a large sample of women, is needed to understand the effects of cannabis use on birth outcomes to construct a body of evidence that can support the development of guidelines for cannabis use in pregnancy. Our study aimed to examine whether there was an association between cannabis use in pregnancy and risk of stillbirth, spontaneous preterm birth (<37 weeks), and small for gestational age (SGA) (<10th percentile).

METHODS

Study Population

Our study population was drawn from births in British Columbia by using data contained in Perinatal Services British Columbia's Perinatal Data Registry for the period of April 1, 2008 to March 31, 2016. The Perinatal Data Registry collects information for greater than 99% of all births in British Columbia. It currently holds records for nearly 700 000 births from the year 2000 onwards. Records with missing gestational ages (GAs), GAs less than 20 weeks or greater than 44 weeks, suspected or confirmed congenital or chromosomal abnormalities, and late terminations were excluded from the analysis. Thus, our research question was examining risks of adverse outcomes associated with cannabis use that occurred through pathways other than congenital anomalies. GA was calculated using an algorithm developed by the Public Health Agency of Canada that incorporates the last menstrual period, first ultrasound (<20 weeks), clinical estimate, and documentation from the maternal chart.[16,17] Only singleton births were included in the study sample.

Cannabis Exposure

Information on lifestyle and social factors including cannabis, tobacco, and alcohol use was collected by the antenatal care provider using an antenatal form administered at the first prenatal visit and updated throughout pregnancy until delivery.[18] Information on cannabis use in pregnancy was collected through maternal self-report at the first prenatal visit.

Outcomes

Stillbirth was defined as the complete expulsion or extraction of a product of conception from its mother after at least 20 weeks of pregnancy or after attaining a weight of at least 500 g, in which after the expulsion or extraction, there is no breathing, beating of the heart, pulsation of the umbilical cord, or unmistakable movement of the voluntary muscle. Antepartum stillbirth was defined as stillbirth that occurred before the onset of labour, whereas intrapartum stillbirth was defined as stillbirth that occurred after the onset of labour but before birth. SGA was determined using a growth chart developed by Kierans et al. and based on a GA algorithm.[16,19] Spontaneous preterm birth was defined as spontaneous labour occurring before 37^0 weeks.

Covariates

Neighbourhood socioeconomic status was determined using the adjusted income per person equivalent (QAIPPE) index released by Statistics Canada. The index

measures neighbourhood income per person equivalent adjusted for household size.[20] Maternal records were assigned a QAIPPE quintile score on the basis of six-digit postal codes. Race/ethnicity is not collected in the Perinatal Data Registry, and therefore the Nam Pehchan algorithm was applied to the study sample to classify mothers as Chinese, South Asian, or other using their surname.[21] Maternal characteristics including pre-pregnancy body mass index (BMI), age, tobacco use, alcohol use, and other substance use were collected on the antenatal record administered at the first prenatal visit and updated throughout pregnancy.

Statistical Analysis

Chi-square tests were used to compare cannabis use by maternal sociodemographic characteristics. Logistic regression was performed to determine the association between cannabis use in pregnancy and spontaneous preterm birth (<37 weeks of gestation) and SGA births (<10th percentile).

Cox proportional hazards regression modelling was performed to compare the time to stillbirth between women who used cannabis in pregnancy and those who did not. This type of modelling was selected over logistic regression to avoid the inclusion of live births in the denominator.[22,23] GA was used as the underlying time axis of the analysis. A subanalysis was conducted to determine whether there was a difference in the association between cannabis use and timing of stillbirth (antepartum vs. intrapartum).

All models were adjusted for maternal age in years (≤24, 25−29, 30−34, 35−39, 40+), pre-pregnancy BMI (kg/m^2), tobacco use (yes/no), alcohol use (yes/no), other substance use (yes/no), socioeconomic status (quintiles), and race/ethnicity (Chinese, South Asian, or other). Approximately 30% of BMI values were missing (30% in women who used cannabis vs. 29% in women who did not). These were excluded from the regression analyses. Research ethics approval was granted through the University of British Columbia (H18-01734).

RESULTS

There were 243 140 women in the study sample after applying the exclusion criteria. Table 1 compares the sociodemographic characteristics and birth outcomes of women who used cannabis in pregnancy versus those who did not. Women who used cannabis were significantly younger, of lower socioeconomic status, less likely to be of normal weight (more likely to be either underweight or overweight and obese), and less likely to be

Table 1. Maternal sociodemographic characteristics and singleton birth outcomes by cannabis use among 243 140 pregnant women in British Columbia, April 1, 2008 to March 31, 2016

Maternal sociodemographic characteristics	Cannabis use n = 5801 n (%)	No cannabis use n = 237 339 n (%)	P value
Maternal age			
≤24	2886 (49.8)	34 567 (14.6)	<0.0001
25−29	1491 (25.7)	66 161 (27.9)	
30−34	973 (16.8)	81 094 (34.2)	
35−39	382 (6.6)	45 204 (19.1)	
40+	69 (1.2)	10 313 (4.4)	
Ethnicity			
Chinese	31 (0.5)	16 111 (6.8)	<0.0001
General population	5717 (98.6)	198 524 (83.7)	
South Asian	53 (0.9)	22 704 (9.6)	
Pre-pregnancy BMI[a]			
Underweight	328 (8.0)	9749 (5.8)	<0.0001
Normal	2152 (53.0)	102 164 (60.5)	
Overweight	893 (22.0)	35 072 (20.8)	
Obese	687 (16.9)	21 863 (13.0)	
Pre-existing diabetes	22 (0.4)	1310 (0.6)	0.08
Gestational diabetes	296 (5.1)	21 737 (9.2)	<0.0001
Pre-existing hypertension	273 (4.7)	11 127 (4.7)	0.95
Gestational hypertension	211 (3.6)	7958 (3.4)	0.24
Preeclampsia	51 (0.9)	2214 (0.9)	0.67
LGA	578 (10.0)	30 074 (12.7)	<0.0001
History of anxiety	1039 (17.9)	15 362 (6.5)	<0.0001
History of depression	1662 (28.7)	22 707 (9.6)	<0.0001
History mental illness	2382 (41.1)	37 341 (15.7)	<0.0001
Tobacco use	4038 (69.6)	39 370 (16.6)	<0.0001
Any alcohol use	700 (12.1)	2168 (0.9)	<0.0001
Other substance use	916 (15.8)	2159 (0.9)	<0.0001
Neighbourhood SES (QAIPPE)			<0.0001
1 (lowest)	1940 (34.1)	49 306 (21.0)	
2	1267 (22.3)	49 792 (21.3)	
3	1025 (18.0)	49 025 (20.9)	
4	894 (15.7)	48 056 (20.5)	
5 (highest)	568 (10.0)	38 176 (16.3)	

BMI: body mass index; SES: socioeconomic status; QAIPPE: adjusted income per person equivalent (index).
[a] 30% missing values. Percentages shown are excluding missing values.

Chinese and South Asian. Women who used cannabis had significantly lower rates of gestational diabetes; however, this may reflect variations in ethnicity between women who used cannabis and those who did not because South

Figure. Cannabis use among pregnant women in British Columbia, April 1, 2008 to March 31, 2016.
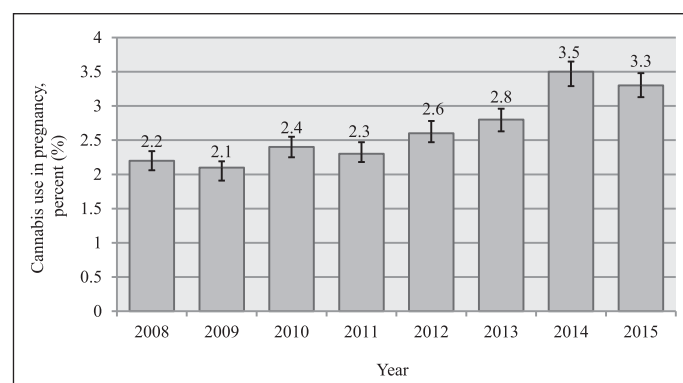
Asian and Chinese women have a significantly higher risk of gestational diabetes.[24] Women who used cannabis were also much more likely to report using other substances than women who did not use cannabis. Nearly 70% of women who used cannabis also reported tobacco use, compared with approximately 17% of women who did not use cannabis. There were significant differences in the history of mental illness by cannabis use. Approximately 40% of women who used cannabis reported a history of mental illness, nearly one-third reported a history of depression, and one-fifth reported a history of anxiety. Rates of stillbirth, including antepartum and intrapartum stillbirth, spontaneous preterm births, and SGA births were significantly higher among women who used cannabis. However, the results for stillbirth need to be interpreted with caution because of the small sample size for this outcome.

The Figure highlights the trends of cannabis use among pregnant women in British Columbia over the past decade. From April 1, 2008 to March 31, 2016, cannabis use among pregnant women in the province increased from 2.2% to 3.3%. The highest rate of use was observed during 2014-2015.

Table 2 summarizes the results of the logistic regression and Cox proportional hazards models to determine the association between cannabis use in pregnancy and SGA, spontaneous preterm birth, and stillbirth. After adjusting for potential confounders, there was a 47% increased risk of SGA and a 27% increased risk of spontaneous preterm birth in women who used cannabis during pregnancy compared with women who did not use cannabis. The association between cannabis use and stillbirth did not remain statistically significant after adjusting for covariates, although the magnitude of the point estimate was comparable to that for spontaneous preterm birth and SGA birth (adjusted HR 1.38; 95% CI 0.95−1.99). Results varied by timing of stillbirth. Antepartum stillbirth was not significantly associated with cannabis use in pregnancy, whereas the risk of intrapartum stillbirth was 2.8-fold higher compared with non-cannabis users.

DISCUSSION

This population-based study found an association between cannabis use in pregnancy and spontaneous preterm birth, SGA, and intrapartum stillbirth, after adjusting for maternal characteristics. This finding suggests that cannabis use may be harmful to fetal growth and development. However, because pregnant women who reported using cannabis were also significantly more likely to report using other substances in early pregnancy (tobacco, alcohol, and other illicit drugs), it is challenging to rule out that our findings are not the result of the use of other substances or associated lifestyle factors.

Table 2. Cannabis use and risk of selected birth outcomes for singleton births in British Columbia, April 1, 2008 to March 31, 2016

| Birth outcomes | Cannabis use during pregnancy | | | |
	Users; n (%)	Non-users; n (%)	Unadjusted OR	Adjusted OR[a]
SGA (<10th percentile)	587 (10.1)	15 463 (6.5)	1.64 (1.50−1.79)	1.47 (1.33−1.61)
Spontaneous preterm (<37 weeks)	433 (7.5)	10 082 (4.3)	1.82 (1.65−2.02)	1.27 (1.14−1.42)
			Unadjusted HR (CI)	Adjusted HR (CI)[a]
Stillbirth	31 (0.5)	632 (0.3)	1.66 (1.19−2.32)	1.38 (0.95−1.99)
Antepartum	21 (0.4)	515 (0.2)	1.47 (0.99−2.18)	1.34 (0.88−2.06)
Intrapartum	8 (0.14)	50 (0.02)	4.84 (2.33−10.1)	2.84 (1.18−6.82)

[a] Adjusted for maternal age, pre-pregnancy BMI, tobacco use, alcohol use, other substance use, socioeconomic status, and race/ethnicity.
SGA: small for gestational age.

Our study found that cannabis use in pregnancy in British Columbia increased in the past decade, with approximately 8000 pregnant women using cannabis in 2015. The prevalence increased from 2.2% to 3.3% between 2008 and 2016. The rise in cannabis use among pregnant women has also been observed in the United States, increasing from 2.4% to 3.9% between 2002 and 2014.[25,26] Pregnant women in British Columbia who used cannabis were significantly younger than women who did not use cannabis. This finding is consistent with other reports of younger maternal age among women who use cannabis.[26,27] The prevalence of cannabis use in Canada ranges between 26% and 46% for 16- to 29-year-olds versus 10% for the general population.[28]

Our results showed no association between cannabis use and stillbirth after adjusting for maternal characteristics. However, results varied by timing of stillbirth, with pregnant women being at higher risk of intrapartum stillbirth with cannabis use. Although research in this area is limited, studies show mixed results between stillbirth and cannabis use in pregnancy. A case-control study from the Stillbirth Collaborative Research Network reported a more than two-fold increased risk of stillbirth among women who used cannabis in pregnancy.[29] However, their results were confounded by tobacco use, which has been found to be associated with growth-restricted stillbirth fetuses but not with appropriate for GA stillbirth fetuses.[30–33]

It is thought that antepartum stillbirth and intrapartum stillbirth result from different etiological pathways.[22,33–35] Antepartum stillbirths, which account for the majority of stillbirths, are more often associated with hypertensive disorders, placental dysfunction including abruption, and growth restriction, whereas intrapartum stillbirth is more often associated with fetal distress, obstructed labour, and quality of care during labour.[22,36] However, there is evidence that women who smoke tobacco during pregnancy are at higher risk of intrapartum stillbirth.[37] This could be further evidence that smoking cannabis and smoking tobacco share a common etiological pathway.

Our results show an association between cannabis use and growth restriction among live births after adjusting for tobacco use and other maternal characteristics. This finding coincides with previous research associating cannabis use in pregnancy and reduced fetal growth, birth weight, and head circumference in a dose-dependent manner.[7] It is possible that smoking cannabis may have etiological effects similar to those of smoking tobacco through fetal oxygen deprivation and reduced blood supply to the placenta, which restricts fetal growth.[7,10] However, we were not able to distinguish between routes of cannabis exposure. The insulin growth factor system plays a critical role in the regulation of fetal and placental growth and is highly sensitive to undernutrition and insulin levels.[11–14] It is possible that cannabis decreases insulin secretion by binding to cannabinoid receptors in the pancreas.[7,15]

Our results indicate an association between cannabis use in pregnancy and spontaneous preterm birth. Previous research on preterm birth showed mixed results. Studies have found associations ranging between a 1.5 and five times increased risk of preterm birth, whereas a meta-analysis showed no association with preterm birth after adjusting for tobacco.[8,9,38,39] However, these studies were not necessarily specific to spontaneous preterm birth, and this may explain the discrepancy in findings. One possible mechanism through which cannabis affects preterm birth is the effect it has on prostaglandins and the role of the cannabinoid receptor in maintaining the ratio of estrogen to progesterone in pregnancy.[40,41]

Our results show that a higher proportion of women who used cannabis had a history of anxiety, depression, and mental illness compared with those who did not use cannabis. Nearly one-third of women who used cannabis reported a history of depression, whereas over 40% reported a history of mental illness, findings which are consistent with previous reports.[27]

Although this study is population based and benefits from a large sample size spanning several years, it is not without limitations. Because women who used cannabis are more likely to use other substances, particularly alcohol and tobacco, it is important to be able to account for these co-exposures.[6,27,29] Separating the effects of cannabis use from other substances that may have similar effects on the developing fetus is challenging and a limiting factor when trying to study the impact of cannabis on pregnancy. A strength of the Perinatal Data Registry is that it collects data on other substance use. However, all data collection on substance use is done through maternal self-report, which may underestimate or overestimate the exposure. Physicians may not always ask women about their use of substances, and women may not feel comfortable disclosing this information to their provider. Although the current standard of care recommends that all providers ask women about substance use during antenatal visits, we were not able to determine whether questions regarding cannabis use were consistently asked of all pregnant women in British Columbia. It is also not possible to account for dose, frequency, or timing of cannabis exposure. A more accurate way to measure cannabis exposure would be through

laboratory confirmation by measuring compounds related to both cannabis and tobacco use in cord blood. This would also allow the comparison of women who have only cannabis exposure with women who have both cannabis and tobacco exposure.

Other limitations include the lack of detailed information on ethnicity and the use of an area-based index to adjust for socioeconomic status instead of an individually based measure. Additionally, one third of pre-pregnancy BMI values were missing, a risk factor known to affect fetal growth and preterm birth. Other factors we could not account for included the potential for poorer nutritional status and antenatal care among women who use cannabis in pregnancy.[42] The lack of association between cannabis use and antenatal stillbirth may reflect the small sample size for this outcome.

CONCLUSION

Our study identified an association between cannabis use and SGA, spontaneous preterm birth, and intrapartum stillbirth. The social characteristics of pregnant women who used cannabis during pregnancy suggest both that younger women should be specifically targeted for prevention messaging on the risks of cannabis use in pregnancy and that poly-substance harm reduction strategies are needed for pregnant women who use cannabis as well as other substances. The role of mental illness in the onset of cannabis use also needs to be better understood. Conducting research on the type of cannabis used (whether inhaled or ingested), the frequency of exposure, and whether this occurred before or during pregnancy would be helpful in answering some important questions regarding the impact of dose, route, and timing of exposure on perinatal outcomes. Understanding the impact of cannabis use in pregnancy on perinatal outcomes is essential to developing guidelines for cannabis use in pregnancy.

Acknowledgements

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