ABSTRACT

Introduction Cannabis use in pregnancy and post partum is increasing. Accessibility to cannabis has expanded due to the legalisation of cannabis in Canada. Therefore, there is a critical need to monitor the impact of cannabis on pregnancy outcomes and infant neurodevelopment. This pilot study will assess the feasibility of modern recruitment and data collection strategies adapted to the current cannabis environment and inform the design of a multicentre prospective birth cohort.

Methods and analysis We will establish a pregnancy and birth cohort of 50 cannabis users and 50 non-users recruited before delivery. We will follow the participants at regular visits from recruitment to 12 weeks post partum. Participants will provide demographic and socioeconomic data, report their cannabis use patterns, and provide biological samples. Biological samples include maternal and infant urine and blood, breastmilk/cheesemilk, cord blood, cord tissue, placenta and meconium. All samples will be processed and stored at −80°C until analysis by immunoassay or liquid chromatography-tandem mass spectrometry to determine the presence of cannabis metabolites. In addition, partners will be invited to provide additional socioeconomic and substance use data.

Ethics and dissemination Ethics was obtained from Ottawa Health Science Network Research Ethics Board through Clinical Trials Ontario (3791). Our findings will be published in peer-reviewed journals, presented at scientific conferences and shared broadly with patients, healthcare decision-makers, and project partners online and through social media.

Trial registration number NCT05309226

INTRODUCTION

Cannabis is a widely used drug in developed and low/middle-income countries, with up to 1 in 10 individuals reporting past-year use in many countries. The prevalence of cannabis use in Canada has increased since 2011 due to increased social acceptability, accessibility and availability. Canada is among multiple countries that have legalised cannabis for any purpose (ie, medicinal and/or recreational purposes). In 2020, it was reported that approximately 20% of Canadians older than 15 years of age consumed cannabis, increasing from a prevalence of 14% in 2018 before legalisation. Notably, the prevalence of cannabis use in pregnancy has increased, and it is the second most commonly used substance in pregnancy, behind tobacco. Legalising cannabis and its increased use in many populations, including pregnant individuals, may contribute to a decreased perception of its harm.

However, findings from retrospective cohort studies suggest that fetal cannabis exposure is associated with adverse neonatal outcomes, including stillbirth, small for gestational age, low birth weight, preterm birth and admission to neonatal intensive care units (NICU). Lasting neurodevelopmental effects in offspring have also been suggested. Although findings from
The lipophilic nature and low molecular weight of cannabinoid compounds contribute to their ability to accumulate in fetal tissues including the brain. Notably, cannabinoids can also be transferred to neonates via breastmilk/ chestmilk when nursing. Although data on breastmilk/ chestmilk are limited, cannabinoids have been detected in the breastmilk/chestmilk of cannabis users and also in the faeces and urine of exposed infants. Challenges in determining the long-term effects of cannabis exposure on fetal and child development include the difficulty of disentangling the influence of socioeconomic status, poly-substance use, frequency, dose, contaminants, mode of consumption, under-reporting of cannabis use and postpartum exposures.

Given the limitations of prior studies and the evolving cannabis environment, new prospective cohorts are needed to collect granular data on cannabis use in the obstetrical population and associations with perinatal and infant outcomes. Cannabis use behaviours are changing rapidly in postlegalisation settings. There are many cannabis products on the market, with varying THC and CBD contents, wide-ranging potency, and various use formats. In addition to user-reported data, it is essential to collect biological samples from which objective measures of cannabis exposures can be derived. Indeed, biosample analysis can alleviate challenges in interpreting self-reported data and unmeasured second-hand or co-exposure.

In contrast, the detection window for chronic users may last for weeks. Other matrices such as meconium, cord blood, cord tissue and placental biopsies can also provide valuable information on exposure in utero. Meconium, the first faecal matter passed by the newborn, has emerged as the gold standard for assessing long-term gestational exposure. Meconium begins to form from 12 to 16 weeks gestation and accumulates until birth. To address the need for contemporary Canadian cohorts to collect robust data on maternal and infant cannabis exposures, we report here the methodology for a pilot study assessing the feasibility of developing a more extensive prospective pregnancy and birth cohort on gestational and postnatal cannabis use.

**METHODS AND ANALYSIS**

**Study design and setting**

The Cannabis Use in Pregnancy and Downstream effects on maternal and infant health (CUPiD) study is a multicentre, prospective, observational cohort pilot study of pregnant individuals and their infants. Participants will be followed throughout pregnancy and into the postpartum period up to 12 weeks after delivery. In addition, participants may invite their partners to participate in a one-time survey.

Recruitment will be in Ottawa and Kingston, Canada, at The Ottawa Hospital (TOH), Ottawa Birth and Wellness Centre and Kingston Health Sciences Centre. Ottawa is the second largest city in Ontario and fourth largest in Canada with 1.4 million population in the Ottawa-Gatineau area. TOH has approximately 7500 births per year. Kingston General Hospital (KGH), located at Kingston Health Sciences Centre, has a smaller population (approximately 172 500); however, KGH has an extensive catchment area of more than 20 000 km² with about 2300 births per year. TOH and KGH are level 3 maternity care hospitals with on-site neonatal and adult intensive care services.

**Exposure**

The exposure of interest is consuming any cannabis-related product in pregnancy. For this study, ‘cannabis’ refers to all forms of cannabis (eg, dry flower, edibles, extracts, concentrates) that may possess any naturally occurring or synthetic cannabinoids such as THC or CBD.

**Outcomes**

The primary outcome is the feasibility of establishing a more extensive multicentre prospective pregnancy cohort in this population. We will consider the primary outcome achieved if our recruitment rate is about 8–10 participants per month and we complete the recruitment of 100 patients within 12 months. We anticipate lower recruitment during study initiation in the first 2 months and that the recruitment rate will increase after we broadly distribute the study materials. We will also examine the enrolment rate, level of engagement, protocol compliance, appropriateness of eligibility criteria, sample size and time frame to achieve target recruitment. The level of engagement will be assessed by calculating the completeness of each study activity (questionnaire data and biological samples). Protocol compliance will be assessed by determining the proportion of participants who complete all study activities and the attrition rate (lost to follow-up or withdrawal of consent). The level of engagement and protocol compliance will help us understand the burden from each study activity and help us tailor data collection activities based on participant level of comfort. The enrolment rate will be the final number of participants enrolled in the cohort after any exclusions due to, for example, other substance use or abuse or pregnancy loss compared with those who agree to participate. We will aim to continue recruitment until 100 participants can be successfully enrolled. Appropriateness of sample size and time frame will be achieved if the target sample size is attained within 12 months.

The secondary outcomes will include perinatal and neonatal outcomes including gestational age at birth, birth weight and size at birth, fetal and neonatal morbidity, pregnancy complications, Apgar score, infant growth, respiratory arrest, neonatal abstinence syndrome, preterm birth, low birth weight, postpartum complications, and maternal outcomes including one-year postpartum mental health, smoking, drug and alcohol use.
Eligibility criteria
Participants and partners must all be able to provide informed consent, comprehend and comply with the study requirements and be 16 years or older at the time of enrolment. The eligibility criteria for this study are summarised in table 1 and figure 1.

Participants
Participants will include individuals planning to deliver at a participating site and have a viable pregnancy at the time of enrolment. Participants will be enrolled in one of the two following groups:
1. Group A: Pregnant individuals who report using any cannabis-related product(s) in pregnancy at the enrolment trimester or within 30 days prior to enrolment, or have used cannabis-related products in the current pregnancy for any reason.
2. Group B: Pregnant individuals who report no use of cannabis-related products at the time of enrolment and who have not used any cannabis-related products for at least 3 months before pregnancy.

Individuals who self-report non-prescription use of controlled and/or illegal drugs, and/or prescription use of opioid medications in their current pregnancy or 3 months before pregnancy will be excluded. We will also exclude individuals who are surrogates or planning to give up their infant for adoption.

Partners
Partners of enrolled participants will be eligible to participate in a one-time survey. The term ‘partner’ will broadly include an individual identified as such by the participant (any sex or gender, any status—marital, common-law or otherwise).

Recruitment and consent
Eligible individuals will be identified through a review of medical charts and recruited from antenatal clinics or via telephone. Individuals who have granted permission to be contacted for research purposes through their local hospitals will be contacted directly by a research
team member. Individuals who did not indicate that they are willing to be contacted for research will otherwise be approached by a member of their circle of care. Eligible individuals may also self-identify themselves to the research team by responding to recruitment material. Recruitment material such as posters and brochures will be distributed around antenatal clinics, obstetricians and family physicians’ offices, midwifery clinics and birth centres, and other establishments within the study catchment area. In addition, we will advertise the study through the professional and personal social media accounts of participating study team members and participating sites. Partners will only be invited to participate if the enrolled pregnant participant chooses to involve them in the study.

Participants will provide informed consent for themselves and on behalf of their infant(s) after they are born. Participants may provide permission for their and their infant(s) data and samples to be used for other future pregnancy and child health-related research. Partners will provide informed consent for themselves. All participants will be made aware of the study procedures, any related risks associated with participation, the potential for secondary use of data and samples, and informed that they have the right to withdraw from the study at any time.

### Study visits and procedures

The study will consist of up to five visits starting in early pregnancy and ending at 6–12 weeks post partum. The total number of visits will vary based on the time of enrolment, and the visit schedule will be adjusted accordingly, maintaining 4 weeks between visits. For patients recruited before 13 weeks, visits 1, 2 and 3 will be in the first, second and third trimesters, respectively. Visit 4 will coincide with the participant’s admission to the hospital or birthing centre for labour and delivery. Visit 5 will be scheduled between 6 and 12 weeks post partum. Data and biological samples will be collected from participants at each visit. Infant involvement will commence at the time of delivery and will also include biological samples and data collection. Partners will complete a one-time survey at any time during the study.

### Data collection

Data will be collected directly from participants and their medical charts (table 2).

All surveys, including the baseline surveys, partner survey, cannabis intake diary and case report form, are included in online supplemental appendix A.

### Biophysical measurements

Anthropometry will be collected throughout the study and include maternal height, weight and waist circumference. Maternal height will be documented at the beginning of the study, and weight and waist circumference will be documented throughout. We will collect maternal blood pressure from participants’ medical charts, where available. After delivery and at each subsequent study visit, infant weight, length, and abdominal and head circumference will be measured.

### Baseline survey

This survey will be administered at enrolment to collect maternal/birthing parent sociodemographic characteristics, details about the household environment such as nature and size of dwelling, nature and number of household members, medical and obstetrical histories, including mental health conditions, previous substance use (any substance use) and current substance use. We will ask about anticipated changes to substance use during pregnancy or after delivery (if any). Among group A, we will ask about the reasons for cannabis use (eg, nausea/vomiting, stress/anxiety, recreational, medical condition), frequency and mode of consumption (eg, smoked, vaped, consumed). Where possible, cannabinoid content and/or brand will be collected. In addition, indoor secondhand exposure to cannabis and tobacco will be documented. We will also include questions to ascertain the nature of counselling participants have received on cannabis use/exposure in pregnancy from their healthcare provider(s) and the extent of information the participant has sought or received about cannabis use (from healthcare providers, independent research or through family/friends/acquaintances).

### Table 2 Schedule of data collection

<table>
<thead>
<tr>
<th>Visit 1 ≤126/7 weeks</th>
<th>Visit 2 13 to 266/7 weeks and ≥4 weeks after visit 1</th>
<th>Visit 3 ≥27 weeks and ≥4 weeks after visit 2</th>
<th>Visit 4 Admission for labour and delivery</th>
<th>Visit 5 6–12 weeks post partum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline survey*</td>
<td>Follow-up survey</td>
<td>Follow-up survey</td>
<td>Follow-up survey</td>
<td>Follow-up survey Infant health survey</td>
</tr>
<tr>
<td>Biophysical</td>
<td>Biophysical measurements</td>
<td>Biophysical measurements</td>
<td>Biophysical measurements</td>
<td>Biophysical measurements</td>
</tr>
</tbody>
</table>

Cannabis intake diary (throughout study)
Partner survey (whenever the partner enrols)
Case report form (throughout study)

*Baseline survey will be administered at enrolment and may replace the follow-up survey.
Follow-up surveys
Following enrolment, these surveys will be administered to mothers/birthing parents in each subsequent study visit. These surveys will capture participants’ cannabis use and cannabis use counselling or information received since the last study visit. In addition, secondhand exposure to cannabis and tobacco in different environmental settings will be documented. These surveys will also collect information related to significant changes in health or well-being (eg, life-changing diagnoses, hospitalisation, emergency health visits).

Infant health survey
Participants will complete this survey on behalf of their infants. It will capture data related to child feeding status (eg, breastmilk/chestmilk, formula or other supplementation, combination) and document significant changes in child health or well-being (eg, life-changing diagnoses, hospitalisation, emergency health visits) reported by the mother/birthing parent. The survey will not be administered if an infant has died before the study visit.

Cannabis intake diary
Participants will be asked to record their cannabis use in a diary. The Cannabis Intake Diary will prompt participants to record details such as date of use, the product format/type, how the product was used/ingested, the amount consumed and the THC and/or CBD content if known.

Partner survey
This survey will be administered to partners and may be completed at any time during the study period. The survey will include questions related to their past and current lifestyle habits (eg, cannabis, tobacco, alcohol use and other substances), and anticipated changes to substance use during their partner’s pregnancy or after delivery (if any). In addition, we will ask partners about their reasons for cannabis use, frequency and mode of consumption, and cannabinoid content and/or brand will be collected. Finally, to inform the design of future prospective cohort studies, we will query partner receptivity to increasing participation, for example, by providing biological samples.

Medical chart review
Chart reviews will be completed to ascertain additional information on participants’ obstetrical and medical histories (eg, gravidity, pre-existing conditions, complications from previous pregnancies), mental health conditions (eg, anxiety, depression), pregnancy complications (eg, hypertensive disorders of pregnancy, diabetes in pregnancy), delivery outcomes (eg, type and mode of delivery, type of labour, live/stillbirth outcome) and newborn outcomes (eg, gestational age at birth, birth weight, Apgar scores, NICU admission, need for resuscitation, intravenous antibiotics and other medications, feeding method from birth to hospital discharge). Medical chart reviews will also be used to supplement missing or unclear data collected from participants and their infants.

Sample collection
Biological samples will be collected from participants throughout the study and their infant(s) after delivery (table 3). No biological samples will be collected from the partners.

Maternal sample collection will include peripheral blood, urine and breastmilk/chestmilk. Peripheral blood will be drawn via venipuncture and serum and plasma will be isolated. Maternal urine and blood samples will be fasting or non-fasting. Breastmilk/chestmilk collection will take place following milk let-down. Although participants will be instructed to collect hindmilk, colostrum and foremilk samples will be accepted. All maternal samples will be stored in aliquots at −80°C until sample analysis.

Fetal/infant sample collection after delivery will include cord blood, umbilical cord tissue, placenta biopsies, meconium and infant urine. Infant sample collection at 6–12 weeks post partum will include urine and dried blood spot samples. The cord blood will be collected immediately after delivery, and serum and plasma will be isolated. Umbilical cords will be flushed and rinsed with saline to remove the blood and patted dry. Umbilical cord segments will be flash-frozen in liquid nitrogen. Chorionic villous tissue biopsies will be collected from evenly spaced locations around the umbilical cord insertion site.

| Table 3 Schedule of biosample collection |
| Visit 1 ≤12 weeks | Visit 2 13 to 26 weeks and ≥4 weeks after visit 1 | Visit 3 ≥27 weeks and ≥4 weeks after visit 2 | Visit 4 Admission for labour and delivery | Visit 5 6–12 weeks post partum |
| Pregnancy samples | Pregnancy samples | Pregnancy samples | Pregnancy samples |
| Peripheral blood | Peripheral blood | Urine | Urine |
| Urine | Urine | Breastmilk/chestmilk | Fetal/Infant samples |
| Meconium | Meconium | Cord blood | Cord Tissue |
| Placenta | Placenta | |
| Infant samples | Infant samples |
| Infant blood | Infant blood |
| Postpartum samples | Postpartum samples |
| Peripheral blood | Peripheral blood |
| Urine | Urine |
| Breastmilk/chestmilk | Breastmilk/chestmilk |
| Infant samples | Infant samples |
| Infant blood | Infant blood |
and flash-frozen in liquid nitrogen. Placental tissue will be collected within 30 min of delivery, and we will follow established methods for placenta sample collection. Placenta biopsies will also be blocked in paraffin wax for later histological evaluation. Meconium will be collected onto diaper liners, and infant urine will be collected into infant urine collection bags. Infant blood at visit 5 will be drawn by heel-prick using a sterile lancet, and blood drops will be collected onto protein saver cards, dried and stored with a desiccant in a sealed bag. All fetal/infant samples will be stored as aliquots where possible and kept at −80°C until sample analysis.

**Biological sample analysis**

Biological samples from all participants (including group A, group B and infants) will be analysed. Data derived from sample analysis will be linkable to the data file generated from data collected from surveys, medical charts and cannabis intake diaries.

The presence or absence of target metabolites may first be identified by immunoassay screening. Presumptive positive samples will be sent for analysis by liquid chromatography-tandem mass spectrometry to confirm and quantify significant interest metabolites using validated methodologies. The extent of analysis will vary depending on the study group (group A vs group B) and/or participant reported substance use at each study time point.

- Samples derived from users of cannabis will be analysed for targeted cannabinoid metabolites including: 11-nor-D9-THC-9-carboxylic acid; THC-COOH; 11-hydroxy-THC; cannabinol; cannabidiol.
- Samples from participants reporting tobacco use or exposure will be analysed for relevant metabolites including but not limited to: cotinine, hydroxycotinine, nicotine to add to our understanding of the potential impact of tobacco exposure on cannabinoid metabolism and the study health outcomes of interest.

**Compensation**

Participants will be compensated for parking expenses or transportation fare related to all study visits excluding visits to hospitals or birthing centres for labour and delivery (visit 4). A breastmilk/chestmilk hand pump will be given to pregnant participants to support breastmilk/chestmilk collection.

To acknowledge their contributions to the study, participants will also be provided with gift cards at each study visit and an additional gift card at the end of the study if they completed all of the study surveys. Partners who complete the partner survey will be provided with a gift card.

**Data management plan**

Participants will be assigned a unique study ID, which will be used to link data and sample information. Data collected from participants, their infants and their partners (if applicable) will be linked. A masterlist linking identifiable information with study IDs will be stored in a password-protected encrypted file. Data from study visits, surveys, and medical chart reviews will be collected into the Research Electronic Data Capture (REDCap) system hosted by participating sites and managed by the Ottawa Hospital Research Institute. REDCap uses 128-bit data encryption and provides modifiable role-based security to protect personal information or personal health information. Members of the research team from the Ottawa Hospital Research Institute will monitor the data to ensure data accuracy and completeness. An audit trail will be maintained for all data entries and modifications. Data generated from the analysis of biological samples will be managed separately in a password-protected encrypted file until it is merged with REDCap data for analysis.

The Ottawa Hospital Research Institute will manage all data and samples and archive them for up to 25 years after study termination. After the retention period, the research data and remaining samples will be securely destroyed per standard institutional procedures.

**Sample size**

We will recruit a maximum of 100 participants (50 participants with cannabis use and 50 without use) over 12 months.

**Statistical analysis**

Our results will be reported using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

**Descriptive statistics**

We will report descriptive summary statistics for the study cohort and across groups according to cannabis use at enrolment. Data will be summarised using frequency distributions for categorical variables and means and medians for continuous variables. We will use toxicological findings and reported use to classify cannabinoid exposure overall and by trimester. We will compare the distribution of sociodemographic characteristics by non-exposure and tertiles of exposure using the following levels: trace exposure/low use versus moderate versus heavy exposures, with final cannabis-use tertiles to be determined during analysis. Sociodemographic covariates will include the age of the maternal/birthing parent and partner, education level, income and race/ethnicity. We will also examine clinical and obstetrical histories according to the study group.

**Analysis of primary outcomes**

Participant recruitment rates, reasons for exclusion, enrolment rates (based on final enrolment following any exclusions), level of engagement (contributing data and biological samples) and rates and reasons for withdrawal from the study will be assessed and summarised descriptively. The recruitment rate will be calculated in monthly intervals with the number of consented participants compared with approached participants. In addition, we examine rates of passive (e.g., participants whose preg
self-identify based on flyers and social media) or active recruitment (eg, invited patients through electronic records searching). An interim analysis at 6 months will be completed to evaluate the primary outcomes. The recruitment strategy will be revised if the recruitment rate is less than our target.

Analysis of secondary outcomes

Perinatal outcomes will be compared between groups based on reported cannabis use and metabolite detection in biological samples and not explicitly according to the group at recruitment. This approach will allow us to analyse group B participants who initiated cannabis use during the study as part of group A. Although we will have a limited sample size, we will conduct exploratory analyses to estimate differences in the risk of perinatal outcomes between the frequency of cannabis use, mode of cannabis consumption, and the timing and duration of use in pregnancy and post partum. We will assess the relative and joint contribution of cannabis use across trimesters on outcomes using mixed/hierarchical models with autoregressive covariance structures.

Interactions between child sex and each indicator of cannabis exposure will be tested to explore sex differences in associations. Potential confounders will be considered a priori. We will control for age, socioeconomic status and maternal/birthing parent tobacco use using self-reported and toxicological data (cotinine).

Considerations for the main study

Analyses of the pilot study will inform the design of the main CUPiD in several critical ways. First, we will ideally recruit participants within the first trimester, before 13 weeks’ gestation. Recruitment in the first trimester will allow an optimal fetal risk assessment due to cannabis consumption, and the timing and duration of use in pregnancy and post partum. We will assess the relative and joint contribution of cannabis use across trimesters on outcomes using mixed/hierarchical models with autoregressive covariance structures.

In recognition that individuals with lived experience (in this case, cannabis use in pregnancy) can have an active and valuable role in research, we have invited patient partners to contribute their perspectives on the design and implementation of this research study. To date, one patient partner has provided feedback on the study design, data collection tools and recruitment materials. We will continue to involve patient partners throughout the study, including reviewing recruitment strategies and study progress, interpreting the results and sharing project findings with the broader public community.

Ethics and dissemination

Ethics

Research ethics approval for this study was obtained through Clinical Trials Ontario (CTO 3791) with the Ottawa Health Sciences Network Research Ethics Board as the board of record. The research team at The Ottawa Hospital Research Institute will be responsible for maintaining provincial-level ethics approval and each participating site will be responsible for obtaining and maintaining site-specific ethics approvals throughout the study.

Dissemination

The results from this pilot study will be disseminated to researchers and clinicians in the form of abstracts and presentations, and manuscripts for publication in peer-reviewed journals. Following publication of the main analyses, deidentified data from this cohort will be made available on request from the corresponding author and with approval from an accredited research ethics board. These results will also be shared with healthcare decision-makers in the form of summaries and technical papers. In addition, the findings will be more broadly disseminated to the academic and clinical community through platforms such as clinicaltrials.gov and the Open Science Framework and to Canadian families through press releases, social media posts and the sharing of lay summaries tailored to each target audience. Overall, our findings will be used to inform the development of a more extensive multicentre pregnancy and birth cohort investigating patterns of maternal cannabis use in pregnancy and the impact of cannabis use and fetal exposure in pregnancy on perinatal outcomes.

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Competing interests
None declared.

Patient and public involvement
Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication
Not applicable.

Provenance and peer review
Not commissioned; externally peer reviewed.

Supplemental material
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