Systematic Reviews

PROTOCOL

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Risk thresholds for the frequency of cannabis use during pregnancy and adverse neonatal outcomes: protocol for a systematic review and dose–response meta-analysis

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Abstract

Background Cannabis use during pregnancy has been increasing and is associated with adverse neonatal outcomes, such as low birth weight (LBW) and preterm birth (PTB). It remains largely unknown whether the association between cannabis use in pregnancy and increased risk of adverse neonatal outcomes is impacted by the frequency of cannabis use and whether thresholds exist below which risk is not significantly increased. The objective of this systematic review is to assess whether the association between cannabis use during pregnancy and the risk of adverse neonatal outcomes is dependent on the frequency of use and whether risk thresholds exist.

Methods For this systematic review and dose–response meta-analysis, the Embase, MEDLINE, PsycINFO, CINAHL, and Web of Science databases will be searched for relevant studies published in English from January 2010 onwards. Studies that include pregnant individuals with singleton pregnancies and evaluate the association between cannabis use in pregnancy and adverse neonatal outcomes using case–control, cohort, or cross-sectional designs will be considered for inclusion. Studies must include information on cannabis use frequency reported according to at least three of the pre-defined categories of no use, yearly (1–11 days per year), monthly (1–3 days per month), weekly (1–4 days per week), and daily/near daily use (5–7 days per week). At least one of the following neonatal outcomes must be reported, according to the frequency of cannabis use: LBW (< 1500 g), PTB (before 37 weeks gestation), neonatal intensive care unit (NICU) admission, and mortality. Studies will be included that report results as risk ratios (RR), odds ratios (OR), hazard ratios (HR), or that include the raw data to be able to calculate them. A two-stage dose–response meta-analysis will be conducted. The risk of bias of included studies will be assessed using the JBI tools for cohort, case–control, and cross-sectional studies. Certainty of the evidence will be reported according to the GRADE approach and the review will be reported according to PRISMA guidelines.

Discussion The frequency of cannabis is one factor that may influence the relationship between cannabis use in pregnancy and adverse neonatal outcomes. This review will quantify this relationship by determining whether risk thresholds exist.

Systematic review registration PROSPERO CRD42023479978.

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Keywords Cannabis, Pregnancy, Systematic review, Neonatal outcomes, Dose–response

Introduction

Cannabis use during pregnancy has been increasing in the past two decades [1]. In Canada, 7.2% of women aged 16–50 who had given birth within the last five years reported using cannabis during their most recent pregnancy in the 2023 Canadian Cannabis Survey (CCS) [2]. Rates of use during pregnancy as high as 15–28% have been reported in the literature, depending on the population studied, mode of detection, and definition of use [3]. Rates of use are highest among those who are of a young maternal age, live in urban areas, and are socioeconomically disadvantaged [4]. Pregnant individuals have cited a multitude of reasons for continued cannabis use, such as the management of pregnancy-related nausea and sleep problems, and as an alternative to other medications [5].

Observed increases in cannabis use in pregnancy have coincided with cannabis legalization in many jurisdictions [4]. Qualitative research evidence shows that pregnant individuals who use cannabis believe that legalization has made it easier to access cannabis, decreased the stigma associated with use, reduced concerns related to involvement with child protective services, and increased the desire to use [4]. Studies have also shown that many individuals who continue to use cannabis during pregnancy believe that there is no or only a slight risk of harm to the fetus from their cannabis use [4, 6]. A lack of clear information surrounding the safety of cannabis use in pregnancy and mixed messages from healthcare providers have also been cited as contributors to continued use [5, 7]. Taken together, changes to cannabis legislation, limited safety information, trends of increasing use, and perceived low risk of use in pregnancy demonstrate the importance of determining the impact of prenatal cannabis use on neonatal outcomes [8].

The main psychoactive ingredient in cannabis, delta-9-tetrahydrocannabinol (THC), readily crosses the placenta and can enter the fetal bloodstream [9]. Prior research has demonstrated that cannabis use in pregnancy is linked to adverse neonatal outcomes, although results have been conflicting [10–13]. Systematic reviews and meta-analyses have shown that cannabis use in pregnancy is associated with an increased risk of preterm birth (PTB), low birth weight (LBW), being small for gestational age (SGA), and admission to a neonatal intensive care unit (NICU) [10, 11, 13, 14]. Contradictory to these results, a systematic review conducted by Connor and colleagues in 2016 concluded that maternal cannabis use in pregnancy was not an independent risk factor for SGA or LBW after adjusting for concurrent tobacco use [12]. Results of this review, however, indicated that the experience of adverse neonatal outcomes may be mediated by the frequency of cannabis use in pregnancy, although they were unable to account for tobacco use in this analysis. Pregnant individuals who used cannabis at least weekly were at significantly higher risk of LBW (two studies, risk ratio [RR] = 1.90, 95% confidence interval [CI] = 1.44–2.45) and PTB (five studies, RR = 2.04, 95% CI = 1.32–3.17) [12].

In the time since the previous review by Connor and colleagues was conducted, additional jurisdictions have legalized cannabis for recreational use and the literature surrounding the safety of cannabis use in pregnancy has expanded [12]. While this review assessed the outcomes of LBW and PTB in relation to the frequency of cannabis use, it was unable to adjust for tobacco use in analyses. The current review will therefore aim to include additional neonatal outcomes (e.g., NICU admission, mortality, SGA), control for concurrent tobacco use, and capture additional studies published since the completion of the existing review. Additional existing reviews have assessed the relationship between cannabis use and adverse neonatal outcomes using only binary categories of cannabis use (e.g., use or no use) [10, 11]. This review will expand on these prior studies by including additional categories of cannabis use frequency.

While there are multiple factors that contribute to the "dose" of cannabis use, such as timing of use in pregnancy (first, second, or third trimester), method of use (e.g., inhalation or oral ingestion), and potency of the product used (THC content), many studies fail to report on both method of use and potency of the product used. Additionally, studies that report on the timing of cannabis use during pregnancy often do not report on the frequency of cannabis use. The focus of this review is therefore on the frequency of cannabis use during pregnancy (e.g., monthly, weekly, daily). Currently, organizations such as the Society of Obstetricians and Gynaecologists of Canada (SOGC) [15] and the American College of Obstetricians and Gynecologists (ACOG) [16] recommend full abstinence from cannabis during pregnancy. This, however, may not be realistic or feasible, especially in jurisdictions, such as Canada, where recreational cannabis use has been legalized. The potential existence of identifiable risk thresholds for the frequency of cannabis use in pregnancy and adverse neonatal outcomes is important from a public health perspective. Such thresholds could be used to inform policy and educational materials towards reducing potential adverse outcomes,

particularly in situations where full abstinence is not a valid option. The objective of this systematic review meta-analysis is therefore to assess whether the association between cannabis use during pregnancy and the risk of adverse neonatal outcomes is dependent on the frequency of cannabis use.

Research question

Do significant, identifiable risk thresholds exist in a dose–response relationship between the frequency of cannabis use (e.g., yearly, monthly, daily) during pregnancy and the development of adverse neonatal outcomes such as low birth weight, preterm birth, mortality, and neonatal intensive care unit admission?

Methods and analysis

This systematic review and dose–response meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. This protocol is reported according to PRISMA for systematic review protocols (PRISMA-P) checklist [18]. The PRISMA-P checklist for this protocol can be found in Additional File 1. This review has been registered with PROSPERO (CRD42023479978). The PROSPERO record will be updated with review amendments as applicable.

Inclusion and exclusion criteria

This review will consider studies that include pregnant individuals. Only those that report on outcomes for singleton pregnancies will be included as multiples gestations are an independent risk factor for many of the outcomes of interest for this study (e.g., PTB) and could thus bias study results [19].

This review will consider studies that evaluate the effect of cannabis use during pregnancy on adverse neonatal outcomes according to predefined categorical levels (frequencies) of cannabis exposure. The predefined categories were derived from the existing cannabis literature and are as follows: (1) never/no use, (2) 1–11 days a year ("yearly"), (3) 1–3 days a month ("monthly"), (4) 1–4 days a week ("weekly"), and (5) 5–7 days a week ("daily/near-daily") [20, 21]. All modes of cannabis use (e.g., smoking, vaping, ingestion) will be considered. Studies on synthetic cannabinoids (e.g., K2 or spice) and that report on cannabis use for medicinal purposes only will be excluded. There will be no restrictions placed on participant age. Only human-subject studies will be included.

This review will consider studies that include the following outcomes: LBW (weight at birth of < 2500 g), SGA (birth weight of less than the 10th percentile for gestational age), PTB (live birth before 37 weeks gestation), NICU admission, and mortality. Birth weight and gestational age reported as continuous variables will also be included as secondary outcomes. These outcomes were chosen due to their clinical importance and because a scoping exercise identified them as being among the most commonly reported outcomes in studies of neonatal effects of cannabis use in pregnancy.

Case–control, cohort, and cross-sectional study designs will be included. Case–control studies with less than ten matched pairs will be excluded due to the increased risk of bias in studies with sample sizes below this threshold [22]. Only studies published from January 2010 onward will be included as the potency of cannabis has increased greatly since that time (e.g., from 8.9% TCH in 2008 to over 17% THC in 2017) [23]. Including older studies from periods where cannabis potency was lower could therefore underestimate the effects of cannabis use during pregnancy on adverse neonatal outcomes. Because it is uncommon for observational studies to report on the potency of cannabis used, controlling for this increase during data analysis would be unfeasible. Studies published in English will be included. Studies published in other languages will be included based on the availability of translations. Studies published as peer-reviewed journal articles as well as grey literature (e.g., conference abstracts, dissertations, government reports) will be considered for inclusion.

Search strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of EMBASE (Ovid) was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles and search strategies of systematic reviews on similar topics were used to develop a full search strategy for EMBASE (Ovid) (Additional File 2) with the aid of a research librarian. The search strategy, including all identified keywords and index terms, was adapted for each database searched. The reference lists of all studies selected for critical appraisal and similar systematic reviews will be screened for additional studies.

The databases to be searched include Embase (Ovid), MEDLINE (Ovid), CINAHL (EBSCOhost), PsycINFO (Ovid), and Web of Science (Clarivate Analytics). Sources of unpublished studies and grey literature to be searched include grey literature databases (e.g., National Grey Literature Collection, Canadian Agency for Drugs and Technologies in Health [CADTH] Grey matters) and the websites of relevant professional organizations (e.g., National Institute on Drug Abuse [NIDA] Canadian Institute for Substance use Research, International Drug Policy Consortium). A full list of grey literature sources to be searched can be found in Additional File 3.

Study selection

Following the search, all identified citations will be collated and uploaded into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia), and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full, and their citation details imported into Covidence. The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies will be recorded and reported in the systematic review. Any disagreements between the reviewers at each stage of the study selection process will be resolved through consensus discussion or with a third reviewer. Inter-rater reliability (IRR) between reviewers will be calculated for both screening by title/abstract and full text. The results of the search and study selection and inclusion process will be reported in full in the final systematic review and presented in a PRISMA flow diagram [17].

Data extraction

Data will be extracted from studies included in the review by two independent reviewers using a standardized data extraction tool developed specifically for this study in Covidence. The data extracted will include specific details about the population, location, study type, cannabis legalization status, method of cannabis use, potential confounders controlled for in each study (e.g., concurrent tobacco and/or alcohol use), and outcomes of significance to the review question listed above. Effect estimates and counts or means for the primary and secondary outcomes will be extracted according to pre-defined frequency of cannabis use categories. If both adjusted and unadjusted effect estimates are reported in a single study, both will be extracted and factors adjusted for will be recorded. For studies that present outcomes/frequency of use information at more than one time point, the most current data will be recorded. Any disagreements in data extraction between reviewers will be resolved through consensus discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required. A full list of variables to be extracted can be found in Additional File 4.

Data synthesis

In this review, relative risk (RR) will be used to measure the association between the frequency of cannabis use during pregnancy and adverse neonatal outcomes. Where hazard ratios (HR) are reported, they will be treated as the RR. Where odds ratios (OR) are reported, they will be transformed to RRs using the formula: $RR = OR/(1 - P_o) + (P_o \times OR)$, where $P_o$is the incidence of the outcome of interest [24]. In studies where no measure of risk is reported, the RRs will be calculated from the raw data where applicable.

The dose–response relationship between the frequency of cannabis use during pregnancy and adverse neonatal outcomes will be estimated using meta-analyses based on random-effects models. Two-stage dose–response multi-variate meta-analysis models will be used [25]. In the first stage, the dose–response associations between log RRs and pre-specified categories of cannabis use frequency will be analyzed within each included study using a linear model. In the second stage, effect estimates will be combined across studies using multi-variate random-effects models [25]. Sensitivity analyses will be performed using both quadratic and flexible non-linear models with restricted cubic splines [25, 26]. Further sensitivity analyses will be conducted to account for the effects of concomitant tobacco use, study design, and using both unadjusted and adjusted RRs where possible. The goodness of fit statistics (deviance, the coefficient of determination [R^2], and the Akaike information criterion [AIC]) will be used to select the best-fitting model [27]. The study-level variables included in this analysis will be the pre-specified categories of cannabis use frequency, the number of cases for each of the primary adverse neonatal outcomes of interest (LBW, SGA, PTB, NICU stay, mortality), and secondary outcomes (birth weight, gestational age), the natural logarithm of the RRs, and the standard error (SE) of the logarithm of the RRs [26]. All data analyses will be conducted in R using the Metafor and dosresmeta packages [28, 29].

The heterogeneity of results will be assessed using the I^2 statistic to describe the variation across studies due to true heterogeneity rather than chance [30]. The recommendations of the Cochrane Training Handbook will be used to assess thresholds for heterogeneity, where 0–40% indicates non-important or minimal heterogeneity, 30–60% may represent moderate heterogeneity, 50–90% may represent substantial heterogeneity, and 75–100% considerable heterogeneity [31]. A funnel plot will be generated in R software to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate.

Risk of bias assessments

Included studies will be critically appraised by two independent reviewers using standardized critical appraisal instruments from JBI for case–control, cohort, and cross-sectional studies [32]. Any disagreements between reviewers will be resolved through consensus discussion or by a third reviewer. The results of the critical appraisal will be reported in a table with the accompanying

narrative. All studies, regardless of their methodological quality, will undergo data extraction and inclusion in the dose–response meta-analyses. The quality of included studies will, however, be taken into consideration when interpreting the results of the meta-analysis. If possible, sensitivity analyses excluding studies deemed to be at high risk of bias will be conducted.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed and a Summary of Findings table will be created using GRADEpro GDT (2023) (McMaster University, ON, Canada) [33]. The Summary of Findings table will present the following information where appropriate: estimates of relative risk for frequency of use categories as compared to no use (reference) and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision, and risk of publication bias of the review results. The outcomes reported in the Summary of Findings table will be LBW, SGA, PTB, NICU admission, and mortality.

Discussion

The aim of this systematic review and meta-analysis is to determine whether risk thresholds exist for the relationship between cannabis use during pregnancy and adverse neonatal outcomes. This research is important as it has the potential to inform public health messaging surrounding the safety of cannabis use during pregnancy. Both pregnant individuals and clinicians have identified the need for further research on cannabis safety. Determining risk thresholds for frequency of use may help clinicians in counseling patients who use cannabis in pregnancy and aid pregnant individuals in reducing their risk, especially in situations where stopping cannabis use completely is not feasible.

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
AIC	Akaike information criterion
CADTH	Canadian Agency for Drugs and Technologies in Health
CCS	Canadian Cannabis Survey
CI	Confidence interval
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard ratio
JBI	Joanna Briggs Institute
LBW	Low birth weight
NICU	Neonatal intensive care unit
NIDA	National Institute on Drug Abuse
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PROSPERO	International Prospective Register for Systematic Reviews
PTB	Preterm birth
RR	Risk ratio
SE	Standard error
SGA	Small for gestational age
SOGC	Society of Obstetricians and Gynaecologists of Canada
THC	Delta-9-tetrahydrocannabinol

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02718-7.

Additional File 1. PRISMA-P Checklist.

Additional File 2. Search Strategy.

Additional File 3. Grey Literature Sources.

Additional File 4. Data Extraction Variables.

Acknowledgements

The authors would like to acknowledge Susanna Galbraith, librarian at McMaster University, for her assistance with search strategy development.

Authors' contributions

TR and BF designed the study. MUA, LK, FF, and SJ provided methodological advice. MB and RH provided clinical advice. TR wrote the first draft of the manuscript. LK and BF provided supervision. All authors critically reviewed the manuscript and approved the final version.

Funding

None.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding authors upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests. BF has held research grants and contracts in the areas of substance use, health, and policy from public funding and government organizations.

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Received: 28 June 2024 Accepted: 15 November 2024
Published online: 19 December 2024

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