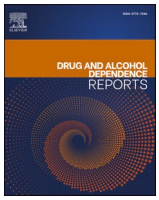
Drug and Alcohol Dependence Reports 13 (2024) 100282

Contents lists available at ScienceDirect

Drug and Alcohol Dependence Reports

journal homepage: www.elsevier.com/locate/dadr



Review

Prenatal cannabis exposure in the clinic and laboratory: What do we know and where do we need to go?

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HIGHLIGHTS

- Open questions remain regarding how cannabis is used in pregnancy.
- Answering these questions could improve laboratory studies.
- Ample evidence suggests potential harm to offspring neurodevelopment.
- Concerns must be addressed if pregnant people are to be dissuaded from use.
- Communication between researchers,health workers, and the public are needed.

ARTICLE INFO

Keywords:
Prenatal cannabis exposure
Offspring neurodevelopment
Lab-to-clinic translation

ABSTRACT

Coincident with the legalisation of cannabis in many nations, rates of cannabis use during pregnancy have increased. Like prior investigations on smoking and alcohol, understanding how prenatal cannabis exposure (PCE) impacts offspring outcomes across the lifespan will be critical for informing choices for pregnant people, clinicians, and policy makers alike. A thorough characterization of the life-long impacts is especially urgent for supporting all of these stakeholders in the decision-making process. While studies in humans bring forth the most direct information, it can be difficult to parse the impact of PCE from confounding variables. Laboratory studies in animal models can provide experimental designs that allow for causal inferences to be drawn, however there can be challenges in designing experiments with external validity in mirroring real-world exposure, as well as challenges translating results from the laboratory back to the clinic. In this literature review, we first highlight what is known about patterns of cannabis use during pregnancy. We then seek to lay out updates to the current understanding of the impact of PCE on offspring development informed by both human and nonhuman animal experiments. Finally we highlight opportunities for information exchange among the laboratory, clinic, and policy, identifying gaps to be filled by future research.

1. Introduction

Prenatal exposure to alcohol, nicotine, and other substances, like heroin, negatively affects foetal development, however, the consequences of prenatal cannabis exposure (PCE) are understudied. Despite evidence that PCE may impact the cognitive, behavioral, and neurological development of offspring (Nashed et al., 2021), there are also recent studies that dispute the clinical significance of such findings (Torres et al., 2020). The lack of clear consensus among scientific studies leaves health professionals cautioning patients against cannabis use during pregnancy without sufficient evidence to properly advise them on the specific impact of use.

Even as medical and scientific professionals remain cautious, many lay resources, such as cannabis dispensaries, encourage cannabis use as a means of managing nausea and vomiting associated with pregnancy (Dickson et al., 2018). Mixed messaging can create confusion for pregnant people weighing the potential benefits of using cannabis but concerned for the health of their foetus (Bayrampour et al., 2019). Thus, to

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https://doi.org/10.1016/j.dadr.2024.100282
Received 4 June 2024; Received in revised form 15 August 2024; Accepted 9 September 2024
Available online 18 September 2024

allow pregnant people to make well-informed decisions about using, decreasing, or abstaining from cannabis, and to allow health professionals to anticipate and mitigate any potential harm from exposure, it is critical for researchers to better establish the impact of PCE on the developing brain and the mechanism(s) by which these alterations emerge.

Cannabis is considered one of the most widely used drugs, even during pregnancy (Gray et al., 2010; Mark et al., 2016; Wendell, 2013). One contributing factor to high use rates is that cannabis is generally considered to be a "safe drug" in terms of its potential for adverse health effects and addictive properties (Bannigan et al., 2022). While cannabis comprises a host of compounds, δ-9-tetrahydrocannabinol (THC) is the main psychoactive component, thought to be responsible for many of the psychiatric alterations following chronic, adolescent exposure (Luzi et al., 2008). As the content of THC in widely-accessible cannabis has been increasing in recent decades, the effect of exposure to this compound in particular has been the focus of much of the PCE, or, in this case, prenatal THC exposure (PTE), research in laboratory settings. Nevertheless, there are existing gaps in the human literature regarding methods of use, dosages, and preparations of cannabis potentially limiting the utility of existing PTE animal models when generalising to humans.

Because research on the effects of PCE is still relatively nascent, there is great potential to identify such gaps in the communication between researchers investigating the topic across humans and model organisms and with different methodologies to ensure the models that reflect human use are used and to promote the efficient and accurate translation of neuroscientific findings back to the clinic. To shed light on this topic, this literature review seeks to review three main topics: What do we know about 1) patterns of cannabis use during pregnancy and 2) the impact on the offspring, and 3) how does this knowledge inform the exchange between the laboratory, clinic, and policy? While not exhaustive, included studies represent a comprehensive literature review from experts involved in PCE research from both the laboratory (L. C. and M.M.C) and clinic/policy (K.A.D.C and J.I.N.M) perspectives.

2. Patterns of use

2.1. Rates of cannabis use during pregnancy

The prevalence of cannabis use during pregnancy varies significantly across studies, with reports from survey data ranging from 0.24 % to 35 % (Metz and Stickrath, 2015; Nashed et al., 2020; Singh et al., 2020). The lowest rate is from a retrospective analysis of hospital case files in the United Kingdom identified with self-report between 2003 and 2007, 17,856 pregnancies (Goel et al., 2011). The highest rate is from a relatively small sample (~300) in Baltimore, United States of America (USA) assessed through an anonymous survey between 2015 and 2016 (Mark et al., 2017). Another source of discrepancies among prevalence estimates is the methodologies used to trace use during pregnancy. A minority of studies supplement self-report data with biological assays such as maternal saliva (Gray et al., 2010), urine (Hurd et al., 2005), and neonatal meconium analyses (Gray et al., 2010; Hurd et al., 2005). Assessing prevalence of use with a combination of self-report, maternal oral samples, and meconium analyses in a population of 86 pregnant people in Buffalo, USA revealed 46.5 % of participants used cannabis at some point during pregnancy (Gray et al., 2010), which exceeds the 35 % reported from surveys alone mentioned above (Mark et al., 2017). Notably, as the legalisation of non-medical cannabis use increases across countries, members of the medical community anticipate increased rates of use, including in pregnant individuals (Everson et al., 2019; Metz and Stickrath, 2015).

Several studies have specifically examined the differences in prevalence estimates based on methodology, finding self-report estimates are lower than those identified with positive urine toxicology in a California health care system dataset including a large sample (279,457) of pregnant people (Young-Wolff et al., 2017). Of the pregnant people who used cannabis, 15.9 % were positive on self-report only (potentially indicative of false-negatives in urine toxicology), 54.9 % were positive in urine toxicology only, and 29.2 % were positive on both tests (Young-Wolff et al., 2017). In addition to the methodological concerns, public health considerations must be taken into account as well, with social factors contributing to differences in rates of cannabis use and rates of reporting. In some places, laws have been considered to regard substance use during pregnancy as felonious "child abuse" or endangerment, creating a culture of fear among pregnant people who live there (Angelotta and Appelbaum, 2017 Paris et al., 2020; Wolfson et al., 2021). Even where cannabis is legal, stigma around substance use during pregnancy impacts participants' and patients' decisions to disclose (Weber et al., 2021). This interacts with other sociodemographic factors, with the highest risk of stigma for marginalised people, such as people of colour (Paris et al., 2020; Shirley-Beavan et al., 2020; Weber et al., 2021; Wolfson et al., 2021).

Legalisation status at the time and place of assessment should be taken into account as well. The work by Young-Wolff and colleagues also provides evidence that rates of cannabis use during pregnancy have been increasing. Between 2009 and 2016, in California, rates of cannabis use during pregnancy (as assessed by a combination of urine toxicology and self-report) increased from ~4 % to ~7.5 % (Young-Wolff et al., 2017). Another study by the same group investigated trends in the use of cannabis only, as opposed to polydrug use, finding that between 2009 and 2018, rates of cannabis use alone during pregnancy increased from 2.39 % to 6.3 % (Young-Wolff et al., 2022). This represented a 1.11 relative rate of increase, whereas the rates of polydrug use increased at a slower rate, suggesting that pregnant people are preferentially using cannabis (Young-Wolff et al., 2022). These data provide evidence that cannabis use during pregnancy is increasing. It is still an open question how legislation will affect rates of cannabis use during pregnancy. One recent study from British Columbia, Canada, found that rates of cannabis use *preconception* did increase following legalisation, however in this study there was no significant increase in cannabis use *during pregnancy* following legalisation (Bayrampour and Asim, 2021). Of note, evidence suggests increasing rates of cannabis use disorders (CUDs) in recent years follow trends of cannabis legalisation; of the seven U.S. states with the highest rates of CUDs, five states recently legalised recreational consumption, potentially suggesting an association between legalisation and emergence of CUDs (Martínez et al., 2023; Meinhofer et al., 2022). Further data must be acquired to examine the impact of legalisation in different regions and countries, with specific attention paid to potential biases in the samples (e.g. socio-economic status, levels of formal education and race/ethnicity).

2.2. Why do people use cannabis during pregnancy?

Understanding *why* people use cannabis during pregnancy is key to reducing PCE. While many popular and medical sources caution pregnant people against drug use, including cannabis, there are several reasons why pregnant people may initiate or continue use. Some pregnant people suffer from a CUD, or comorbid substance use disorders (Meinhofer et al., 2022). Of 21 million hospitalizations of pregnant people between 2010 and 2018 from 35 U.S. states, 1.19 % involved a CUD. This small percentage actually represents ~250,000 pregnancies, and the proportion of hospitalizations of pregnant people involving a CUD increased from 0.008 in 2010–0.02 in 2018 (Meinhofer et al., 2022).

Some pregnant people use cannabis to help manage the symptoms associated with morning sickness (Westfall et al., 2006). Morning sickness generally occurs during the first trimester of pregnancy (Einarson et al., 2013). A majority of pregnant people experience symptoms of morning sickness ranging from mild to extreme nausea and vomiting (Westfall et al., 2006). One study surveying 79 participants found 65 % (51) of participants reported using cannabis, with seven participants

using it only therapeutically, 14 using it only recreationally, and the other 30 using it for both (Westfall et al., 2006). Of the respondents who used cannabis as a treatment for morning sickness, 92 % considered it extremely effective (Westfall et al., 2006). Data from a recent publication supports these findings, with 35 of 103 participants indicating they had previously used cannabis during pregnancy, and 89 % of these respondents indicating treatment for morning sickness as the primary reason for use (Daniels et al., 2022).

Pregnant people also report using cannabis to manage their mood. A Toronto-based focus group from a program for pregnant and parenting mothers with substance use disorders reports that participants discussed external stressors (such as financial and social stressors and concern about withdrawal from substances), internal stressors (guilt over substance use, leading to a vicious cycle), substance use as a coping strategy, and a misunderstanding of the potential consequences for their children (Latuskie et al., 2019; Paris et al., 2020; Shirley-Beavan et al., 2020). Some pregnant people also believe cannabis is a safer alternative to pharmaceuticals that may be prescribed or recommended to treat their mood-disorders and morning sickness (Chang et al., 2019).

Finally, some pregnant people continue cannabis use recreationally, sometimes because they are not yet aware of their pregnancy or doubt the long-term harm. Increased legalisation may give the perception that cannabis can be consumed without consequences for the developing foetus, increasing the perceived acceptability of use during pregnancy (LaSalle, 2021). In one study from 2013 to 2017, the majority of pregnant people reporting past-month cannabis use were classified as using for non-medicinal purposes (Volkow et al., 2019) based on their answer to the question "if any cannabis use was recommended by health care professionals" (Volkow et al., 2019). A major limitation of this survey question is the resulting characterization of self-medication for morning sickness as recreational use.

2.3. When do people use cannabis during pregnancy?

Recreational use prior to knowledge of pregnancy, and the use of cannabis to alleviate the symptoms of morning sickness may contribute to the fact that the highest levels of use occur early in pregnancy. Accordingly, there is ample evidence that cannabis use during pregnancy is most frequent during the first trimester, reduced in the second, and further reduced in the third (Ko et al., 2015; Moore et al., 2010; Volkow et al., 2019). This pattern is characterised in one early study (The Maternal Health Practices and Child Development Study [MHPCD]) with 763 low-income parents from Pittsburgh, Pennsylvania. Here authors assessed cannabis use with an interview at the end of each trimester of pregnancy, finding 41.7 % of their sample consumed cannabis in the first trimester, 23.2 % continued to the second trimester, and 19.1 % continued to the third (Goldschmidt et al., 2004).

Two other critical periods of cannabis use necessitating research include preconception and postpartum, during lactation. A recent study identified increased cannabis use both preconception and postnatally, although not in pregnancy, following cannabis legalisation by comparing surveys of 73,551 pregnant people in two U.S. states that had legalised cannabis (Maine and Alaska) and two states that had not (Vermont and New Hampshire) (Skelton et al., 2021). While it is possible that rates of cannabis use during pregnancy were underestimated due to concern over stigma, these data suggest rates during reproductive years and periods may be increasing, and it is important to design studies examining whether cannabis use preconception could impact foetal development. A relatively recent review highlights the importance of understanding the impact of preconception cannabis use on fertility and ovulation, and the impact of both preconception and postpartum use on offspring development (Corsi et al., 2021).

2.4. How much and how do people use cannabis during pregnancy?

Dosage is even more challenging to assess in pregnant populations than frequency of use. The MHPCD study characterised use as "light", meaning less than one "joint" (cannabis cigarette) per day, or "heavy" meaning one or more joints per day (Goldschmidt et al., 2004). While there is missing data for this variable in the studies, "light" usage declined from 27.4 % of the total sample in the first trimester to 17.9 % in the second trimester and 14.2 % in the third. Meanwhile, "heavy" use declined from 14.4 % in the first trimester to 5.3 % in the second and 5 % in the third. Importantly, the authors collected no information about the size of joints or potency of the cannabis consumed. Of note, this study employed a longitudinal design with up to 10 years follow up, and most of the data were acquired in the 1990's when cannabis was still illegal and heavily stigmatised. Cannabis would have been purchased from dealers without information (or with unreliable information) about the THC and cannabidiol (CBD) content of cannabis, which alters the balance of psychoactive and non-psychoactive constituents. As a brief overview, psychoactive THC induces a host of motor and psychological effects unobserved after exposure to non-psychoactive CBD. These differential effects make the THC:CBD balance important when assessing exposure, rather than just a characterization of "light" or "heavy", an outcome that has been neglected to date.

Additionally, the mean potency of cannabis (THC content) is estimated to have tripled from ~4 % in 1995 to ~12 % in 2014 (ElSohly et al., 2016), and almost ~14 % in 2019 (ElSohly et al., 2021). The studies reporting this increase analysed samples of cannabis seized by the USA's Drug Enforcement Agency, reflecting illicit cannabis and reported a decline in the content of CBD. The preference for this increased THC:CBD ratio is reflected in legal cannabis on the market as well, where it is common to see preparations with high THC and almost no CBD. For example, THC levels in cannabis advertised online in the USA, contained on average 19.2 % ±6.2 for medical and 21.5 % ±6.0 for recreationally used cannabis (Cash et al., 2020). Unless pregnant participants are actively recording and reporting the cannabis they purchase and consume, it is very challenging for studies to assess dosage. As a result, like in the MHPCD study (Goldschmidt et al., 2004), researchers often use frequency of use as a proxy for a dosing variable, such as in the Generation R (Gen R) study acquired in Rotterdam, the Netherlands between 2002 and 2006 (El Marroun et al., 2009). In this study the participants reported whether cannabis use was daily, weekly, or monthly. In addition to the MHPCD study and the Gen R study, an older study published in 1980, the Ottawa Prenatal Prospective Study (OPPS), reported participants as non-users, irregular users (on average no more than one joint per week), moderate users (on average 2–5 joints per week), and heavy users (more than 5 joints per week) (Fried, 1980). With the legalisation of cannabis and increased access to information regarding potency of preparations, future studies may be able to more accurately assess dosage during pregnancy to better characterise long-term impact on offspring.

A final variable impacting severity of foetal exposure is the method of use. It has been demonstrated that THC can cross the placenta into the foetal compartment (Baglot et al., 2022). Route of administration can alter circulating metabolites of cannabinoids in the maternal blood and the levels that reach the foetus. In humans, much of the available information regarding the impact of routes of administration on the pharmacokinetics of cannabis involves oral or smoked exposure, as these methods are most common. Following inhalation, THC levels in blood serum peak rapidly in a matter of minutes, however bioavailability of THC varies drastically based on inhalation technique, inhalation depth, and frequency of use (McGilveray, 2005). THC is then rapidly metabolised into a psychoactive metabolite, 11-hydroxy-THC, peaking ~15 minutes after THC peaks (McGilveray, 2005). Over the course of the subsequent 1.5–2.5 hours, it is then converted to the inactive 11-nor-9-carboxy-THC, which is excreted in urine and faeces. Following oral exposure, THC is absorbed slowly over the course of hours, and unreliably, depending on individuals' metabolisms (McGilveray, 2005). Peak THC values following oral exposure are lower when compared with efficient smoking, however rates of 11-hydroxy-THC (the psychoactive

metabolite) are relatively higher and longer-lasting than after smoking (McGilveray, 2005).

The MHPCD, Gen R, and OPPS studies all characterise use in joints, potentially overlooking other routes of administration such as edibles, vaping, nasal spray, or topical administration. Historically, smoking cannabis through joints, blunts, pipes, or water pipes (bongs), has been the most popular route of administration and remains so today, however the other methods are also gaining popularity, and may be over-represented in pregnant people who want to avoid smoking (Spindle et al., 2019). Vaporisers heat cannabis or extracts to sub-combustion temperatures aerosolizing the product for inhalation, and have become increasingly common in part because of a perceived reduction in the health risk (Spindle et al., 2019). Edibles are of special interest to the pregnancy literature as these preparations are more commonly used among women, older adults, and people who use cannabis for medicinal purposes (Spindle et al., 2019). Again, there is a perception of reduced health risk, however edibles are often inaccurate as to reports of the potency of cannabis (Spindle et al., 2019). Route of administration is important not only to accurately assess dosing of various cannabis metabolites, but also when translating to and from animal models.

3. Modelling PCE in nonhuman animals

Modelling the effects of prenatal exposure to cannabinoids in animals presents opportunities to understand what effects there may be, however there are certain limitations to such approaches that must be acknowledged as well. One decision researchers must make is which route of administration to employ. While regimens of injecting cannabinoids are common in rodent models, they lack external validity, as injecting cannabis is not a common method of use in humans (McLaughlin, 2018). This discrepancy between lab and real-world use is especially important as the pharmacokinetics and dynamics of cannabinoid metabolism differ when they are injected subcutaneously, intraperitoneally, or inhaled (Baglot et al., 2021).

The choice of administration route can also affect the compounds used. While vaporisation chambers can make use of cannabis comprising naturalistic combinations of cannabinoids and terpenes, injected or oral preparations tend to use a single compound such as pure THC or pure CBD (McLaughlin, 2018). This does allow for specificity of associating observed effects with a compound, however ignores possible entourage effects which have been well-documented. For example, CBD inhibiting THC binding in balanced preparations of these compounds (Laprairie et al., 2016). Possibly because of strict regulations of cannabinoids through much of research history, potent synthetic cannabinoids, such as WIN 55,212–2 (WIN) have been favored in research over cannabis preparations (McLaughlin, 2018), however these synthetic cannabinoids differ in functional selectivity when compared with phytocannabinoids and endocannabinoids (Laprairie et al., 2014).

Depending on what compound is used, dosing may differ drastically, or be challenging to estimate in comparison with human use. As discussed later in more detail, it is difficult to obtain accurate information on how much cannabis people, especially pregnant people, are using. Nevertheless, lab experiments using pure THC tend to use high dosages in comparison to known human exposure (McLaughlin, 2018).

Finally, animal models of gestation must account for differences in the gestational timelines between humans and nonhuman animals. Rats and mice are altricial, giving birth at what corresponds roughly to the end of the second trimester in humans (Gumusoglu and Stevens, 2019). Much of the development that occurs within the protected and isolated womb in humans occurs postnatally in these species, posing challenges to interpreting developmental effects. Nevertheless, animal models do allow researchers to differentiate the effects of PCE and the milieu of social factors that complicate quasi-experimental studies in humans, providing a valuable, if imperfect, tool to research the effects.

4. Effects on development

Several reviews have been published on the impact of PCE on humans and nonhuman animals (Nashed et al., 2020), sex-differences in prenatal and adolescent cannabis exposure (Tirado-Muñoz et al., 2020), and the impact of PCE on white matter in the brain (Baranger, 2024). Here, we provide an overview of the evidence for outcomes following PCE, updating these reviews and focusing on the interface between the lab and clinic. A summary of findings following PCE in humans can be seen in Supplementary Table 1, and in nonhuman animals, Supplementary Table 2.

4.1. Gross physiology and obstetric complications

Cannabis has no documented teratogenic effects (Orsolini et al., 2017). Additionally, despite examinations, there is no evidence for increased risk of foetal mortality or perinatal death with moderate prenatal exposure to cannabis (Fergusson et al., 2002). A recent meta-analysis found that cannabis use during pregnancy was associated with increased probability of preterm birth, an example of obstetric complications that may follow gestational cannabis use (Duko et al., 2022). Mouse models with inactive cannabinoid(CB)-1 (but not CB2) receptors reportedly demonstrate early onset of labour (GD 19.3–19.6 instead of GD 20) (Wang et al., 2008). Few other studies report examining early onset of labour.

Gross morphological and physiological metrics are amongst the most ubiquitous outcome measures recorded in humans and experimental animals following prenatal exposure to cannabinoids. In neonates, one of the major questions is whether cannabis exposure leads to low birth weight (LBW) or foetal growth restriction (FGR). LBW has been associated with prenatal exposure to nicotine (Ko et al., 2014), but the literature is mixed on the association of PCE and LBW. One factor could be the difficulty in separating prenatal polydrug exposure (Nashed et al., 2021). A number of studies investigate potential correlations between cannabis use during pregnancy and LBW (Gunn et al., 2016) or FGR (El Marroun et al., 2009). While some studies report LBW and FGR (Gray et al., 2010), others find no difference (Fergusson et al., 2002), and yet others report increased birth weight following prenatal cannabis exposure (Day et al., 1991).

Animal studies control for factors like polydrug use, inaccurate self-report, and socioeconomic status, but the literature does not lend a clear answer to the question of whether PCE impacts weight at or before birth. Indeed, results paint as variable a picture as human studies, with some papers reporting subtle FGR or LBW following inhalation (Benevenuto et al., 2017; Roeder et al., 2024) and injections (Gillies et al., 2020; Natale et al., 2020), and others reporting no difference following inhalation (Breit et al., 2020) and injections (Newsom and Kelly, 2008; Silva et al., 2012). Some papers that report initial LBW also report characteristic catch-up growth by postnatal day (PND) 21 (Natale et al., 2020). It has been suggested that variability in results could be due, in part, to route of administration, with LBW more often reported in studies administering cannabinoids with intraperitoneal (IP) injection, null results reported after oral administration, and mixed results following vapour exposure (Nashed et al., 2020). Dosage and species must also be considered, as well as age of assessment, as some studies examine foetuses (Chang et al., 2017; Natale et al., 2020) and others birth weight (Gillies et al., 2020; Natale et al., 2020). Longitudinal studies are particularly valuable as they would allow researchers to assess how weight might change over the course of the lifespan. In humans, high quality data has recently been made available, but such studies still struggle to delineate THC, CBD, or the ratio between them (Nashed et al., 2020).

4.2. Behavioural and clinical outcomes

Behavioural and cognitive outcomes have been a focus of PCE in the

human literature. Measures related to behaviour and cognition have been examined in children as young as 18 months through adolescents. Overall, findings are quite subtle and are somewhat varied. In a large study relying on self-reported PCE and child developmental delay, delays were observed in social communication at 12 months, but statistical differences went away when controlling for multiple comparisons (Watts et al., 2024). In 18 month old toddlers, there is evidence for increased risk of ASD, however the same study found no increased risk for other behavioural disorders, such as ADHD at 4 years of age (Corsi et al., 2020). PCE is also associated with anxiety, hyperactivity, and aggression (in girls) (Rompala et al., 2021). Consistent with anxiety, the authors found increased cortisol levels in the hair of the young children included in the experiment (Rompala et al., 2021). Exposure to cannabis after maternal knowledge of pregnancy was associated with adverse outcomes in 9–11 year old children, including psychotic-like experiences, externalising, attention, thought, and social problems (Paul et al., 2021). While the outcomes are examined at an early age for psychiatric disorders to first appear, they could indicate a risk for disorders to emerge during adolescence. Ten-year-olds exposed to one or more joints per day in the first trimester of pregnancy show worse reading and spelling scores, and school teacher assessments (Goldschmidt et al., 2004). Second trimester exposure was also associated with reduced reading comprehension and academic underachievement (Goldschmidt et al., 2004). At age 14, prenatal cannabis exposure was associated with increased frequency and earlier age of onset of cannabis consumption (Day et al., 2006). There is some evidence for a catch-up effect and normalisation in cognition or behaviour by adolescence. Despite early changes in academic performance, in adolescence a study found no differences in performance on memory, attention, or impulse control tasks (Smith et al., 2006).

In terms of animal models, assessments for anxiety-like behaviours, motor behaviour, and sensorimotor gating have been conducted from neonates to adulthood. In pups, anxiety-like behaviour can be examined by recording ultrasonic vocalisations (USVs) when pups are separated from their dams. One study tested male offspring and found 2.5 and 5 mg/kg of THC administered orally at GD 15 to PND 9 in rats increased the number of USVs pups made, while 5 mg/kg alone reduced social play at PND 35 and decreased time in the open arm of the elevated plus maze at PND 80 (adulthood), all indicating anxiety-like phenotypes (Trezza et al., 2008). Yet, another study found reductions of USVs in rat pups at PND 10 exposed to lower levels (0.5 mg/kg) of the cannabinoid-receptor agonist, WIN, administered by injection GD 5–20 (Antonelli et al., 2005). The opposite directions of their findings could be related to differences in the methodology, associated either with alterations in the drug administered (THC or WIN), the differing dosages, that cannot be directly compared across drugs, or the different ages of administration (into postnatal life in the first study). In adolescence, one study examined the impact of oral exposure to THC (5 mg/kg) throughout pregnancy on a novelty suppressed feeding task, finding increased latency to approach food (representative of anxiety-like behaviour) in males, but not females (Lallai et al., 2022).

Anxiety is commonly comorbid with other mood and psychiatric disorders such as depression (Pollack, 2005), bipolar disorder (Pavlova et al., 2015), psychosis (Dernovsek and Sprah, 2009), and ASD (Zaboski and Storch, 2018), and there is evidence in humans and animals to highlight the importance of considering levels of anxiety as an outcome of interest. Adult spontaneous locomotion is frequently tested in offspring prenatally exposed to cannabinoids. While increased spontaneous locomotion can be interpreted as a marker of increased exploration, and immobility is seen as another marker of anxiety or fear, many factors can impact locomotion, including sensory processes, environmental novelty, hunger/thirst, and time of day (Kelley, 1993). Generally, increased spontaneous locomotion is still interpreted as exploratory, however the translation of "activity" to humans is nonspecific (Crusio, 2001), as it could implicate cognitive, motor, or sensory neural circuits and processes relating to fear, need, or "curiosity". Experiments have examined the impact of a range from 0.1 mg/kg to 5 mg/kg exposure to THC during the pre- and perinatal periods (GD5 to PND24) (Moreno et al., 2005; Navarro et al., 1994; Rubio et al., 1995). The results are often sex-specific, with some studies finding prenatal oral exposure to 5 mg/kg THC increased locomotion in females only (Rubio et al., 1995), and others describing a timing effect, with increased locomotion in females at PND 70, but increased locomotion in males only at PND 20 following oral PTE exposure (Navarro et al., 1994). While THC injected at doses of 0.5 or 2 mg/kg decreases locomotion in males, in females there was evidence of a dose-effect, with levels of 0.1 or 0.5 mg/kg THC associated with decreased locomotion, but 2 mg/kg associated with increased locomotion (Moreno et al., 2005). Another study examining dosage effects exposed pups to vaporised THC at either 10 mg/kg or 40 mg/kg doses, finding increased distance travelled in the OFT following exposure to either dose until adolescence (~PND 37) (Roeder et al., 2024). The mixed results necessitate further investigation of the impact of prenatal cannabis exposure on locomotion, however, they further highlight sex-specific effects and the importance of including female subjects, which several of the anxiety studies did not include (Antonelli et al., 2005; Trezza et al., 2008).

Assessments of sensorimotor gating with prepulse inhibition (PPI) provide one of the few tests that can be implemented in humans. Impairments in sensorimotor gating are relevant trans-diagnostically, and have been observed in several neuropsychiatric disorders including schizophrenia, obsessive compulsive disorder, ASD, Tourette syndrome, and Huntington's disease (Swerdlow et al., 2016). Prenatal exposure to an injected cannabinoid-receptor agonist, WIN, did not affect sensorimotor gating, as measured with PPI, at PND 40, 60, or 80 in rats exposed from GD 5–20 to either a low dose (0.5 mg/kg) or a high dose (1 mg/kg) (Bortolato et al., 2006). Rat pups exposed to 5 mg/kg THC orally throughout the course of pregnancy displayed sex-differential effects, with males only exhibiting deficits in sensorimotor gating (Lallai et al., 2022).

Short-term memory has been explored following prenatal THC exposure. In both sexes, prenatal exposure to THC (oral exposure throughout pregnancy, 5 mg/kg) impaired short-term memory in rats (Drazanova et al., 2019; Lallai et al., 2022). Impaired cognition could relate to the difficulty in school performance observed in humans, however further research would be required to confirm alterations in short-term memory and other aspects of cognition.

Finally, recent studies have investigated the potential role of PTE in alterations to circadian rhythms and metabolism. Metabolic consequences of PCE have been reviewed, highlighting the impact of PCE on foetal growth by altering placental perfusion (Lee and Hardy, 2021). In turn PCE and FGR has also been associated with alterations in lipid and glucose metabolism (Lee and Hardy, 2021). In one experiment, rats were exposed to THC via vaporisation (100 mg/ml) across entire gestation, assessed for glucose metabolism, adiposity, and feeding behaviour as adults, and then placed on high-fat or low-fat diets for four months, after which they were re-assessed (Hume et al., 2023). PCE was associated with reduced pup weight at PND 22 and less weight gain regardless of diet. The impact on glucose metabolism and feeding behaviour differed by diet and sex (Hume et al., 2023). In humans there is also evidence for the impact of PCE on adiposity and metabolism in children around 4.7 years of age (Moore et al., 2022). Cannabis exposure was assessed with maternal urine samples, and 15 % were considered positive for cannabinoids. Fetal exposure was associated with increased fat mass and adiposity, as well as higher glucose levels (Moore et al., 2022). The interaction between circadian rhythm and metabolism was studied as well: rats were exposed prenatally to either a low (10 mg/kg) or high (40 mg/kg) dosage of THC via vaporisation and examined for 24-hour locomotor activity at 4 and 7 weeks of age, as well as weight gain after being placed on a low or high-fat diet at weaning (Roeder et al., 2024). The authors found there was no significant difference in food intake or weight gain for the THC pups, however rats exposed to the

low-dose of THC did show reduced dark-cycle activity (when they are usually awake) (Roeder et al., 2024).

4.3. Neuroanatomical, functional, and molecular outcomes

Neuroanatomy *in vivo* can be examined non-invasively with magnetic resonance imaging (MRI) and *ex vivo* with cellular and molecular assays such as immunohistochemistry (IHC) and RNA-sequencing (RNAseq). While the scale of the assessments differ with MRI examining gross morphometry and IHC examining cellular composition, the techniques are complementary, as they both provide information about the structure of the brain and can be sensitive to insults, both genetic and environmental.

In children aged 6–8, increased cortical thickness in frontal regions was observed after prenatal exposure to cannabis (El Marroun et al., 2016). Another study reports reduced cortical grey matter in children 10–14 years of age prenatally exposed to cannabis, however these results must be considered carefully: the sample size was small and children were scanned in a polydrug study and only three of the eight participants were exposed to cannabis alone (Rivkin et al., 2008). More recent studies have specifically investigated the impact of prenatal exposure to cannabis on white matter. Diffusion MRI was used in a large sample of children (11,530; 690 with PCE), average age ~10, from the ABCD cohort to examine the relationship between PCE, defined as a binary variable representing positive retrospective report from the caregiver, and white matter tracts (Evanski et al., 2024). Fractional anisotropy (FA) was found to be reduced in the bilateral fornix, potentially indicative of reduced white-matter integrity (Evanski et al., 2024). These findings highlight the benefit of including neuroimaging in assessments of the impact of PCE.

In nonhuman animals, the results are also scarce. One study used Arterial Spin Labelling (ASL), an MRI technique that noninvasively magnetically tags blood flowing into the brain to trace the path of cerebral blood flow. This study found perinatal exposure to THC orally in rats (5 mg/kg, GD 13 - PND 9) found no difference in ventricle size or regional blood perfusion when examining the Circle of Willis, hippocampus, sensorimotor cortex, PFC, or caudate putamen (Drazanova et al., 2019). Importantly, with the authors' implementation of the technique, they pre-selected regions of interest from two coronal slices in the brain, limiting their sensitivity to whole-brain or volumetric changes.

Human brain function following prenatal cannabis exposure garnered more attention in early MRI work. The OPPS dataset included several batteries of cognitive tests during task-based fMRI paradigms, including visuospatial and letter 2-back tests for working memory, the go/no-go task for response inhibition, and a counting Stroop task for cognitive Interference (Bush et al., 2006; Smith et al., 2016)]. While the participants exposed prenatally to cannabis did not differ from the controls in performance on the tasks, there were significant changes in Blood Oxygen Level Dependent (BOLD) activity during tasks, such that cannabis-exposed adolescents required greater activation in posterior areas than controls across tasks (Smith et al., 2006, 2016).

5. How results affect lab-clinic-policy exchange

5.1. Addressing the motivation for use is critical to reduce use during pregnancy

One critical finding emerging from studies that investigate the motivation of cannabis use in pregnant people is that many take cannabis for therapeutic reasons and because they think it is more natural and therefore safer than prescription pills (Barbosa-Leiker et al., 2022). For example, pregnant people suffering from anxiety have reported concern about pharmacological interventions and low willingness to take prescription drugs during pregnancy (Lemon et al., 2020). These concerns need to be carefully considered, not dismissed as ignorance, especially as there are some studies of prenatal exposure to pharmacotherapies such as serotonin reuptake inhibitors (SRI)s on foetal development that suggest adverse foetal and neonatal events (Creeley and Denton, 2019). Much of this literature, however, suffers from similar issues as the PCE literature, such that few studies follow the early life of prenatally exposed children longitudinally. Further research is certainly necessary to establish comprehensive guidelines for the prescription of pharmaceuticals during gestation and the proper communication of potential risks to pregnant patients. It must also be communicated that just because cannabis is a natural substance does not mean it is inherently safer than the alternatives. Simultaneously, the needs of the pregnant person cannot be disregarded either. First of all, the pregnant person is a patient deserving of state-of-the-art care, necessitating effective strategies to ameliorate the symptoms of mental health disorders such as anxiety and depression. Second, maternal anxiety in-and-of-itself has been demonstrated to impact pregnancy and child development (Correia and Linhares, 2007). There is some evidence that cognitive behavioural therapy and interpersonal psychotherapy may afford significant benefit to pregnant patients with psychiatric disorders and may be as effective as SRIs, without negatively impacting child development, however further research is required (Nillni et al., 2018). Pairing such psychotherapies with information on potential consequences of prenatal cannabis exposure is critical for pregnant people who are unwilling to treat their symptoms with pharmaceuticals while pregnant.

5.2. Information laboratory scientists need from the clinic to design more generalizable experiments

There are several key pieces of information from the clinic that could assist laboratory scientists in designing experiments that will better reflect cannabis use during pregnancy. For one, as summarised previously, many studies in humans use frequency of use as a proxy for dosages. This makes it difficult to accurately model in the laboratory, because someone using a low THC-cannabis several times a week compared to someone using a high THC-cannabis once a week will have a very different profile of exposure. There are difficulties in assessing dosages of exposure, with biological samples susceptible to confounders such as frequency of use, and self-report often being inaccurate. One study received donated joints from recreational cannabis users and analysed the THC content in them (Casajuana Kögel et al., 2017). A similar methodology of collecting donated joints could be employed in a pregnant population (where cannabis is legal) to better estimate exposed dosages. Researchers have also recently been calling for "Standard THC units", much as alcohol units exist irrespective of alcohol preparation, in order to overcome challenges of assessing dosage of exposure based on route of administration (Freeman and Lorenzetti, 2020). This could improve model design in the laboratory, allowing for more relevant studies and easier back-translation of results. Additional information, such as the most common routes of administration for pregnant people are also important, given the differences in THC metabolism between different routes of administration.

5.3. Information needs to be translated from the laboratory to clinicians to assist in their approach to patients

While not unique to the study of PCE, the need for strengthened communication among researchers, medical professionals, policy makers, and the public is critical in this field. It is a benefit for all that cannabis legalisation may increase the quality of available data, government oversight, and access to care for users, however it is worth noting that preliminary data from regions with legalised cannabis also suggest an increase in use among adults (but potentially not youth), reduction of the price, and increase in potency, which may increase prenatal exposure to THC (Hall and Lynskey, 2020). There is significant evidence that pregnant people want more concrete information about

the potential harms of cannabis use during pregnancy (Young-Wolff et al., 2020). While national guidelines in the United States and Canada suggest pregnant people should refrain from cannabis use, both health-care providers and budtenders (cannabis retailers) are consulted for information regarding perinatal cannabis use, and there is evidence that they perceive an insufficient body of knowledge and training to provide counselling (Barbosa-Leiker et al., 2022). One way in which governments attempt to warn users is with health labels on products. For example, in Canada, there are 8 different warnings that must be rotated on products, including one advising against potentially harmful effects if consumed during pregnancy (Health Canada, n.d.). Evidence from regular cannabis users suggest they do take note of these health labels (Goodman and Hammond, 2021). In the United States, however, such marketing is handled state-by-state, without general requirements, and inconsistent labelling can reduce the efficacy of warnings and information (Kruger et al., 2022).

Together these data highlight the need for increased lines of communication between laboratory studies, where evidence about the potential harms of PTE are accumulating, and health care providers, budtenders, and the general public. While care must be taken to ensure results are not over-generalized and are properly contextualised, as with any science communication, there are several ways that connections could be forged among these groups. Lay abstracts could be published alongside papers, openly accessible to the public. Increased contact could also be established between laboratory researchers and health care providers/budtenders in the form of information sessions or discussion groups. Finally, public forums and conferences could be arranged to increase the accessibility of scientists to the general public.

The intention of this review is not to downplay the challenges of appropriately translating between the laboratory and clinic or communicating to the general public and lawmakers. There are significant limitations to nonhuman animal studies, as discussed above, that impact how directly results can be translated. Additionally, popular science communication often lacks the nuance necessary to accurately represent the findings of academic articles, with potential disconnection between the creators' intent and the audience's reception (Szu et al., 2017). The topic of nuance is especially salient when information is transmitted predominantly online where simple, emotionally-charged messages garner the most attention (Taddicken and Reif, 2020). A balance must be struck on making accurate, current, and nuanced information as accessible as possible.

6. Conclusions

Lines of evidence from both human studies and laboratory experiments in nonhuman animals increasingly converge to characterise the impact of PCE on offspring development, highlighting this field as critical for further investigation. This topic is especially urgent as current data from pregnant people suggest use of cannabis during pregnancy is increasing, coincident with rising rates of THC in cannabis preparations. Whether pregnant people are actually using high THC cannabis remains an open question which would aid the generalizability of laboratory studies. Overall, increased lines of communication between cross-disciplinary research groups could bridge clinical and preclinical studies, improving the laboratory models and directing human studies in specific outcomes or timeframes to establish cross-species concordance in results. Here we highlight the importance of understanding why pregnant people use cannabis and addressing their concerns with further research as key to ultimately reducing PCE. In time, further interdisciplinary research could contribute to increasing the knowledge base available for clinicians as they advise their patients and provide the most up-to-date information for pregnant people deciding whether to cease cannabis use.

Role of funding sources

L.C. supported by Fonds de recherche du Québec Santé Doctoral Award at time of manuscript drafting.

Contributors

Manuscript conceptualized by all authors through collaborative meetings (Early Life and Prenatal Health in Neurodevelopment conference, March 2023; interlab meeting, June 2023). Manuscript drafted by L.C. and critical review provided by all other authors.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dadr.2024.100282.

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