![Scientific Research Publishing logo]

The Safety of Cannabis Use in Pregnancy

Simona Senovaityte, Alexander Nguyen*, Solhee Han, Brenda La, Faithful Anane-Asane, Rouna Mohran, Sterling Lee, Anthony Monzon, Omar Samara, Derrick Murcia, Shrey Purohit

University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA
Email: *alex.t.nguyen@cuanschutz.edu

Abstract

Based on self-reported surveys conducted by the Substance Abuse and Mental Health Services Administration, cannabis use in pregnant females has increased over the years. Despite the increasing trend, the relationship between cannabis use and fetal outcomes is not fully understood. This review paper evaluates the literature investigating the short-term and long-term fetal outcomes resulting from cannabis use during pregnancy. Additionally, the risk of chronic marijuana use leading to cannabis hyperemesis syndrome has been highlighted in this paper using conclusions compiled from several case studies. Several studies linked delayed mental growth and reduced cognitive function with prenatal cannabis use, but the literature was limited to lower-quality observational studies and could not establish causality. One systematic review investigated short-term outcomes of low birth rates and preterm deliveries, where marijuana use in conjunction with tobacco use was associated with more preterm deliveries. Another study found that six-year-old patients exposed to cannabis prenatally were more likely to score lower in different categories on the Stanford-Binet scale test, which measures intelligence. The exposure in the first, second, or third trimester was associated with lower composite or subcategory scores such as verbal reasoning or short-term memory. Despite these results, the studies evaluated had limitations. They could not establish a clear relationship between cannabis use and fetal outcomes, but the literature showed a similar pattern of health, social and economic inequities among the populations who self-reported cannabis and substance use and non-users. Current organization guidelines advise against the use of cannabis use during pregnancy due to mixed and limited literature. However, they emphasize the importance of the clinician in the public health efforts of education and resource-distribution in addressing these inequities.

Keywords

Causality, Preterm Deliveries, Low-Birth Rates, Stanford-Binet Scale Test,

Trimester, Inequities

1. Background on Cannabis

Cannabis, also known as marijuana, refers to a species of plant, *Cannabis sativa*, *Cannabis ruderalis*, and *Cannabis indica* that has been utilized for medicinal and recreational purposes [1]. Cannabis contains over 500 chemical compounds and over 100 cannabinoids (CBDs) that contribute to its medicinal properties, while others like tetrahydrocannabinol (THC) contribute to its psychoactive effects [1]. Currently, in the United States, cannabis and its components are classified as a Schedule I drug under the Controlled Substances Act, recognized as a drug with high abuse potential and little medical application [2]. Therefore, possession, use, and distribution are subject to federal criminalization. Although cannabis use remains illegal on a federal level, multiple states have legalized its use to eliminate state prosecution [2]. Since its legalization, the number over counter of cannabis-containing products has increased [3]. Internationally, policy towards cannabis use varies per country but generally follows a trend towards increasing medicinal usage and governmental regulation, though these do create discordance between United Nations (UN) regulatory law between nations [4]. In the United States, cannabis and all cannabis-containing products contain varying THC concentrations, where most cannabis sold from dispensaries contains content greater than 0.3% [3]. Cannabis with a THC content of less than 0.3% is hemp-based (genus of cannabis) and is used to make over the counter CBDs derivatives [5]. Epidiolex is a plant-derived schedule-V cannabinoid used to treat Lennox-Gastaut syndrome and Dravet syndrome in ages two and older [6]. Cannabis has been used for various medical conditions ranging from seizures to pain, to autism, to depression, to anxiety, and so on [7]. The use of cannabis in pregnancy has grown over the years, where 5.4% of pregnant women report using cannabis within the last month from a 2019 survey [8] [9]. One study found that about 22% of pregnant females aged less than 18 years old screened positive for cannabis based on toxicology reports, while 19% of pregnant females from 18 to 24 years also tested positive [10] [11]. The use of marijuana in pregnancy has been reported to alleviate symptoms with severe nausea and vomiting, while others report using it for other conditions as previously discussed [8] [9] [10] [11].

1.1. Pharmacokinetics and Pharmacodynamics of Cannabis in Pregnancy

The pharmacokinetics (PK) of cannabinoids in cannabis varies on the route of administration [7]. For example, the T max (time at which the drug is at the maximum concentration in the blood) of THC is achieved within a few minutes for smoking, while the absorption via the oral route is slower, with peak concentrations attained within one to three hours [7]. The pharmacokinetics via the

inhalation route can be altered through various mechanisms such as patient variability, number of puffs, and duration of inhalation, while the PK of oral administration varies among patients due to PK variability between patients, digestion within the stomach, and hepatic breakdown via first-pass metabolism [12]. Of note, administration via the inhalation route leads to the formation of noxious chemicals due to combustion reactions from the heat compared to ingestion [7] [12]. The different cannabinoids within cannabis have varying properties that contribute to their PK profiles and ultimately affect fetal exposure [7]. For example, THC easily partitions into fat tissue and readily crosses the placenta due to its lipophilic properties [12] [13]. In conjunction, the long half-life of THC ranges from 1 - 13 days depending on how frequently the patient uses cannabis and decreased fetal clearance results in increased levels [12]. For lactating mothers, THC passes through breast milk to the infant [7] [12]. Of note, though THC potency is labeled on products, there is no regulation on labeling due to the differences between state and federal laws on cannabis use [3]. Therefore, the accuracy of the labeling of cannabis-containing products varies, especially CBDs, where most suppliers are either under label or over label, with the average concentration being above 15% of THC [3]. Therefore, all the factors discussed increase cannabis exposures to the developing embryo. However, the short-term and long-term outcomes of the fetus and mother have not been fully established but will be discussed in the following sections.

Cannabinoids exert their effects on the endogenous receptors, cannabinoid 1 receptor (CB1Rs) and cannabinoid 2 receptor (CB2Rs) [7] [12] [13]. CB1Rs predominately reside in central and peripheral nervous systems neurons, while CB2Rs primarily reside on immune cells and some neurons [7] [12] [13]. Activation of CB1Rs from cannabinoids produce psychoactive and clinical effects such as hypoactivity, hypothermia, vasodilation, short-term memory impairment, drowsiness, euphoria, and dizziness, while the antiemetic effects result from CB1R agonism and indirect activation of serotonergic receptors located in the midbrain [7] [12] [13]. The median lethal dose of oral THC varying in different animal models with doses reaching up to 9000 mg/kg in monkeys [7], but fatalities reported in humans are rare, and the relationship of all-cause mortality from cannabis use remains unclear [14].

1.2. Hyperemesis in Pregnancy

Cannabinoid hyperemesis syndrome (CHS) is a novel clinical entity that involves cyclic vomiting, nausea, and abdominal pain that develops in susceptible individuals with a history of chronic cannabis abuse [15]. The syndrome can be explained by the role of CB1 receptors in the enteric nervous system, which influences peristalsis and gastric emptying, specifically emesis [15]. In addition, THC can quickly be sequestered in the fat tissue, further increasing the risk of CHS with chronic use [12]. Once THC reaches a toxic level, it is hypothesized that the peripheral effect at the gut bypasses the body's centrally mediated antiemetic effects [12] [14] [15] [16]. Interestingly, case studies commonly report a

strong association with patients taking frequent hot baths to relieve CHS symptoms of nausea and vomiting [15] [17]. One hypothesis explaining this linking behavior is the body's reaction to the psychoactive hypothermia outcome from chronic use of cannabinoids and taking a hot bath is a natural thermoregulatory response [17]. Additionally, symptom relief can be attenuated via dilation of blood vessels, decreasing the blood flow to the cannabinoid vasodilated splanchnic vessels [17]. As a result, several complications can arise from significant dehydration of recurrent bathing behavior [17]. There is an increased risk of hypotension-related falls and possibly inducing preterm labor when the body responds to dehydration with the release of the antidiuretic hormone oxytocin [17]. Additionally, CHS-related weight loss of pregnant mothers can further exacerbate preterm labor and increase the risk of neural tube defects, esophageal atresia, omphalocele, and gastroschisis during the first trimester with greater than 30 minutes of use of hot tub [17]. When dehydration is involved, fluid resuscitation, as well as antiemetics, can help. However, the best treatment is the cessation of cannabinoid use with education [17].

1.3. Cannabis and Fetal Outcomes

Unlike the established relationships between tobacco and alcohol use and fetal development, the outcomes related to cannabis use and embryo development have not been clearly defined [13] [18]. The studies published have shown associations between cannabis and fetal outcomes such as preterm deliveries, low birth weight, decreased cognitive function, poor attention, and academic performance [19] [20]. However, none have shown causality, while other findings seem to conflict and are limited to lower quality studies such as cohort or case-control. Currently, no human studies have established a relationship between miscarriages and cannabis use, yet some animal studies suggest that the risk for miscarriage increases if used early in pregnancy [8] [18].

In a systematic review that investigated primary outcomes of low birth weight (defined less than 2500 g) and preterm delivery (defined by delivery less than 37 weeks of gestation) from self-reported surveys of cannabis use, pregnant women reported as less than weekly users in comparison to non-users were at an increased risk for low birth rates (12 studies: RR 1.43, 95% CI 1.27 - 1.62) and preterm deliveries (14 studies: 15.3% compared with 9.6%, RR 1.32, 95% CI 1.14 - 1.54) [21]. However, when adjusting for heterogeneity factors such as tobacco use within the two populations, there was no significant difference in low birth rates in pregnant women using cannabis less than weekly in comparison to non-users (two studies: RR 1.22, 95% CI 0.91 - 1.64) or preterm deliveries (five studies: RR 1.09, 95% CI 0.91 - 1.32). Similar results were seen in weekly cannabis users with and without tobacco stratification, respectively. Pregnant women who used both cannabis and tobacco were more likely to have preterm deliveries than non-users of both tobacco and marijuana (two studies: RR 1.85, 95% CI 1.21 - 2.810) [21]. From this study, marijuana use alone did not contribute to low-birth rates and preterm deliveries, yet concurrent use of tobacco with mari-

juana in comparison to no use carried a risk of preterm deliveries. Despite the clinical and statistical stratification of heterogeneity factors, methodological heterogeneity was not accounted for, contributing to the study's bias. Additionally, the lack of standardized scoring systems and reliance on self-reported usage across different studies may have affected the validity of the results, considering the outcomes may not have been accurately measured or groups adequately separated. Regardless of these short-comings, adverse birth outcomes were not clearly associated with self-reported low to moderate marijuana use during pregnancy unless paired with concomitant tobacco use. Little can be said about any dose response as again these were self-reported surveys and dosing of marijuana is extremely variable by method and purity. Second-hand exposure to marijuana smoke has not been systematically studied in any population including pregnant women but most authors agree that the effects are likely similar to second-hand tobacco smoke exposure on the developing fetus [22].

A prospective cohort study followed pediatric patients who are six years of age exposed to cannabis prenatally and assessed their intellectual development by using an IQ test [23]. Of the 648 patients included, children who were prenatally exposed to marijuana with one or more cigarettes per day had lower composite scores in Stanford-Binet scale tests than children who were not exposed in the second trimester (p-value = 0.01), when adjusting for baseline factors [23]. Cannabis exposure within the first-trimester was associated with lower scores in verbal reasoning (p-value = 0.01). Second-trimester exposure resulted in lower scores on short-term memory and quantitative reasoning (p-values of 0.005 and 0.01, respectively). Study considerations include that the prospective study design could not show causality, and exposure stratification was limited to self-reported questionnaires and surveys, which predisposes to bias. Of note, cofounding factors such as race, social support, substance use, number of people in the household, alcohol problems with a parent, number of illnesses, and maternal depression were significant predictors for the composite score and other categories [23]. Other variables are that pregnant women were more likely to report using marijuana if they did not graduate high school, use tobacco or alcohol, and report a history of abuse or depression [24]. In addition, having a lower household income and being a single-parent were also additional co-variables seen across multiple studies [21] [23] [24].

2. Methods

On June 7, 2021, an electronic systematic search was conducted on a variety of databases, which consists of Web of Science, Cochrane Controlled Register of Trials (CENTRAL), as well as PubMed. Search terms included "cannabis", "CBD", "cannabinoid", or "cannabinoids" were combined with either "pregnancy", "fetal outcomes", "embryo outcomes", "pharmacokinetics", "hyperemesis", "pregnancy hyperemesis", "laws", "clinical guidelines", "contaminants", "pregnancy polysubstance", "trimester", "fetal growth", "fetal development", "embryo growth", "embryo development", "mechanism", "clinicians", "consen-

sus statements", "regulations", "gestation", "breastfeeding", "toxicities", "safety", and "efficacy". Eligibility of identified articles was evaluated based on title and abstracts. The reference lists of included articles were also individually examined to determine whether further citations would be required.

3. Guideline Recommendations

As evidenced by the earlier studies, the literature surrounding cannabis use in pregnancy is limited and mixed. Despite this, multiple guidelines strongly advise against the use of cannabis-containing products due to its unknown effects on neurodevelopment with the increased risk of hyperemesis [25] [26] [27]. The recommendations include avoiding or discontinuing cannabis use before, during, and after pregnancy to avoid adverse outcomes and asking about concurrent polysubstance abuse. The women who self-reported cannabis-use also were more likely to use substances such as tobacco or alcohol [25] [26] [27]. There has been a moderate level of evidence to suggest that cannabis use in pregnancy is associated with lower physical and mental fetal growth, cognitive function, and attention outcomes, while there is limited, insufficient, or mixed data to indicate that cannabis use is linked to low birth weight or newborn behavioral issues [28]. Guidelines stress the importance of education and providing alternatives to marijuana use in pregnant women [25] [26] [27] [28]. Additionally, clinicians should remind patients that the goals of drug screening tests seek to promote well-being for both the mother and the fetus, yet patients should be informed on the mandatory reporting associated with positive tests based on state-specific guidelines [25]. Federal FDA recommendations also do not support the use of marijuana in pregnancy due to the points mentioned earlier and the lack of regulation of cannabis-containing products. Therefore, cannabis-containing products may differ in concentrations and be contaminated with components such as heavy metals, pesticides, and fungus that pose a risk to pregnant patients and developing embryos [18] [29].

4. Role of the Clinician

The literature supporting the short-term and long-term effects of cannabis use on the mother and developing fetus remains mixed, though some evidence suggests long-term neurodevelopment complications [23] [25] [26] [27]. However, the obstetric and fetal outcomes of marijuana use remain unclear due to conflicting evidence, lower-quality studies, smaller sample sizes, and cofounding factors (*i.e.*, tobacco, alcohol, and other substance use). Guidelines and federal agencies advise against the use of cannabis in pregnancy. Additionally, these resources stress the importance of the clinician, not only in the discontinuation of cannabis use but overall improvement of health from a clinical, behavioral, and socioeconomic standpoint. As mentioned earlier, the studies evaluated showed similarities where patients with reported cannabis use were more likely to share the demographics like lower-income status, single-parenting, mental illness his-

tory, lack of social support, substance abuse, and lower education [23] [24] [25]. Therefore, clinicians play an essential role in public health efforts directed toward pregnant patients, which seek to address the disparities and inequities affecting these patients. Based on collaborative efforts, clinicians should educate families and direct resources, all of which could empower patients and remove the stigmas associated with marijuana use and pregnancy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Atakan, Z. (2012) Cannabis, A Complex Plant: Different Compounds and Different Effects on Individuals. *Therapeutic Advances in Psychopharmacology*, **2**, 241-254. https://doi.org/10.1177/2045125312457586

[2] Pacula, R.L., Chriqui, J.F., Reichmann, D.A. and Terry-McElrath, Y.M. (2002) State Medical Marijuana Laws: Understanding the Laws and Their Limitations. *Journal of Public Health Policy*, **23**, 413-439. https://doi.org/10.2307/3343240

[3] Bonn-Miller, M.O., Loflin, M.J., Thomas, B.F., Marcu, J.P., Hyke, T. and Vandrey, R. (2017) Labeling Accuracy of Cannabidiol Extracts Sold Online. *JAMA*, **318**, 1708-1709. https://doi.org/10.1001/jama.2017.11909

[4] Barrett, D. (2019) Canada, Cannabis and the Relationship between UN Child Rights and Drug Control Treaties. *International Journal of Drug Policy*, **71**, 29-35. https://doi.org/10.1016/j.drugpo.2019.02.010

[5] Niesink, R.J. and van Laar, M.W. (2013) Does Cannabidiol Protect against Adverse Psychological Effects of THC? *Frontiers in Psychiatry*, **4**, Article No. 130. https://doi.org/10.3389/fpsyt.2013.00130

[6] Abu-Sawwa, R., Scutt, B. and Park, Y. (2020) Emerging Use of Epidiolex (Cannabidiol) in Epilepsy. *The Journal of Pediatric Pharmacology and Therapeutics*, **25**, 485-499. https://doi.org/10.5863/1551-6776-25.6.485

[7] Grotenhermen, F. (2003) Pharmacokinetics and Pharmacodynamics of Cannabinoids. *Clinical Pharmacokinetics*, **42**, 327-360. https://doi.org/10.2165/00003088-200342040-00003

[8] NIDA (National Institute on Drug Abuse) (2021) Can Marijuana Use during and after Pregnancy Harm the Baby? https://www.drugabuse.gov/publications/research-reports/marijuana/can-marijuana-use-during-pregnancy-harm-baby

[9] McCance-Katz, E.F. (2020) 2019 The National Survey on Drug Use and Health: Women. Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/sites/default/files/reports/rpt31102/2019NSDUH-Women/Women%202019%20NSDUH.pdf

[10] Young-Wolff, K.C., Tucker, L.Y., Alexeeff, S., Armstrong, M.A., Conway, A., Weisner, C. and Goler, N. (2017) Trends in Self-Reported and Biochemically Tested Marijuana Use among Pregnant Females in California from 2009-2016. *JAMA*, **318**, 2490-2491. https://doi.org/10.1001/jama.2017.17225

[11] Weisner, C. and Goler, N. (2017) Trends in Self-Reported and Biochemically Tested Marijuana Use among Pregnant Females in California from 2009-2016. *JAMA*, **318**,

2490-2491. https://doi.org/10.1001/jama.2017.17225

[12] Friedrich, J., Khatib, D., Parsa, K., Santopietro, A. and Gallicano, G.I. (2016) The Grass Isn't Always Greener: The Effects of Cannabis on Embryological Development. *BMC Pharmacology and Toxicology*, **17**, Article No. 45. https://doi.org/10.1186/s40360-016-0085-6

[13] Boggs, D.L., Nguyen, J.D., Morgenson, D., Taffe, M.A. and Ranganathan, M. (2018) Clinical and Preclinical Evidence for Functional Interactions of Cannabidiol and Δ^9-Tetrahydrocannabinol. *Neuropsychopharmacology*, **43**, 142-154. https://doi.org/10.1038/npp.2017.209

[14] Calabria, B., Degenhardt, L., Hall, W. and Lynskey, M. (2010) Does Cannabis Use Increase the Risk of Death? Systematic Review of Epidemiological Evidence on Adverse Effects of Cannabis Use. *Drug and Alcohol Review*, **29**, 318-330. https://doi.org/10.1111/j.1465-3362.2009.00149.x

[15] Alaniz, V.I., Liss, J., Metz, T.D. and Stickrath, E. (2015) Cannabinoid Hyperemesis. *Syndrome, Obstetrics & Gynecology*, **125**, 1484-1486. https://doi.org/10.1097/AOG.0000000000000595

[16] Flament, J., Scius, N. and Thonon, H. (2020) Cannabinoid Hyperemesis Syndrome in the Pregnant Patient: Clinical Case and Literature Review. *International Journal of Emergency Medicine*, **13**, Article No. 52. https://doi.org/10.1186/s12245-020-00311-y

[17] Kim, H.G., Moon, J., Dixon, H. and Tullar, P. (2018) Recurrent Nausea and Vomiting in a Pregnant Woman with Chronic Marijuana Use. *Case Reports in Obstetrics and Gynecology*, **2018**, Article ID: 9746062. https://doi.org/10.1155/2018/9746062

[18] Cash, M.C., Cunnane, K., Fan, C. and Romero-Sandoval, E.A. (2020) Mapping Cannabis Potency in Medical and Recreational Programs in the United States. *PLoS ONE*, **15**, Article ID: e0230167. https://doi.org/10.1371/journal.pone.0230167

[19] Young-Wolff, K.C., Tucker, L.Y., Alexeeff, S., Armstrong, M.A., Conway, A. and Groce, E. (2018) The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. *Journal of Medical Regulation*, **104**, 32. https://doi.org/10.30770/2572-1852-104.4.32

[20] Mark, K., Desai, A. and Terplan, M. (2016) Marijuana Use and Pregnancy: Prevalence, Associated Characteristics, and Birth Outcomes. *Archives of Women's Mental Health*, **19**, 105-111. https://doi.org/10.1007/s00737-015-0529-9

[21] Conner, S.N., Bedell, V., Lipsey, K., Macones, G.A., Cahill, A.G. and Tuuli, M.G. (2016) Maternal Marijuana Use and Adverse Neonatal Outcomes. *Obstetrics & Gynecology*, **128**, 713-723. https://doi.org/10.1097/AOG.0000000000001649

[22] Wilson, K.M. (2016) Secondhand Marijuana Smoke Is Not Benign. *Journal of the American Heart Association*, **5**, Article ID: e004004. https://doi.org/10.1161/JAHA.116.004004

[23] Goldschmidt, L., Richardson, G.A., Willford, J. and Day, N.L. (2008) Prenatal Marijuana Exposure and Intelligence Test Performance at Age 6. *Journal of the American Academy of Child & Adolescent Psychiatry*, **47**, 254-263. https://doi.org/10.1097/CHI.0b013e318160b3f0

[24] Ko, J.Y., Coy, K.C., Haight, S.C., Haegerich, T.M., Williams, L., Cox, S., Njai, R. and Grant, A.M. (2020) Characteristics of Marijuana Use during Pregnancy—Eight States, Pregnancy Risk Assessment Monitoring System, 2017. *Morbidity and Mortality Weekly Report*, **69**, 1058-1063. https://doi.org/10.15585/mmwr.mm6932a2

[25] Carson, G., Cox, L.V., Crane, J., Croteau, P., Graves, L., Kluka, S., Koren, G., Martel, M.J., Midmer, D., Nulman, I. and Poole, N. (2010) Alcohol Use and Pregnancy

Consensus Clinical Guidelines. *Journal of Obstetrics and Gynaecology Canada*, **32**, S1-S2. https://doi.org/10.1016/S1701-2163(16)34633-3

[26] Committee on Obstetric Practice (2017) Committee Opinion No. 722: Marijuana Use during Pregnancy and Lactation. *Obstetrics & Gynecology*, **130**, e205-e209. https://doi.org/10.1097/AOG.0000000000002354

[27] Krist, A.H., Davidson, K.W., Mangione, C.M., Barry, M.J., Cabana, M., Caughey, A.B., Donahue, K., Doubeni, C.A., Epling, J.W., Kubik, M. and Ogedegbe, G. (2020) Primary Care-Based Interventions to Prevent Illicit Drug Use in Children, adolescents, and Young Adults: US Preventive Services Task Force Recommendation Statement. *JAMA*, **323**, 2060-2066. https://doi.org/10.1001/jama.2020.6774

[28] Ghosh, T.S., Van Dyke, M., Maffey, A., Whitley, E., Erpelding, D. and Wolk, L. (2015) Medical Marijuana's Public Health Lessons—Implications for Retail Marijuana in Colorado. *New England Journal of Medicine*, **372**, 991-993. https://doi.org/10.1056/NEJMp1500043

[29] Joseph, P. and Vettraino, I.M. (2020) Cannabis in Pregnancy and Lactation—A Review. *Missouri Medicine*, **117**, 400-405.