

Cannabis Use in Pregnancy and Neonatal Exposure: What we know!

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THC and Pregnancy

- Throughout the world the use of marijuana for both medicinal and recreational use has increased dramatically over the past decade and especially in the last few years.
- Along with the opioid crisis, the use of many drugs has become commonplace.
- It has been difficult to design randomized controlled investigations which investigate the effects of marijuana on the developing fetus, newborn, infant, and child.
- Cannabis has been legalized worldwide, our lack of information regarding its safety in the pregnant and lactating population has become apparent.
- Cannabis is the most commonly used illicit drug during pregnancy. Self reported rates of use in pregnancy are 2% to 5%; however, these likely represent an underestimate.

THC and Pregnancy

- In one study exploring the outcomes of prenatal cannabis and alcohol exposure on academic achievement, Goldschmidt et al reported on the frequency of concurrent cannabis and alcohol use during pregnancy.
- In their study, 14% of women reported heavy use of cannabis (ie, smoking 1 or more joints per day) during the first trimester of pregnancy, compared with 5.3% and 5.0% during the second and third trimesters of pregnancy, respectively.
- Risk factors for continued use include single or unmarried status, lower income, less education, or a partner who also uses cannabis.
- Women using cannabis in pregnancy are more likely to use alcohol, tobacco, and illicit drugs, which might have additive or synergistic effects.
- At the same time, studies have demonstrated that cannabinoids readily cross the placenta and appear in human breast milk, resulting in fetal and neonatal exposure.

Facts on the Matter!

- In utero exposure to cannabis has been associated with long-term neurodevelopmental outcomes that persist into young adulthood.
- Pregnant women should be counseled regarding these risks and encouraged to abstain from use.
- Maternal risks of cannabis use are related to the mode of ingestion and its addictive potential. Harm reduction options should be offered to those not able to quit completely.
- The relationship between cannabis and nausea in pregnancy is complex and remains poorly defined. While women using it in pregnancy often find it effective, chronic use might be associated with cannabinoid hyperemesis syndrome, a condition characterized by episodes of acute abdominal pain, nausea, and vomiting.

Facts on the Matter!

- There are other safe and effective treatments for nausea and vomiting that should be used first line.
- Tetrahydrocannabinol is excreted in human breast milk. Human data have suggested possible impaired infant motor development at 1 year in children exposed to cannabis while breastfeeding; however, these data are limited.
- There is no known safe level of cannabis use during pregnancy or lactation. Pregnant women should be counseled regarding the risks of in utero exposure and encouraged to abstain from use in pregnancy and while breastfeeding

Marijuana history and legislation

- Marijuana was part of a list of drugs in the United States Pharmacopeia from 1850 to 1942.
- In 1930 the United States Federal Bureau of Narcotics produced literature saying that marijuana was an addicting substance which led users to narcotics addiction.
- It was then portrayed as a “gateway drug”.
- The Marijuana Tax Act of 1937 placed a tax on the sale of cannabis.
- In the 1950s marijuana was known as an accessory to the “beat generation”.
- In the 1960s there was increased use by college students and hippies as its widespread acceptance became a symbol of rebellion against authority.
- In 1970, the Controlled Substance Act repealed the Marijuana Tax Act and marijuana was listed as a Schedule I drug along with heroin, LSD and ecstasy.
- In 1972 the National Commission on Marijuana and Drug Abuse recommended “partial prohibition” and “lower penalties” for possession of a small amount of marijuana

Marijuana history and legislation

- In 1996 the Compassionate Use Act in California (also known as Proposition 215) was the first state to legalize marijuana for medicinal use for chronic illness.
- The United States Supreme Court (2005) opined that the Federal government had the constitutional authority to prohibit marijuana for all purposes. The Court indicated that Congress and the Food and Drug Administration should resolve this issue. Complicating matters, many states have passed laws recognizing marijuana's medicinal value.
- In 2012 California and Washington became the first states to legalize marijuana for recreational use.
- In 2014, the Rohrabacher-Farr or Commerce Justice Science Amendment was signed into law. This amendment does not just prevent Federal direct interference with state implementation, but it also ends Federal medical cannabis raids, arrests, criminal prosecutions, and other Federal interference.
- It is clear that Federal agencies are grappling with state conflicts. In 2016 guidelines and policies were produced to manage the conflict between Federal and State Laws dealing with marijuana.

Marijuana history and legislation

- As of 2019 there are five categories of state legalization descriptions. These categories are:
 - Legalized
 - medical and decriminalized
 - Medical
 - decriminalized
 - Fully Illegal
- Ten states have completely legalized the sale of marijuana for medical, recreational purposes.
- Recent polls in the United States have represented that the majority of Americans now favor some form of marijuana legalization.
- With the increasing prevalence of cannabis use there is a decreasing perception of risk of harm from cannabis products.
- The conflict is increased as the Federal government through the Controlled Substances Act does not recognize the difference between medical and recreational use of cannabis

A Booming Business!

- Further complicating matters is that marijuana production and its various types have created a new “cottage industry”.
- New products have been produced which concentrates the THC and delivery systems such as vaping and eating the THC (dabbing) and allows a more immediate and longer lasting effects on the central nervous system.
- There are over 700 cannabis strains that have been recognized as new marijuana products.
- Growers are experimenting with cannabis cultivation. Varieties of names are chosen and can reflect different properties of the plant (taste, color, and smell). Growers are also experimenting with hybrid varieties which can be cultivated to vary clinical effects.
- New product names of these strains include, Acapulco Gold, Bedrocan, Blue Dream, Charlotte’s Web, Green Crack, and Skunk to name a few. Fiscally, marijuana economics is potentially a billion dollar business.

Endocannabinoid System

- The endocannabinoid system (EDS) is involved in regulating and modulating movement, memory, thinking, coordination, appetite, thermoregulation, sleep, pain, pleasure sensations, the immune system response, and sensory and time perception.
- THC is a phytocannabinoid which is similar in structure to anandamide. Because of this similarity in chemical structure, THC attaches to the cannabinoid receptors on the neurons, activates them, and the final effects are those described above.
- This EDS is critical to normal function. Children, adolescents and adults that THC may alter function of the hippocampus and orbitofrontal cortex which deals with memory and focus. (Sucking Reflex)

Endocannabinoid System

- Another area of concern is the effect of THC on the dopamine release system in the newborn. The interaction between cannabinoids and dopamine are complex and evidence in both human and animal studies are conflicting.
- THC causes an increase in dopamine release and neuronal activity. It is interesting however that long term use of THC blunts the dopamine system.
- If brain metabolic activity is studied using functional magnetic resonance imaging and positron emission tomography, it is noted that indirect measurement of dopamine's effect can be identified through changes in cerebral blood flow and glucose metabolism.
- These interactions need further investigation to determine the effects on neonatal behavior and biochemistry

Endocannabinoid System

- Endocannabinoids and their receptors (CB1, CB2) are present in early gestation.
- These cannabinoid receptors are part of the EDS which is imperative to many physiological processes. These receptors are in a class of the G protein-coupled receptors superfamily.
- There are two main cannabinoid receptors, CB1 and CB2. The CB1 receptors are present in the placenta, brain, kidney, lungs, and liver.
- The CB1 receptor in the placenta is involved in the regulation of serotonin transporter activity. The fetal brain requires serotonin in the development of critical neural circuits.
- The CB1 cannabinoid receptor (CB1R) is presynaptic and acts as an important signaling platform. The neuromodulatory role of CB1R signaling is most important during prenatal development as mature synaptic activity is not present.

Endocannabinoid System

- The CB1 receptor when stimulated by cannabinoids induces a reduction in GABA (Gamma-aminobutyric acid) which is a prevalent inhibitory transmitter in the central nervous system
- THC activates these protein-coupled receptors. CB1 receptors in the placenta can impair fetal growth by inhibiting cytotrophoblastic proliferation. Cannabinoids acting on the CB1 receptors influence the differentiation embryologically of neural cells from stem cells in the brain.
- Cannabinoids have a direct effect on cellular processes which potentially can influence embryogenesis and fetal development. These include disruption of normal angiogenesis, inducing apoptosis leading to premature cellular death, impairment, and reduced cellular migration and disruption of DNA replication. In animal studies prenatal exposure to cannabinoids evoked long-lasting functional alterations on developing cortical neurons.
- Fetal exposure to THC has a negative potential for neonatal and childhood development.

Cannabis and Pregnancy

- Pharmacokinetics of cannabis is variable depending upon the route of administration and therefore absorption.
- Smoking allows for rapid drug delivery while ingestion depends upon absorption, breakdown of the drug in the stomach, and metabolism in the liver.
- Since cannabinoids are lipophilic, when present in the bloodstream they readily cross the placenta into the fetus

Cannabis and Pregnancy

- Metabolically, THC decreases fetal folic acid uptake which is essential for placental and embryo development.
- Folic acid is essential for fetal growth and since it is not synthesized de novo, dietary supplementation is necessary during pregnancy.
- Folic acid deficiency is well known to produce neural tube defects. THC interferes with folic acid by disturbing syncytiotrophoblast development.
- Acute cannabinoid consumption results in no effect on the uptake of folic acid while chronic use of cannabinoids is more consistent in the effects of disturbing folic acid metabolism.

Cannabis and Pregnancy

- On a cellular level, cannabinoid disrupts DNA replication, cellular motility, and cellular migration and replication.
- The latter is a critical process in embryogenesis, especially in fetal brain development.
- CB1 receptors are in the fetal brain and play an important role in the differentiation into neurons and supporting tissue such astrocytes or oligodendrocytes.
- Neural stem cells (NSCs) can proliferate incorrectly leading to anatomical cerebral dysgenesis. NSCs vary in different areas of the brain and if this signaling process is disrupted the results on the growing fetus can be extensive.

Fetal Development

- Interference with:
 - Vascular endothelial growth factor (VEGF)
 - Neurotrophic factor (brain-derived neurotrophic factor—BDNF)
 - Microtubule-binding protein in axons identified as superior cervical ganglion 10 (SCG10/stathmin-2)
 - Pathway called the “MAPK/ERK” pathway

Breast Feeding and Cannabis

- Molecular weight, solubility, and the pH of the drug must be considered.
- THC is 99% protein bound and has a low molecular weight and increased lipid solubility.
- There is storage of THC in lipid predominate tissue such as the brain. There continues to be insufficient data to conclude that maternal marijuana use during breastfeeding is safe.
- It is because of this lack of information that the recommendation from both the American Academy of Pediatrics (AAP) and The American College of Obstetricians and Gynecologists (ACOG) is that marijuana use should be discouraged during this breastfeeding period.

Breast Feeding and Cannabis

- Studies have evaluated the concentration of Δ -9-tetrahydrocannabinol, 11-hydroxy- Δ -9-tetrahydrocannabinol, CBD, and cannabidiol in breastmilk using liquid chromatography mass spectrometry electrospray ionization.
- Results showed that Δ -9 THC was detectable for up to 6 days after reported use.
- Even though definitive data is lacking, both the AAP and the American Congress of Obstetricians and Gynecologists advise that marijuana use should be discouraged while breastfeeding.
- Conflicting information regarding marijuana metabolites in breastmilk revolves around the macronutrient components of foremilk and hind-milk.
- The number of times that a mother used marijuana per day was a predictor of THC concentrations in milk.
- There is a critical need for research to measure concentration of marijuana products in breastmilk and subsequent neonatal plasma concentrations.

Prenatal Exposure Research

- Alvarez et al. [31] completed a chart review to assess developmental milestones during well-child visits at 6, 9, 12, 15, 18, and 24 months of age.
- Logistic regression revealed that prenatal marijuana exposure was associated with developmental delay.
- The affected developmental domains were fine motor and social in nature.
- There are longitudinal studies in children of women who smoke marijuana during pregnancy and there are consistent outcomes regarding development.
- These include an increase in impulsivity, hyperactivity, delinquent behavior, memory dysfunction, and decrease IQ scores.

Breast Feeding and Cannabis

- There is reason for concern, but the results are variable with changes in habituation, sleep patterns, and motility during the first several weeks of life.
- Unlike the neonatal abstinence syndrome (NAS) with guidelines for therapy, there is no well-defined clinical approach to withdrawal in neonates who are exposed only to marijuana through breastmilk.
- Based upon the pathophysiology of marijuana's effects, there is certainly “justification” to advise against any type of marijuana exposure in the breastfed infant.

Breast Feeding and Cannabis

- Unfortunately, the literature is unclear about cannabis use during breastfeeding and the effects on the newborn and infant.
- The baby gets on an average 2.5% of the maternal THC dose through breastmilk.
- The accuracy of these numbers depends upon the collection of the breastmilk and if the assay was done on the foremilk versus hindmilk .
- The highest concentration of THC in breastmilk occurs 1 h after cannabis consumption. There are falling concentrations over the next 8 h.
- Even though this section discussed cannabinoid and breastfeeding, there are also infant complications with paternal cannabis use. There remains a possible risk of SIDS in babies who have been exposed to marijuana through paternal smoking

Conflicts!

- As marijuana exposures during pregnancy increases, there will be more scientific studies which better define marijuana's effects on the fetus and newborn.
- As the numbers are still small, the results are variable and oftentimes conflicting.
- Prenatal exposure to cannabis did not have a statistically negative effect on length or head circumference.
- **Some systemic reviews concluded that there was no association between cannabis exposure and IUGR/SGA infants.**
- Other investigations believe that cannabis exposure does affect fetal growth.
- There apparently is no association between cannabis use and gestational age.
- There is also no correlation between maternal cannabis use and Apgar scores, development of jaundice, hypoglycemia, and or sepsis.

Committee on Substance Abuse and Prevention and Section on
Breastfeeding (Ryan et al. 2018)

“In summary, the evidence for independent, adverse effects of marijuana on human neonatal outcomes and prenatal development is limited, and inconsistency in findings may be the result of the potential confounding caused by the high correlation between marijuana use and use of other substances such as cigarettes and alcohol, as well as sociodemographic risk factors. However, the evidence from the available research studies indicate the reasons for concern, particularly in fetal growth and early neonatal behaviors.”

Based upon a review of the literature and the pathophysiology of the effects of marijuana we should be faced with a large number of infants with signs and symptoms which can be attributed to marijuana:

1. Increased moro-reflex (startle response)
2. Tremors
3. High pitched cry
4. Abnormal sleep pattern
5. Increased muscle tone
6. Uncoordinated suck-swallow reflex
7. Increased irritability
8. Tachycardia
9. Increased blood pressure
10. Seizures
11. Thermoregulation instability
12. EEG—sleep disturbance

Treatment of the Neonate with Cannabis Withdrawal

1. A dimly lit room environment
2. Minimal sensory or environmental stimulation (noise reduction)
3. Positional support
4. Swaddling
5. Gentle handling
6. Skin-to-skin contact (kangaroo care)
7. Gentle vertical rocking (supports self-regulation, use of rocking beds, or mechanical swings)
8. Frequent smaller volume feedings with higher calories
9. Nonnutritive sucking
10. Maintaining temperature stability
11. Consideration of neonatal sleep states and altering environmental approaches with consideration of physiologic principles
12. Use of family-integrated neonatal care.

ACOG and AAP Positions:

- Cannabinoids do have an effect on pregnancy and these effects are due to activation of the endocannabinoid system and their receptors (CB1, CB2).
- Marijuana withdrawal often mimics the clinical features exhibited with the NAS.
- The treatment for the symptomatic infant secondary to marijuana exposure is behavioral rather than medicinal
- The ACOG discourages the use of marijuana during pregnancy.
- The AAP recommends encouraging mothers not to breast feed while using marijuana.
- It is clear that in order to answer many of these questions further investigations which are evidence-based must be developed.

Challenges with studying Cannabis and Pregnancy

- Within the literature there is an overall lack of good-quality research on cannabis use in pregnancy and post-partum.
- For obvious reasons, there are no randomized controlled trials on cannabis use in pregnancy, and many studies do not exclude or control for polysubstance use.
- A reliance on self-reported measures might underestimate the prevalence of drug use in pregnancy, and the rising tetrahydrocannabinol (THC) potency in cannabis products during the past decade might act as a confounder.
- Finally, pregnant women who use cannabis are more likely to be underweight, have less education, and have a lower household income, and are less likely to take folic acid, compared with nonusers.

Three Studies Worth a Close Look!

- 3 important prospective longitudinal cohort studies that are ongoing and have provided some insight into both short-term and long-term effects of in utero exposure to cannabis products:
 1. **The Ottawa Prenatal Prospective Study (OPPS)**
 2. **The Maternal Health Practices and Child Development (MHPCD) study.**
 3. **Generation R (GenR)**
- These studies all recruited women who were pregnant and have followed their children into early childhood (GenR), adolescence (MHPCD), and early adulthood (OPPS).
- They all controlled for sex, ethnicity, home environment, maternal socioeconomic status, prenatal alcohol and tobacco exposure, and current maternal substance use.

Table 1. Comparison of characteristics of 3 important prospective longitudinal studies

| CHARACTERISTIC | OPPS ⁹ | MHPCD ^{2,10} | GENERATION R ^{1,11} |
|--|---|--|--|
| Year study began | 1978 | 1982 | 2001 |
| Population | Caucasian, primarily middle class | Largely African American (57%) and single (71%), with low SES | Multiethnic cohort; slightly higher SES compared with nonresponders or incomplete responders |
| Recruitment | Self-referral for study participation based on posters in prenatal clinics and information from prenatal providers | Actively recruited from an inner-city prenatal clinic in the 4th or 5th mo of pregnancy | Enrolled based on residence in the study area with a due date during recruitment. Recruited from early pregnancy until birth |
| Cannabis-exposed population and total sample size, n/N | 78/698 | 307/763 | 220/7531 |
| Polysubstance use | Yes: tobacco (21%) and alcohol (76%) | Yes: alcohol (65%), tobacco (53%), cocaine (3.6%), and other illicit drugs (8.6%) | Yes: alcohol (31%), tobacco (39%), and other substances (4.5%) |
| Method of data collection to determine cannabis use | Repeated interviews largely within each woman's home by the same trained, female interviewer for each interview | Standardized interviews | Self-reported questionnaires |
| Categorization of cannabis exposure | Nonuser, light user (≤ 1 joints/wk), moderate user (2-5 joints/wk), or heavy user (> 5 joints/wk) | Based on ADJ: light (0-0.4 ADJ), moderate (0.5-1 ADJ), or heavy (> 1 ADJ) use | Nonuse, occasional (monthly), moderate (weekly), or heavy (daily) use |
| Cannabis use measured | Each trimester | First, second, and third trimester, and 8 mo, 18 mo, and 36 mo postpartum | Prepregnancy, early pregnancy, and late pregnancy |
| Retention rate | At 22 y only 49 (63%) of the group exposed to cannabis remained | Of the total sample, 636 (83%) followed up at 10 y, 580 (76%) at 14 y, and 608 (80%) at 22 y | Follow-up rates for the total sample at 6 y exceed 80% for most measures |
| Limitations | <ul style="list-style-type: none"> • Small sample with small number of heavy (n = 25) and moderate (n = 37) users • Low-risk sample • Self-reported use, although used the same interviewer for all interviews in an effort to build rapport | <ul style="list-style-type: none"> • Large, high-risk sample with potential for multiple confounding variables • Substantial polysubstance use with alcohol, tobacco, cocaine, and other illicit substances • Self-reported use of cannabis | <ul style="list-style-type: none"> • Likely highest-potency THC products owing to increasing potency over time and increased potency of Dutch cannabis products • Self-reported use of cannabis • Use of self-report questionnaires skewed the sample to a higher SES and more educated sample compared with nonresponders or incomplete responders |

Neonatal Outcomes: Birthweight

- Large number of studies on cannabis use in pregnancy focus on fetal growth. Results are mixed, with some studies showing lower birth weights and others showing no effect.
- Of the large prospective studies, GenR alone showed a statistically significant decrease in birth weight associated with cannabis use while controlling for tobacco smoking.
- This result was dose dependent, with those continuing to use cannabis throughout pregnancy showing a mean reduction in birth weight of 277 g compared with 156g in those who only used it in early pregnancy.
- A recent meta-analysis by Gunn et al showed a pooled mean difference for birth weight of 100 g, which is like previous estimates. There is debate as to whether this represents a clinically meaningful difference, but it certainly identifies a fetal effect.
- Others have proposed that with increasing THC potency over time, we might see a greater magnitude of difference between users and nonusers.

Neonatal Outcomes: Neurodevelopment

- Probably the greatest contribution that the OPPS, MHPCD, and GenR studies have provided is information on the effects of cannabis on neurodevelopment and mental health.
- In utero exposure to marijuana has been linked to a “withdrawal”-like syndrome in newborns, demonstrated by an increase in startles and tremors and reduced habituation to light.
- In the GenR population, increased aggressive behavior and attention deficits were seen as early as at 18 months.
- By preschool age, difficulties with verbal and visual reasoning, hyperactivity, attention deficits, and impulsivity became apparent in both the OPPS and the MHPCD populations and persisted throughout the school years.
- At age 10, depressive and anxious symptoms became apparent and were found to predict earlier cannabis use and poorer adolescent and early adult achievement.

Neonatal Outcomes: Neurodevelopment

- While these findings suggest that marijuana is not without potential harm, these studies are limited in terms of their ability to control for several environmental and socioeconomic factors.
- Furthermore, some findings were not reliably reproduced between the cohort studies, suggesting a complex relationship between the effects of marijuana on neurodevelopment.
- For example, in the OPPS and MHPCD studies, the preschool population was found to have lower scores on memory and verbal reasoning testing, a finding not reproduced by the GenR study.
- Further information and clarity on the effects of cannabis on the developing brain will require future study, but at this time, it does not appear that cannabis use in pregnancy portends a specific phenotype that can be reliably reproduced.

Maternal Risks

- Maternal risks of marijuana use are related to the mode of ingestion and its addictive potential.
- Approximately 8% of people who try marijuana will develop cannabis dependence. Cannabis use disorder, like other substance use disorders, is characterized by impaired control, social difficulties, risky use, tolerance, and withdrawal as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition.
- Treatment programs are limited, and no single method has been proven superior. Any treatment appears to be better than none, and where outpatient treatment programs are available, they should be used.
- No pharmacotherapy has been shown to be effective at mitigating withdrawal symptoms other than THC replacement.
- Harm reduction options include using vaporizers or edibles instead of smoking (reducing the maternal carcinogenic risk, but not risk to the fetus), avoiding smoking indoors and around children, and using prescribed tapering doses of a synthetic cannabinoid.

Case Presentation

Julie is a 23-year-old nulliparous woman who is currently at 18 weeks' gestation. Her pregnancy has been uncomplicated to date. She presents to your office with an urgent concern of diffuse abdominal pain and intractable nausea and vomiting. Findings of investigations, including bloodwork and imaging, are unremarkable. On history she admits to increasing cannabis use during the past week to mediate worsening symptoms of "morning sickness." Nausea and vomiting were not an issue in her first trimester. You wonder whether her cannabis use is contributing to the overall clinical picture.

Nausea and Vomiting in Pregnancy

- The antiemetic properties of cannabis products are widely known to the public and even depicted in Hollywood films and popular media.
- There is a prevalent belief that cannabis is “natural” and an “herb” that can be safely used for nausea in pregnancy.
- Pregnant women with access to cannabis products have been reported to use it for the treatment of nausea and vomiting in pregnancy.
- In a survey of women using medical cannabis products, 77% reported nausea and vomiting in pregnancy, and 68% reported using cannabis specifically for this purpose.

Nausea and Vomiting in Pregnancy

- Most pregnant women using cannabis for nausea and vomiting (92%) found it “effective” or “extremely effective.”
- Paradoxically, marijuana use before pregnancy has been associated with increased reports of nausea in pregnancy.
- Adding to the confusion, cannabinoid hyperemesis syndrome (CHS), a syndrome of episodic abdominal pain, nausea, and vomiting in chronic cannabis users, is being increasingly identified clinically.
- Thus, the relationship of cannabinoid products and nausea in pregnancy appears to be complex and poorly defined.

Nausea and Vomiting in Pregnancy

- Cannabinoid hyperemesis syndrome is largely described in case series and small retrospective studies in the emergency medicine literature
- Episodes of diffuse abdominal pain, nausea, and vomiting are typically acute in onset and last 24 to 48 hours.
- They are often preceded by a prodromal phase of escalating nausea, which leads to increased use of cannabis products.
- The symptoms of CHS are often alleviated by hot showers. Cannabinoid hyperemesis syndrome is thought to be largely underdiagnosed and over-investigated, and it responds poorly to traditional antiemetics.

Nausea and Vomiting in Pregnancy

- Proposed effective treatments include topical capsaicin cream (applied to the abdomen every 4 hours), haloperidol, and benzodiazepines, although long-term resolution requires the cessation of cannabis products. Consideration of a diagnosis of CHS might be warranted in patients with nausea and vomiting in pregnancy that is atypical and difficult to treat.
- As a treatment option, cannabis products have a greater side effect profile than alternate options, with insufficient data for safety.
- Given the potential for neurodevelopmental effects, cannabis is not recommended for the treatment of nausea and vomiting in pregnancy, and pregnant women should be encouraged to abstain from use.

Cannabinoid Hyperemesis Syndrome

Box 1. Characteristics of cannabinoid hyperemesis syndrome

The following are characteristics of cannabinoid hyperemesis syndrome:

- Chronic marijuana use
- Acute-onset nausea, vomiting, and abdominal pain
- Symptoms alleviated by hot showers
- Episodes typically last 24 to 48 h

Data from Richards,²⁷ Simonetto et al,²⁸ and Hernandez et al.²⁹

More on Breastfeeding

- Tetrahydrocannabinol is a fat-soluble molecule excreted in human breast milk in moderate amounts.
- In chronic heavy users, the milk-to-plasma ratio can be as high as 8:1 and metabolites of cannabis are found in infant feces and urine, suggesting that it might be absorbed and metabolized by the infant.
- Animal studies suggest that exposure to cannabis while breastfeeding has implications on neurodevelopment similar to in utero exposure.
- Human studies are few and generally small. In 1990, a prospective cohort study by Astley and Little found that exposure to THC through breast milk in the first month of life was associated with a mean (SD) increase of 14 (5) points on the Bayley Scale of Infant Development at 1 year of age.
- The adverse effect was persistent after controlling for maternal smoking, alcohol drinking, and cocaine use during pregnancy and lactation.

More on Breastfeeding

- The results, however, were confounded by maternal marijuana use in the first trimester, and it was unclear which exposure was to blame for the effect seen.
- Given the small sample sizes of studies to date and the lack of more recent studies, there is a paucity of data from which to make a conclusion about the risks of cannabis use in lactating mothers.
- While the Academy of Breastfeeding Medicine urges careful consideration of the risks and benefits of breast-feeding in the setting of moderate, long-term marijuana use, they also acknowledge that the data remain “not strong enough” to recommend against breastfeeding with any marijuana use.

Infant Safety and Maternal Use

- Further considerations include the risks of second-hand cannabis exposure and impaired caregivers.
- Second-hand cannabis exposure is an independent risk factor for sudden infant death syndrome.
- Considering that breastfeeding is protective for sudden infant death syndrome, this warrants a careful weighing of the risks and benefits of breastfeeding while using cannabis.
- At the very least, lactating mothers should be counseled to smoke outside of the home and change their clothing before caring for their infant.

Infant Safety and Maternal Use

- Although **no studies** have been done on the subject, a mother's ability to care for her child while she is impaired might be compromised owing to cannabis's effect on mood and judgment.
- What implications this might have with regard to the involvement of child protective services will likely depend on an assessment of elements such as support systems, other substance abuse, and the extent of their cannabis use.
- Cannabis use itself is not an indication for involvement of child protective services, and punitive discussions can lead to further harms such as discontinuation of prenatal care.

Infant Safety and Maternal Use

- Instead, an assessment for dependency, education regarding the risks of marijuana use, an assessment of willingness to quit, and a discussion of harm reduction options as described above are the mainstays of interventions available at this time.
- While community resources for marijuana substance use disorder are currently scarce across the country, with the legalization of marijuana, we might see this change in the coming years.
- Recently, the Society of Obstetricians and Gynecologists of Canada has created excellent online educational tools including interactive websites, videos, and posters on marijuana use in pregnancy and lactation.
- These are valuable resources examples to which we can point our patients to further explore these topics and concerns.

Case Resolution

Julie is admitted to the hospital for 48 hours of intravenous fluids and antiemetic medications. Her symptoms do not respond to most interventions during her admission other than hot showers, where she spends most of her time. After 48 hours her symptoms resolve spontaneously and she requests discharge home. Before discharge she is counseled regarding the safety of cannabis and its contribution to her clinical picture, and is given the following information:

Fact Sheet on Cannabis and Pregnancy

- Cannabis is a complex plant with more than 400 chemicals that pass from the mother to the baby in pregnancy and in breast milk postpartum.
- Cannabis use in pregnancy has been associated with a “withdrawal” syndrome in the newborn and can make your baby more irritable.
- Exposure in the uterus might have long-term effects on your child’s brain development and mental health.
- Chronic cannabis use can lead to cannabinoid hyperemesis syndrome, which causes episodes of diffuse abdominal pain, nausea, and vomiting often relieved by hot showers. These symptoms last 24 to 48 hours. The only way to stop them from recurring is to stop using cannabis products.
- There are alternate options for management of nausea and vomiting in pregnancy that have been proven to be safe and effective, with fewer side effects.
- If you are having trouble with nausea and vomiting in pregnancy, please contact your pregnancy care provider.

Table 2. Summary of findings of 3 important longitudinal prospective studies

| CATEGORY | OPPS ⁹ | MHPCD ^{2,10} | GENERATION R ^{1,11} |
|----------------------------------|--|--|--|
| Gestational age and birth weight | <ul style="list-style-type: none"> • Delivery at earlier gestational age in exposure group • No differences in birth weight | <ul style="list-style-type: none"> • Shorter gestation for exposure after first trimester only • Increased birth weight after third trimester exposure | <ul style="list-style-type: none"> • Fetal growth reduced from second trimester onward • Lower birth weight in exposed group |
| Neonatal | <ul style="list-style-type: none"> • Increased startle response | <ul style="list-style-type: none"> • No differences in neonatal behaviour | <ul style="list-style-type: none"> • Not examined |
| Infant | <ul style="list-style-type: none"> • 6 mo to 3 y: no neurobehavioural defects | <ul style="list-style-type: none"> • Not examined | <ul style="list-style-type: none"> • 18 mo: increased aggression and inattention problems in exposed girls only |
| Preschool | <ul style="list-style-type: none"> • 4 y: poorer performance on verbal and memory subscales • No effect on global intelligence | <ul style="list-style-type: none"> • 3 y: lower short-term memory and verbal reasoning scores | <ul style="list-style-type: none"> • 3 y: no significant deficits in cannabis-exposed group |
| School age | <ul style="list-style-type: none"> • 6 y: poorer sustained attention. No effect on impulse control • Higher parental ratings of inattention and misconduct • 6 to 9 y: impaired visual perception, visual memory, and language comprehension • Increased distractibility | <ul style="list-style-type: none"> • 6 y: more impulsivity, hyperactivity, and delinquency • 9 y: impaired abstract and visual reasoning • Impaired executive functioning • Poorer reading, spelling, and academic achievement • Depressive and anxious symptoms | <ul style="list-style-type: none"> • 6 to 8 y: altered brain morphology in the frontal cortex |
| Teens and young adults | <ul style="list-style-type: none"> • 14 to 16 y: deficits in visual-cognitive functioning • 17 to 22 y: deficits in executive functioning, response inhibition, and visual-spatial working memory • Increased smoking and early substance use | <ul style="list-style-type: none"> • 14 to 16 y: deficits in academic achievement (especially reading), information processing speed, and visual motor coordination • Increased rates of delinquency • 17 to 22 y: increased rates of smoking and early initiation of substance use | <ul style="list-style-type: none"> • Not yet examined |

In Summary!

- In utero exposure to cannabis has been associated with long-term neurodevelopmental outcomes that persist into young adulthood.
- Pregnant women should be counseled regarding these risks and encouraged to abstain from use.
- Maternal risks of cannabis use are related to the mode of ingestion and its addictive potential. Harm reduction options should be offered to those not able to quit completely.

In Summary!

- The relationship between cannabis and nausea in pregnancy is complex and remains poorly defined. While women using it in pregnancy often find it effective, chronic use might be associated with cannabinoid hyperemesis syndrome, a condition characterized by episodes of acute abdominal pain, nausea, and vomiting.
- There are other safe and effective treatments for nausea and vomiting that should be used first line.
- Tetrahydrocannabinol is excreted in human breast milk. Human data have suggested possible impaired infant motor development at 1 year in children exposed to cannabis while breastfeeding; however, these data are limited.