



Cannabis use should be discouraged during pregnancy and lactation.

Cannabis in Pregnancy and Lactation – A Review

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Abstract

Cannabis (marijuana) is now legal for either medicinal use or recreational use in 33 states with more states considering legalization for medicinal and/or recreational use. More women planning pregnancy, pregnant, or breastfeeding will present with exposure to marijuana. A familiarity with the pharmacology and potential effects for pregnancy and lactation is important for the obstetrical care provider to permit optimal counseling for the gravida. This paper provides a pertinent review of cannabis for the obstetrical care provider. The literature available for review concludes that no amount of marijuana and associated product use in pregnancy and lactation is safe. Cannabis and associated product use has the potential for adverse maternal, fetal, and long-term childhood development and its use should be discouraged during pregnancy and lactation.

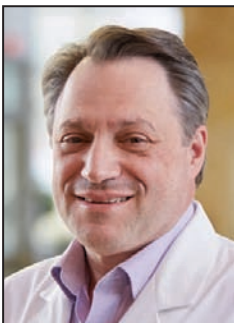
Introduction

Marijuana or cannabis is also known by many slang terms including weed, herb, pot, grass, bud, ganja, and Mary Jane. Cannabis has a long history with evidence of use for medicinal, spiritual, and recreational use dating at least 5000 years ago.^{1,2} Historical texts show most ancient civilizations utilized cannabis for medicinal and spiritual properties.³ Cannabis use as a medicinal has been reported in the United States during the 19th and early 20th centuries.⁴ Medical marijuana was first described in the United States in 1850. The various modes of use include smoking, dabbing, eating, and most recently vaping.

As of June 2019, 11 states have adopted laws legalizing recreational use of marijuana. Another 22 states allow for the use of medical marijuana.⁵ The federal government does not recognize cannabis as a legal drug. Cannabis

is the most commonly used illegal drug in the United States of America (USA). Approximately 22.2 million individuals use marijuana each month. One in 10 individuals will become addicted if over the age of 18 years and 1 in 6 will become addicted if use occurs under the age of 18 years.⁶ Long term and frequent use have been associated with increased risk for psychosis and schizophrenia.

As legalization of marijuana has spread across the USA, the perception of safety in pregnancy has also increased.^{7,8,9} Approximately 1 in 25 pregnant women are estimated to use marijuana during pregnancy.¹⁰ In a research letter using data from



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the National Surveys of Drug Use and Health from 2005 to 2012 reported that the percentage of women who reported “no risk” of harm rose from 25.8 % in 2005 to 65.4 % in 2012.¹¹ This paper will review the pharmacology and the potential effects of marijuana use in pregnancy and lactation.

Pharmacology

Marijuana is composed of the leaves and flowers of the Indian hemp plant. The potency varies based on location of origin, method of cultivation, and method of storage. The active ingredient tetrahydrocannabinol (THC) is present in all parts of the plant. However, the most concentrated and strongest marijuana comes from the resin in the flowering tops of the female plants. The plant contains greater than 400 other chemicals including approximately 60 compounds chemically related to THC known as cannabinoids. Additionally, there are over 2000 compounds produced by thermal decomposition during smoking.¹²

The psychoactive metabolite of cannabis is delta-9-tetrahydrocannabinol (THC) that acts on cannabinoid receptors within the central nervous system (CNS) and peripheral tissues.¹³ THC acts on cannabinoid receptors – CB1 found in CNS and CB2 found in peripheral tissues.¹⁴ THC is similar in chemical structure to the human brain chemical anandamide. Anandamide is an endogenous cannabinoid which functions as a neurotransmitter within the endocannabinoid system.^{13,15} This system plays a critical role in the normal functioning of the nervous system and homeostasis. The endocannabinoid system is involved in a wide variety of processes including pain, memory, mood, appetite, stress, sleep, metabolism, immune function, and reproductive function. Therefore, interfering with this system can have profound effects. For example, THC can alter functioning of the hippocampus affecting memory and focus. THC also can disrupt functioning of the cerebellum and basal ganglia resulting in loss of balance, coordination, and a decrease in reaction time.¹⁶ This similarity in structure between THC and anandamide allows the brain to recognize THC in a manner like anandamide.

Psychological effects include euphoria as THC can increase the release of dopamine. This effect may lead to psychological habituation noted below. Effects of THC can vary amongst individuals. Some

will experience visual disturbance, laughter, increase in appetite, and distortion in judgment, time, and space. Visual hallucinations, anxiety, depression, psychosis, mood disturbance can also occur. If marijuana is used as an edible or beverage, the effects can be delayed by approximately 30 minutes to an hour due to tablets and within the digestive tract. Eating or drinking marijuana results in significantly less THC in the bloodstream when compared to smoking an equivalent amount. Because of these delayed effects, increased consumption of THC can lead to toxicity.¹⁷

The physical effects of cannabis use include but are not limited to red eyes, dryness of the mouth, increase in heart rate, chest tightness when smoked, drowsiness, and unsteadiness with decreased muscle coordination.

Chronic use does not appear to lead to physical dependence. Therefore, withdrawal is not a known effect of cannabis use when discontinued. However, this drug can be psychologically habituating. THC remains in the body for approximately 48 hours after smoking. Therefore, the residual effects on cognitive function including memory can last up to 48 hours.¹⁸

THC is metabolized within the liver, brain, lung, and intestine to hydroxylated and carboxylated metabolites. These metabolites are stored within the peripheral tissues and eventually excreted in the urine or feces dependent upon mode of use, inhalation or edible, respectively. Within a 5 day window, approximately 80 to 90 percent of THC is eliminated.¹⁹

Indirect exposure can occur during passive smoking of cannabis. Fifty percent of THC survives pyrolysis during smoking with 6 to 53 % released in the air. Therefore, passive inhalation can occur if the individual is within proximity of the smoker. A positive drug screen is possible following passive exposure.²⁰

Marijuana Exposure in Pregnancy

The incidence of marijuana use in pregnancy has increased. According to Centers for Disease Control (CDC) estimates, approximately 1 in 20 women self-reports the use of marijuana in pregnancy.^{21, 22} As with most self-reporting, this likely underestimates the number of women utilizing marijuana in pregnancy. A recent study found that this number has increased to approximately 18% or approximately 1 in 6 women. These numbers are likely to further increase as more states legalize recreational use of marijuana, resulting



in the perception that marijuana use is safe. A research letter using data from the National Surveys of Drug Use and Health from 2005 to 2012 reported that the number of women who recently used marijuana and believed the drug to be safe in pregnancy increased over this time frame from 25.8 % to 65.4 %.⁷ Women prior to pregnancy and during pregnancy utilize cannabis by many different routes including but not limited to smoking, edibles, vaping, lotions and other.²³

Maternal Effects

The maternal risks of marijuana use are related to method of ingestion, associated risk behaviors, polysubstance abuse, and associated mental health complications. Cannabis use disorder is defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition by impaired control, social difficulties, risky use, tolerance, and withdrawal.²⁴

Multiple studies have shown an association with depression, anxiety and other psychiatric conditions.^{25, 26} Such associated mental health conditions can lead to addiction as the marijuana is used to treat the underlying psychiatric illness. Screening for and referral for management of co-existent psychiatric conditions is imperative to decrease the use of marijuana in pregnancy.

Also important for the obstetrical care provider is awareness of cannabinoid hyperemesis syndrome.^{27, 28} Cannabinoid hyperemesis syndrome (CHS) can be challenging to differentiate from hyperemesis gravidarum. CHS should be considered in patients presenting with hyperemesis gravidarum with a history of chronic marijuana use, atypical presentation, and failure to improve with the usual course of management. CHS is characterized by a history of chronic marijuana use; acute-onset nausea, vomiting, and abdominal pain; symptoms alleviated by hot showers; and episodes lasting 24 to 48 hours.^{28, 29, 30} Resolution requires discontinuation of marijuana use.^{28, 30}

Although robust studies are lacking in regard to maternal complications of marijuana use in pregnancy, the data available to date suggests that pregnant women need to be educated

to the potential adverse effects on their health and encouraged to discontinue marijuana use in pregnancy.

Fetal and Long-Term Childhood Effects

Studies regarding the use of marijuana in pregnancy have provided conflicting results.³¹⁻⁴³ This is likely due to the challenges in controlling for confounding factors including but not limited to other associated drug use, challenges in quantifying the amount of drug used, difficulties in evaluating childhood development due to other familial/socioeconomic economic factors. Thus, definitive guidelines regarding marijuana use in pregnancy are challenging.

The American College of Obstetrics and Gynecology (ACOG) published a committee opinion in 2017.⁴⁴ In this opinion, the ACOG recommends that women attempting pregnancy, currently pregnant, or breastfeeding avoid marijuana use. The American Academy of Pediatrics also recommends against marijuana use in women who are breastfeeding.⁴⁵

The literature regarding marijuana use in pregnancy is varied and many of the studies have limitations as would be expected in studying a drug in pregnancy. There are recall biases for self-reporting amount and timing of use, confounding variables difficult to control, and meta-analyses with variability in study design. Taking the aforementioned in consideration, the following findings are applicable at this time pending further study.

The inherent physiologic endocannabinoid system is known to be important in human pregnancy. This system has been shown to be important for implantation and pregnancy maintenance.⁴⁶ The role of THC use in implantation and pregnancy maintenance is unclear at this time.

There has not been consistent data to date to suggest an increase in fetal anatomic abnormalities. Likewise, there is no consistent data to show an association with preterm delivery and other adverse pregnancy outcomes in patients reporting only marijuana use.^{31, 32, 33} Preterm labor and delivery can be increased in women using other substances such as tobacco.³⁴ Earlier data suggested that perinatal morbidity/intrauterine fetal demise does not appear



to be increased in patients using marijuana alone in pregnancy. Like preterm delivery, use of other substances such as tobacco may slightly increase the risk of stillbirth in this patient population. A recent retrospective cohort analysis controlling for many of the confounders that affected other studies showed newborns exposed to marijuana had increased rates of lower birth weight - 218 g less; low birth weight, deliver preterm; admitted to the neonatal intensive care unit, and have lower Apgar scores than matched newborns not exposed to marijuana.³⁵ This adds to the literature for concern regarding marijuana exposure in pregnancy.

Regarding neurobehavior development, THC crosses the placenta and enters the fetus at a level of approximately 10% maternal levels.⁴⁷ This level is likely increased with heavy and repetitive use as the half-life of THC can vary based on amount and repetition of use. Fetal brain development can therefore be impacted as the fetal brain contains cannabinoid receptors type 1 as early as 14 weeks' gestation necessary for normal brain development. The THC can preferentially bind to these cannabinoid receptors potentially resulting in abnormalities in brain development and response to endogenous neurotransmitters.^{47, 48} Newborns with in utero exposure to THC can undergo a neonatal abstinence like syndrome characterized by tremors, increased startle reflex and reduced habituation to light.⁴⁹

Children exposed *in utero* to have been found to have lower scores on tests of visual problem solving, visual-motor coordination, and visual analysis, decreased attention span, behavioral challenges than children who were not exposed to marijuana in utero.^{50, 51, 52} There have been no consistent findings regarding cognition and school performance. This is likely due to the multiple confounding variables in studies involving education and school performance. However, studies have shown these children have challenges throughout the educational milestones.

Most recently, a large retrospective analysis of live births in Ontario, Canada has shown an association between cannabis use in pregnancy and the incidence of autism spectrum disorder in their offspring. Women who reported cannabis use without associated tobacco, alcohol or opioid use had an adjusted hazard ratio of 1.51 (confidence interval of 1.17 to 1.96) for a child with a diagnosis of autism.⁵³ This study also found an increase

incidence of intellectual and learning disabilities in the children of women who used cannabis in pregnancy. These results support previous studies reporting similar findings as referenced above.

Lactation

To date, most of the literature assessing the effects of marijuana exposure to the neonate through breastfeeding have studied the pharmacokinetics of THC and breast milk.^{54, 55, 56} As cannabinoids are lipophilic, cross the blood brain barrier, affects to the developing fetal brains raise significant concerns. Studies have shown that the concentration of THC in breast milk is variable based on the amount and frequency of maternal ingestion. Unlike many other drugs and medications that are excreted into breast milk but are not concentrated in breast milk, THC is excreted and concentrated in the breast milk. Breast milk can have up to eight times the concentration of maternal plasma and can be detectable for up to 6 days.⁵⁶

Additionally, THC can be found in breast milk approximately 1 hour following ingestion.⁵⁶ Therefore, pumping and dumping between feeds is not likely to significantly decrease the exposure to the neonate.

As individuals with passive inhalation of secondhand marijuana smoke have been shown to have THC present in bodily fluids, one must assume that secondhand exposure can also effect the breast milk and therefore the neonate. Passive or secondhand exposure to marijuana while breastfeeding should be avoided given the potential for harm.⁵⁷

Medical Marijuana

A review of the literature regarding the effectiveness of medical marijuana in decreasing pain and in management of chronic pain syndromes is outside the scope of this paper.

Medical marijuana is not regulated by the Food and Drug Administration. Given that maternal, fetal, and neonatal effects are present as noted above, women managed with medical marijuana should be encouraged to discontinue the medical marijuana and adopt more traditional strategies for management of their underlying medical condition(s) in pregnancy.

Cannabidiol

Cannabidiol (CBD) is a chemical obtained from the Cannabis sativa plant primarily from the hemp



type.^{58, 59, 60} Hemp and marijuana are both in the Cannabis family, but hemp contains very little (less than 0.3 percent) of the psychoactive compound delta-9-tetrahydrocannabinol (THC). CBD, unlike marijuana, does not produce a psychoactive response. The FDA has approved only one CBD product as a prescription drug indicated for the management of rare forms of seizure disorder in children.⁵⁹

The Farm Bill passed in 2018 made the sale of hemp and hemp products legal in the United States. It remains illegal to tout medicinal properties of CBD. Despite lack of scientific evidence for efficacy, CBD has gained in popularity in products such as cosmetics, creams and ointments for pain relief, dietary supplements, treatments for anxiety, management of some neurologic disorders as seizures and Parkinson's, and in edibles. The science and pharmacology of CBD is unknown. Effects on the brain is a proposed mechanism of action. There are no approved dosing regimens. The amount of CBD in these products is variable and the safety of CBD is unclear. Reported side effects include but are not limited to: dry mouth, low blood pressure, light headedness, and drowsiness. Liver injury has been reported. Possible interactions with prescription medications, alcohol, or other illicit drugs remains unknown potentially causing serious side effects.⁵⁹

The Food and Drug Administration (FDA) citing lack of data and concern from animal studies strongly advises against the use of cannabidiol (CBD) in any form during pregnancy or while breastfeeding.⁵⁹ High doses of CBD given to pregnant test animals suggest abnormalities in the reproductive system of developing male fetuses including decreased testicular size, low testosterone, and abnormalities of spermatogenesis.⁶¹ There is an extrapolation from information available to suggest that some amount of CBD will be transferred to babies through breast milk.

There are the additional concerns for CBD products to be contaminated with other potentially harmful substances to the developing fetus or neonate including but not limited to: THC, pesticides, heavy metals, bacteria, and fungus.

In summary, the use of CBD in any form should be discouraged during pregnancy and during lactation.⁵⁹

Conclusion

As states continue to legalize medical and recreational marijuana, more women planning pregnancy, pregnant, or breastfeeding will present with exposure to marijuana. In summary, the literature available for review suggests that no amount of marijuana use in pregnancy and lactation is safe. Marijuana use has the potential for adverse maternal, fetal, and long-term childhood development. Women contemplating pregnancy or pregnant should discontinue marijuana use. Consultation with an addiction specialist and/or mental health provided may be indicated. Passive or secondhand exposure to marijuana also may have potential effects and should also be avoided. Given the concerns regarding the potential for adverse pregnancy outcome, prenatal care should be adjusted to screen for the potential adverse outcomes.

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Disclosure

None reported.

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