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Marijuana Use during Pregnancy

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Abstract

In recent years, there has been a considerable rise in the prevalence of marijuana use during pregnancy in the United States. Our study aimed to thoroughly review the current prenatal and postnatal studies and to evaluate the harmful effects of cannabis use during pregnancy. Our literature review has demonstrated that the use of cannabis can have various detrimental effects on development, effects that show up at various developmental stages, including the prenatal, newborn, and adolescent stages. Serious prenatal impacts include poor birth weight, anemia, and other long-term impacts such as poor neurocognitive development. Adolescents whose mothers used cannabis during pregnancy have been reported to suffer from decreased attention, increased hyperactivity and impulsivity, and the earlier onset of substance use. Cannabis use during pregnancy is of great concern, and further research is needed to understand and prevent the harmful prenatal and postnatal effects of cannabis.

Keywords: Endocannabinoid system; CB1-Receptor; Cognitive abilities; Screening; Pre-natal exposure; Pharmacotherapy; Psychotherapy

Abbreviations: THC: Delta-9-tetrahydrocannabinol; ECS: Endocannabinoid System; OPPS: Ottawa Prenatal Prospective Study; MHPCDP: Maternal Health Practices and Child Development Project; TSF: Twelve-Step-Facilitation; MET: Counseling, Motivational Enhancement Therapy; CBT: Cognitive-Behavioral Therapy; CM: Contingency Management; BMDC: Brief Marijuana Dependence Counseling; FMRI: Functional Magnetic Resonance Imaging ; MTP: Marijuana Treatment Project

Introduction

As society's views and laws soften in regard to cannabis, there has been a significant increase in the prevalence of cannabis use in the United States. Currently, twenty-nine states and the District of Columbia have laws regulating the use of medicinal cannabis. In the period of 2001-2002, the past-year prevalence of cannabis use was 4.1%, and in the period of 2012-2013, the past-year prevalence of cannabis use rose to 9.5%. These increases were observed across various demographic categories, including age, sex, race, education, income, region [1]. Interestingly, cannabis is the most commonly used illicit drug among pregnant mothers [2]. The National Survey of Drug Use and Health speculates that at least 10% of pregnancies in the US are associated with fetal cannabis exposure [3]. Further studies have indicated that 3.85% of pregnant women between the ages of 18 and 44 reported past-month marijuana use in 2014, compared with 2.37% in 2002 [4]. In self-reporting studies, the prevalence of past-month cannabis use during pregnancy rose to 62% between 2002 and 2014 [5]. The perceived safety of cannabis, compared to other recreational drugs such as heroin or cocaine, may contribute the mounting use during pregnancy. More than 65% of UK adults surveyed in 2015 reported that cannabis was "not very harmful" or "not at all harmful," whereas, less than 5% of those surveyed had similar thoughts regarding to heroin or cocaine [6]. Moreover, some pregnant women use the drug to mitigate nausea and vomiting associated with pregnancy [7]. One 2014 study reported that pregnant women who experienced severe nausea were significantly more likely to report cannabis use during pregnancy (3.7% vs 2.3%; PR=1.63, 95% CI: 1.08-2.44) [8].

In combination with the persistent increase in the prevalence of cannabis use over the last 20 years, the potency of the active cannabis components has also increased significantly within the same time frame, from ~4% in 1995 to ~12% in 2014 [9]. Although the number of women who use marijuana during

pregnancy continues to rise, impact on fetal outcomes is not yet clearly understood, especially with the newer and stronger strains of cannabis. There is growing evidence from human and animal studies emphasizing the negative effect on the fetus; however, these studies cannot be usefully generalized to humans. These negative effects include low birth weight and anemia, as well as more long-lasting effects such as alterations in neurocognitive development, higher rates of depression, and anxiety, all of which can manifest in childhood, and impaired higher-order executive functions (e.g., impulse control, visual memory, and attention) [10]. The potential impairment of executive functions is especially worrisome due to their importance in day-to-day functioning. Integral neural development assists in executive functions, the sort of cognitive skills we run use to analyze, plan, and execute a task aiming to achieve desirable outcomes. This ability is used in various daily settings such as work, school, and social interactions. Although the executive functions continue to develop in adolescence and adulthood, prenatal neural development of these functions creates the base upon which later abilities build. The use of cannabis during pregnancy may impair this growth and thus may possibly affect executive functions in adulthood. Thus, research on cannabis use during pregnancy is necessary and of interest to the larger medical community [11].

Endocannabinoid System during Neural Development

Cannabis preparations, such as marijuana, are derived from the female plant of Cannabis Satvia, which is comprised of approximately 60 plant-derived cannabinoid compounds. Of these compounds, Delta-9-tetrahydrocannabinol (THC) is the main psychoactive constituent [12]. Smoking, ingesting, or consuming vaporized cannabis preparations ("vaping") lead to feelings of tranquility and euphoria, an increased sensitivity to stimuli (e.g., colors), an altered perception of time, and appetite stimulation. However, there is another side to cannabis use that is more negative. Besides these generally sought-after effects, use can lead to deterioration in cognition, judgment and motor coordination. Additionally, when the serum blood of THC rises, cannabis users may experience agitation, fear, paranoia, and hallucinations [13].

Research targeting the effects of THC on the brain led to the discovery of the endocannabinoid system [10]. The endocannabinoid system (ECS) is composed of a group of endogenous cannabinoid receptors, their interacting proteins (the endogenous cannabinoids), and the enzymes responsible for the formation and degradation of the endogenous cannabinoids. The ECS is involved in a number of physiological processes throughout the central and peripheral nervous systems. Such processes affect mood regulation, appetite, and the metabolic impact of glucose homeostasis, memory, analgesic modulation, and mediating the psychoactive effects of cannabis [14]. One of the primary endocannabinoid receptors, cannabinoid receptor type 1 (CB1-R) is found in the central and peripheral nervous systems. CB1 receptors are expressed in the cerebral cortex, hippocampus, caudate nucleus, putamen, and cerebellar cortex of the human fetal brain. CB1-R is also a major neuronal target of THC and synthetic derivatives (e.g. "K2/Spice"), in both the adult and embryonic brain [15].

Scholars have proposed theories which argue that using cannabis during pregnancy may interfere with the neurodevelopment of the fetus. The ECS develops in the embryo at around day 16 of gestation and is thought to be a leading factor in neurodevelopment and brain formation. Furthermore, the endocannabinoids regulate brain development by controlling neural proliferation, migration, and the differentiation of lineage-committed cells. Additionally, the ECS has been shown to have a prominent role in the migration and genesis of neurons, as well as the outgrowth of their axons and dendrites. Endocannabinoids affect short- and long-term synaptic plasticity and also attenuate presynaptic neurotransmitter release. Disruption of CB1-R-mediated control of synaptic plasticity may lead to neuronal circuitry failures.

THC freely crosses the placental barrier and may directly have an effect on the CB1-receptor that has been found in the human placenta and developing fetal CNS. The limbic region within the brain is responsible for mood and conscious behaviors in humans and other mammals. The primary structures within the limbic system include the amygdala, hippocampus, thalamus, hypothalamus, basal ganglia, and cingulate gyrus. These regions are rich in dopaminergic neurons and their D1, D2 dopamine receptors.

Recent animal studies that examined the effect of prenatal cannabis exposure have observed alterations in neurotransmitter and neuroendocrine systems in the offspring of exposed rats, particularly within the dopaminergic pathways [16]. These changes were usually observed weeks after the initial exposure to THC. A decrease of dopamine, its metabolites, and D1 receptors were detected in the second postnatal week of female rats. However, all measures returned to normal levels within one month. By the end of the first postnatal month in male rats, the dopamine synthesis rate-limiting enzyme, tyrosine hydroxylase, and dopamine metabolites were increased. No changes in the levels of dopamine receptors were observed. Studies using rodents, detect a multitude of lasting neurobiological alterations in the off-spring of cannabinoid treated mothers, such as different neuroendocrine and neurotransmitter systems with the most profound effects reported in the dopaminergic system [17]. Hyperactivity and alterations in locomotor habituation and exploratory behavior in adulthood were most pronounced in female rats, although some marginal behavioral alterations were also reported in males. No lasting effects were found on startle magnitude and sensorimotor gating in male rats on different ages tested. Chronic cannabinoid treated rats showed deficient sensorimotor gating and higher anxiety-related behavior, however no lasting effects in short term memory processing and locomotor activity in general were detected.

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As noted earlier, findings from animal studies cannot be generalized directly to humans; however, they may help in better understanding to some of the mechanisms by which cannabis may affect neurodevelopment. Our comprehension of how THC affects the human neuropsychiatric system increased exponentially with the ability to use situ hybridization techniques to visualize messenger RNA (mRNA) distribution in human fetuses. A decrease in D2 receptor mRNA expression was observed in the basal amygdala, and this alteration was correlated with the amount of maternal cannabis use. This observation was specific, as no similar changes were noted in the hippocampus or striatum. In addition, only human male fetuses displayed marked D2 receptor reduction, and similar sex-related variances were reported in animal studies. These sex-specific differences highlight male susceptibility to cannabis exposure when tested for performance in attention, learning, and memory. Furthermore, those neural structures involved are significant in the development of behavioral and mood disorders and the shifting of dopamine receptor expression may be attributable to the impaired social behaviors and depressive symptoms reported in longitudinal studies of children whose mothers used cannabis when pregnant.

Exposure to TCH affects the dopaminergic signaling in the nigrostriatal tract, too, beyond the mesolimbic system. In perinatally exposed rats, decreased tyrosine hydroxylase activity is observed, in conjunction with an increase in the concentration of receptors in the striatum. This suggests that the diminished presynaptic activity, induced by the THC exposure, may upregulate postsynaptic D1 and D2 receptors. Furthermore, presynaptic activation of D2 receptors may modulate the synthesis of neurotransmitters and their release [18]. However, human fetuses with prenatal cannabis exposure reported no changes in dopamine receptor mRNA expression in the striatum or in non-mesolimbic dopamine systems. Longitudinal human studies have not shown an association between perinatal cannabis and motor impairment, such as Parkinson's disease in human studies of adults who were prenatally exposed to THC, the nucleus accumbens showed decreased coding for D2 receptors [19].

Short Term/Acute Consequences of Prenatal Substance Use in the Newborn

Cannabis has a long half-life and can be measured in the body for up to 30 days after use, a circumstance which may leave the fetus vulnerable for an extensive period of time after the initial use of cannabis. Additionally, the THC concentration found in human breast milk may be up to eight times higher than levels found in maternal plasma [20]. This may contribute to the possibility of continued neurological effects even after delivery when there is a continuation of maternal cannabis use. Longitudinal studies in humans with prenatal cannabis exposure have demonstrated exaggerated startle responses and poor habituation to novel stimuli in infants as well as hyperactivity, inattention, and impaired executive function in adolescents. In the first week after delivery, neonates prenatally exposed to cannabis were observed to have tremors and prolonged, exaggerated startle responses. Such a response was observed with both mild and spontaneous stimuli. In the same study, the exposed newborns spent less time in quiet sleep and exhibited a high-pitched cry. In addition, these newborns evinced poor habituation to novel stimuli. There are some studies that also suggest that cannabis exposure may affect fetal growth and may modulate the regulation of insulin and glucose. Fetuses exposed to cannabis earlier in the pregnancy grew 11.2grams per week more than the fetuses that were not exposed, and this effect was more significant in women who used cannabis throughout pregnancy. However, there are some contradictory results; for instance, some studies have observed a decrease in birth weight, and others observed no difference. The clinical significance of this diminution is arguable, as the reported growth differences are on the order of 100g.

The Ottawa Prenatal Prospective Study (OPPS) and the Maternal Health Practices and Child Development Project (MHPCDP) are two studies that have followed groups of children and their mothers over a long period of time. Both have demonstrated that prenatal cannabis exposure in the fetus has various detrimental effects, include neurocognitive challenges in the areas of short-term memory, as well as verbal outcomes, aspects of attention, impulsivity and abstract visual skills. These effects manifest after the age of three and continue into adolescence. At six years of age, prenatally exposed children demonstrated more impulsivity and hyperactivity, difficulties which continued into adolescence and coincided with challenges with abstract and visual reasoning, as well as visuo-perceptual functioning.

Chronic Neurobehavioral and Cognitive Functioning Consequences of Prenatal Cannabis Use through Adolescence to Adulthood

Longitudinal studies on children exposed to cannabis prenatally have found that these children demonstrate significant depressive symptoms at 10 years of age. Expanded analysis discovered that exposure during the first trimester increased the likelihood of depression [21,22]. Further studies have revealed that prenatal cannabis alters the expression of opioid-related genes in the human fetus and mesolimbic forebrain. An increase in mu and kappa receptor concentrations was found in the amygdala and medio-dorsal thalamic nucleus, respectively. Prenatal cannabis exposure may lead to impairments in the opioid system and the behavioral deficits seen later in adulthood. This effect has been found in animal studies: Prenatal THC-exposed rats have exhibited higher heroin-seeking behaviors during mild stress and drug extinction and seem inclined toward drug use. Alterations in the limbic system of cannabis-exposed human fetuses mean that as children and young adults, they display impairments in executive function and academic

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achievement. In addition, they often suffer from depression, anxiety, inattention, delinquency, and psychosis.

Data in the MHPCD cohort have demonstrated that children who were exposed to cannabis during the first and third trimester of the mother's pregnancy showed reduced levels of attention and increased hyperactivity and impulsivity by the time they were ten years old. Reading and spelling skills-as measured by academic reports-were poorer in the prenatally exposed group of children. By the age of 14, those prenatally exposed children were more likely to have low scores in math, reading, and spelling. Additionally, those children were associated with an earlier onset of substance use and greater duration of use than their matched counterparts, even after adjustment for the home environment and parental substance use.

Follow-up studies using functional magnetic resonance imaging (FMRI) showed that in the 35 OPPS participants (aged 18-22), there was a significant relationship between the quantity of prenatal cannabis exposure and brain activity in several regions. The participants performed four executive functioning tasks, and the neuroimaging results showed the continuing neurophysiological impact of prenatal cannabis exposure on those cognition areas. The results of all four executive functioning tests routinely showed that the exposed group required high neural activity in the posterior brain regions to conduct the tasks, higher than the non-exposed group needed. Both groups were able to successfully complete the tasks, but the increased activity of the prenatally exposed group suggests an apparent need for a compensatory response. We postulate that either additional brain regions are required to perform the tasks or that more activity in typically activated regions is necessary. Additionally, the results are suggestive of a required compensation or altered blood flow pattern that correlates with prenatal cannabis exposure.

Management of Cannabis Use during Pregnancy

Cannabis use during pregnancy has adverse effects on both maternal health and the developing fetus, either directly from the drug use itself or indirectly from the environment and social milieu associated with illicit drug use. It is likely that the number of women who use and report use of marijuana during pregnancy will increase due to legalization of recreational marijuana in many states. However, many pregnant women often underreport marijuana use to their health-care providers because of guilt, associated stigma, and the criminal consequences. For instance, fear of the losing custody of their children might prevent them from saying anything. It is also possible that inadequate understanding of the effects of cannabis use in pregnancy might mean that they do not think it is important enough to report to health-care providers. Nevertheless, early antenatal care and appropriate interventions can improve both maternal and fetal outcomes and prevent maternal and fetal morbidity, even mortality.

Screening for substance use in pregnancy plays a vital role in identifying women who are engaging in substance abuse. Substance use questionnaires should be included in the initial assessment for pregnant woman and subsequently repeated at each prenatal visit. Such a questionnaire might include various simple questions such as the amount, pattern, route, and frequency of marijuana use and whether any substance dependence is present. The interview should be open-ended and non-judgmental in order to allow physicians to become closer to their patients and obtain an accurate history, thus keeping care uninterrupted. If a woman acknowledges cannabis use, more detailed assessment is required to disclose the concomitant substance abuse, as well as other possible issues with substance abuse such as drinking, smoking, or misusing over-the-counter or prescribed medications. By doing so, we can relocate them to the addiction specialist services accordingly.

Identification of intoxication and withdrawal symptoms plays a vital role in treatment. The symptoms of marijuana intoxication include a unique combination of calmness and euphoria. Once intoxication progresses to acute intoxication, the user's sociability and sensitivity to certain stimuli (e.g., colors) are very high, the perception of time is altered, and appetite for sweet and fatty foods is stimulated. These pleasant changes are often associated with and outlast substantial impairments in cognition, judgment, and motor coordination. The DSM-5 (American Psychiatric Association 2013) introduces diagnostic criteria for marijuana withdrawal, which are the concurrence of at least three of the following symptoms: irritability, anger, or aggression; nervousness or anxiety; sleep difficulty; decreased appetite or weight loss; restlessness; depressed mood; or one or more physical symptoms causing significant discomfort (e.g., stomach pain, headache, sweating, shakiness) [23].

Table 1: Summary of the WHO recommendation principles for identification and management of substance use disorder in pregnancy [28].

	Principle	Summary
1	Screening and brief intervention	Health-care providers should ask about the past and present history of substance abuse and offer treatment.
2	Psychosocial interventions	Health-care providers should offer inclusive assessment and individualized care.
3	Detoxification	As early as possible, health-care providers should advise pregnant women to stop substance abuse and provide detoxification services. Considering the psychiatric disorders in withdrawal management is paramount.
4	Dependence management	Pharmacotherapy is not recommended for routine treatment, and the risk-benefit ratio should be always counted for each woman.

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5	Infant feeding	Mothers should be motivated to breastfeed unless it is hurtful. Skin-to-skin contact is important to gratify her baby's needs.
6	Management of infant withdrawal	Construct protocols for identifying, assessing, and monitoring those in risk. Neonatal withdrawal syndrome can be initially managed through Phenobarbital.

There is no specific gold standard for the treatment of cannabis use in pregnancy. Health care providers should advise pregnant women to minimize or better stop cannabis use during pregnancy, counseling them to become aware of the long-term negative cognitive and behavioral outcomes in their babies. Regular cannabis users can be supported with a range of alternative interventions that include brief interventions, short counseling, educational sessions, psychologically based treatments like CBT, and motivational enhancement. Multiple sessions are more efficient than single intervention, and these will mainly focus on problem solving in regard to triggers for use. The WHO and SAMHSA strongly suggest brief interventions for all pregnant women in reducing cannabis use during pregnancy. Table 1 provides a summary of the main principles of the WHO's recommendations to identify and manage drug abuse during pregnancy.

Quitting marijuana use during pregnancy requires a combination of approaches to address the physical, emotional, and psychological aspects of dependence. Currently, there are no medications approved by the U.S. Food and Drug Administration for cannabis use during pregnancy. Psychopharmacological interventions for cannabis use have been barely studied in pregnancy and are less frequently utilized than psychotherapeutic interventions. Promising preliminary findings with NAC and gabapentin have recently emerged, but these medications require further examination. NAC, an antioxidant that has modulatory effects on glutamatergic transmission, was evaluated in an RCT with adolescent marijuana users and was more effective than placebo in reducing marijuana use [24]. Gabapentin has also shown promise in treating marijuana dependence in a RCT; however, there is no research on its use during pregnancy [25].

Habitual cannabis users are offered inpatient treatment programs in which these women are placed in a safe and a medically supervised environment. They are provided with various treatment options, group activities, psychotherapies; and they address any underlying issues regarding this dependence. Treatment of addiction to marijuana often starts with behavioral therapy. Several different psychotherapies have been studied as potential treatments for cannabis dependence. The most commonly used therapies are Twelve-Step-Facilitation (TSF) counseling, motivational enhancement therapy (MET), Cognitive-behavioral therapy (CBT), and contingency management (CM). To date, there have been no efficacy trials for TSF counseling for marijuana dependence. Cognitive-behavioral therapy (CBT) and motivational enhancement therapy (MET) may be efficacious when combined with contingency management (CM) strategies, especially in promoting initial abstinence. In two RCTs, CM was superior to other psychotherapeutic approaches and to the combination of psychotherapy and CM in maintaining abstinence during the trial period. However, during later follow-ups, the combined treatment groups in both studies CBT+CM [26] or MET+CBT+CM [27,28] had the highest percentages of abstinence among participants. There are also other forms of therapies which many programs incorporate into their treatment which include mindfulness, yoga and meditation, acupuncture, art therapy, biofeedback, etc. for cannabis dependence.

According to SAMHSA guidelines, The Brief Marijuana Dependence Counseling (BMDC) approach, which is designed to treat adults with the diagnosis of cannabis dependence, is an intervention consisting of ten weekly one-on-one sessions, which utilize a client-centered approach and target a reduction in the frequency of marijuana use. It is based on a research protocol which was used by the counselors in the center for Substance Abuse Treatment's Marijuana treatment project (MTP) conducted in the late 1990's. The BMDC manual provides guidelines for counselors, social workers, and psychologists in both public and private settings who treat adults dependent on marijuana. It is comprised of three key intervention components: motivational enhancement, cognitive behavioral skills training, and case management.

Discussion

Based on the recent statistics, the prevalence of marijuana use has been increasing since 2002 across all demographic domains. Importantly, we highlight the increasing use of marijuana in pregnant women aged 18-44. The prevalence of past-month of marijuana is increasing compared to other substances such as cocaine and heroin. This is attributable to the relative safety of marijuana use and its efficacious role in mitigating pregnancy symptoms like nausea and vomiting. However, the safety of marijuana use during pregnancy is questionable, not only because of the active cannabis components with higher potency, but also because of the growing understanding about the immediate and long-term harmful outcomes of fetal marijuana exposure. The deleterious effects are due to the long half-life of marijuana which may pass be longer than thirty days and the elevated concentration in breast milk (8-folds) compared to maternal plasma. These harmful effects include low birth weight, anemia, and premature birth, and exaggerated startle response, poor habituation to new stimuli, decreased quiet sleep time, and high-pitched crying.

Additionally, it affects prenatal neural development, growth which forms the basis of executive and neurocognitive functions during adolescent and adulthood. As a result, anxiety

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and depression can be manifested as early as 10 years of age; inattention, delinquency, psychosis, and decreased ability in math, reading, and spelling can be manifested by the age of 14. THC, the active component in cannabis, crosses freely through the human placenta and disrupts CB1R mediated synaptic plasticity, which plays an important role in neurodevelopment and brain formation, around the sixteenth day of gestation. Later, it causes an alteration in the dopamine levels in the limbic system. Animal models show hyperactivity in female rats and increased socio-sexual approach behavior in male rats. These findings cannot be directly generalized to humans, but a decrease in messenger RNA was observed in basal ganglia, a lessening which may substantiate sex-related variances in fetuses with prenatal cannabis exposure. The cannabis effects were further established by functional magnetic resonance imaging (FMRI) studies which noted increased neural reactivity in the posterior brain regions and compensated blood flow pattern during functional tests involving executive-function tasks in prenatally exposed individuals compared to controls. The most important step in decreasing the incidence of fetal exposure to marijuana is enhancing awareness about its lethal effects by incorporating screening questionnaires about possible substance use during ante-natal visits. Since there are no FDA-approved medications for intoxication or withdrawal symptoms from marijuana use, psychotherapies such as CBT, CT and MET-individually or combined for synergistic effects-may be efficacious

Future Recommendations

Future large-scale interventional studies are required to find safe and effective medications to lessen the lethal effects of marijuana. Furthermore, more robust research is warranted to provide evidence-based counseling for pregnant women on the known negative outcomes of marijuana use in pregnancy. Meanwhile, women should be advised not to use marijuana during pregnancy and lactation. Educational and outreach programs may assist in enhancing general awareness and decrease the incidence and prevalence rate of fetal marijuana use among child-bearing mothers.

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