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Marijuana and Breastfeeding: Applicability of the Current Literature to Clinical Practice

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Abstract

With recent legalization of marijuana in numerous U.S. states, the risk of marijuana exposure via breast milk is a rising concern. This review analyzes the available human and animal literature regarding maternal use of marijuana during lactation. The findings can be categorized into four areas of analysis: effects of marijuana on the mother, transfer into milk, transfer to the offspring, and effects on the offspring. Human and animal data have reported decreased prolactin levels as well as potential maternal psychological changes. Animal and human studies have reported transfer into milk; levels were detected in animal offspring, and metabolites were excreted by both human and animal offspring. Further, animal data have predominately displayed motor, neurobehavioral, and developmental effects, whereas human data suggested possible psychomotor outcomes; however, some studies reported no effect. Despite these results, many human studies were marred by limitations, including small sample sizes and confounding variables. Also, the applicability of animal data to the human population is questionable and the true risk of adverse effects is not entirely known. There are large gaps in the literature that need to be addressed; in particular, studies need to focus on evaluating the short- and long-term consequences of maternal marijuana use for the infant and the potential for different risks based on the frequency of maternal use. Until further evidence becomes available, practitioners need to weigh the benefits of breastfeeding for mother and child, with the potential influence of marijuana on infant development when determining the infant's most suitable form of nutrition.

Keywords: breastfeeding, lactation, marijuana, cannabis, THC, infant exposure

Introduction

The use of marijuana for medical and recreational purposes is a controversial topic that continues to acquire enormous attention by the public and healthcare professionals. Currently, medical marijuana is legal in 28 U.S. states along with the District of Columbia; in addition, recreational marijuana is legal in 8 states (Colorado, Washington, Oregon, Alaska, Massachusetts, California, Nevada, and Maine) and the District of Columbia.[1] As more citizens and governments are favoring the legalization of marijuana, it is evident that the use of this substance is increasing.[2] Currently, marijuana is used medicinally to alleviate chemotherapy-induced nausea and vomiting, increase appetite in patients with acquired immune deficiency syndrome, lower intraocular pressure in glaucoma, and reduce spasticity and chronic pain.[3,4] Marijuana may also be used in patients with epilepsy or multiple sclerosis to reduce pain and spasticity.[4]

Although potential clinical benefits exist, it is critical to consider that very few breastfeeding women suffer from the disease states demonstrating benefit at this time. Often, women use marijuana to treat conditions for which there are alternative therapies that have safety data in lactation.[5] Consequently, with its growing popularity, the use of marijuana in pregnant and breastfeeding women is raising significant concern with clinicians. A previous report from the American College of Obstetricians and Gynecologists states that 2–5% of women use marijuana in pregnancy; however, certain demographics are known to have higher rates of use.[6] In particular, 15–28% of socioeconomically disadvantaged young women in cities self-reported use in pregnancy. One longitudinal study that assessed the use of marijuana in adolescent pregnancy found that although the use of marijuana and other substances may have declined during pregnancy, the patterns of use rose in the first 6 months postpartum.[7] Thus, knowing that marijuana use may increase in the postpartum period, the primary question at hand for most clinicians remains: Do the maternal and neonatal benefits of breastfeeding reduce or offset the potential sequelae from exposure to marijuana in milk?

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The chief psychoactive compound in marijuana is delta-9-tetrahydrocannabinol (THC), which functions as an agonist of cannabinoid (CB) receptors.[8] CB receptors comprise the endocannabinoid system, which is essential for attention, cognition, memory, emotion, movement, and the peripheral immune system.[9] These receptors are detected starting at an early stage in utero; in particular, humans have active CB1 receptors by the 19th week of gestation.[10] Along with the endocannabinoid system, THC also exerts its effects by influencing the dopamine, opioid, GABA, glutamate, and serotonin-associated systems.[9] In the anterior pituitary, THC promotes corticotropin secretion, and it prevents the secretion of gonadotropin, thyroid-stimulating hormone, prolactin, and growth hormone.[11]

In adults, the use of marijuana results in relaxation, reduced motor function, and pain relief.[12] The most common adverse effects of marijuana, which usually resolve with symptomatic care, include tachycardia, agitation, and nausea.[13] More serious adverse effects of marijuana use include cardiovascular events, acute kidney injury, seizures, and psychiatric events (e.g., psychosis, paranoia, and suicidal ideation).[13–15] The prevalence of these adverse effects is difficult to determine based on the current available research, and the subsequent long-term consequences are unknown. Of note, one recent publication did find an increasing rate of visits to the emergency department, hospital admissions, and healthcare costs in states that have legalized marijuana over a 5-year period.[14] In addition, one state reported an increase in unintentional pediatric exposures (median age 2.4 years old) presenting to hospital or requiring assistance from a local poison center after legalization.[16] This study reported the following adverse events from unintentional marijuana exposure in children: drowsiness, dizziness, seizures, agitation, respiratory depression, tachycardia, bradycardia, hypotension, vomiting, dystonia, and muscle rigidity.

Cannabis may also suppress the immune system in adults at both innate and adaptive levels.[17] This is evident by increased concentrations of anti-inflammatory mediators (transforming growth factor beta-1 and interleukin-10) in adult cannabis users. Adult users also present with decreased levels of pro-inflammatory chemical mediators (interleukin-2), natural killer cells, and reduced lymphocyte proliferation. Marijuana use has also been associated with infertility. Long-term use by men has been correlated with a decline in luteinizing hormone; this decline leads to low testosterone levels and, consequently, a decrease in sperm production.[18,19] Chronic use in women has been correlated with suppressed ovulation, lower levels of prolactin, follicle-stimulating hormone, luteinizing hormone, and estrogen.[20]

A critical point to consider when assessing these effects is that the concentration of the psychoactive component of marijuana continues to increase. In the past two decades, the average concentration of THC in marijuana has risen from $3.96\% \pm 1.82\%$ to $11.84\% \pm 6.60\%$ (data from 1995 to 2014, respectively).[21,22]

Further, numerous marijuana studies assessing in-utero exposure have reported negative findings.[20,23–25] Although marijuana has not been associated with specific congenital anomalies, its use in pregnancy has been associated with complications such as growth restriction, lower gestational age, and increased admissions to neonatal intensive care units. Warner et al.[20] reviewed the effects of in-utero marijuana exposure and found poorer scores on executive functions, including memory scores and verbal skills as well as difficulty with attention. In later years, these children also had difficulties with impulsivity, abstract reasoning, and visual problem solving. In addition, data from three longitudinal studies have reported similar findings regarding lower gestational age, changes in fetal growth, and multiple behavioral changes when followed up to adolescence (e.g., changes in memory, impulsivity, and verbal reasoning).[26] Even though these data suggest a potential risk with use in pregnancy, there are multiple studies demonstrating no risk; thus, additional studies are needed to confirm these results and to rule out the influence of other substances and social factors.[23–26]

Although breast milk delivers essential nutrients and bioactive molecules, such as lipids, proteins, and immunological factors, it can also carry medications and their metabolites to the child. Hence, it is essential to study the transfer of drugs, including marijuana, into breast milk and their possible effects on the child. To date, the transfer of marijuana into human milk and the short- and long-term effects on infant development are poorly characterized, making it nearly impossible for clinicians to weigh the benefits and risks of breastfeeding while using marijuana, especially when the infant is exposed in utero.

The Academy of Breastfeeding Medicine acknowledges the presence of conflicting data and currently recommends lactating mothers to decrease or completely stop marijuana consumption due to the potential neurobehavioral consequences of prolonged exposure to the child.[27] The Academy also encourages lactating mothers to be cautious if using cannabis, as there is inadequate evidence to support the discontinuation of breastfeeding. Both these recommendations are based on a grade III level of evidence since further research is needed, but, nevertheless, raise important concerns.

Objective

The purpose of this article is to review the available literature regarding marijuana use during lactation and to evaluate the risks of exposing infants to this medication in breast milk.

Human and animal data will be analyzed from four perspectives: (1) the effects of THC on the mother in relation to lactation and care of the offspring, (2) transfer of the chemical into breast milk, (3) transfer to the offspring, and (4) the indirect and direct effects of THC on the offspring. Assessment from these four perspectives will assist in evaluating the safety of the drug for use in lactation and outlining areas for future research.

Methods

A literature search was performed up to June 2017 by using the following search engines: Google Scholar, University Library Search Engine, PubMed, Google, Elsevier ScienceDirect, and Springer Link. Various combinations of the following search terms were employed: marijuana, CB, cannabis, breastfeeding, milk, human milk, breast milk, mother's milk, lactation, infant, prenatal effects, postnatal, and development. The literature search was open to both animal and human studies, and it was not restricted by publication date. A total of 48 articles were obtained, of which 29 were primary research studies, and 19 were review articles.

Overall, 2 primary articles and 4 review articles were excluded due to their lack of significant focus on the topic of review or because their information overlapped with the primary studies. Each article was analyzed for information pertaining to the study type, population, intervention, and results.

Results

Effects of THC on the mother

Human studies. The potential effects of marijuana on breastfeeding women (Table 1) are largely due to its principal chemical, THC. Research examining the correlation between marijuana use and prolactin levels have shown lower concentrations of the hormone in chronic human users.[29] Compared with placebo, one study reported prolactin levels that were 50% lower in the luteal phase of women who smoked marijuana; however, concentrations still remained in the normal range.[28]

In addition to the hormonal effects, THC could also alter the mothers' psychological state.[37] Use of the drug can alter a mother's perception of her environment and her ability to react to changes in the environment. Once the effects of marijuana fade, deep sleep can occur.

Animal studies. With regards to animal data, studies performed on lactating rats and non-pregnant rhesus monkeys also displayed lower prolactin levels in subjects given injections of THC (Table 1).[31,32] For instance, Asch et al.[32] reported a maximal reduction in prolactin levels of 74% (in male monkeys) and 85% (in female monkeys) over the first 30- to 90-minute period. Bromley et al.[31] reported the following changes in prolactin levels from baseline over a 30- to 60-minute interval: >70% reduction after a 1.25 mg/kg dose of THC, and greater than 90% reduction from a 4 mg/kg dose. Further, lactating rats given THC displayed lower blood oxytocin concentrations.[35] The authors of this study concluded that THC prevented suckling-induced oxytocin secretion by the posterior pituitary, which led to a longer delay in the initial ejection of milk and between successive ejections.

Additional effects seen in monkeys and rats include lethargic behavior, reduced maternal care, and anxiety.[31,34,36] This is especially important considering that high quantities of the chemical remain in the brain.[38]

Transfer of THC into milk

THC is a fairly lipophilic compound and, based on its physiochemical characteristics, should readily transfer into breast milk.[39] This medication has a low molecular weight (314 Da), high volume of distribution (4–19 L/kg), and long elimination half-life (25–57 hours), so it is extensively distributed into peripheral adipose tissue.[39,40] After a single injection of the drug into rats, one study found 10 times more THC in fat, as compared with other tissues.[40]

Human studies. With regards to humans, a study following a mother who smoked marijuana once a day for 7 months reported up to 105 ng of THC per mL of breast milk (Table 2).[41] Another mother who used the drug seven times per day for 8 months had 340 ng of THC per mL of milk. Overall, the second mother had 8 times more THC in her breast milk than in her plasma. Although this milk-to-plasma ratio is greater than one, at this time we cannot conclude that the relative infant dose will be high, as this depends primarily on maternal dose and concentration.

A study conducted in 2011 to verify a method of quantifying drugs in milk analyzed breast milk samples from two women with a history of substance use.[43] One of these women had smoked cannabis but the dose, frequency, and timing of use before obtaining the milk sample were not reported. The milk samples obtained from this woman contained 5 ng of 11-OH-THC per mL and 86 ng of THC per mL of breast milk.

Further, in another quantification study, 109 breast milk samples were obtained from lactating women for analysis.[44] The participants completed a questionnaire to assess drug use throughout their life and during pregnancy. Although 19 women reported drug use, one had THC present in her breast milk (concentration of 20 ng/mL), without the presence of cannabinol or cannabidiol. CBs were also detected in this participant's urine sample. In another woman, THC was detected in breast milk (concentration of 31 ng/mL) and cannabidiol was present but at a concentration below the limit of quantification; however, she had not reported prior drug use. The authors estimated that the infants of these mothers would ingest 2 and 3.1 μg of THC, respectively, for each 100 mL of breast milk. Thus, the infants would subsequently absorb 0.24 and 0.37 μg of THC, after considering the oral bioavailability of 12%. These estimated values are absolute infant doses rather than relative infant doses as the maternal dose and timing of milk sample collection and marijuana use were unknown.

Animal studies. Numerous animal studies have also reported the transfer of THC into breast milk (Table 2). For instance, 50% of milk samples from buffalos that consumed marijuana plants contained a metabolite of THC.[42] Lactating squirrel monkeys given labeled THC accumulated 0.2% of the label as hydrophilic and lipophilic metabolites in their milk within a period of 24 hours.[30] Moreover, milk from lactating ewes contained less of the radiolabel than the feces or urine; levels were detected in milk when examined 4 and 96 hours after the THC injection.[46]

Transfer of THC to human and animal offspring

Human studies. Levels of THC and its metabolites have been detected in the organs of offspring after transfer into mother's milk (Table 2). In humans, a study following two women who smoked marijuana while breastfeeding concluded that infant fecal samples contained low levels of THC metabolites.[41] Data also suggest that infants and children who ingest marijuana via milk may further eliminate the drug in their urine.[37,42]

Passive inhalation of smoked cannabis is another means for this drug and its byproducts to enter the infant's body other than direct ingestion of maternal milk.[48] However, there is no research analyzing this means of transfer to infants.

Animal studies. A study where labeled THC was injected into lactating rats found that suckling pups contained the radioactive marker 4 hours after administration to the

Table 1. Maternal Effects of Delta-9-Tetrahydrocannabinol

Author(s)	*Study type*	*Population*	*Intervention*	*Results*
Human studies				
Mendelson et al.[28]	Experiment (double-blind, randomized crossover design)	Non-pregnant women (each woman was her own control/comparator)		Marijuana users had decreased prolactin concentrations in the luteal phase compared with placebo (measured at 60–120 and 150–180 minutes after marijuana use)
		$n=16$	Smoked marijuana (1 g [1.83% THC]) cigarette	
		$n=16$	Smoked placebo (1 g) cigarette	
Ranganathan et al.[29]	Experiment (double blind)	Men and non-pregnant women		Prolactin levels before and after THC administration were lower in marijuana consumers
		$n=40$	Used marijuana on a regular basis: Received IV placebo (ethanol) or THC (0.0357, 0.0286, or 0.0714 mg/kg)	THC administration was associated with increased cortisol concentrations in both groups (but slower rise in regular users)
		$n=36$	Did not use marijuana: Received IV placebo (ethanol) or THC (0.0357, 0.0286, or 0.0714 mg/kg)	
Animal studies				
Chao et al.[30]	Experiment	Lactating squirrel monkeys and their young		Both groups of lactating monkeys produced similar amounts of milk
		n (mothers) = 11	Received oral doses of THC (2 mg/kg) 2 or 5 times per week, followed by 2 doses of ^{14}C-THC	Mothers given ^{14}C-THC had 1% of the label in their urine and 42% in their feces
		n (mothers) = 6	Received oral doses of placebo	
Bromley et al.[31]	Experiment	Lactating rats (total $n=14$) and their offspring		THC group: Had decreased suckling-stimulated prolactin discharge Had decreased care provided by the mothers
		$n=$ Not clearly specified	Mothers received an IV injection of THC (1.25 or 4 mg/kg)	
		$n=$ Not clearly specified	Mothers received an IV injection of the vehicle	
Asch et al.[32]	Experiment	Male and oophorectomized female rhesus monkeys		Males and females given THC: Had decreased prolactin levels within 30–120 minutes Subjects given TRH with THC: Had normal levels of prolactin
		n (males) = 4, n (females) = 5	All nine subjects received an IM injection of THC (2.5 mg/kg) Four subjects also received an IM injection of TRH (5 μg)	
		n (males) = 4, n (females) = 5	Received an injection of the vehicle (2.5 mg/kg)	

(*continued*)

Table 1. (Continued)

Author(s)	*Study type*	*Population*	*Intervention*	*Results*
Frischknecht et al.[33]	Experiment	Male and lactating female adult mice, and their offspring		THC group:
		n = Not clearly specified	Adult mice received oral doses of a hashish product (20 mg/kg THC) 3 times per week from birth to the time their offspring were weaned from nursing	Initially, had reduced maternal nonsocial behavior and locomotion. Resumed usual level of care for offspring after the 5th dose (i.e., day 10 postpartum)
		n = Not clearly specified	Remaining adults received oral doses of olive oil (2 mL/kg)	
Asch and Smith[34]	Experiment	Lactating female rhesus monkeys and their offspring		Mothers were tired/lethargic during nursing
		n (mothers) = 8, n (offspring) = 8	Mothers received IM THC (2.5 mg/kg/day) injections during lactation	
Tyrey and Murphy[35]	Experiment	Lactating rats and their pups		THC group:
		n (mothers) = 8	Received an IV injection of THC (0.5 mg/kg)	Longer delay before initial ejection of milk and between further ejections
			Five mothers received an injection of oxytocin (0.5 mU) after their dose of THC	Proposed that THC prevented oxytocin secretion via the posterior pituitary
		n (mothers) = 8	Received an IV injection of the vehicle (0.5 mg/kg)	
Vilela and Giusti-Paiva[36]	Experiment	Nursing rats and their pups		WIN55,212-2 group:
		n = Not clearly specified	Mothers received an injection of the cannabinoid receptor agonist WIN55,212-2 (1 or 3 mg/kg)	Had lower maternal oxytocin concentrations, less care maternal care, and reduced aggressive activity
		n = Not clearly specified	Mothers received an injection of the vehicle (1 mL/kg)	Had more maternal anxiety

IM, intramuscular; IV, intravenous; THC, delta-9-tetrahydrocannabinol; TRH, thyrotropin-releasing hormone.

Table 2. Transfer of Delta-9-Tetrahydrocannabinol into Breast Milk and the Offspring

Author(s)	*Study type*	*Population*	*Intervention*	*Results*
Human studies				
Perez-Reyes and Wall[41]	Observational study	Breastfeeding mothers (total $n=2$) and their infants		Mother 1: Had 105 ng THC/mL milk
		Mother 1	Smoked marijuana once per day for 7 months (one milk sample obtained)	No 9-carboxy-THC or 11-OH-THC in milk
		Mother 2	Smoked marijuana 7 times per day for 8 months (2 milk samples obtained)	Mother 2: (Sample 1): Had 340 ng THC/mL milk, 4 ng 11-OH-THC/mL milk. No presence of 9-carboxy-THC in milk (Sample 2): Had 60.3 ng THC/mL milk, 1.6 ng 9-carboxy-THC/mL milk, and 1.1 ng 11-OH-THC/mL milk. Had 7.2 ng THC/mL plasma, 19 ng 9-carboxy-THC/mL plasma, and 2.5 ng 11-OH-THC/mL plasma. Overall, had eight times more THC in breast milk than blood plasma. Fecal sample of infant contained 347 ng THC, 611 ng 9-carboxy-THC, and 67 ng 11-OH-THC. Infant feces contained a greater metabolite: parent compound ratio compared with breast milk
Ahmad and Ahmad[42]	Observational study	Buffalo (diet 5–10% marijuana) and human children (6 months to 3 years old) who drank buffalo milk		50% of buffalo milk samples contained THC or its metabolites (mean concentration of THC-COOH was 51 ± 20 ng/mL milk)
		Buffalo: n (milk samples) = 10, n (urine samples) = 10	Determined the concentration of a THC metabolite in buffalo milk and urine samples	60% of buffalo urine samples had the metabolite THC-COOH (mean concentration of THC-COOH was 67 ± 30 ng/mL urine)
		Human children: n (urine samples) = 7	Determined the concentration of a THC metabolite in child urine samples	29% of child urine samples contained THC-COOH (in low concentrations)
Marchei et al.[43]	Observational study	Breast milk samples obtained (total $n=400$) from a milk bank; mothers self-reported drug use		Breast milk from the mother who smoked cannabis: Contained 5 ng OH-THC/mL milk and 86 ng THC/mL milk
		n (Smokes cannabis) = 1 (unknown dose, frequency, and time of use to milk sample)	Determined concentrations of substances and their metabolites in breast milk samples to test a quantification technique	No pediatric outcome data

(*continued*)

Table 2. (Continued)

Author(s)	*Study type*	*Population*	*Intervention*	*Results*
de Oliveira Silveira et al.[44]	Observational study	Breastfeeding women (details regarding study population not provided) *n* (Breast milk samples) = 109 (randomly collected samples from a poison center)	Analyzed samples for the presence of THC, cannabinol, and cannabidiol by using a headspace solid-phase microextraction technique	Positive THC milk samples obtained from two women: Woman 1: had 20 ng THC/mL milk, but no cannabinol or cannabidiol; positive urine sample for cannabinoids. Estimated 2 μg absolute dose ingested by infant/100 mL breast milk, and 0.24 μg absorbed Woman 2: had 31 ng THC/mL milk; cannabidiol level below limit of quantification. Estimated 3.1 μg absolute dose ingested by infant/100 mL breast milk, and 0.37 μg absorbed
Animal studies				
Jakubovic et al.[45]	Experiment	Lactating rats and their offspring *n* = Not clearly specified	Lactating rats received an SC injection of ^{14}C-THC (53 mg/kg) 3 days after giving birth	THC and its byproducts were detected in milk and newborns' organs (exact moieties and metabolites not reported)
Kreuz and Axelrod[40]	Experiment	Female rats *n* = 4	Received SC THC (1 mg/mL) injection(s)	After 1 injection: had 10 times more THC in fat compared with other tissues After multiple injections: had more THC and metabolites in fat tissues Metabolites stayed in fat for 14 days
Jakubovic et al.[46]	Experiment	Lactating ewes and lamb offspring *n* (ewes) = 5, *n* (lamb) = 1	Lactating ewes received an IV injection of labeled THC (0.013, 0.02, or 1 mg/kg) 1 week after weaning or while nursing	Ewe milk samples: had less radioactive label than feces or urine Within 48 hours, 15% of label entered the milk, urine, and feces (exact moieties not determined) Milk samples contained radioactivity at all testing intervals, ranging from 4 to 96 hours
Chao et al.[30]	Experiment	Lactating squirrel monkeys and their young *n* (mothers) = 11 *n* (mothers) = 6	Received oral doses of THC (2 mg/kg) 2 or 5 times/week, followed by 2 doses of ^{14}C-THC Received oral doses of placebo	Within 24 hours, mothers had 0.19% of the labeled drug in their milk Label excreted most into the milk 2 hours after the mothers received the drug Within 18 hours of milk intake, the young had 0.12% of their mothers' labeled drug dose in their feces, and 0.01% in their urine

(*continued*)

TABLE 2. (CONTINUED)

Author(s)	*Study type*	*Population*	*Intervention*	*Results*
Dalterio[47]	Experiment	Mice (during pregnancy and lactation) and their male offspring		THC group: Milk contained 1% of the label from THC and cannabinol
		n (Mothers) = not clearly specified; *n* (males, THC group) = 52; *n* (males, cannabinol group) = 57	Mothers received oral doses of THC or cannabinol (50 mg/kg)	Maximum labeled THC detected in offspring 4 hours after feeding (peak detected earlier in the brain)
		n (mothers) = Not clearly specified; *n* (males) = 61	Mothers received oral doses of sesame oil	
Asch and Smith[34]	Experiment	Lactating female rhesus monkeys and their offspring		THC entered the mothers' milk to reach the offspring
		n (mothers) = 8, *n* (offspring) = 8	Mothers received IM THC (2.5 mg/kg/day) injections during lactation	THC reached peak serum concentrations in offspring after 8 hours
		n = Not clearly specified	Mothers received IM vehicle (2.5 mg/kg/day) injections during lactation	

SC, subcutaneous.

Table 3. Effects of Delta-9-Tetrahydrocannabinol on the Offspring

Author(s)	*Study type*	*Population*	*Intervention*	*Results*
Human studies				
Perez-Reyes and Wall[41]	Observational study	Breastfeeding mothers (total $n=2$) and their infants		Both children had normal development, as per pediatricians (no details provided regarding developmental measures)
		Mother 1	Smoked marijuana once per day for 7 months (one milk sample obtained)	
		Mother 2	Smoked marijuana 7 times per day for 8 months (two milk samples obtained)	
Tennes et al.[49]	Prospective observational study	Children whose mothers belonged to a low-income prenatal clinic	Assessed their development (motor, mental, growth [height, weight]), and behavior) at 1 year of age by using the Bayley Infant Scale of Mental and Motor Development and Behavior Checklist, and maternal interviews	Weaning age similar among both groups of children Developmental measures did not differ
		$n=27$	Children whose mothers consumed marijuana while nursing	
		$n=35$	Children whose mothers either consumed or did not consume marijuana while nursing	
Astley and Little[50]	Prospective observational study	Children of mothers who were primarily married, and college educated	Measured mental and motor development at 1 year of age by using the Bayley Scale of Infant Development (Mental Developmental Index and Psychomotor Developmental Index)	Lower motor development at 1 year if mother used marijuana in the first month after giving birth Mental development unaffected
		$n=68$	Children of breastfeeding marijuana users	
		$n=68$	Children of breastfeeding non-marijuana users	
Animal studies				
Jakubovic and McGeer[38]	Experiment	Adult male rats and their offspring		Less label entered RNA, proteins, nucleic acids secondary to THC exposure
		$n=$ Not clearly specified	Exposed adult and infant cerebral cortex samples to labeled leucine, uridine, and THC	High levels of THC remained in brain samples (larger retention in adult samples)
Jakubovic et al.[45]	Experiment	Lactating rats and their offspring		Infant brain cells had fewer ribosomes bound to nuclear membranes, as observed at 4–24 hours after maternal injection
		$n=$ Not clearly specified	Lactating rats received an SC injection of ^{14}C-THC (53 mg/kg) 3 days after giving birth	
Chao et al.[30]	Experiment	Lactating squirrel monkeys and their young		The young from both groups did not differ in weight gain
		n (Mothers) $=11$	Received oral doses of THC (2 mg/kg) 2 or 5 times per week, followed by 2 doses of ^{14}C-THC	
		n (Mothers) $=6$	Received oral doses of placebo	

(*continued*)

Table 3. (Continued)

Author(s)	*Study type*	*Population*	*Intervention*	*Results*
Dalterio[47]	Experiment	Mice (during pregnancy and lactation) and their male offspring		Male progeny: Had increased LH and decreased testes weight at prepubertal and adult stages, and reduced sexual activity in adulthood
		n (Mothers) = not clearly specified; *n* (males, THC group) = 52; *n* (males, cannabinol group) = 57	Mothers received an oral dose of THC or cannabinol (50 mg/kg) and nursed their offspring	
		n (mothers) = Not clearly specified; *n* (males) = 61	Mothers received an oral dose of sesame oil and nursed their offspring	
Frischknecht et al.[33]	Experiment	Male and lactating female adult mice, and their offspring		The offspring exposed to THC had less weight gain relative to the control group on days 4–7, 7–11, and 11–15 after birth
		n = Not clearly specified	Adult mice received oral doses of a hashish product (20 mg/kg THC) 3 times per week from birth to the time their offspring were weaned from nursing	
		n = Not clearly specified	Remaining adults received oral doses of olive oil (2 mL/kg)	
Asch and Smith[34]	Experiment	Lactating female rhesus monkeys and their offspring		Offspring did not differ in mean weight when they were weaned Between birth and weaning, offspring unexposed to THC gained weight faster than the treatment group
		n (mothers) = 8, *n* (offspring) = 8	Mothers received IM THC (2.5 mg/kg/day) injections during lactation	
		n = Not clearly specified	Mothers received IM vehicle (2.5 mg/kg/day) injections during lactation	Offspring exposed to THC seemed lethargic during nursing
Vela et al.[51]	Experiment	Mice (during pregnancy and lactation), and their adult offspring		Adult female offspring whose mothers received THC had greater binding to μ-opioid receptors and a greater tendency to self-administer morphine
		n = Not clearly specified	Mothers received an oral dose of THC (5 mg/kg) each day	
		n = Not clearly specified	Remaining mothers received an oral dose of oil each day	
Fride E et al.[8]	Experiment	Newborn mice *n* = 12	Received SC SR141716A (CB-1-receptor antagonist) (5–20 mg/kg) injection(s) plus vehicle	THC group: Had greater development and milk suckling, largely undoing the harm of the cannabinoid-1 receptor blocker SR141716A
		n (vehicle) = 10, *n* (THC plus vehicle) = 12, *n* (SR141716A plus THC) = 12, *n* (2-arachidonyl glycerol) = 15	Received vehicle, or THC (20 mg/kg) plus vehicle, or SR141716A (5–20 mg/kg) plus THC (20 mg/kg), or 2-arachidonyl glycerol (20 mg/kg) injections	Decreased deaths and increased body weight

(*continued*)

TABLE 3. (CONTINUED)

Author(s)	*Study type*	*Population*	*Intervention*	*Results*
Moreno et al.[52]	Experiment	Mother rats during pregnancy and lactation, and their adult offspring		THC (effects on offspring at adulthood): Adult females had higher blood concentrations of corticosterone, whereas males had lower concentrations Adult female locomotor behavior was reduced at lower doses (0.1 and 0.5 mg/kg), but it increased at higher doses (2 mg/kg) Adult males had lower mobility as a result of the 0.1 and 2 mg/kg doses (measured at 120 minutes)
		n = 17–24 per regimen	Mothers received oral doses of THC (0.1, 0.5, or 2 mg/kg)	
		n = 17–24	Mothers received oral doses of the vehicle (0.1 mL of sesame oil)	
Trezza et al.[53]		Mother rats during pregnancy and nursing, and their offspring		Effects of 5 mg/kg THC on selected male offspring: Decreased play and social interactions during adolescence Increased anxiety in adulthood
		n = Not clearly specified	Mothers received an injection of THC (2.5–5 mg/kg) during pregnancy and lactation	
		n = Not clearly specified	Mothers received an injection of the vehicle during pregnancy and lactation	
Newsom and Kelly[54]	Experiment	Pregnant female rats and their male offspring		THC group: Pups had increased anxiety; greater anxiety risk in adulthood No effect on weight gain
		n (Mothers) = 8, n (male offspring) = 8	Pregnant rats and their male pups received SC THC (2 mg/kg) injections BID	
		n (Mothers) = 8 for each regimen, n (male offspring) = 8 for each regimen	Pregnant rats and their male pups received no treatment or vehicle (1.06 mL/kg) injections BID	
Vilela and Giusti-Paiva[36]	Experiment	Nursing rats and their pups		WIN55,212-2 group: Less weight gained by the young
		n = Not clearly specified	Mothers received an injection of the CB receptor agonist WIN55,212-2 (1 or 3 mg/kg)	
		n = Not clearly specified	Mothers received an injection of the vehicle (1 mL/kg)	

BID, twice daily; LH, luteinizing hormone.

mothers (Table 2).[45] The label was distributed in the milk, in addition to the offspring's stomach, liver, spleen, brain, lungs, and heart.

After THC enters the nursing squirrel monkey, it is further metabolized.[30] Within 18 hours of milk intake, nursing squirrel monkeys were found to have 0.12% of their mothers' labeled drug dose in their feces, and 0.01% in their urine. Only the presence of radioactivity was determined in this study, not the specific compounds such as metabolites.

Effects of THC on human and animal offspring

In addition to the effects of THC on mothers, the compound is believed to influence infant development (Table 3). Such effects are likely to occur in infants because CB receptors are detected in the brain very early in life and the blood–brain barrier is under-developed at this age.[10,55] The endocannabinoid system is essential for infant development as it regulates several vital processes in the body.[8,37,50] Based on rodent and human data, it controls factors such as motor development, cognitive function, and suckling patterns.[8,50,56] In general, the development of suckling patterns is essential for effective breastfeeding. Breastfeeding, in turn, has numerous benefits to both the mother and offspring.

Human studies. A prospective study published in 1990 evaluated the motor and mental skills of infants exposed to marijuana via breast milk by using the Bayley scales of infant development; assessments were performed at 1 year of age.[50] This study used participants from a previous project that analyzed diet, alcohol, and smoking in lactation as well as their impact on infant growth and development. Among these participants, 68 women were found to use marijuana in lactation (reported use in the first and third month); these women were then matched to 68 women who did not use marijuana in lactation but did have similar use of marijuana in pregnancy and similar use of alcohol and cigarettes in pregnancy and lactation. Eighty-four percent of women who used marijuana during pregnancy continued to use marijuana in lactation. In this study, 20–24% of women reported using marijuana, most commonly 1 joint, at least once per week in pregnancy or lactation. Five to 10% of women reported higher doses of 2 to 5 joints per day. It was found that infants with higher marijuana exposure in the first trimester or first month of lactation had significantly lower psychomotor development index scores as compared with infants with no exposure during these periods at 1 year of age. The authors reported that neurobehavioral development did not seem to be affected in the same manner.

Tennes et al.[49] followed 62 breastfed children. Thirty-five of these women did not consume marijuana while lactating, whereas the remaining 27 women did. Their children were assessed at 1 year for potential effects on infant development. The authors reported no difference in motor and mental development (based on the Bayley Infant Scale and maternal interviews) as well as weaning age in breastfed children of maternal marijuana users.

However, there are numerous limitations with both the Astley and Little[50] and Tennes et al.[49] studies that need to be considered. For instance, it is difficult to isolate the impact of marijuana intake via breast milk from in-utero exposure. The use of other illicit substances by these mothers remains a confounding factor, and the heterogeneity of the small sample sizes limits the validity of the results.

Animal studies. A study where male rat pups were injected with THC found that the pups displayed an elevated sense of anxiety at an adult age.[54] Their anxiety was marked by increased time spent sniffing and inspecting their surroundings, as well as inhabiting the outer regions of the activity area, rather than the middle. In another study, female and male adult rats whose mothers were given injections of THC during pregnancy and lactation were reported to have reduced locomotor behaviour.[52] Despite these results, human data are required to evaluate both the short- and long-term effects of marijuana.

Mouse pups whose mothers consumed food containing hashish during lactation weighed significantly less (by 10–14%) than control pups from day 11 onward; it was suggested that this occurred due to malnutrition (which could be the result of poorer milk production in the mothers or the direct influence of THC on the pups).[57] In another study, rhesus monkeys unexposed to THC between birth and weaning from milk gained weight faster than the treatment (2.5 mg/kg/day THC) group; however, these groups did not differ in mean weight at birth or weaning.[34] Both the lactating rhesus monkeys and their offspring appeared fatigued during feeding after exposure to THC.

In addition to generalized effects on the offspring, gender-specific effects have also been observed. For instance, when THC was given to mother rats during pregnancy and lactation, their adult female offspring had a greater density of μ-opioid receptors in various areas of the brain and displayed a greater tendency to self-administer morphine.[51] Comparatively, when mother mice were given THC in pregnancy and lactation, their male progeny presented higher levels of luteinizing hormone and decreased testicular weight at the prepubertal and adult stages.[47] THC exposure at an early age was also associated with reduced sexual behavior in the adult male rats. This is yet another area where further research is required.

Although the data cited earlier suggest potential harm, some studies have shown no changes in growth in monkey and mice offspring exposed to marijuana in mother's milk.[30,57]

Limitations and Discussion

The current evidence for marijuana use in lactation is poor. However, studies do suggest that marijuana use during breastfeeding may have potential short- and long-term consequences for both the mother and child. Based on animal data, marijuana may reduce maternal oxytocin levels; in addition, animal and human data suggest that marijuana may reduce prolactin levels. These hormonal changes could, consequently, decrease maternal milk supply. THC readily enters milk in both animal and human studies, and it is then, subsequently, metabolized by the breastfed infant. Once consumed by the infant, THC potentially increases the risk for psychomotor, neurobehavioral, and developmental sequelae. Although such effects have been reported, conflicting data also exist and evidence suggests that weaning age does not seem to be affected by marijuana exposure via breast milk.

Overall, the main limitation of this review and the ability to guide informed decision making is the lack of rigorous human data. Although notable findings have been reported in animal studies, the correlation of animal studies to the human population, particularly in evaluating neurobehavioral changes, is questionable. In addition, the doses used in animals were usually greater than those found in human studies and administration was usually intravenous, so the comparison of pharmacokinetics would be difficult. Intravenous THC also lacks many of the compounds that are found in smoked and orally consumed forms of marijuana. Most research focuses on the effects of THC, but there are more than 70 other natural CBs that may have clinical effects.[55] Thus, more studies are required to analyze these additional compounds and their potential actions. Moreover, there is considerable dose variation among human studies; hence, further research is necessary to investigate the difference between smoking infrequently (e.g., weekly or monthly) and smoking regularly (e.g., a few times per day), as well as the different means of intake (e.g., smoking or incorporating marijuana into food). Finally, confounding in-utero exposure(s), the accuracy of maternal self-reporting, and the ethical considerations when studying this population are just a few of the limitations that need to be overcome in future research.

It is essential that studies analyzing marijuana use in breastfeeding mothers review long-term outcomes in human infants. In the future, it is necessary that such studies extend beyond the period of lactation and follow mothers and their children until school age or longer. A well-designed study with a large sample size, minimal confounding factors, and careful assignment of an appropriate control group is required.

One of the many questions that remains unanswered in this literature review is whether THC affects an infant's immune system. Since the immune system of an infant is immature, the clinical relevance of these findings are unknown. This raises the question of whether or how chronic exposure to THC may affect a child's development and long-term health, and thus highlights the need for further research.

Until such discrepancies in the literature can be resolved with larger prospective human research, the information available must be used to guide clinical decision making. It is important to consider that despite the limitations cited earlier, many of the effects observed in animal data are also seen in humans.

Conclusion

Although the evidence for marijuana use in lactation is limited and lacks scientific rigor, the number of studies that have found concerning evidence (human and animal) outnumber the studies that have concluded no effect. The time an infant is breastfed is a crucial period for growth and development; thus, a conservative approach is suggested until evidence can strongly support otherwise. Mothers should refrain from recreational use of marijuana during this period. Healthcare professionals should also recommend and encourage other therapeutic options (that are suitable for use in lactation) in cases where marijuana is being used to treat maternal health conditions during breastfeeding.

Although the objective of this article was to evaluate the safety data of marijuana use in lactation, this article ultimately highlights the lack of short- and long-term data in breastfeeding women and their infants, as well as the many questions that remain unanswered. Further research regarding this topic and its potential implications should be encouraged among researchers and healthcare professionals to help determine the true benefits of marijuana for maternal health and the short- and long-term risks and benefits of its use in lactation. At this time, it is impossible to make a well-informed decision regarding the use of this drug in lactation. As clinicians, we must often make difficult recommendations based on limited evidence, thus a conservative approach is endorsed at this time.

Based on the information available, in the instance where a mother presents to the delivery room and reports marijuana use or screens positive for marijuana, the clinician should counsel the mother carefully regarding the use of this substance in lactation and the significant lack of safety data at this time. Although mothers should be encouraged to avoid marijuana or limit its use in lactation, the final decision is ultimately up to the individual woman.

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