CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Marijuana Use During Pregnancy and Breastfeeding: Implications for Neonatal and Childhood Outcomes

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Marijuana is one of the most widely used substances during pregnancy in the United States. Emerging data on the ability of cannabinoids to cross the placenta and affect the development of the fetus raise concerns about both pregnancy outcomes and long-term consequences for the infant or child. Social media is used to tout the use of marijuana for severe nausea associated with pregnancy. Concerns have also been raised about marijuana use by breastfeeding mothers. With this clinical report, we provide data on the current rates of marijuana use among pregnant and lactating women, discuss what is known about the effects of marijuana on fetal development and later neurodevelopmental and behavioral outcomes, and address implications for education and policy.

PREGNANCY AND MARIJUANA USE

Epidemiology

Data from 2016 reported in the National Survey on Drug Use and Health (NSDUH) revealed that 4.9% of pregnant women 15 through 44 years of age reported use of marijuana* in the past month, compared with 11% of nonpregnant women in the same age group.[1] This was an increase from the prior year, 3.4% and 10.3%, respectively. Among 18- through 25-year-old pregnant women, 8.5% reported past month marijuana use in 2016, compared with 3.3% of pregnant 26- through 44-year-old women.

* For the purposes of this report, the word "marijuana" is used intentionally to denote all substances derived from the cannabis plant, in lieu of the word cannabis, even when specifically designated as such by cited research to avoid confusion; the exception is when the term cannabis is part of a quotation. "Cannabis" is less typically used in most clinical settings and currently refers more to commercial products. Using the term marijuana also is consistent with many previous publications on this topic.

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Although 2016 data are not available for pregnant 15- through 17-year-old women, 2012–2013 data revealed 14.6% reporting use of illicit† drugs in the past month. Among these illicit substances, marijuana is the substance most commonly used by pregnant women. Widely variable rates are reported among published studies in both the United States and the United Kingdom. Authors of a US multicenter lifestyle study in 2001 reported a prevalence of δ-9-tetrahydrocannabinol (THC), the psychoactive substance in marijuana, in infant meconium samples to be 7.2%.[2] Authors of a 2006 United Kingdom–based pilot study found that 13.25% of a cohort of Scottish newborn infants had meconium samples that had positive results for tetrahydrocannabinol and/or tetrahydrocannabinol-9-carboxylic acid.[3] In studies of urban, young, and socioeconomically disadvantaged pregnant women, reported rates of marijuana use ranged between 15% and 28%.[4–6] Using NSDUH data from 2002 to 2014, Brown et al[7] reported that the prevalence of "past month" marijuana use among pregnant women 18 through 44 years of age increased from 2.37% to 3.84%, with the highest use rates reported in 18- through 25-year-old women (7.47% in 2014). Several state-specific surveys have also been used to document increasing rates of marijuana use among pregnant women. The Pregnancy Risk Assessment Monitoring System (PRAMS), a surveillance project of the Centers for Disease Control and Prevention and state health departments, collects state-specific, population-based data on maternal attitudes and experiences before, during, and after pregnancy (available at cdc.gov/prams). PRAMS has conducted surveys on a sample of women in Vermont with live births since 2001 and has included questions about marijuana use during pregnancy since 2009.[8] In 2013, 9.4% of women in Vermont reported marijuana use during their pregnancy, with no significant change in rates since 2009. PRAMS data from Hawaii revealed that women who reported experiencing significant nausea during their pregnancy reported higher rates of marijuana use (3.7%) compared with pregnant women without nausea (2.3%).[9] The 2012 NSDUH found that pregnant women reported a decrease in their marijuana use from 9.0% to 4.8% in the first and second trimesters, respectively, to 2.4% by the third trimester. Reported rates of tobacco use during pregnancy decreased from 19.9% to 13.4% and to 12.8% in the first, second, and third trimesters, respectively. Authors of other studies have found that 48% to 60% of marijuana users report continuing use during their entire pregnancy, believing it to be safer than tobacco.[4,10,11] In the Longitudinal Development and Infancy Study from the United Kingdom, Moore et al[11] found that most pregnant women who used cocaine, ecstasy, methylenedioxymethamphetamine, and other stimulants stopped using these substances by the second trimester, but 48% of previous marijuana users continued to use marijuana as well as alcohol (64%) and tobacco (46%) throughout their entire pregnancy. In addition, the Longitudinal Development and Infancy Study revealed that the frequency and amounts of both marijuana and tobacco use were sustained throughout the entire pregnancy, similar to prepregnancy levels, whereas the extent of reported alcohol use was reduced. PRAMS data from Vermont also revealed that for 2013 births, 44.6% of women who reported being marijuana smokers before pregnancy continued to use marijuana during their pregnancy.[8] In contrast to these studies, Forray et al[12] found that, of 101 women who reported using marijuana at the beginning of pregnancy and who received substance abuse counseling, 78% were abstinent at a mean of 151 days later and remained abstinent until delivery.

Mark et al[13] demonstrated in a retrospective cohort study of urban, predominantly African American women that, of patients receiving prenatal care and delivering at their institution, 21.8% initially had positive screen results for marijuana use (by either self-report or urine toxicology), but only 1.9% had positive urine screen results for marijuana at the time of delivery. They attributed their high rate of cessation of marijuana use during pregnancy to be related to opportunities for education about adverse effects of drug use, including tobacco and marijuana, during prenatal visits.[13]

Marijuana use during pregnancy has been found to be associated with higher rates of licit and illicit substance use and certain socioeconomic and demographic characteristics. For example, in the Vermont PRAMS study, researchers found that pregnant women who reported marijuana use were more likely to be younger (<25 years of age), to be from households with lower income, to smoke cigarettes, and to report having experienced a significant emotional stressor (traumatic, financial, or partner related) before or during the pregnancy.[8] Mark et al[13] found that use of marijuana was more common in women who reported being unemployed, without a high school diploma, users of either alcohol or cigarettes, depressed, or a victim of abuse. In the Generation R study in the Netherlands, El Marroun et al[14] found in a sample of more than 7000 pregnant women that 85% of marijuana smokers were also

† The NSDUH defined illicit drug use to include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically.

cigarette smokers. Schempf and Strobino[6] found that marijuana use was not independently related to prenatal care. In their population of poor, urban women, lack of adequate prenatal care, defined as 1 or no prenatal visits, was significantly more likely among cocaine and opiate users but not marijuana users.[6] Reasons reported for this correlation with cocaine and opiate use included fear of being reported to police or child protective services and lower perceived benefit of prenatal care. Emphasized in these studies is the importance of considering the potential confounding of additional demographic and behavioral variables when evaluating the independent role of marijuana on pregnancy and fetal and infant outcomes.[15,16]

It is important to note that reported marijuana use rates can vary depending on the method of screening used. Current guidance recommends routine screening of all pregnant women for substance use by way of validated questionnaires or conversations with patients.[5,17] Authors of most studies to date have relied predominantly on self-report, which may have resulted in significant underestimation compared with questionnaires or objective measures using urine screening or meconium samples. However, even these objective measures will provide variable results, depending on the chronicity and intensity of use and the recency of use related to the time that a urine sample is obtained. With the increasing number of states legalizing marijuana use and with marijuana being touted on the Internet as a safe treatment of nausea during pregnancy, current rates of use of marijuana during pregnancy are a concern. Health care providers may see increases in the number of pregnant women using marijuana during at least a portion of their pregnancy.[18]

It is unclear why pregnant women are choosing to use marijuana during their pregnancy, because there are few data available on the benefits of marijuana use during pregnancy. Roberson et al[9] found that women reporting marijuana use during pregnancy were more likely to report experiencing severe nausea and vomiting (3.7%) compared with those not experiencing these severe symptoms (2.7%). In a second study of women using marijuana during their pregnancy, 51% reported using it for relief of nausea and vomiting, and 92% of those women reported its effectiveness; no controls were included in this study.[19] Although the use of marijuana is being touted on social media as an effective and safe treatment of nausea and vomiting of pregnancy, there are currently no indications for its use during pregnancy; the American College of Obstetricians and Gynecologists (ACOG) clearly stated this in its Committee Opinion in 2015.[5] Of note, none of the states with legal medicinal marijuana laws list pregnancy as a contraindication for recommending or dispensing medicinal marijuana.[18]

Pharmacokinetics of Cannabinoids During Pregnancy

Marijuana can affect the normal transport functions and physiologic status of the placenta throughout pregnancy.[20] One study has revealed that short-term exposure to cannabidiol, a nonpsychoactive substance found in marijuana, can enhance the placental barrier permeability to pharmacologic agents and recreational substances, potentially placing the fetus at risk from these agents or drugs.[21] El Marroun et al[22] found that marijuana use during pregnancy, as compared with either no marijuana use or tobacco use, results in increased resistance index and pulsatility index of the uterine artery, with resulting potential effects on uterine blood flow, such as increased placental resistance and reduced placental circulation.

Studies that have been used to assess the ability of metabolites of drugs of abuse, including marijuana, to cross the placenta are not recent and have revealed that recreational and licit substances directly cross the placenta, either through passive diffusion or, less commonly, through active transport or pinocytosis.[23] Among the numerous cannabinoids present in marijuana, the substance most responsible for the psychoactive effects, THC, has been shown to readily cross the placenta.[24] The THC molecule is highly lipophilic and is distributed rapidly to the brain and fat of the fetus after ingestion or inhalation by the pregnant woman. After maternal ingestion, concentrations of THC in fetal blood are approximately one-third to one-tenth of maternal concentrations.[24,25] These concentrations can vary depending on the permeability and biological capacity of the placenta.[26] In addition, when marijuana is smoked, serum carbon monoxide concentrations in the pregnant woman are 5 times higher than those when tobacco is smoked, resulting potentially in impaired maternal respiratory gas exchange and subsequent adverse effect on the fetus.[27] Given these known effects of marijuana on the placenta and placental transport, it is biologically plausible that marijuana use during pregnancy could affect both maternal and fetal outcomes.

Adverse Effects of Marijuana on Pregnancy and on the Neonate, Infant, Child, and Adolescent

Outcomes During the Neonatal Period

Two recent systematic reviews and meta-analyses have been published to determine the independent effect of marijuana use during pregnancy on both maternal and early neonatal outcomes. The first study by Gunn et al[28] was used to review 24 studies to determine the effect of marijuana use on maternal anemia; neonatal growth parameters, such as birth weight, head circumference, and length; admission to the NICU;

gestational age; and preterm birth. They found that women who used any marijuana during pregnancy had a higher likelihood of developing anemia, and infants exposed prenatally to marijuana had a decrease in birth weight (mean difference in weight of 110 g for exposed versus unexposed neonates) and a higher likelihood of needing admission to an NICU. They found no relationship between marijuana use and any of their other selected outcomes. The authors pointed out, however, that a major limitation of their study was their inability to determine the independent effect of marijuana, given that most of the studies assessed did not exclude individuals with polysubstance use, including tobacco or alcohol, or measure use of those substances. The authors also cited additional limitations, such as how the use of marijuana was identified mainly by self-report, and few of the outcomes assessed were standardized across studies.

Conner et al[29] has attempted to address the limitations cited in the review by Gunn et al[28] by adjusting the effects of marijuana exposure during pregnancy for tobacco use and other confounders, such as other drug use, wherever possible, in a second meta-analysis. Their study included the systematic review of 31 studies (from 1982 to 2015) in which they specifically evaluated the effect of maternal marijuana use on neonatal outcomes that included low birth weight (<2500 g), preterm delivery (<37 weeks' gestation), birth weight, gestational age at delivery, admission to the NICU, small-for-gestational-age status, stillbirth, spontaneous abortion, low Apgar scores, placental abruption, and perinatal death.[29] A major strength of this review was the inclusion of cohort studies used to measure use of other substances, such as tobacco and other recreational drugs, and socioeconomic and demographic factors to control for these confounders and determine the independent role of marijuana use. Exposure to marijuana was defined as any amount, frequency, or duration during the pregnancy, assessed through self-report or objective means when available; comparison groups were women who did not use any marijuana during their pregnancy. When analyses controlled for concomitant tobacco use, women who smoked marijuana only were not at risk for preterm delivery, but those who smoked both tobacco and marijuana did experience higher rates of preterm delivery compared with those not using either marijuana or tobacco. They also found no independent relationship between marijuana use and small-for-gestational-age status, placental abruption, need for NICU admission, or spontaneous abortion. They did find that women using marijuana during pregnancy were more likely to deliver an infant with lower mean birth weight or lower Apgar scores and to experience stillbirth, but these results were unadjusted, because the authors were limited in their analytic ability to provide adjusted relative risk rates for these outcomes. They concluded that maternal marijuana use during pregnancy was not an independent risk factor for several outcomes, given the confounding effect with factors such as tobacco use. They stated that the "increasing frequency of marijuana use during pregnancy may play a role in risk for adverse neonatal outcomes" but cautioned that "women who use marijuana more frequently are also more likely to use higher amounts of tobacco and other drugs," which could not be accounted for completely in their review.

Both systematic reviews included longitudinal cohort studies used to provide data that are mixed in terms of adverse outcomes in infants exposed to prenatal marijuana during pregnancy. These include the Ottawa Prenatal Prospective Study (OPPS), a longitudinal cohort study of low-risk, white, predominantly middle-class families[30,31]; the Maternal Health Practices and Child Development Study (MHPCD), a cohort study of high-risk, low socioeconomic–status women, representing both white and African American women[32]; the Generation R study, a population-based study from the Netherlands[14]; and the United Kingdom–based Avon Longitudinal Study of Pregnancy and Childhood.[33] Researchers of the OPPS and the MHPCD found no independent relationship between prenatal marijuana use and preterm births, miscarriages, pregnancy complications, or Apgar scores or physical anomalies in the neonates, but researchers of the OPPS did find a decrease in the length of gestation by 0.8 weeks associated with heavy marijuana use.[34,35] Researchers of the MPHCD study found that weight at birth was increased for neonates prenatally exposed to marijuana in the third trimester of pregnancy.[35] In the Generation R study, fetal growth was measured by using ultrasonography, and the researchers found an independent effect of marijuana use, over and above the effect observed with concomitant tobacco use, on decreased fetal growth that was observed beginning in the second trimester and resulted in lower birth weight, specifically when marijuana use was begun early in pregnancy and continued throughout the entire pregnancy.[14] The Generation R study was also used to assess the role of paternal marijuana use, and no independent association with fetal growth was found. In the Avon Longitudinal Study, Fergusson et al[33] found an association between prenatal marijuana use and smaller birth lengths, smaller head circumferences, and lower birth weights among those reporting marijuana use in pregnancy, compared with women in the control group who did not report use.

Authors of another recent large, population-based cohort study found that self-reported marijuana use, without concomitant use of nicotine and/or tobacco, was not associated with pregnancy complications, preterm birth, or changes in neonatal outcomes such as Apgar scores and growth parameters.[36] However, concomitant use of both marijuana and tobacco, compared with tobacco use alone, resulted in an increased risk of multiple adverse perinatal outcomes, higher rates of maternal asthma and preeclampsia, preterm births, and infants with decreased (<25th percentile) head circumferences and decreased (<25th percentile) birth weights. Less than 1% of the total sample of 12 069 women reported use of marijuana, which raises concerns about the representativeness of the sample or validity of self-reported use of substances.

A small number of studies have been used to assess the role of marijuana in outcomes not addressed in the 2 systematic reviews above, such as outcomes in preterm infants, neonatal behavioral outcomes, and fetal anomalies. Dotters-Katz et al[37] published a secondary data analysis on a group of preterm infants born before 35 weeks' gestation comparing the neonatal outcomes of those with prenatal marijuana exposure by maternal report or drug screening (n = 138) versus infants with no marijuana exposure (n = 1732). They found that prenatal marijuana exposure had no detrimental effect on death before hospital discharge, grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, cerebral palsy, and/or a Bayley Scales of Infant Development–II <70 at 2 years of age.[37] van Gelder et al[38] found a higher rate of anencephaly in fetuses of women who smoked marijuana immediately before and during the first trimester of pregnancy, although the authors did not control for whether these women took supplemental folic acid during early pregnancy. Immediate newborn behaviors that have been observed in those infants who were exposed to marijuana in utero include altered arousal patterns, regulation, and excitability, as measured by the NICU Network Neurobehavioral Scale.[39] Increased tremors and prolonged and exaggerated startle reflexes, as measured by the Neonatal Behavioral Assessment Scale, were observed in the first week and persisted at 9 and 30 days of life.[40] Poor habituation and responses to visual but not auditory stimuli,[41] abnormal high-pitched cries,[42] and abnormal sleep patterns with decreased quiet sleep and increased sleep motility[43] have also been noted in the first week of life. A study by Dreher et al[44] of Jamaican infants exposed to marijuana prenatally did not reveal any abnormalities. Although researchers have suggested that these behaviors share some similarities with symptoms observed in the neonatal abstinence syndrome as well as with opioid withdrawal, there are no data being used now to support a clinical withdrawal syndrome with marijuana exposure.

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

Later Effects During Childhood, Adolescence, and Early Adulthood

Two longitudinal studies (the OPPS and the MHPCD, which have been described in the previous section) have been used to observe cohorts of prenatally exposed individuals from infancy through adolescence and early adulthood, and these provide most of the limited available evidence on the long-term adverse neurodevelopmental effects resulting from prenatal exposure to marijuana.[30,32] Authors of both studies have assessed long-term outcomes in the areas of executive function, cognition, academic achievement, and behavior.

Researchers of OPPS have observed its cohort since 1978 (original total of 84 pregnant women who use marijuana) and have demonstrated that, independent of tobacco and other drugs, marijuana exposure has significant and pervasive effects that are noticeable in children beginning at 4 years of age and continuing into young adulthood. Initial observable effects at 4 years of age included lower scores in verbal reasoning and memory tasks.[45] At 6 years of age, children exposed to marijuana, compared with nonexposed children in the control group, showed deficits in global measures of language comprehension, memory, visual and/or perceptual function, and reading tasks that require sustained attention, with a dose response observed, in that those exposed to higher amounts of marijuana prenatally demonstrated higher dysfunction on impulsive and hyperactive scales.[46–48] At 9 through 12 years of age, marijuana exposure was not independently associated with global intelligence or verbal subscales on intelligence testing but was associated with deficits in executive function tasks, such as impulse control and visual problem-solving.[49–52] At 13 through 16 years of age, problems were seen in attention, problem-solving, visual integration, and analytic skills requiring sustained attention.[51,53–55] A functional MRI study of this cohort at ages 18 through 22 years revealed

changes in neural activity with working memory tasks that were not observed in unexposed matched children in the control group.[56] Fried et al have postulated that the behavioral problems and decreased performance on global measures observed throughout childhood and into early adulthood reflect deficits in executive functioning, not overall intelligence.[31,54,57,58]

Researchers of the MHPCD have observed a cohort of exposed infants since 1982 to determine the independent effects of marijuana on cognition, behavior, temperament, mental health disorders, and substance use from infancy through adolescence and early adulthood. At 9 months of age, impaired mental development was seen.[59] At 3, 4, and 6 years of age, deficits in executive function tasks similar to those observed in the OPPS, with poorer memory and verbal measures were found[60,61]; at 6 years of age, impaired sustained attention on vigilance tasks and verbal reasoning and increased impulsivity and hyperactivity was observed with those exposed during the first trimester whose mothers smoked at least 1 joint per day.[61] Adverse consequences in later childhood included impaired executive functioning and visual problem-solving at 9 through 12 years of age and increased hyperactivity, impulsivity, and inattention at 10 years of age for those whose mothers had smoked marijuana during both the first and third trimesters.[62] Unlike the OPPS, whose authors did not find deficits in intellectual abilities and on measurements of standardized academic tests at ages 6 through 9 or 13 through 16 years, authors of the MHPCD did find lower reading and spelling scores in 10-year-old children whose mothers reported smoking at least 1 joint per day during the first trimester of pregnancy and deficits in reading comprehension and underachievement, as measured by the Wide Range Achievement Test–Revised, with mothers who reported smoking marijuana during the second trimester.[62] Lower global achievement, reading, spelling, and math scores were also seen at 14 years of age.[63] Measures of problem behaviors and mental health symptoms were also reported in both cohort studies. The authors of the OPPS found higher rates of reported problem behaviors at 6 through 9 years of age[64] and higher rates of depressive symptoms at 16 through 21 years of age.[65] Authors of the MHPCD also found higher rates of depressive symptoms and externalizing behaviors via parent and teacher report in the exposed cohort at 10 years of age and an increased risk of psychosis in young adults.[66,67] Higher rates of substance use were also reported by these 2 cohort studies. Authors of the OPPS found earlier onset and greater use of both marijuana and tobacco in the exposed cohorts, observed at ages 16 through 21 years,[65] and authors of the MHPCD found higher rates of marijuana and tobacco use across the ages of 14 through 21 years, even after controlling for home environment and parental substance use.[66,68] Sonon et al[69] have also demonstrated higher rates of marijuana use in young adulthood after prenatal exposure to marijuana.

In summary, it is essential to note that the studies discussed above have limitations that may threaten the validity of the findings. For example, the studies in which authors look at proximal results, such as fetal or early neonatal outcomes, rely in most part on self-report of marijuana use, and there is little standardization across studies in the amount of marijuana used and frequency of use. Many of these studies included pregnant women who used other substances in addition to marijuana, such as tobacco, alcohol, or other drugs, and analytic methods were used to control for the confounding effects of these other substances.

For more distal outcomes, such as later childhood and adolescent cognition and behavior, studies were limited in the environmental and sociodemographic variables that the authors could control, which could be expected to influence development across childhood and adolescence.[70,71] Despite these limitations and the relative paucity of research in this area, the findings regarding growth variables[72] and neurodevelopmental and behavioral outcomes can be used to suggest that marijuana use during pregnancy may not be harmless. In addition, the existing cohort studies were conducted when the available marijuana had a much lower potency than what is available today, which raises concern that the adverse consequences of prenatal exposure in currently pregnant women may be much greater than what has been reported to date.[18] (See the "Other Considerations" section for discussion on potency.) Rigorous research is needed to determine the independent effects of marijuana, as well as tobacco and other drugs, on neonatal and later childhood and adult outcomes.

Mechanisms Used to Explain Underlying Effects on the Developing Fetus

Cannabinoids mediate their effects through the cannabinoid receptors, type 1 and 2. The endocannabinoid system (ECS) comprises these receptors, along with the neurochemical cannabinoids anandamide and 2-arachidonoylglycerol. This has been studied in both animal as well as human models, specifically for its effect on the immune system and the central nervous system.[23] Although the consequences of prenatal marijuana exposure in pregnant women, both behavioral and developmental, have been documented in epidemiological studies, the molecular mechanisms that are postulated to be associated with these effects of prenatal

drug exposure are only now being elucidated. The ECS is detectable from the early stages of embryonic development (as early as 5 weeks' gestation) and has been found to play an essential role in the early stages of neuronal development and cell survival.[73] Researchers of new data elucidate how this system is involved in the control of neuronal developmental processes such as cell proliferation, migration, and differentiation; thus, it is not surprising that cannabinoid exposure during early developmental stages can result in the long-term neurobehavioral consequences described previously.

Although authors of early studies relied on animal models, authors of recent studies conducted on electively aborted fetuses have provided specific human data, which have been used to support findings observed with animal models. Tortoriello et al[20] have used sophisticated quantitative and qualitative molecular analyses and pharmacologic methods to study human fetuses electively aborted during the second trimester, in both pregnant women who smoked marijuana and pregnant women in a control group who did not use marijuana.[19] They found that in fetuses exposed prenatally to marijuana, levels of molecular substances essential for neuronal cell axonal elongation (SCG10) are significantly reduced, which affects the disassembly of microtubules essential for axonal elongation and the "pathfinding" essential for the development of normal neuronal circuitry during early brain development. THC acts as a partial agonist and binds to the cannabinoid receptors (CB1) during fetal development by reducing endogenous endocannabinoid synthesis (especially 2-arachidonoylglycerol) and subsequent CB1 expression. This results in a functional "hijacking" or supraphysiological modulation of the normal ECS during early fetal brain development. The result is a disruption of the precisely orchestrated signaling and sequencing functions of the ECS, affected by the CB1 receptors, and mediated through the excessive degradation of the intracellular substances such as SCG10 and JNK1.[74] Researchers have also found that unlike the adult brain, in which CB1 receptors are widely distributed throughout most areas of the brain, in the fetus, CB1 receptors are found primarily in the mesocorticolimbic structures such as the amygdaloid complex, the hippocampus, and the ventral striatum, all areas that are important for emotional regulation, cognition, and memory.[75] Researchers have also found that male fetuses may have a greater vulnerability to early developmental effects of prenatal marijuana exposure.[65,76] It is still unclear to what extent this disruption or alteration of developmental synaptic organization is responsible for early neonatal birth effects, longer-term neurodevelopmental effects, or increased vulnerability of later teenagers and adults for addiction or psychiatric illness. With the limited data, it is suggested that the neuronal systems involved in early development need to be studied further for us to understand more fully the molecular mechanism underlying the effects of maternal marijuana on the human fetal brain and specifically for those systems involved in neurocognition, impulsivity, and addiction vulnerability.[76]

Epigenetic mechanisms are also being proposed as one of the explanations for the consequences of prenatal marijuana exposure on fetal neurodevelopment and to explain why adolescents and adults who have been exposed to marijuana prenatally demonstrate an increased vulnerability to later addiction and psychiatric disorders.[77] Epigenetics refers to the mechanism by which gene expression is altered without changes to the genetic code that occur after the genetic makeup of the individual is determined, either prenatally or postnatally. These genetic alterations include microRNAs, DNA methylation, and posttranslational modifications of nucleosomal histones.[77] They are stable alterations that occur during critical developmental periods and result in enduring phenotypical abnormalities.[77] For example, researchers have found that marijuana exposure in early fetal life decreases the expression of genes (through histone lysine methylation) for dopamine receptors (DRD2) in those areas of the brain important for reward recognition (ventral striatum, nucleus accumbens), which may explain higher rates of drug addiction in adults exposed prenatally to marijuana.[78] THC also causes substantial changes in gene expression levels of several other significant systems in the brain that are linked to the ECS, such as the opioid, glutamate, and γ-aminobutyric acid systems, which may persist well into adulthood.[79]

Linkages of the ECS to Other Neurotransmitter Systems

The ECS has been found to have a strong interaction with the opioid systems, through the μ, δ, and κ opioid receptors,[80] Jutras-Aswad et al[79] have found that early marijuana exposure influenced the expression and activity of opioid receptors that have been found to be important in reward and subsequent addictive behaviors. The ECS has also been found to be associated with the serotonergic, adrenergic, glutamate, and γ-aminobutyric acid systems.[78]

Issues for the Clinician

The American Academy of Pediatrics (AAP), the ACOG, and the American Society of Addiction Medicine recommend that all women considering pregnancy, pregnant women throughout their

pregnancy, and those attending predelivery pediatric visits be screened routinely for alcohol and other drug use, including marijuana, by using a validated screening questionnaire.[17,81] Screening and brief intervention techniques are recommended to counsel abstinence for individuals using substances and to refer for treatment those individuals meeting criteria for any substance use disorder.[81] Despite these recommendations, in 1 study, Holland et al[82] found that of the 19% of women reporting current marijuana use (53%) or past marijuana use at their initial prenatal visit, only 52% received any kind of counseling. In addition, the counseling that was provided was focused mainly on legal and child protective consequences of detection at delivery, rather than specific medical or health effects of marijuana use. In July 2015, the ACOG published a position statement that was specifically used to advise against the "prescribing or suggesting the use of marijuana for medicinal purposes during preconception, pregnancy and lactation."[5] Most states that have legalized medicinal marijuana have not specifically limited its dispensing to pregnant women. Oregon is the only state that has legislated specific point-of-sale warnings to dispensaries for women who are pregnant or breastfeeding.[83] It is beyond the scope of this report to discuss specific validated questionnaires that are available or various means for objective screening.

Health care providers are mandated to report to child protective services any cases of suspected child abuse or neglect. The 2010 Child Abuse and Prevention and Treatment Act requires all states to have policies and procedures for reporting newborns and other children who are exposed to illicit substances under the definition of child abuse and/or neglect. Because marijuana is still an illicit substance under federal law, this law applies to marijuana exposure in all states regardless of the legal status of marijuana use by adults in each state. Individual states may have other requirements for the reporting of newborn infants exposed to drugs and other exposures to children.[84]

Given these legal requirements, it is advisable for all health care providers who see pregnant women to be aware of the specific reporting requirements of their state and the potential adverse legal and social consequences of identifying substance use in their patients. When a legal or medical obligation exists for a health care provider to test a patient, he or she should counsel patients about these potential consequences before ordering drug tests and make a reasonable effort to obtain informed consent.[5] Of note, in states with requirements for the reporting of newborn infants exposed to drugs, these supersede federal law on confidential protection of patient records when receiving addiction treatment (42 Code of Federal Regulations Part 2).[81]

BREASTFEEDING AND MARIJUANA USE

Breastfeeding is recognized as the ideal feeding method for infants because of the numerous short-term and long-term benefits of breastfeeding for the mother and the infant. These benefits include but are not limited to decreased infections, such as gastroenteritis, ear infections, and severe respiratory diseases; decreased obesity and diabetes mellitus; decreased rate of sudden infant death syndrome; improved intellectual development; decreased postpartum blood loss; increased child spacing; and decreased risk of type 2 diabetes mellitus for the mother.[85]

When pregnant mothers take medications prescribed or recreationally, the benefits of breastfeeding must be weighed against the effects of the drug on the infant to make a decision that is in the infant's and mother's best interests. Many medications that mothers use while breastfeeding are also taken during pregnancy. It can be difficult to determine whether effects of the drug on the infant are attributable to exposure during pregnancy or from breastfeeding. Additionally, a mother's ability to care for her infant may be impaired because of her use of marijuana. Infants can also be exposed to marijuana through inhalation of marijuana smoked in the presence of the infant.[86,87]

Epidemiology

There are few data about the frequency of use of marijuana by women while breastfeeding. A report from Colorado, where marijuana is legal for some, surveyed women attending the Special Supplemental Nutrition Program for Women, Infants, and Children program in the state's largest local health department. It revealed that 7.4% of mothers younger than 30 years of age and 4% of mothers older than 30 years of age were current marijuana users. Of all marijuana users (past, ever, current), 35.8% said that they had used at some point during pregnancy, 41% had used since the infant was born, and 18% had used while breastfeeding.[88]

Pharmacokinetics of Marijuana in Human Milk

The excretion of medications into human milk depends on chemical factors about the drug, including ionization, the molecular weight, the solubility in lipids and water, and the pH of the drug. The major psychoactive cannabinoid of marijuana, THC, is 99% protein bound, is lipid soluble, and has a molecular weight of 314.[89] The low molecular weight and high

lipid solubility combine to cause marijuana transfer into human milk. It also causes storage of THC in lipid-filled tissues such as the brain. Little is known about the other cannabinoids in marijuana and their transfer into human milk. There are few data about the transfer of THC into human milk. With Table 1, we list the results from the only 2 primary references about concentrations of THC in human milk. These limited data by Perez-Reyes and Wall[90] and Marchei et al[91] reveal that THC transfers into human milk. There is no information about how the amount transferred is related to the concentration of THC in the marijuana, the frequency of use, or the concentration in maternal plasma.

TABLE 1 Primary Sources for the Concentrations of THC Transmission Into Human Milk

Mother	Maternal Marijuana Dose	Amount of THC in Maternal Plasma	Amount of THC in Human Milk
A[91]	Smoked in pipe 1 time per day	—	105 ng/mL
B[91]	Smoked in pipe 7 times per day	7.2 ng/mL	60.3 ng/mL
C[90]	No information	—	86 ng/mL

—, not applicable.

The Effect of Marijuana on Breastfed Infants

There are 2 small studies by Tennes et al[92] and Astley and Little[93] from the 1980s in which the authors attempt to evaluate the effect of maternal marijuana use while breastfeeding on the infant. Both studies included mothers who also used alcohol, other drugs, and tobacco. Tennes et al[92] studied 258 mothers using marijuana and compared them to mothers who did not use marijuana. They examined the infants at 24 to 72 hours of age and a subgroup at 1 year of age. They found the following results: (1) marijuana users were more likely to use illicit drugs and alcohol with a significant linear dose-response relationship between the use of marijuana and alcohol ($R = 0.45$; $P < .01$); (2) infants exposed to marijuana were slightly shorter; (3) most mothers decreased use of marijuana during pregnancy; and (4) no differences were noted in the 1-year growth and scores on the Bayley Scales of Infant Development; however, only 27 of the infants tested at 1 year were exposed to marijuana while being breastfed. These results are limited by the small number of infants exposed to marijuana through breastfeeding, self-selection of mothers who participated in the 1-year follow-up, and lack of control for use of other substances, particularly alcohol.[92]

Astley and Little[93] studied diet, alcohol, and tobacco use during lactation in a group of middle-class mothers. Developmental evaluation at 1 year was completed on 68 infants whose mothers used marijuana while breastfeeding who were matched with mothers with similar alcohol and tobacco use who did not use marijuana while breastfeeding. Of the breastfeeding mothers, 79% reported marijuana use while pregnant, compared with 15% of mothers of infants who were fed formula. In multivariate regression analysis, the infant's exposure to marijuana during breastfeeding in the first month was associated with 14 ± 5 points decrease in motor scores after controlling for tobacco, alcohol, and cocaine use during pregnancy and lactation. There was no effect of marijuana use in the third month of life while breastfeeding. Marijuana use in the first trimester of pregnancy confounded these results, and it was not clear whether exposure prenatally or during breastfeeding had more association. The studies by Tennes et al[92] and Astley and Little[93] had small sample sizes, were completed more than 30 years ago, were associated with use of marijuana during the mother's pregnancy, and had no long-term follow-up. These limitations make it difficult to separate independent effects of marijuana use during breastfeeding from prenatal exposure.

Another area of concern is the use of expressed maternal milk for feeding preterm infants when the mother has reported marijuana use or receives positive test results for marijuana. Expressed maternal milk has been shown to significantly improve outcomes in preterm infants by decreasing the rate of necrotizing enterocolitis (both surgical and nonsurgical), contributing to earlier attainment of full enteral feeds, decreasing the rate of sepsis, and improving neurodevelopmental outcomes, especially for the preterm infants with a birth weight of less than 1500 g.[85]

Published Recommendations From Other Organizations

The 2012 AAP policy statement, "Breastfeeding and the Use of Human Milk," included the following guidance: "maternal substance abuse is not a categorical contraindication to breastfeeding." "Street drugs such as PCP (phencyclidine), cocaine, and cannabis can be detected in human milk, and their use by breastfeeding mothers is of concern, particularly regarding the infant's long-term neurobehavioral development and thus are contraindicated."[85] Although this has been interpreted by some professional organizations to indicate that in the parent using marijuana, the choice to breastfeed is "contraindicated," this was not the intent of that statement. It is suggested instead that the mother be encouraged to breastfeed while, at the same time,

it is strongly encouraged that she abstain completely from using marijuana as well as other drugs, alcohol, and tobacco. This position has been supported by several other professional organizations and resources. For example, LactMed (a free searchable database from the National Library of Medicine) recommends that mothers be encouraged to abstain from or reduce their marijuana use while breastfeeding and to minimize infant exposure to marijuana smoke. The LactMed peer review panel, which reviews published data to ensure scientific validity and currency, recommends continuing breastfeeding.[86] This is similar to the recommendations of the ACOG, which state, "There are insufficient data to evaluate the effects of marijuana use on infants during lactation and breastfeeding, and in the absence of such data, marijuana use is discouraged."[5] The Academy of Breastfeeding Medicine states "A recommendation of abstaining from any marijuana use is warranted. At this time, although the data are not strong enough to recommend not breastfeeding with any marijuana use, we urge caution."[94] After Colorado legalized the use of marijuana by adults ≥21 years old, the Colorado Department of Public Health and Environment developed educational material about marijuana use during pregnancy and while breastfeeding. These materials include patient education handouts that may be helpful to pediatricians and families and are available at the following link: www.colorado.gov/pacific/sites/default/files/MJ_RMEP_Pregnancy-Breastfeeding-Clinical-Guidelines.pdf. Other states that have legalized marijuana may have similar educational information for health care providers and families.

OTHER CONSIDERATIONS

The potency of marijuana now routinely available is much higher than what was available a decade ago. The potency of THC in samples studied in 1983 averaged 3.2%, and the average in 2008 was 13.2%; the authors of that same study identified isolated samples with THC contents as high as 27.3% and 37.2%.[95] These higher potencies as well as new practices of marijuana use, such as dabbing or vaping, can significantly increase the concentration of THC being consumed. Studies have revealed that the development of marijuana strains with higher THC concentrations has reduced the concentration of cannabidiol, possibly decreasing the medicinal benefits for a select number of conditions. There are many other substances contained in the marijuana plant in addition to THC and cannabidiol about which little is known. Additionally, marijuana is often grown with the use of pesticides, herbicides, rodenticides, and fertilizers, many of which are toxic.[96,97] Exposure to marijuana may also expose the fetus and infant to these toxins.

CONCLUSIONS AND RECOMMENDATIONS

Pediatricians are in a unique position to counsel women of childbearing age about the potential negative consequences of marijuana use during pregnancy and breastfeeding. Discussing what is known about adverse consequences of marijuana use during pregnancy and breastfeeding at prenatal visits with either the pediatrician or the obstetric provider is an important component of promoting the best health outcomes for both the pregnant woman and the infant. Legalization of marijuana may give the false impression that marijuana is safe. Given ethical concerns, there are no randomized controlled trials on the effect of marijuana use by pregnant and lactating women, and the available longitudinal studies must be viewed with caution given the potential confounding of the effect of marijuana during pregnancy by other licit and illicit substances and sociodemographic and environmental risks factors. However, highlighted in the available epidemiological and animal data are concerns regarding both short-term growth and long-term neurodevelopmental and behavioral consequences of prenatal exposure to marijuana. Our current understanding of the ECS and its role in the development of neural circuitry early in fetal life also provides "theoretical justification" for the potential of marijuana substances, particularly THC, to affect neurodevelopment.[18]

Breastfeeding has numerous valuable health benefits for the mother and the infant, particularly the preterm infant. Limited data reveal that THC does transfer into human milk, and there is no evidence for the safety or harm of marijuana use during lactation. Therefore, women also need to be counseled about what is known about the adverse effects of THC on brain development during early infancy, when brain growth and development are rapid.

The importance of the published findings and the emerging research regarding the potential negative effects of marijuana on brain development are a cause for concern despite the limited research and are the basis for the following recommendations:

1. Women who are considering becoming pregnant or who are of reproductive age need to be informed about the lack of definitive research and counseled about the current concerns regarding potential adverse effects of THC use on the woman and on fetal, infant, and child development. Marijuana can be included as part of a discussion about the use of tobacco, alcohol, and other

drugs and medications during pregnancy.

2. As part of routine anticipatory guidance and in addition to contraception counseling, it is important to advise all adolescents and young women that if they become pregnant, marijuana should not be used during pregnancy.
3. Pregnant women who are using marijuana or other cannabinoid-containing products to treat a medical condition or to treat nausea and vomiting during pregnancy should be counseled about the lack of safety data and the possible adverse effects of THC in these products on the developing fetus and referred to their health care provider for alternative treatments that have better pregnancy-specific safety data.
4. Women of reproductive age who are pregnant or planning to become pregnant and are identified through universal screening as using marijuana should be counseled and, as clinically indicated, receive brief intervention and be referred to treatment.
5. Although marijuana is legal in some states, pregnant women who use marijuana can be subject to child welfare investigations if they have a positive marijuana screen result. Health care providers should emphasize that the purpose of screening is to allow treatment of the woman's substance use, not to punish or prosecute her.
6. Present data are insufficient to assess the effects of exposure of infants to maternal marijuana use during breastfeeding. As a result, maternal marijuana use while breastfeeding is discouraged. Because the potential risks of infant exposure to marijuana metabolites are unknown, women should be informed of the potential risk of exposure during lactation and encouraged to abstain from using any marijuana products while breastfeeding.
7. Pregnant or breastfeeding women should be cautioned about infant exposure to smoke from marijuana in the environment, given emerging data on the effects of passive marijuana smoke.
8. Women who have become abstinent from previous marijuana use should be encouraged to remain abstinent while pregnant and breastfeeding.
9. Further research regarding the use of and effects of marijuana during pregnancy and breastfeeding is needed.
10. Pediatricians are urged to work with their state and/or local health departments if legalization of marijuana is being considered or has occurred in their state to help with constructive, nonpunitive policy and education for families.

RESOURCES

Additional resources include the AAP Resources on Marijuana (www.aap/marijuana), the AAP Section on Breastfeeding (www.aap.org/breastfeeding), the Academy of Breastfeeding Medicine (www.bfmed.org), the ACOG (www.acog.org/About-ACOG/ACOG-Departments/Breastfeeding), and LactMed (toxnet.nlm.nih.gov/newtoxnet/lactmed.htm).

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ABBREVIATIONS

AAP: American Academy of Pediatrics
ACOG: American College of Obstetricians and Gynecologists
ECS: endocannabinoid system
MHPCD: Maternal Health Practices and Child Development Study
NSDUH: National Survey on Drug Use and Health
OPPS: Ottawa Prenatal Prospective Study
PRAMS: Pregnancy Risk Assessment Monitoring System
THC: δ-9-tetrahydrocannabinol

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