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Update on the developmental consequences of cannabis use during pregnancy and lactation

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Abstract

There is a strong increase in prevalence trends for cannabis use during pregnancy and lactation as more states legalize use of this drug. Information on the teratogenic risk of cannabis is limited but some important themes can be gleaned. Studies have not found a unique phenotypic signature of prenatal exposure but an increased risk of congenital anomalies, particularly gastroschisis, has been reported. Changes in fetal growth have been described in some epidemiological studies but long-term patterns of physical growth appear unaffected. Prenatal exposure to cannabis is not generally associated with reductions in global IQ but specific cognitive skills, especially attention and memory, can be negatively impacted. Long-term impacts on psychological health include increased rates of depressive symptoms and anxiety as well as delinquency. Relatively little is known about the risk of maternal cannabis use during lactation but data suggest that infant exposure is relatively low compared to maternal exposure. As delta-9-tetrahydrocannabinol (THC) levels increase to meet consumer demand and routes of exposure diversify, there is a strong need for prospective birth-cohort studies that collect biological samples to quantify exposure. Data from such studies will be critical to overcoming the weaknesses of past cannabis research and are essential to establishing reliable information on the risks of maternal use. Until that time, health care providers should be encouraged to talk about the risks and benefits associated with cannabis use during pregnancy and lactation with their patients, emphasizing that fetal and neonatal risks cannot be excluded at this time.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

Keywords

birth defects; cannabis; child development; exposure; lactation; marijuana; pregnancy

1 | BACKGROUND

Marijuana (*Cannabis sativa*) is an herbal remedy that has been used for thousands of years to treat conditions that range from leprosy to dandruff. *C. sativa* contains more than 80 phytocannabinoids, but the most studied and frequently used are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the predominant psychoactive compound in cannabis. CBD can be derived from either marijuana or hemp; cannabidiol oils contain low amounts of THC and thus avoid intoxicating side effects. Hemp is a variant of *C. sativa*, which is fiber producing and contains no more than 0.3% of THC (VanDolah, Bauer, & Mauck, 2019). There are many routes of exposure for cannabinoids including smoking the flowers and leaves, vaping concentrates, applying a vaporized spray to the buccal area, ingesting capsules, liquids, or foods and applying topical lotions. Potency and timing of effects on the user vary greatly according to method used (Meier, Docherty, Leischow, Grimm, & Pardini, 2019).

1.1 | Legalization/prevalence of use

California legalized medical marijuana in 1996. “Recreational” marijuana is legal for adults in 11 states; medical marijuana is legal in 33 states plus the District of Columbia, and there are currently bills being considered in other state legislatures (Kharbanda et al., 2020). Federal law has also changed, with the Agricultural Improvement Act of 2018 making cannabis derivatives with very low levels of THC (defined as less than 0.3% on a dry weight basis) no longer a controlled substance. Prevalence of cannabinoid use in women who are pregnant has increased over the past decade, at least in part due to social acceptability and legalization. Data from the 2016 Pregnancy Risk Assessment Monitoring System (PRAMS) was used to assess the prevalence of exposure in women living in three states that have legalized recreational marijuana compared to three states that have not. Usage was significantly greater in the preconception, prenatal and post-partum period in women living in the states with legalized marijuana (Skelton, Hecht, & Benjamin-Neelon, 2020). A Canadian study found that use by pregnant women went from 1.2% to 1.8% between 2012 and 2017, a relative increase of 61% (Corsi, Hsu, Weiss, Fell, & Walker, 2019). Canada recently legalized use of marijuana, so it is anticipated that cannabinoids will become more widely available and use during pregnancy will continue to increase.

In the United States, the National Survey on Drug Use and Health interviewed women aged 12–44 years over a period of time ranging from 2002 to 2017. Women were asked about frequency and prevalence of medical and nonmedical cannabis use. Among women who were in any trimester of their pregnancy, self-reported past month cannabis use increased from 3.4% in 2002 to 7.0% in 2017. Use was highest in the first trimester (5.7% in 2002 vs. 12.1% in 2017) (Volkow, Han, Compton, & McCance-Katz, 2019).

It is widely believed that data utilizing self-report frequently provides an under-estimate of use. For example, a study that recruited 500 women from obstetrical practices and utilized urine drug screens in addition to self-report found 22% of women used cannabis, a much higher prevalence than that reported in prior studies (Oga, Mark, & Coleman-Cowger, 2018).

1.2 | Medical versus recreational use

The legalization of medical marijuana in many states has resulted in cannabinoids increasingly being proposed as novel approaches for treatment of a variety of difficult to control conditions (Hill, 2020). In situations where cannabinoids are demonstrated to be as effective or even more effective than conventional prescribed medications, the risk vs. benefit consideration regarding use in pregnant or breastfeeding women becomes more difficult. However, in many cases there is limited evidence of efficacy, and dangers of use have been poorly delineated. There is concern that medical use of cannabis for unproven therapies may deter women from using standard medical treatments that have gone through the FDA drug approval process and have been determined to be both safe and effective (Hill, 2020; Young-Wolff et al., 2019).

A systematic review of 15 randomized controlled trials of medical cannabinoids concluded that there is reasonable evidence for improvement of chemotherapy-induced nausea and vomiting, patient “perception” of improvement with multiple sclerosis-associated spasticity, and uncertainty as to whether cannabinoids improve neuropathic pain (Allan et al., 2018). With regard to mental health conditions, a systematic review and meta-analysis of 83 studies involving 40 small randomized controlled studies on medical cannabis and pharmaceutical grade CBD found limited evidence of effectiveness in treating mental health conditions such as depression, anxiety, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), or psychosis when compared to placebo. Many participants reported side effects associated with treatment including sleepiness and dizziness (Black et al., 2019).

The most common reasons women cite for using medical marijuana are nausea and vomiting of pregnancy, chronic pain, and anxiety (Metz & Borgelt, 2018). A Canadian study of 84 women who used medical cannabis during pregnancy, reported that 77% used it to treat nausea and vomiting of pregnancy (NVP). Of those who used it for NVP, 92% indicated that it was effective (Westfall, Janssen, Lucas, & Capler, 2006). A subsequent study utilizing data from pregnant women in the Kaiser Permanente health care system who either self-reported cannabis use or had a positive urine screen for THC found that while prevalence increased over time in both groups, it was higher among women who had NVP when compared to those who did not. Between 2009 and 2016 the prevalence increased from 6.5% to 11.1% in women with NVP, and 3.4% to 5.8% in pregnant women who did not have NVP (Young-Wolff et al., 2019). There are no randomized controlled studies on efficacy of cannabis in treating NVP, and ACOG recommends that women discontinue use of cannabis during pregnancy (Volkow et al., 2019).

1.3 | Perception of risk associated with use

The American College of Obstetricians and Gynecologists (ACOG) (Braillon & Bewley, 2018), the American Academy of Pediatrics (AAP), the FDA, and the U.S. Centers for Disease Control and Prevention (CDC) all recommend that women avoid cannabis use during pregnancy or while breastfeeding. Despite these recommendations, women's perception that use of cannabis during pregnancy is without risk continues to increase. This perception of safety is encouraged by legalization, permissive social norms, and personal recommendations by nonmedical employees at places such as medical and retail cannabis dispensaries (Bayrampour, Zahradnik, Lisonkova, & Janssen, 2019; Dickson et al., 2018). Women's false sense of safety may also thrive in an environment where healthcare providers are uncertain as to the safety and risk of use during pregnancy. Instead of following medical recommendations, women may obtain their information from family and friends, social media, and Internet searches (Metz & Borgelt, 2018). In a study utilizing interviews with pregnant and nonpregnant women of reproductive age collected by the National Survey on Drug Use and Health between 2005 and 2015, annual changes in the perception of "no risk of regular marijuana use" were examined. In that time period, the overall perception in women of reproductive age that regular marijuana use has "no risk" increased three-fold. Impressions of safety in pregnant women reporting use in the past 30 days increased from 25.8% to 65.4% (Jarlenski et al., 2017). Another study explored the perspectives and reasons for cannabis use during pregnancy (Chang et al., 2019). Interviews were conducted with 25 pregnant women who self-reported current cannabis use, or who had positive urine tests for cannabinoids. Women cited medical reasons for use including help with nausea and to improve mood. Many women reported that they were uncertain about potential risks, but were trying to reduce use. However, they also described cannabis as "safe and natural," compared to other recreational drugs, tobacco, and alcohol (Chang et al., 2019).

Jarlenski et al. (2017) interviewed 26 women receiving prenatal care and who either self-disclosed that they were using cannabis or tested positive for cannabis in urine samples. The women were asked about where they obtained information on the effects of marijuana use in pregnancy. Internet searches and anecdotal information from family and friends were the most common sources of information, and few women indicated that they had received helpful information from their healthcare provider. Women indicated that information obtained from various sources was inconsistent and did not provide evidence of specific harms that cannabis might present to the pregnancy or fetus. Some women reported that since health care providers did not address perinatal cannabis use, they assumed that it did not present a significant risk to their pregnancy. Recommendations for what would have been useful included improved communications from healthcare workers and resources specific to the impact of the perinatal cannabis exposure on the baby's health.

1.4 | Potency/contaminants

Retail marketing of cannabinoids had led to concerns because of varying THC levels and general lack of regulation. In prior decades, smoked cannabis generally had a THC level of 3–6%. In recent years the potency of cannabis has increased from 5% to more than 15% (Hall et al., 2019). With legalization, there are business reasons to increase THC concentration, and new cultivars are being grown that have potency as high as 30%.

Cannabis concentrate, made by extracting THC from the marijuana plant, may have a THC content ranging from 39% to 69% (Meier et al., 2019). Cannabinoids are not regulated or approved by the U.S. Food and Drug Administration (FDA), with the exception of one prescription CBD medication and two prescription THC products. In a March 2020 news announcement, the FDA expressed concerns that there may be false claims and omitted ingredients in nonprescription cannabis product labeling, such as pesticides and heavy metals, that may present health hazards (FDA, 2020).

1.5 | Pharmacokinetics

While the pharmacokinetics of cannabinoids in pregnancy have not been studied, in the general adult population, disposition of the drug varies by form and route of administration. Smoking marijuana is the principle route of cannabis administration. It provides a rapid and efficient method of drug delivery from the lungs to the brain. THC is detectable in plasma almost immediately following inhalation and reaches peak concentrations rapidly. However, bioavailability of THC via inhalation has ranged widely in various studies from 2–56%, in part due to variability in individual smoking style (Huestis, 2007).

There are a limited number of studies on the disposition of THC and its metabolites after oral administration of cannabis. Absorption is slower when cannabinoids are ingested, with lower, more-delayed peak THC concentrations. Dose, route of administration, vehicle, and physiological factors, such degradation of drug in the stomach, and significant first-pass metabolism in the liver, can influence drug concentrations in circulation. In one study, peak THC concentrations ranged from 4.4 to 11 ng/mL, 1–5 hr following ingestion of 20 mg of THC in a chocolate cookie. Bioavailability in that study was estimated to be 6% (Huestis, 2007).

1.6 | Limitations of available data

Efforts have been made to study the impact of prenatal cannabis exposure in animal models and humans. However, methodological issues, especially in human studies, make findings inconsistent, difficult to interpret, and problematic when trying to synthesize results to inform clinical recommendations (El Marroun et al., 2018). Randomized controlled studies of treatments in pregnant women are often not ethically possible, and much of the existing data on cannabis use in pregnancy involves case reports and observational studies. In many studies there is no standardized formulation or dose of cannabis. Observational studies on substance abuse are prone to misclassification, especially if self-report is not accompanied by biomarker testing. They are also prone to unmeasured or poorly measured confounding by factors such as socioeconomic status, use of tobacco and concurrent use of alcohol and other recreational drugs, which may pose their own risks to the fetus (Oga et al., 2018; Silverstein, Howell, & Zuckerman, 2019; Singh, Filion, Abenhaim, & Eisenberg, 2020).

2 | EFFECTS OF PRENATAL CANNABIS EXPOSURE ON NEONATAL OUTCOMES AND CHILD

2.1 | Neurodevelopment

The body of information on maternal cannabis use during pregnancy and child outcomes suggests that effects are often subtle and may become more pronounced with age, often manifesting during middle childhood or adolescence (Scheyer, Melis, Trezza, & Manzoni, 2019). The interpretation of results from published studies is challenging for several reasons, including maternal poly-drug use and reliance on measures of self-report to quantify or typify exposure. Because many women do not provide reliable estimates of cannabis use, misclassification of exposure can lead to biased results. This has been clearly demonstrated in studies where the adverse impact of prenatal cannabis exposure was only revealed after statistical analyses were restricted to women with positive THC urine toxicology results (Rodriguez et al., 2019; Zuckerman, Amaro, & Cabral, 1989). Additionally, the possible influence of covariates such as carbon monoxide exposure from smoking cannabis must be considered when interpreting study results. In this update of the teratogenic risk associated with cannabis, we have organized the information into three general outcome areas; (a) congenital anomalies, (b) other adverse perinatal outcomes, and (c) cognitive and behavioral development from infancy through adolescence.

2.2 | Congenital anomalies

Most studies, including prospective longitudinal birth cohorts, have not found an association between maternal use of cannabis during pregnancy and an increased frequency of congenital anomalies (Day et al., 1991; Fried, 1980; Gunn et al., 2016; Kharbanda et al., 2020). Results suggest that there is not a unique phenotypic signature of prenatal cannabis exposure and the morphology of exposed newborns is normal. However, some studies using aggregate data from health records have found evidence that supports an association between cannabis use and congenital anomalies. An increased risk of anencephaly (posterior OR 1.9, 95% CI 1.1–3.2) after first trimester cannabis exposure was identified in an analysis of data from the National Birth Defects Prevention Study (van Gelder, Donders, Devine, Roeleveld, & Reefhuis, 2014). Gastroschisis, a defect in the infant abdominal wall, has been associated with maternal cannabis use in a matched case–control study using data from the California Birth Defects Monitoring Program (OR = 2.2, 95% CI 1.0–4.8) (Lam & Torfs, 2006). An increase in isolated ventricular septal defects (OR = 2.35, 95% CI 1.43–3.86) (Williams, Correa, & Rasmussen, 2004) and severity of gastroschisis (OR = 4.0, 95% CI 1.0–15.7) (Weinsheimer & Yanchar, 2008) have also been reported in two additional case–control investigations of prenatal cannabis exposure.

A population-based study of gastroschisis and lifestyle variables found that young, disadvantaged women with a history of drug use, including cannabis, in the 3 months before pregnancy were at the greatest risk for having a child with this congenital anomaly (Torfs, Velie, Oechsli, Bateson, & Curry, 1994). Rates of maternal cannabis use were significantly higher than expected for 21 of 54 selected congenital anomalies in a record linkage study that covered 18 years (Forrester & Merz, 2007). A number of organ systems appeared to be affected but a specific relationship between cannabis exposure and defects

of the gastrointestinal system was identified. While suggestive and potentially important, studies that have found an association between prenatal cannabis exposure and congenital malformations are correlative in nature. Such ecological associations cannot demonstrate increased risk for the individual exposed pregnancy (Corsi, 2020). Data from prospective cohort investigations with biological markers of exposure will be necessary to clearly understand the impact of this drug on fetal development but until then, a small increased risk of congenital anomalies cannot be excluded.

2.3 | Other adverse perinatal outcomes

The published results on prenatal cannabis exposure and perinatal outcomes are inconsistent. Some studies have reported no effect of maternal cannabis use on fetal growth, birth outcomes and postnatal health (Conner, Carter, Tuuli, Macones, & Cahill, 2015; Sturrock, Williams, Ambulkar, Dassios, & Greenough, 2020; van Gelder et al., 2010). Other investigations however, have found evidence that prenatal exposure affects early development in a variety of ways. A recently published study, notable for its extensive control for covariates including maternal comorbidities, examined health records from pregnant women that included a urine toxicology screening for THC (Kharbanda et al., 2020). Results indicated a 70% increase in risk of small-for-gestational age (SGA) infants in women who used cannabis during pregnancy. An elevated risk of SGA infants has been found in other studies using THC urine assays to confirm exposure (Rodriguez et al., 2019; Warshak et al., 2015) and in studies relying on maternal self-report (Corsi, Walsh, Weiss et al., 2019; Luke, Hutcheon, & Kendall, 2019; Saurel-Cubizolles, Prunet, & Blondel, 2014). The association between maternal cannabis use during pregnancy and SGA infants remained significant in a study where women cousing tobacco were excluded from the analysis (El Marroun et al., 2009). In contrast, a records analysis of data from the Stillbirth Collaborative Research Network cohort found that maternal cannabis use during pregnancy was not associated with adverse pregnancy outcomes including SGA infants but was associated with an increased risk of neonatal death (Metz et al., 2017).

When compared to unexposed controls, prenatally-exposed infants may also be at an increased risk for prematurity and reduced birthweight (Baer et al., 2019; Corsi, Walsh, Weiss et al., 2019; Howard, Dhanraj, Devaiah, & Lambers, 2019; Luke et al., 2019; Petrangelo, Czuzoj-Shulman, Balayla, & Abenhaim, 2019; Rodriguez et al., 2019). Despite research findings that suggest prenatal exposure is associated with changes in early growth trajectories, there is no robust evidence of an enduring negative effect. Children enrolled in longitudinal cohort studies with a history of prenatal exposure showed normal patterns of long-term physical growth despite some evidence of differences in infancy (Day, Richardson, Geva, & Robles, 1994; Fried, Watkinson, & Gray, 1999) and pubertal milestones were unaffected (Fried, James, & Watkinson, 2001).

2.4 | Cognitive and behavioral development from infancy through adolescence

Gestational cannabis exposure has been studied from birth through adolescence using a wide range of psychometric instruments in a small number of studies. Most of the information that is available on neurodevelopment comes from three longitudinal birth cohort studies: the Ottawa Prenatal Prospective Study in Canada (Fried, Watkinson, Grant, & Knights, 1980),

the Maternal Health Practices and Child Development Project in the United States (Day, Wagener, & Taylor, 1985) and the Generation R Study in the Netherlands (Jaddoe, van Duijn, & van der Heijden, 2010). One of the earliest reports described increased tremors/startle and diminished visual responses among neonates born to women who were moderate or heavy users of cannabis during pregnancy (Fried, 1980; Fried, Watkinson, Dillon, & Dulberg, 1987). Increased body movements and decreased time in quiet sleep were reported in a study using electroencephalogram (EEG) testing in young infants with a history of daily gestational exposure (Scher, Richardson, Coble, Day, & Stoffer, 1988). Similar results were obtained in this cohort of exposed children at 3 years of age, suggesting a persistent disruption of the brain mechanisms that control arousal and cycles of sleep (Dahl, Scher, Williamson, Robles, & Day, 1995).

Studies of cognition during infancy have reported no relationship between maternal cannabis use and mental abilities (Astley & Little, 1990; Fried & Watkinson, 1988) or transient effects that did not persist at follow-up (Richardson, Day, & Goldschmidt, 1995). Diminished short-term memory and attentional capacity have, however, been identified in exposed children as early as preschool age but intelligence quotient (IQ) scores fall within the normal range (Fried & Watkinson, 1990; Noland et al., 2005). At the time of school entrance, findings on intellectual development as measured by standardized tests lack consistency (Fried, O'Connell, & Watkinson, 1992; Fried, Watkinson, & Gray, 1992; Goldschmidt, Richardson, Willford, & Day, 2008). During middle-childhood and adolescence, higher-dose prenatal exposure has been associated with poorer performance on assessments of memory, visual analysis, attention, inhibitory control and academic achievement (Fried, Watkinson, & Gray, 1998, 2003; Goldschmidt, Richardson, Cornelius, & Day, 2004; Richardson, Ryan, Willford, Day, & Goldschmidt, 2002). An overall synthesis of the data suggests that while global IQ is preserved in exposed children, certain components of cognition are affected (Fried et al., 1998, 2003). Many of the skills most vulnerable to cannabis exposure, for example, attention, working memory and inhibitory control, are part of a domain of cognitive performance known as executive functioning (Fried & Smith, 2001; Smith et al., 2016). Executive functioning allows for the top-down processing of information and is a key predictor of academic and professional success (Diamond & Ling, 2016). Children with a history of prenatal exposure may be at a disadvantage for the full realization of their life goals because of deficits in executive functioning skills.

There is increasing recognition that maternal use of cannabis during pregnancy may also have long-term effects on psychological health in exposed children. Increased levels of aggression were observed at 18 months in female infants with a history of prenatal exposure (El Marroun et al., 2011). By early school age, impulsivity and hyperactivity have been reported at higher rates in exposed children (Fried, O'Connell, & Watkinson, 1992; Fried, Watkinson, & Gray, 1992). A recent publication from the Generation R study showed teacher ratings of externalizing behaviors such as aggression and rule-breaking were more frequent among children whose mothers used cannabis during pregancy (El Marroun et al., 2019). Findings from this cohort are particularly noteworthy because maternal THC levels in urine were used to quantify gestational exposure. By middle-childhood, increases in depressive symptomology, anxiety, hyperactivity and impulsivity have been reported and in

some cases, the effects were dose and timing dependent (Goldschmidt, Day, & Richardson, 2000; Gray, Day, Leech, & Richardson, 2005; Leech, Larkby, Day, & Day, 2006). During this period of development, a small increase in psychoses (Fine et al., 2019) and a greater frequency of psychotic-like experiences (Bolhuis et al., 2018) has been observed in children whose mothers and/or fathers used cannabis during pregnancy. Cannabis-related effects on behavior continue into adolesence where increased rates of juvenile delinquency have been documented (Day, Leech, & Goldschmidt, 2011). Prenatally exposed adolescents at the highest risk for delinquency reported experiencing depression at age 10. However, in a seperate study, no increase in risk for psychotic symptoms was observed in young adolescents with a hisory of prenatal cannabis exposure (Zammit et al., 2009) (see Table 1 for a summary of the observed effects of prenatal exposure on child development).

As with other outcomes described in this review, the available data are limited in some cases by use of cannabis products that were historically of lower potency, relatively small samples sizes that decline in number at later follow-up assessments, and inability to completely control for other factors in the postnatal environment that influence development.

2.5 | Messages from research with animal models

Studies using model species such as monkeys, rats and mice provide the opportunity to control many of the environmental factors that impact study outcomes in human research. Results from investigations of prenatal cannabis exposure with animal models lend support to the general themes that can be extracted from the human literature, particularly changes in cognition and social interactions (for reviews see Grant, Petroff, Isoherranen, Stella, & Burbacher, 2018; Scheyer et al., 2019; Tirado-Muñoz et al., 2020). No congenital anomalies were described in infant rhesus monkeys exposed to THC in-utero during the second and third trimester (Asch & Smith, 1986). Similarly, fetal malformations have not been reported in rodent offspring born to dams treated with THC during pregnancy in laboratory studies spanning several decades (Benevenuto et al., 2017; Campolongo et al., 2007; Fried, 1976; Harbison, Mantilla-Plata, & Lubin, 1977; Hutchings, Morgan, Brake, Shi, & Lasalle, 1987; Moreno, Trigo, Escuredo, Rodríguez de Fonseca, & Navarro, 2003; Natale et al., 2020). There is some evidence of fetal growth restriction but recent data in mice suggest that significant postnatal catch-up growth normalizes the early effects of exposure (Natale et al., 2020). Some investigations in rodent models have found that neurobehavioral development is not disrupted by prenatal cannabis exposure (Abel, 1984; Hutchings et al., 1987; Hutchings & Dow-Edwards, 1991) while others have identified persistent changes in learning and memory (Campolongo et al., 2007; Fried, 1976; Gianutsos & Abbatiello, 1972). Altered social interactions and increased anxiety-like behaviors have also been reported (Trezza et al., 2008; Trezza et al., 2012). Recent research on paternal exposure prior to mating has been associated with impaired attentional processing and abnormal activity levels in offspring (Levin et al., 2019). This finding highlights the important contribution of the sire to developmental outcomes in offspring. Treatment-related effects on growth and cognition in rodents are often expressed differently between the sexes and male offspring are typically more affected than females (Bara et al., 2018; de Salas-Quiroga et al., 2020; Holloway et al., 2020).

3 | CANNABIS USE DURING LACTATION

While there are few data on the prevalence of cannabis use during lactation, based on estimates of use during pregnancy, it is thought that cannabis consumption while breastfeeding is common. However, infant exposure to THC and other metabolites through breastmilk has not been well-studied. Several case reports published over 30 years ago demonstrated detectable quantities of THC in breast milk and in one case in the feces of a breastfed infant (Perez-Reyes & Wall, 1982). More recently, validated analytical methods for assaying cannabis in milk have been developed (Wei, McGuffey, Blount, & Wang, 2016). Two recent studies using these methods have quantified cannabis metabolites in milk samples from women, one under experimental conditions, and one in an observational setting. In the first, eight lactating women were asked to inhale a single 0.1 g premeasured dose of cannabis containing 23.18% THC. Serial milk samples were collected in the 4 hr following that exposure. The investigators estimated the relative infant dose (RID) to be 2.5% (range 0.4–8.7%) of the maternal level (Baker et al., 2018). In the second study, 50 breastfeeding mothers who had used cannabis products in the previous 2 weeks provided 54 milk samples. THC was measurable in 34 (63%) of the samples; levels were dependent on hours since last use and number of uses per day. In at least one sample, THC was detectable 6 days after the last reported maternal dose. Based on several assumptions, the investigators estimated that the plasma concentration of THC in a fully breastfed infant would be several orders or magnitude lower than maternal levels (Bertrand, Hanan, Honerkamp-Smith, Best, & Chambers, 2018).

Two older studies have examined motor and mental performance in one-year old infants born to mothers who consumed cannabis while breastfeeding, with conflicting results. The first involved 27 breastfed infants in the cannabis group compared to 35 breastfed infants who were unexposed; the authors found no significant differences between the groups on the Bayley Scales of Infant Development Motor or Mental Developmental Indices (Tennes et al., 1985). The second study involved a sample of 55 infants breastfed by mothers who were using cannabis and 81 comparison infants breastfed by mothers who did not. On the Bayley Scales of Infant Development, there were significant differences between the groups on motor skills performance at 1 year of age among infants whose mothers used marijuana in the first month postpartum but no differences with exposure at later time points. In that study, the authors acknowledged that they could not completely account for the potential contribution of prenatal exposure to cannabis in those infants (Astley & Little, 1990).

In summary, indications from two small studies of cannabis use during lactation suggest that the infant dose of THC resulting from breastfeeding is likely to be small; however, these studies did not measure infant dose directly. In addition, it is unclear from these studies to what extent there could be accumulation of THC in milk with chronic use. The neurodevelopmental data available to date are limited by samples exposed to lower potency products available more than 30 years ago and by follow-up that was limited to one standardized test at 1 year of age. Further studies are required to address these issues.

4 | DISCUSSION AND CONCLUSIONS

Although the data on in utero cannabis exposure and child development are often equivocal, some clinical messages can be gleaned. It is unlikely that cannabis has a unique phenotypic signature in exposed newborns. An increased risk of adverse perinatal outcomes, including SGA infants, prematurity and low birthweight, has been reported in some, but not all, epidemiological studies. Findings on cognitive development indicate that global IQ is probably not affected but subtle deficits in memory, attention and impulse control may impact long-term success in school and the workplace. There is a growing recognition of the relationship between prenatal cannabis exposure and psychological health. Symptoms of anxiety and depression are elevated in exposed children as are rates of externalizing and delinquent behavior. THC, the principal psychoactive component of cannabis, can be measured in the breast milk of women who use cannabis during lactation. Infant exposure through lactation appears to be limited in dose relative to maternal levels; however, direct measurements of infant dose have not been well studied, and data are lacking on the relationship between exposure through breastfeeding and longer term growth and development.

Women report that they want information on whether maternal cannabis use can affect the health of their fetus or breastfed infant (Chang et al., 2019). However, physicians and other medical providers indicate that they are largely unfamiliar with risks and benefits of medical marijuana and specific concerns regarding use in a pregnant or breastfeeding woman (VanDolah et al., 2019; Young-Wolff et al., 2019). The lack of consistent results and the belief that the available studies are flawed interferes with a reliable message that healthcare providers can embrace and effectively convey to their patients. Given the difficulty in interpreting the existing data, healthcare providers may fail to address the topic at all, or fall back on avoidance of liability as the rationale for recommending that women abstain from perinatal cannabis use. Legalization makes that particular argument less persuasive, and women may conclude that concerns are only with regard to legality and not actual safety for the fetus (Bayrampour et al., 2019; Mark et al., 2017). Disturbingly, women report an assumption that if cannabis use is not addressed within the health care setting, it does not present a risk for adverse reproductive outcomes (Jarlenski et al., 2016).

Cannabis is increasingly present in various forms and potency in many retail products. Questions about cannabis use in all forms for both recreational and medical reasons should be included in the prenatal intake for all women. Without this information, healthcare providers cannot effectively address the issue with their patients.

When cannabis is prescribed for medical indications, risks and benefits in pregnancy and breastfeeding should be addressed in a similar fashion to that used with other prescription medications. This entails weighing the adequacy of the data and considering whether alternative medications that are lower risk, better studied, or both will effectively treat the maternal condition. A discussion of recreational use might involve the potential contamination of product with other hazardous agents, and difficulty in ensuring safety to the fetus and breastfed infant.

Healthcare providers need education on strategies to convey risk in situations where data are inconclusive and incomplete (Conover & Polifka, 2011). Provider-patient discussions should be clear and honest about uncertainty. This allows for a conversation about risks and benefits, and whether there is a conventional therapy that is likely to be safer (Rubin, 2019; Young-Wolff et al., 2019). Information suggesting that safety has not been proven is a potent strategy in convincing women to quit use of cannabis. At the same time, caution should be used in drawing premature conclusions about risks associated with cannabis exposures in pregnancy and breastfeeding. Exaggerating risk can lead to loss of confidence in expert opinion and lowered expectations for prenatally exposed children (Silverstein et al., 2019).

Healthcare providers and their patients need reliable and readily available information on the impact of maternal cannabis use on the fetus and breastfed infant. Table 2 includes recommended resources including the North American Antiepileptic Drug Registry which is gathering data to explore the impact of Epidiolex and other medical CBD exposures in pregnancy. Information on medical CBD exposures (where there is a controlled product and dose) is needed to assist in determining whether there are potential hazards to these medications. Healthcare providers are encouraged to refer appropriate patients and contact the registry for additional information. MotherToBaby, the patient information service of the Organization of Teratology Information Specialists, has a wide range of patient materials including fact sheets, blogs, and podcasts. Healthcare providers can call the toll free number to discuss specific cases and receive current and comprehensive information on the potential reproductive hazards of cannabis.

With changing policies and more widespread legalization of cannabis for recreational use, it can be anticipated that there will be increasing prevalence of cannabinoid use in pregnancy and breastfeeding, and greater need for health care providers to address the issue with their patients. This makes it crucial to have good quality data on the outcomes of cannabis use in pregnant and breastfeeding women, a commitment by providers to address cannabis use with their patients, and enhanced information sources for health care providers and their patients.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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TABLE 1

Observed effects of prenatal cannabis exposure on child development

Infancy (*0–2 years*) 
No robust effect on early mental development (Astley & Little, 1990; Fried & Watkinson, 1988; Richardson et al., 1995)
Some evidence of alterations in fetal growth, particularly SGA infants (El Marroun et al., 2009; Saurel-Cubizolles et al., 2014; Rodriguez et al., 2019; Warshak et al., 2015)
Disturbance in sleep cycling (Scher et al., 1988)
Increased aggression and attentional problems in females (El Marroun et al., 2011)
Early and mid-childhood (*3–11 years*) 
Disturbance in sleep cycling (Dahl et al., 1995)
Possible effect on cognition, particularly verbal reasoning, attention, and memory, but unlikely to impact global IQ (Fried & Watkinson, 1990; Fried, O'Connell, & Watkinson, 1992; Fried, Watkinson, & Gray, 1992; Day et al., 1994; Goldschmidt et al., 2004; Goldschmidt et al., 2008)
Increase in externalizing behaviors such as aggression, impulsivity, and delinquency (Goldschmidt et al., 2000; Leech et al., 1999)
Greater frequency of depressive symptoms and anxiety (Gray et al., 2005; Leech et al., 2006)
Adolescence (*12–18 years*) 
No effect on long-term physical growth and timing of pubertal milestones (Fried et al., 2001)
Diminished scores on tests of academic achievement (Goldschmidt, Richardson, Willford, Severtson, & Day, 2012)
Higher rates of juvenile delinquency (Day et al., 2011)
Subtle impairments in attention, working memory and inhibitory control suggest diminished executive functioning skills (Fried et al., 2003; Fried & Smith, 2001; Smith et al., 2016)

TABLE 2

Resources

a.	Epidiolex and mother medicinal CBD exposures in pregnancy are now being followed by the North American Antiepileptic Drug Pregnancy Registry http://www.aedpregnancyregistry.org/ [aedpregnancyregistry.org]
b.	MotherToBaby fact sheet https://mothertobaby.org/fact-sheets/marijuana-pregnancy/ [mothertobaby.org]
c.	FDA, https://www.fda.gov/consumers/consumer-updates/what-you-should-know-about-using-cannabis-including-cbd-when-pregnant-or-breastfeeding [fda.gov]
d.	ACOG, https://www.acog.org/patient-resources/faqs/pregnancy/marijuana-and-pregnancy [acog.org]
e.	AAP, https://www.healthychildren.org/English/ages-stages/prenatal/Pages/Marijuana-Use-During-Pregnancy-Breastfeeding.aspx [healthychildren.org]
f.	SAMHSA, https://www.samhsa.gov/marijuana/marijuana-pregnancy [samhsa.gov]