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REVIEW ARTICLE

Outcomes of mothers and newborns to prenatal exposure to kratom: a systematic review

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Abstract

Kratom is a legal, widely available substance that contains opioid agonist alkaloids. Due to the marketing of kratom as an opioid alternative for treatment of pain, anxiety, depression, or to reduce opioid withdrawal symptoms, the use of kratom has increased among persons in the USA including pregnant women. This systematic review of the peer-reviewed literature regarding kratom in relation to maternal and infant outcomes resulted in analysis of six case reports of prenatal kratom exposure. Maternal and infant withdrawal from kratom exposure was described in each case, resulting in pharmacologic treatment for both mothers and infants.The original online version of this article was revised: Madison Sherbondy has been added to the author list.

Introduction

The opioid epidemic has brought attention to perinatal substance exposures and the resulting effects on pregnancy, maternal, and newborn outcomes. Besides the substances of use that are identified by routine history and toxicology, novel psychoactive substances (NPS) often are not routinely part of the health history obtained and remain undisclosed or undetected during pregnancy. NPS are legally sold on the internet and in retail locations such as gas stations, herbal stores, and "head shops" [1]. From 2000 to 2017, the United States poison control reported roughly 67,500 calls reporting exposure to NPS [2]. Kratom was one of the four leading substances that had the highest rates of hospitalization and serious medical outcomes. While most exposures to natural psychoactive substances have decreased over the years, exposures to kratom have increased drastically, by 4948.9%, from 2011 to 2017 [2].

cKratom, a derivative of *Mitragyna speciosa*, is in the coffee plant family and originated from Southeast Asia. Kratom is sold as tea, capsules, tablets, raw leaves, and concentrated extracts. The two main alkaloid substances found in kratom are mitragynine pseudoindoxyl and 7-hydroxymitragynine. Mitragynine is an opioid agonist with a small affinity for receptors. Conversely, 7-hydroxymitragynine has a much smaller presence in kratom, yet an increased potency as an opioid agonist [3, 4]. The alkaloid 7-hydroxymitragynine has been reported to have a higher potency than morphine [5]. A major challenge in understanding the actions and effects of kratom is the varying dosage of the alkaloids, additives, or alterations of kratom, the variability of dosage, and simultaneous polysubstance use by consumers [6, 7].

Metabolites of kratom will not appear on a standard urine toxicology. Standard analytical screening techniques for mitragynine and its metabolites, as with other NPS, require a more sophisticated liquid chromatography–mass spectrometry [8–10].

The primary reasons for use of kratom given by persons with past or present substance use disorder include pain, anxiety, depression, and to stop or reduce opioid use by reduction of withdrawal symptoms [11–13]. Kratom is popularly used and marketed in the USA as an opioid substitute and for the reduction of withdrawal symptoms [14–18]. In 2016, the Food and Drug Administration (FDA) attempted to list kratom as a Schedule 1 controlled substance [19], which generated a massive response from pro-kratom advocates. In 2018, the FDA released a report of 36 kratom-related overdose deaths with potential deadly

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interactions with other substances [20]. In the same year, the FDA released a warning of kratom contamination with multiple strains of Salmonella, which resulted in 199 people infected across 41 states and 38% of infected individuals were hospitalized [21]. A subset of states and cities in the USA has banned kratom (Alabama, Arkansas, Tennessee, San Diego, California, Indiana, Rhode Island, Vermont, Wisconsin). The debate on the benefits of kratom versus the risks continues, and highlights the need for research to inform clinical practice guidelines [22].

Prenatal use of kratom incidence is not fully known. The specific effects on pregnant women and their infants/children are unknown. The purpose of this systematic review was to analyze the current evidence published in peer-reviewed journals of the effects of kratom on human mothers and infants.

Methods

The peer-reviewed literature including prenatal kratom exposure and effects on mothers and newborns was analyzed using the following databases: PubMed, Cochrane Review, CINAHL, EBSCOhost, and Google Scholar. Search terms included kratom and pregnancy, kratom, kratom and neonatal effects, kratom and neonatal abstinence syndrome, kratom and infancy, kratom and newborn, and kratom and perinatal exposure. Inclusion criteria for the studies included: (1) the literature using English language; (2) peer-reviewed journals; (3) research studies; (4) studies of kratom when the use was during pregnancy; (5) studies that included effects on the mother and/or infant associated with use of kratom prenatally; and (6) case reports that included prenatal use of kratom and effects on the mother and/or infant. Exclusion criteria for the studies included: (1) non-English language literature; (2) journals that are not peer-reviewed; (3) the literature that was not research; (4) studies of kratom that did not include use during pregnancy; and (5) studies of kratom that did not include effects on the mother and/or the infant.

A total of 31 articles were found in the search of the databases using the search terms described (Fig. 1). Eighteen of the articles were duplicate and were excluded from the review. Abstracts of the remaining 13 articles were reviewed. Five of the articles did not pertain to infant or maternal outcomes relating to kratom prenatal exposure. The remaining eight articles were reviewed in full text. Three articles were excluded due to not being research or case reports in addition to not pertaining to infant or maternal outcomes related to prenatal kratom exposure. Five published case reports in peer-reviewed journals that pertained to prenatal kratom use and maternal/infant outcomes were included in the review (Fig. 1).

Results

The review of the five case reports of prenatal kratom use and maternal and infant outcomes are summarized in Table 1. The five articles included six mothers with an age range of 39–37 years and used kratom during pregnancy [23–27]. The reasons mothers reported using kratom for included: (1) pain relief such as fibromyalgia, back pain, and restless leg syndrome; (2) anxiety; (3) relief of opioid withdrawal symptoms; and (4) desired opioid-like effects. Four of the six mothers used kratom 3–4 times per day for the entire pregnancy [23–27]. The cost of the kratom was reported by one mother as $40.00 per day [24]. Two mothers were treated with prescribed buprenorphine or buprenorphine and naloxone after weaning off kratom during pregnancy [27].

Descriptions of the mothers' withdrawal symptoms from kratom use were reported in the case studies and included anxiety, piloerection, diaphoresis, and restlessness. Symptoms of withdrawal were described as severe resulting in returning to kratom use or being treated with buprenorphine or buprenorphine and naloxone. One mother had to go to the emergency department due to the initial severity and presentation of her withdrawal symptoms when discontinuing kratom use [27]. Prior to pregnancy, one mother reported that if she missed a kratom dose for 4–6 h or if she tried to taper her kratom dose, she experienced symptoms that included diaphoresis, rhinorrhea, myalgia, anxiety, nausea, diarrhea, and piloerection [24]. Psychological dependence was also described by a mother as not being able to function at home or work without taking kratom [24].

Polysubstance use was reported in four cases and included prescribed substances for comorbid conditions [23, 25] (Table 1). Two cases had no other substances identified except kratom [24, 26].

The gestational age of five of the infants ranged between 37 weeks and 5 days to description of full term [23–27]. Infant outcomes included symptoms of neonatal abstinence syndrome in five out of six infants in the case reports, including the two infants that were only exposed to kratom prenatally. Symptoms of neonatal abstinence syndrome appeared to begin as early as 6–8 h after birth and could be detected up to 4 days after birth. The average length of stay in the hospital was ~10 days with a minimum stay of 3 days and a maximum stay of 12 days [23–27].

The five infants that exhibited withdrawal symptoms were pharmacologically treated with a morphine weaning protocol. One of the five was started on morphine then switched to clonidine after signs of over sedation. The infant developed sinus bradycardia on both morphine and clonidine and had no reported prenatal substance exposures other than kratom [26]. A Finnegan score of 18, prior to

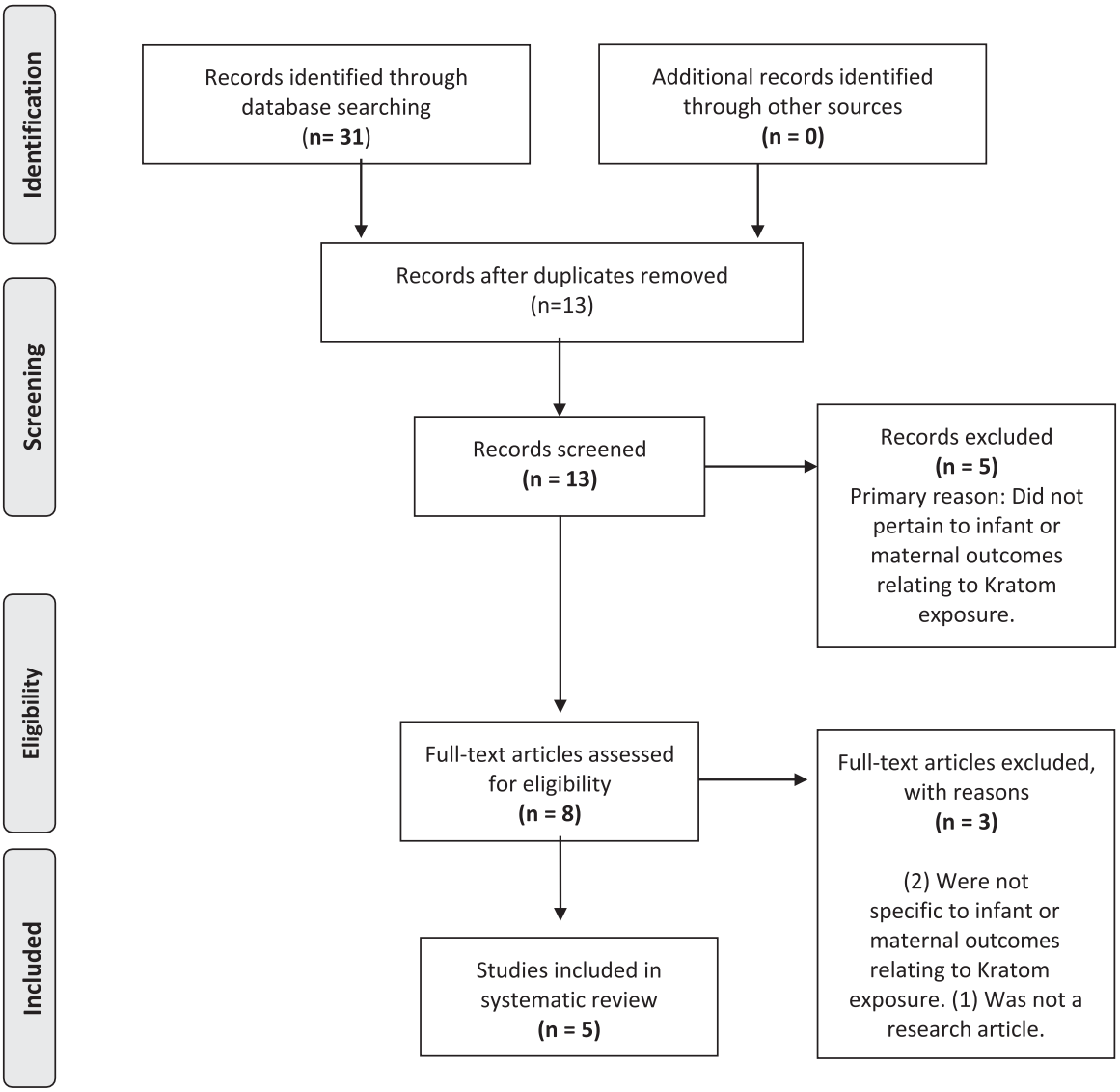

Fig. 1 Prisma flow diagram. Databases used: PubMed, CINAHL, Cochrane Review Google scholar, and EBSCOhost. Key search terms: "Kratom and neonatal abstinence syndrome," "Kratom and neonatal effects," and "Kratom and pregnancy".

morphine treatment, was reported for the infant exposed to kratom (tea used 3–4 times per day), selective serotonin reuptake inhibitors, acetaminophen-methocarbamol, diphenhydramine, valacyclovir, ranitidine, loratadine, salbutamol, and citalopram [25]. One of the infants who was only exposed to kratom, with a maternal daily use pattern of kratom 18–20 g three times per day, developed abstinence symptoms day 2 postpartum. Symptoms included feeding intolerance, jitteriness, irritability, and emesis requiring IV morphine 10 mg/kg/h and was switched on day 7 to oral morphine when able to tolerate oral intake [24].

The one infant that did not exhibit neonatal withdrawal symptoms was not exposed to kratom at the end of pregnancy, but instead the mother was given 2 mg of buprenorphine to alleviate maternal symptoms of withdrawal [27]. In addition, this baby was discharged from the hospital when 3 days old without evidence of withdrawal symptoms and there was no without report in the case study of follow-up of the infant to monitor symptoms post discharge from the hospital.

Discussion

The systematic review of the literature of prenatal kratom use and effects on maternal and infant outcomes revealed case reports of both maternal and infant withdrawal symptoms after kratom use in pregnancy. The majority of mothers in the case studies were using kratom daily prior to their pregnancy. All mothers reported consumption of

Table 1 Prenatal kratom exposure literature on maternal and infant outcomes.

Case study	Maternal characteristics	Other substances during pregnancy	Maternal outcomes	Infant outcomes	Comments
Davidson et al. [23]	29-year-old female	Other substances during pregnancy:	Delivery: Spontaneous vaginal delivery	Gestational age:	Call for research
	Chronic smoker	Gabapentin	Mother's treatment: Maternal treatment not specified in case study	Full term	Safety and efficacy of kratom for prenatal maternal use and effects on the fetus during pregnancy.
	Second pregnancy	Clonazepam		Feeding: Formula Fed	Polysubstance exposure complicates the causal relationship of kratom and withdrawal.
	Mother's kratom use pattern: Chronic kratom user				Further research is needed on polysubstance exposures.
	Reasons for kratom use:	Prenatal vitamins		Signs/symptoms of infant withdrawal: Symptoms 24 h after birth	Clinicians understanding specific spectrometry to identify kratom, routine toxicology will not identify kratom.
	Chronic low back pain, fibromyalgia, and anxiety			Included:	
		Daily over the counter herbal supplements		Reduced oral intake, jitteriness, sneezing, hypertonia, excessive crying. Intermittent tachypnea, excessive suck, hyperthermia.	
		Penicillin prophylaxis		Finnegan 10 and above	
		Nicotine		Pharmacologic Wean: Yes, morphine	
				Length of hospital stay: 14 days	
Mackay and Abrahams [24]	29-year-old female	Other substances during pregnancy:	Delivery: Delivered 37 weeks 5 days	Gestational age: 37 weeks and 5 days	Clinicians need to ask patients about kratom use and observe infants exposed for neonatal withdrawal.
	Gravida 4	No other substances described	Unremarkable pregnancy	Signs/symptoms of infant's withdrawal: On postpartum day 2, exhibited feeding intolerance, jitteriness, irritability, and persistent vomiting	Maternal withdrawal needs to be assessed and treated.
	Para 1-3-0-0		Mother's length of stay in the hospital:	Pharmacologic treatment for infant withdrawal:	Authors suggest the nonpharmacologic measure of rooming-in with mother and breastfeeding for infant withdrawal.
	Mother's kratom use pattern:		4 weeks in perinatal addiction unit	IV then oral morphine	
	18–20 g three times per day prior to and during pregnancy.		Mother's treatment:	Length of infant's stay in the hospital:	
	Reasons for kratom use:		Postpartum day 2 oral morphine	NICU 2 days	
	Back pain		moderate withdrawal symptoms anxiety, piloerection, diaphoresis and restlessness Improved over 2 days	Tertiary NICU 7 days	
	Functioning		4 weeks slow taper	Total length of stay not specified	
	Withdrawal symptoms if dose delayed 4–6 h			Feeding: Breastfed Infant was breastfed at the beginning of day 7	
	Symptoms included				
	anxiety, piloerection, diaphoresis, and restlessness				
Murthy and Clark [25]	37-year-old female	Other substances during pregnancy:	Mother's length of stay in the hospital:	Gestational age:	Maternal kratom demonstrated
	Gravida 2	Selective serotonin reuptake inhibitors	7 days after delivery	Term	withdraw symptoms with clinical features similar to narcotic withdraw.
	Reasons for kratom use:	Acetaminophen-methocarbamol	Delivery:	Feeding: Breastfed	Demonstrates importance of maternal history and practitioners' familiarity of kratom and kratom with polysubstance use.
	Anxiety	Diphenhydramine	C-section		Management principles for managing NAS with maternal kratom use are needed.

Table 1 (continued)

Case study	Maternal characteristics	Other substances during pregnancy	Maternal outcomes	Infant outcomes	Comments
				Signs/symptoms of infant's withdrawal: Within 6–8 h after birth jittery and increased tone	
	Restless leg syndrome	Valacyclovir	Mother's treatment (postpartum): Rapid 7 day detoxification program	12 h, excessive sucking and irritability	Prolonged withdrawal symptoms in infant need further evaluation.
	Mother's kratom use pattern:	Ranitidine		22 h, irritability, sleeplessness between feeds and excessive sucking Finnegan score of 18	
	Kratom tea was used daily 3–4 times per day	Loratadine		Pharmacologic treatment for infant withdrawal:	
		Salbutamol		Morphine with two unsuccessful weans of morphine	
		Citalopram		Length of hospital stay:	
				Discharged home on day 12 on oral morphine. Total wean off morphine took 2 months	
Eldridge et al. [26]	Mother's kratom use pattern: Daily drank kratom tea during pregnancy, which she purchased at a smoke shop, to self-treat opioid dependence	Other substances during pregnancy:	Delivery: Uncomplicated C-section	Signs/symptoms of infant's withdrawal: 33 h post birth, sneezing, jitters, excessive suck, facial excoriations, irritability, resting tremors, high pitched cry	Pediatricians should be aware of the increasing use of kratom as a self-treatment and "opioid alternative" in pregnant mothers and should expect to see more babies with NAS.
	Reasons for kratom use:	No other substances reported during pregnancy	Mother's length of stay in the hospital:	Pharmacologic treatment for infant's withdrawal: Morphine	Pediatricians need to ask mothers specifically about this drug when taking histories because it does not show up in urine samples.
	Opioid withdrawal symptoms	Maternal urine toxicology:	Not reported in case report	Appeared overly sedated and developed sinus bradycardia. Discontinued morphine after 3 days. Finnegan scores rose to 11–13	There is a lack of literature to guide pediatricians in management of babies with NAS due to kratom and more research needs to be done.
	Sleep	Negative	Mother's treatment:	Clonidine for 2 days until sinus bradycardia reoccurred so weaned off day 5	
			Not reported in case report	Length of infant's stay in the hospital: 8 days	
Smid et al. [27]	**Case One**	Other substances during pregnancy:	Delivery: Scheduled repeat C-section	Gestational age:	Kratom exposure in beginning of pregnancy switched to buprenorphine for remaining of pregnancy at a decreased dose.
	32-year-old woman	Buprenorphine:	Mother's length of stay in the hospital: After giving birth, mother remained in the hospital for 3 additional days (infant with her)	39 weeks	Infant was discharged on day 3 postpartum after prenatal exposure to buprenorphine but suggest follow-up if symptoms develop.
	Gravida 4 Para 2-0-1-2	8 mg after period of abstinence from kratom, tried to self-wean in pregnancy with severe depression so began 2 mg of buprenorphine for remainder of pregnancy	Mother's treatment (postpartum):	Signs/symptoms of infant's withdrawal: No evidence of neonatal abstinence syndrome, however child was discharged on day 3 after exposure to buprenorphine	Obstetricians should be aware of kratom use among individuals with opioid use disorders including pregnant women.
	Medical history:	Other substances during pregnancy:	Oxycodone for post cesarean pain	Length of infant's stay in the hospital: 3 days	Suggests that buprenorphine or methadone may be viable options for opioid replacement pharmacotherapy.
	Hodgkin's lymphoma	Switched from kratom to prescribed buprenorphine 16 mg and naloxone 4 and 2 mg, respectively	Buprenorphine	Feeding: BreastfedBreastfeeding:	Further studies should be done on prenatal use of kratom.
				Feeding: Breastfed	

Table 1 (continued)

Case study	Maternal characteristics	Other substances during pregnancy	Maternal outcomes	Infant outcomes	Comments
	Hx of oxycodone use for pain weaned in prior pregnancy	At 36 weeks gestation due to withdrawal symptoms switched to 20 mg buprenorphine and 3 mg naloxone daily			
	Reasons for kratom use:	Escitalopram, lamotrigine, and quetiapine (to treat bipolar disorder)	Length of mother's stay in the hospital:	Signs/symptoms of infant's withdrawal: Diagnosed with neonatal abstinence syndrome on day 4 after birth	
	Used to treat chronic pain and anxiety	Quit smoking cigarettes and switched to using an e-cigarette two to six times daily	2 days after giving birth	Treatment for infant's withdrawal: Treated with morphine	
	Mother's use pattern: Daily use for 7 months prior to discovering she was 16 weeks pregnant. She initially discontinued use, to self-wean, but was unsuccessful so she continued use of kratom		Delivery: Induced vaginal delivery	Length of infant's stay in the hospital: After being weaned off morphine, was discharged after 12 days after birth	
	Case Two		Mother's treatment (prenatal): Maintained 4 mg of buprenorphine and 2 mg of naloxone four times per day, switched to e-cigarettes, increased to 20 mg buprenorphine and 3 mg naloxone daily at 36 weeks of gestation for increased withdrawal symptoms	Feeding: Breastfed	
	28-year-old woman		Mother's treatment (postpartum): Maintained on same dosage of buprenorphine and naloxone until discharge	Infant was breastfed	
	Gravida 5			Gestational age:	
	Para 3-0-1-3			39 weeks	
	Presented to emergency department at 19 weeks gestation with withdrawal symptoms secondary to kratom. After 10–12 h of abstinence from kratom experienced opioid-like withdrawal symptoms			Apgar scores:	
	Past medical history:			8 and 8 at 1 and 5 min	
	History of intravenous methamphetamine and heroin use. Last use 6 months prior to presentation at emergency department			Finnegan scores:	
	Hospitalized several times for suicide attempts, but denied any active suicidal ideation			Not reported in case study	
	Reasons for kratom use: Desired opioid-like effects				
	Mother's use pattern: Smoking kratom for 4 months until reaching 19 weeks of gestation				

kratom because of its opioid-like effects and 66.67% of mothers reported previously being dependent on opioids. Although the previous drug history of all mothers was unclear in the case studies, the women who attempted to decrease or stop their kratom usage reported symptoms similar to opioid withdrawal and expressed psychologic dependence on kratom. Women of childbearing age are using kratom and becoming pregnant without knowing or being advised of consequences of continued use during pregnancy.

Of the case reports that included toxicology results, the results were negative. The presence of kratom metabolites needs specific spectrometry [22] and the standard toxicology testing would be negative if not specifically ordered. Clinicians need to review toxicology panels and understand the limitations of routine testing to detect NPS such as kratom.

Polysubstance exposure was described in the case studies. One mother reported taking prescribed gabapentin during her pregnancy along with a variety of other drugs. Gabapentin while taking opioids has shown an increase in the opioid's effects, and it is unknown whether kratom produces these same effects [28, 29]. The severity of the symptoms could not be fully analyzed due to inconsistent reporting of Finnegan scores in the case study reports; however, pharmacologic wean was needed whether or not the infants had polysubstance exposure or single exposure to kratom.

The treatment plan for the mothers was similar to typical opioid treatment plans. The various treatments performed to discontinue kratom usage included prenatal medically assisted therapy using buprenorphine or buprenorphine and naloxone, partial replacement of kratom with oral morphine (which both were completely weaned off after 4 weeks), and a rapid detoxification program with assistance of psychiatry and an addiction program. All of the treatment plans reported successfully weaning the women off kratom.

Infants experienced withdrawal symptoms that created a need for pharmacologic wean using morphine and in one case clonidine and morphine. In the only case report that did not require pharmacologic treatment, the mother was only using prescribed buprenorphine during the last months of pregnancy [27]. The infant was sent home 3 days after birth, which makes it possible that symptoms may have developed after discharge. Timing of infant withdrawal to prenatal kratom exposure is an area of research that is needed to guide timing of postbirth observation for withdrawal in infants.

Clinicians are educated to take a medical history that includes any drugs or other substances taken by a patient, especially during pregnancy. The public impression that herbal substances do not fall into the category of needing to be disclosed is based on the principal that these substances are "natural" and therefore do not need any special consideration. Due to marketing of kratom that claims it is a nonaddictive alternative for opioids without risk, mothers do not know the potential of risk if they use kratom [30]. In a qualitative study of pregnant or parenting mothers with substance use disorder, mothers expressed their concern on effects of substance use on their infant and were motived to discontinue use for the sake of their child(ren) [31]. Kratom use is not reported to child protective services because it is "legal." All of these factors may lead to misinterpretation of the safety of prenatal exposure to kratom and other legal psychoactive substances. Clinicians providing services to childbearing age, pregnant, or parenting women should specifically ask about the use of any substance. It should be explained to mothers that any substance exposure for the growing fetus may have effects—some that are known and some that are just being discovered as different substances become more available. The lack of incidence data is a result of the current state of undiscoverable use of kratom in pregnancy. Adoption of a validated tool, such as the kratom dependence scale, may assist in screening for the increasing use of psychoactive substances [32]. Understanding the presence of exposure to psychoactive substances during pregnancy assists in anticipating the observation of withdrawal symptoms for both mother and infant in the postpartum period, and scheduling the appropriate timing of discharge to home. Offering substance use treatment, such as detoxification, counseling that includes motivational interviewing, trauma informed care, and medically assisted therapy, is a standard of practice to address substance use disorders and should be made available to all childbearing age and pregnant women.

Research is needed to study the potential impacts of prenatal kratom in maternal and infant outcomes. In order to study the effects of perinatal kratom use, foundational areas of research are needed that include: (1) patterns of maternal use during pregnancy; (2) reasons for use in pregnancy; (3) maternal symptomatology; and (4) reactions to self-weaning during pregnancy. Infant outcomes need to address the crossing of kratom through the placenta, the determination of toxicology identification of kratom exposure, the amount of kratom in breast milk transmission to infants, and the timing, severity, and signs of infant withdrawal from prenatal exposure. Kratom combined with other prescribed and nonprescribed substances is an area of research needed to determine if there is an increased severity of negative maternal and infant outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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