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Maternal Kratom Use: A Cause of Neonatal Opioid Withdrawal Syndrome - A Case Series and Literature Review

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"Kratom is a psychoactive herbal supplement with opioid activity and is marketed as a non-opioid remedy for opioid withdrawal. Many health care professionals are still unaware of kratom use and availability. Kratom is undetectable by standard drug screens."

Abstract:

Maternal opioid use is a well-known cause of neonatal opioid withdrawal syndrome (NOWS). Pregnant women may seek non-opioid alternatives to manage opioid dependence to avoid NOWS. Kratom is a psychoactive herbal supplement with opioid activity and is marketed as a non-opioid remedy for opioid withdrawal. Many health care professionals are still unaware of kratom use and availability. Kratom is undetectable by standard drug screens. Neonates are withdrawing and developing NOWS when their mother's history is positive for kratom use. We present two NOWS cases secondary to maternal kratom exposure. Both neonates developed withdrawal signs and symptoms within the first 36 hours of life. Subsequently, they were successfully treated with methadone. Awareness of the effects of maternal use of kratom is essential for better care for neonates by both pregnant women and healthcare providers.

Keywords: Kratom, Neonatal Abstinence syndrome, withdrawal

Introduction:

NOWS is a withdrawal syndrome observed in neonates after exposure to opioids *in utero*. (1-2). The incidence of NOWS alarmingly increased fivefold in the previous decade. Public health strategies have been implemented to increase awareness with mutual efforts to prevent and treat opioid use before and during pregnancy among patients and healthcare personnel. Recognition of potential NOWS has driven many women of reproductive age to less studied herbal remedies. Recently, *Mitragyna speciosa*, more commonly known as kratom, has been found as an emerging substance of abuse that can cause NOWS due to maternal use during pregnancy.

Kratom is a plant-derived substance that can cause a stimulant effect, which may increase energy levels and help combat fatigue when used in low doses (3). When used in higher doses, kratom has been shown to mimic the analgesic and sedative effects of opioids (1). When used regularly, like substances that act on opioid receptors, dependence on kratom can develop, resulting in withdrawal after cessation of use (4). Kratom is legally and readily available in stores and via Internet sales in the United States (5). There have been estimates of 3–5 million users within the United States (6). An online cross-sectional study obtained over 10,000 individual responses primarily from within the United States in under a month from an announcement on the American Kratom Association's homepage, demonstrating kratom's increasing prevalence and popularity (6).

Diagnosis of kratom dependence relies largely on history as it is not detected on standard toxicology screens. Several case reports describing adult patients with kratom dependence and consequential withdrawal currently exist in the literature (7, 8). However, a limited number of NOWS cases have been reported secondary to maternal kratom use. Neonates whose mothers have a history of kratom use have exhibited comparable symptoms to adults who have shown kratom withdrawal. Although the management of NOWS due to kratom lacks sufficient guidelines, affected neonates respond to traditional NOWS management.

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Case Presentation:

Case 1: A white male born at 38 weeks' gestation vaginally to a 29-year-old G6 P4 A2 mother was transferred to our facility from a sister institute at the age of life eight hours. The patient was suspected of having NOWS in the newborn nursery since he was exhibiting tremulousness without any other etiologies. Upon arrival, the newborn had hypertonia, tremulousness, and inconsolable high-pitched cry. Mother had a history of polydrug use, including marijuana, methamphetamines, suboxone (combination buprenorphine and naloxone), and tobacco for ten years but reported undergoing successful rehabilitation. Her last use of any opioid or sedative substance was at least one year before the delivery. The patient's urine and meconium drug screens (MDS) were positive for marijuana only.

Similarly, the mother's UDS was also only positive for marijuana. However, the mother later revealed that she was using kratom as a non-opioid alternative to help relieve the pain associated with uterine contractions over the last two weeks before delivery. He was suspected of having NOWS from kratom withdrawal. The patient then had seizure-like activities. He was treated with a load-

ing dose of phenobarbital. MRI brain and EEG were normal. His Finnegan scores were persistently above 12. He was started on methadone per unit protocol. Slowly methadone was weaned as tolerated, and he was discharged after 17 days.

Case 2: A term white male born vaginally to a 34-year-old G6P2A4 mother was transferred from the newborn nursery at 36 hours of age. He demonstrated tachypnea, hypertonia, high-pitched cry, and jitteriness. The mother had a history of heroin dependence. The infant's MDS and UDS were negative. The mother's UDS was also negative. The mother reported that to stay away from heroin, she had been taking kratom purchased over the counter and at gas stations over the past four years. The patient required a 32-day methadone wean before he was discharged home.

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Discussion:

Kratom leaves are indigenous to Southeast Asia and have long been used recreationally and medicinally (9). The pharmacological activities of kratom are primarily due to the indole alkaloids, mitragynine, and 7-hydroxymitragynine (10). These components act as partial agonists at μ-opioid receptors and competitive antagonists at κ-opioid and δ-opioid receptors (11). Mitragynine and 7-hydroxymitragynine demonstrate biased agonism at μ-opioid receptors, activating G-protein receptors without engaging β-arrestin, a signaling molecule linked to noxious opioid side effects such as constipation and respiratory depression (11). Mitragynine is less potent than morphine, while 7-hydroxymitragynine has a higher potency than morphine, with fewer gastrointestinal effects. Although 7-hydroxymitragynine is structurally different from morphine, chronic exposure to μ-opioid receptors can result in dependence, tachyphylaxis, and cross-tolerance to morphine (12). Unlike traditional opioids, kratom is not associated with respiratory depression; its biased agonism may be explained by μ-opioid receptors, δ-opioid antagonism, and its action at non-opioid receptors, including α-2 adrenergic, serotonin, and dopamine receptors (13).

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The main objective of our report is to raise awareness among pediatricians, particularly neonatologists, about the unconventional substance kratom that is commercially available yet can lead to the development of withdrawal in neonates who have had intrauterine exposure. This highlights the need to inquire specifically about the consumption of herbal and over-the-counter substances on at-risk patients, facilitating maternal counseling, early recognition, and prompt treatment of NOWS.

Another objective that this report focuses on is the paucity of data on managing withdrawal with kratom. Previously, NOWS caused by maternal kratom use has been reportedly managed with clonidine and morphine. The reported cases were successfully managed with the unit's standard NOWS treatment with methadone for commonly used opioids.

Kratom is a legal, widely-available herbal supplement with opioid-like properties increasingly used by those with opioid dependence to self-treat opioid withdrawal (7). Although internet-based surveys of kratom users report less severe withdrawal from kratom compared to traditional opioids (14), there is sufficient evidence to support a dose-dependent abstinence syndrome similar to opioid withdrawal (10). Reports of kratom use among pregnant women are increasing, especially among women with histories of chronic opioid use (12). Reports of NOWS due to maternal kratom use are also increasing (11). Infants usually exhibit withdrawal symptoms 1-2 days after birth (10). Mitragynine has an estimated terminal half-life of ~24 ± 16 hours (14).

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Reported cases of NOWS suspected from kratom were managed with morphine, clonidine, and benzodiazepines (2). However, our patients were treated with methadone successfully. The length of pharmacological treatment for NOWS due to kratom has been reported from 5 days to 2 months (19). Although there are no formal studies of kratom transmission through breastmilk, The American Kratom Association (https://www.americankatom.org/ science) recommends against use among pregnant or breastfeeding women. (7)

Kratom cannot be detected by routine toxicology screening. Definitive testing requires Liquid Chromatography or Tandem Mass Spectrometry, although qualitative immunologic-based tests are in development (10). It is unclear for what duration kratom can be detected in urine; however, one case reports the detection of kratom 48 days after last use (13). Without readily available testing, medical providers must solely rely on history taking (10). To provide optimal care for pediatric patients, obstetricians, neonatologists, and pediatricians must remember to ask about kratom use in those with histories of opioid dependence.

Conclusion:

Kratom use in the United States is increasing, especially among those with histories of opioid dependence, to alleviate opioid withdrawal. Physicians caring for those with histories of opioid dependence will likely encounter kratom users and kratom-related morbidity. Providers must familiarize themselves with the substance

and its consequences for adult and pediatric patients' dependence, withdrawal, and toxicity. Currently, physicians are limited to history-taking to diagnose kratom use as it is not detected on routine toxicology screening. Patients should disclose kratom use to their medical providers as they would other legal substances such as alcohol or tobacco. In turn, medical providers should counsel patients on the risks of kratom use. Further research is needed to educate the general public about kratom's side effects and help guide medical providers in the optimal management of kratom-related complications.

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References:

1. *Nellhaus E, Andrews L, Haas J, Miskell D, Kurek K, Hansen Z et al. Neonatal withdrawal following in utero exposure to kratom. International Journal of Clinical Pediatrics. 2018 Dec 26;7(4):55-8.*
2. *Eldridge WB, Foster C, Wyble L. Neonatal Abstinence Syndrome Due to Maternal Kratom Use. Pediatrics. 2018;142(6):e20181839. doi:10.1542/peds.2018-1839*
3. *Centers AA. Kratom withdrawal, detox, and tapering. 2018. Available from: https://americanaddictioncenters.org/withdrawal-timelines-treatments/kratom/.*
4. *Anwar M, Law R, Schier J. Notes from the field: Kratom (Mitragyna speciosa) exposures reported to Poison Centers - United States, 2010-2015. MMWR Morb Mortal Wkly Rep. 2016;65(29):748-749.*
5. *Diep J, Chin DT, Gupta S, Syed F, Xiong M, Cheng J. Kratom, an emerging drug of abuse: a case report of overdose and management of withdrawal. A&A Practice. 2018 Apr 15;10(8):192-4.*
6. *Grundmann O. Patterns of kratom use and health impact in the US—results from an online survey. Drug Alcohol Depend. 2017;176:6370.*
7. *Eldridge WB. Kratom: An Opioid-like Herbal Supplement Pediatricians Should Know About. J Pediatr Pediatr Med. 2019; 3(1): 1-5*
8. *Takayama H. Chemistry and Pharmacology of Analgesic Indole Alkaloids from the Rubiaceous Plant, Mitragyna speciosa. Chem Pharm Bull. 2014; 52(8): 916-928.*
9. *Kreugel A, Gassaway M, Kapoor A, Váradi A, Majumdar S, Filizola M, Javitch JA, et al. Synthetic and receptor signaling explorations of the Mitragyna alkaloids: Mitragynine as an atypical molecular framework for opioid receptor modulators. J Am Chem Soc. 2016; 138(21): 6754-6764.*
10. *Takayama H, Ishikawa H, Kurihara M, Aimi N, Ponglux D, Koyama F, et al. Studies on the Synthesis and Opioid Agonistic Activities of Mitragynine-Related Indole Alkaloids: Discovery of Opioid Agonists Structurally Different from Other Opioid Ligands. J Med Chem. 2002; 45: 1949-1956.*
11. *Boyer EW, Babu KM, Macalino GE. Self-treatment of opioid withdrawal with a dietary supplement, kratom. Am J Addict. 2007; 16 (5): 332- 336.*
12. *Murthy P, Clark D. An unusual cause for neonatal abstinence syndrome. Paediatr Child Health. 2018; pxy084. Doi: 10.1093/pch/pxy084.*
13. *Khazaeli A, Jerry J, Vazirian M. Treatment of Kratom Withdrawal and Addiction with Buprenorphine. J Addict Med. 2018; 12(6): 493-495*
14. *Smid MC, Charles JE, Gordon AJ, Wright TE. Use of Kratom, an opioid-like traditional herb, in pregnancy. Obstetrics & Gynecology. 2018; 132(4): 926-928.*

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