Narrative Review

Emerging Substances and Perinatal Health

A Narrative Review

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Perinatal substance exposure is evolving rapidly, often before data on exposure outcomes are available. New exposures to substances include adulterants found in established drug supplies such as fentanyl, xylazine, nitazenes, and medetomidine, and substances promoted as herbal or natural supplements such as kratom and tianeptine. In addition, there are prescription medications being used in new or unintended ways, such as ketamine. This narrative review details some of the most common substances currently emerging in the United States and discusses the potential effects on pregnancy outcomes. It also highlights the importance of comprehensive inquiry into substance exposure and discussion regarding minimizing the risks of exposure in the setting of limited perinatal data.

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Approximately 8% of pregnant individuals in the United States reported nonprescribed substance use other than nicotine or alcohol in 2020.[1] Although treatment options for perinatal substance use such as opioids and tobacco are well established,[2,3] there is rising concern regarding novel or emerging substances for which far less is known regarding perinatal exposure. This narrative review details emerging exposures related to nonprescribed substance use and summarizes the published literature on the potential effects in pregnancy and recommendations to reduce perinatal harm.

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WHAT ARE EMERGING SUBSTANCES?

Emerging substances are those that are relatively new or resurging and may pose novel human health threats, including during pregnancy (Table 1). Emerging substances include adulterants within an established illicit substance supply (fentanyl, xylazine, nitazenes, and medetomidine); substances that are readily available online or in convenience stores due to lack of controlled substance classification (kratom or tizanidine); and prescriptions medications with increasing use in nonstandard scenarios (ketamine).

Fentanyl

Much focus has been placed on the transition of the illicit opioid supply to fentanyl and fentanyl analogs,[4] and fentanyl increasingly contributes to peripartum overdose deaths.[5] Fentanyl is a synthetic opioid with potency that exceeds that of other commonly used opioids, including heroin and prescription opioids. It was initially developed for use in human anesthetic and analgesic treatments. Synthesis outside the legal pharmaceutical industry has led to its initial presence as an illicit drug supply adulterant, in both opioids and stimulants. It is now a leading contributor in substance-related overdose deaths in the United States.[6] It is typically used by injection, smoking, or nasal insufflation, and has replaced heroin as the most commonly used illicit opioid in most U.S. markets.[7] Fentanyl is known to cross the placenta, including in early pregnancy, and can be detected in fetal brain tissue.[8,9] A recent case series[10] reported the finding of a novel syndrome in 10 individuals with prenatal fentanyl exposure, in which individuals were noted to have physical findings similar to those seen with Smith-Lemli-Opitz syndrome such as short stature, microcephaly, and distinctive facial features. Prenatal fentanyl exposure also was associated with congenital malformations such as facial clefting,

Table 1. Emerging Substances Within the Nonprescribed Substance Supply

Substance	Mechanism	Accessibility	Reversal With Naloxone	Clinical Concerns
Fentanyl	Synthetic opioid agonist	Prescription, illicit manufacture	Yes	MOUD (eg, methadone, buprenorphine); more severe neonatal withdrawal
Nitazenes	Synthetic opioid agonists	Illicit manufacture	Yes	Increased potency relative to fentanyl
Xylazine	α-2 adrenergic agonist	Veterinary sources, illicit manufacture	No	Association with nonhealing wounds; prolonged sedation with exposure
Medetomidine	α-2 adrenergic agonist	Veterinary sources, illicit manufacture	No	Prolonged sedation with exposure; withdrawal includes severe autonomic dysfunction, often requiring ICU care and dexmedetomidine treatment

MOUD, medications for opioid use disorder; ICU, intensive care unit.

talipes equinovarus, and hypoplastic corpus callosum in the case series, raising concerns for teratogenicity. Smith-Lemli-Opitz syndrome typically is caused by genetic mutations in genes that metabolize cholesterol. Unlike Smith-Lemli-Opitz syndrome, the abnormalities described in cholesterol metabolism in these cases were present at birth but resolved over time. This case series raises concern that fentanyl might be associated with an interference in prenatal cholesterol metabolism. In addition, animal models have suggested other neurodevelopmental sequelae with prenatal fentanyl exposure, including impaired sensory adaptation lasting into adolescence.[11] These reports have yet to be validated in larger scale studies and the relationship to prenatal fentanyl exposure remains theoretical at this time.

Children with prenatal exposure to fentanyl may have a higher incidence of neonatal opioid withdrawal syndrome than those with exposure to other opioids. Fentanyl exposure may be associated with an increased incidence of severe neonatal opioid withdrawal syndrome and an earlier initiation of neonatal opioid withdrawal syndrome treatment, as well as a longer length of stay at birth admission.[12] However, the treatment of neonatal opioid withdrawal syndrome after fentanyl exposure remains consistent with treatment after other prenatal opioid exposure, with the utilization of Eat, Sleep, Console care approach as the standard of care for all opioid-exposed neonates at risk for withdrawal symptoms.[13]

The major fentanyl metabolite, norfentanyl, can have prolonged clearance times, which complicates the interpretation of the timing of exposure when detected on urine toxicology testing. Urine toxicology performed during pregnancy has identified the presence of norfentanyl up to 70 days after confirmed last use[14] and low levels up to 294 days after last use.[15] Although prolonged detection of fentanyl metabolites also has been described in nonpregnant patients,[16] it is perhaps more critical to recognize when testing pregnant individuals for substance use, given the potential consequences for child welfare involvement in a patient without active ongoing illicit opioid use at the time of birth.

Limited research on the excretion of fentanyl into breast milk is available in the context of fentanyl use for analgesia during labor. These data indicate some excretion into human breast milk, but with insufficient transfer to recommend withholding breastfeeding.[17] When examining the safety of breastfeeding in the context of ongoing illicit fentanyl use, however, current breastfeeding guidelines recommend against breastfeeding in the context of all nonprescribed opioid use.[18] The prolonged presence of fentanyl metabolites in urine is less well understood with regards to human breast milk, and needs to be considered when making shared decisions for breastfeeding individuals with a history of chronic fentanyl exposure, even when use is discontinued before birth admission. Additional research is needed to address this topic to better counsel patients regarding anticipated outcomes and amounts of exposure.

Best practices for perinatal opioid use disorder, including methadone and buprenorphine treatment,[19] are based primarily on treatment success with heroin or prescription opioid use. In nonpregnant individuals, there is an increased risk of buprenorphine-precipitated withdrawal in individuals with chronic fentanyl use,[20] and these data can likely be extrapolated to pregnant individuals. Thus, there is ongoing

work to improve treatment options and increase the rate of sustained recovery for individuals with fentanyl exposure. At this time, there are no standard treatment protocols to initiate buprenorphine in the context of chronic fentanyl use in pregnancy, but initial work suggests that the use of high dose (macroinduction)[21] and low dose (microinduction)[22] protocols may be associated with a lower risk for precipitated withdrawal. Others also have described a role for long-acting injectable buprenorphine,[23] with research on this treatment in pregnancy still ongoing.[24] In addition, recent literature suggests that changes in methadone titration, including a faster escalation in dosing, might increase success when initiating treatment for opioid use disorder in individuals with chronic fentanyl exposure.[25,26]

Xylazine

A current adulterant of concern with illicit opioid exposure is xylazine, which contributed to approximately 11% of overdose deaths from illicitly manufactured fentanyl in the United States in 2022.[27] Xylazine is an α-2 adrenergic agonist that stimulates central α-2 receptors similarly to clonidine, causing hypotension and sedation.[28] It was developed in 1962 as an antihypertensive, but trials were stopped due to hypotension and central nervous system depression.[29] It was approved for use in veterinary medicine but was never clinically used in humans.

A concern with human xylazine exposure is the inability to reverse its effects with naloxone administration. Although there is ongoing research into reversal agents, none are currently identified as efficacious for human use.[30] Nonetheless, naloxone administration is still recommended for suspected xylazine exposure given the high likelihood of opioid co-use. It is important to also implement timely supportive care, including medications that address bradycardia (atropine) and hypotension (IVF, vasopressors).[31] There are limited data on the management of xylazine withdrawal. A recent review suggested management of withdrawal with clonidine, benzodiazepines, and gabapentin in nonpregnant individuals[32]; however, these therapies have not been investigated for use in pregnancy.

There are limited data on the prevalence of xylazine in human pregnancy, but available data suggest increasing prevalence of use. In a cross-sectional study of the toxicology screens that identified nonprescribed opioids in 2022–2023,[33] 47.2% identified xylazine. This trend in detection of xylazine increased over time, from 0% in December 2022 to 100% in July 2023.

Data from human umbilical cord samples also suggest transplacental transfer,[34] although effects on the human fetus and neonate are poorly understood outside of one case report with suspected neonatal xylazine toxicity.[35] In a 2023 review,[36] animal and human studies on xylazine in pregnancy were evaluated. Animal studies identified decreased uterine blood flow, increased uterine vascular resistance, and decreased maternal and fetal heart rates,[37,38] as well as decreased fetal growth.[39] Human studies identified profound bradycardia and respiratory depression after xylazine exposure[40] and identified xylazine within umbilical cord tissue of patients with prenatal exposure.[34] A case report introduced α-2 receptor agonists as a possible treatment for a reported case of neonatal xylazine withdrawal.[35] There are no published data on xylazine exposure and human lactation. Likewise, there are no available data examining neonatal or childhood outcomes in the context of prenatal or breastfeeding exposure to xylazine.

For obstetric clinicians, it is important to consider the potential for xylazine exposure in patients who present with exaggerated hypotension and lack of full response to naloxone in the context of opioid overdose. The presence of nonhealing skin lesions also is linked to xylazine exposure, and requires a thorough skin inspection of patients with known use and early engagement with wound specialists to minimize secondary infections and optimize healing.[41] Toxicology testing for xylazine exposure may not be part of standard care, but can be obtained, if indicated.[28] Point-of-care test strips for xylazine also are available[42] and should be considered in areas of high xylazine prevalence in the illicit fentanyl supply, as a perinatal harm-reduction strategy. Test strips often can be obtained through local harm-reduction organizations, as well as for purchase commercially online through point-of-care testing supply manufacturers.

Nitazenes

A group of substances with increasing prevalence in the opioid and stimulant supplies are nitazenes, which were first identified in the United States' illicit substance supply in 2019[43] and are noted to be a significant contributor to opioid overdose in the United Kingdom.[44] Nitazenes were developed in the 1950s as human analgesics but were never approved for medical use. However, recent synthesis using historical pharmacologic research is now being identified as a group of substances currently termed novel potent opioids.[45] Some nitazenes have been placed as Schedule 1 controlled substances by the U.S. Drug Enforcement Administration.[46]

A serious concern with nitazene exposure is the increased relative potency when compared with heroin. The most prevalent nitazene, isotonitazene (known as iso or tony), has a relative potency of 250 times that of heroin.[47] This high potency may decrease the efficacy of naloxone in the case of an overdose, and there are limited data on whether multiple or higher doses of naloxone can provide benefit.[48]

There are limited data on treatment of nitazene exposure outside of pregnancy, and there is, likewise, no published information on perinatal use. Medication for opioid use disorder can be considered for nitazene use disorders, given the likely co-use with other opioids, but the effectiveness of medication for opioid use disorder with nitazene exposure has not been elucidated. Currently, it is most important to educate patients on potential nitazene exposure in illicit substance use and on the increased potential for overdose. As always, harm-reduction tools (Table 2), such as not using substances alone, sterile use supplies, testing strips when available,[49] and naloxone distribution, can be lifesaving.[50]

Medetomidine

Recently, an additional veterinary medication medetomidine has emerged within the illicit drug supply,[51] and is now noted to be present in more than 70% of tested samples of nonprescribed opioids in Pennsylvania[52] and 2.4% of all submitted nonprescribed samples between 2022 and 2025 in a national drug checking program.[53] Medetomidine is an α-2 adrenergic agonist that contains a racemic mixture of inactive levomedetomidine and dexmedetomidine, the latter of which is approved for human sedation and has been proposed for use in obstetric anesthesia.[54] Medetomidine was first identified in the illicit opioid supply in 2022, and often is seen in association with xylazine.[55] It has been identified in overdoses across the United States and presents with prolonged sedation, bradycardia, and hypotension.[56] It is not reversible with naloxone but is often used in associated with opioids,[57] so naloxone administration is still encouraged. Medetomidine is associated with a withdrawal syndrome that includes severe autonomic dysfunction with hypertension and tachycardia as well as encephalopathy, tremor, and vomiting. Case series suggest that the majority of medetomidine withdrawal cases will need critical care services such as dexmedetomidine infusion and intubation.[58]

At this time, there are no data that specifically address illicit exposure to medetomidine and pregnancy outcomes. A high suspicion for this exposure is warranted with perinatal substance use in communities with a high prevalence of medetomidine, because withdrawal symptoms such a as severe hypertension and seizures may have significant overlap with the presentation of preeclampsia with severe features.[58] Clinical pearls for care[57–59] are provided in Box 1.

Kratom

Kratom originates from the leaves of a tree native to Southeast Asia, *Mitragyna speciosa,* and is marketed as an herbal supplement.[60] It is sold as tea, capsules, tables, raw leaves, and as a concentrated extract. Kratom is a partial opioid agonist that is used for analgesia and mood-enhancing effects but also is marketed as a natural alternative to medication for opioid use

Table 2. Harm-Reduction Tools for Perinatal Substance Use

Situation	Tool
Nonprescribed substance exposure	• Substance test strips (eg, fentanyl, xylazine, medetomidine) • Sterile use supplies (syringes and needles, pipes, alcohol wipes) • Discussion of safer-use routes (ie, nasal insufflation vs injection)
Overdose prevention and treatment	• Naloxone distribution • Overdose training, such as rescue breathing • Substance test strips (eg, fentanyl, xylazine) • Reverse motion detectors that can detect occupancy with lack of motion or depressed breathing in areas with more frequent nonprescribed substance use (eg, public bathrooms)[97]
Infectious disease care	• Point-of-care testing and treatment • Co-located hepatis C and HIV treatment • Distribution of condoms • Co-located wound care
Engagement in prenatal care	• Co-located prenatal care • Point-of-care pregnancy testing and ultrasonography for gestational age • Obstetric care partnership with harm-reduction programming

HIV, human immunodeficiency virus.

Box 1. Clinical Pearls for Medetomidine Exposure and Withdrawal[56–58]

- Key features of intoxication include prolonged sedation, hypotension, respiratory suppression, and bradycardia
- Initial support for medetomidine overdose should focus on respiratory support rather than responsiveness
- Key features of withdrawal include severe hypertension, tachycardia, refractory vomiting, and tremor
- Onset of symptoms within 24 h of last substance exposure
- Ensure access to critical care services for dexmedetomidine infusion and intubation
- Adjunct medication considerations include clonidine, prochlorperazine, and olanzapine

disorder. Up to 80% of pregnant patients who used kratom reported use to manage opioid withdrawal symptoms.[61] Kratom may be more accessible for patients than prescribed treatment medications or even illicit opioids, given the ease of access through multiple direct to consumer purchasing channels such as convenience stores and smoke shops, which are not regulated. The lack of a required prescription may lead patients to believe that kratom and tianeptine (described below) are more natural treatments for health concerns, including during pregnancy.

Individuals who use kratom in pregnancy describe use as a means to reduce opioid exposure, to treat opioid withdrawal, or to manage anxiety and depression.[61] Prevalence in pregnancy, overall, is unknown, but the prevalence of lifetime use in the United States has been reported at 1.5% in the general population.[62] In a single-site survey of patients receiving care at a perinatal opioid use disorder treatment clinic, 32% of patients reported ever using kratom, and 5% reported ongoing exposure in pregnancy.[61]

Physiologic withdrawal from kratom mimics opioid withdrawal, and case series have reported treatment with buprenorphine, including during pregnancy.[60,63] Additional reports of treatment with clonidine, morphine, tricyclic antidepressants, and contingency management are described outside of pregnancy.[64–66] Kratom has been associated with lethal overdose, and limited reversal with naloxone has been identified.[67] Additional clinical concerns with kratom use that have been identified outside of pregnancy include a risk of sudden death due to cardiac dysrhythmia with high dose exposure[68] and reports of a multistate Salmonella gastroenteritis outbreak associated with kratom supply contamination.[69]

It is also important to note a recent increase in the manufacture and marketing of a semisynthetic metabolite of kratom, 7-hydroxymitragynine. This compound recently has been identified as a separate substance of concern that may have a higher potential for misuse due to increased opioid receptor binding,[70] but does not yet have substantial data related to perinatal exposure.

Neonates with prenatal exposure to kratom products may exhibit a phenotype similar to neonatal opioid withdrawal; successful treatment with morphine and clonidine has been described.[71–73] This finding suggests transplacental transfer of kratom. Long-term neonatal or infant outcomes are currently not available, and research examining breast milk excretion also is lacking.

Kratom metabolites are not identified on standard urine toxicology testing in most laboratories, and specific spectrometry (liquid chromatography mass spectrometry) tests may need to be ordered separately. It can take up to 1–2 weeks for results,[74] and testing may be available only through select reference laboratories.

Given what is not yet known about perinatal kratom use, it is important to educate patients on the lack of exposure data in pregnancy, the potential for withdrawal symptoms if stopped abruptly, and the potential for withdrawal symptoms in an exposed neonate. Some experts recommend checking baseline liver function tests with chronic kratom exposure.[75] In addition, it is important to identify any indication for which a patient uses kratom, because there may be other better studied and clinically approved alternatives to use instead.

Tianeptine

Tianeptine is an opioid mu-receptor agonist that is available in the United States as a supplement, with names such as ZaZa and Tianna Red.[76] Tianeptine is used as a prescription anxiolytic and antidepressant in some European countries but is available in supplement form at up to 50 times the prescribed medical dose.[77] Although it is available in many U.S. convenience stores, it is banned in a handful of states (Michigan, Alabama, Ohio, Georgia, and Tennessee). Tianeptine is advertised as a supplement for mood, pain, and mental health, similar to its applications as a prescription medication. Chronic exposure can result in withdrawal symptoms such as prolonged agitation. Overdose treatment with naloxone has been reported,[78] but there are no data on treatment of intoxication or withdrawal symptomatology.

Pregnancy data in a rat model have identified inhibition of uterine contractility[79] and changes in dopamine affinity in offspring.[80] In two human cases, prenatal tianeptine exposure resulted in a neonatal withdrawal phenotype that was effectively treated with morphine.[81,82] There are no data currently

available on toxicology testing, breast milk excretion, or fetal and infant effects. If there is concern for exposure to this substance, it will require separate mass spectrometry toxicology testing.[83]

If a pregnant patient confirms tianeptine exposure and is having difficulty abstaining from use, obstetric care professionals should discuss the risk of overdose and the limited perinatal research. In addition, given the indications for prescription use and the prevalence of peripartum mood disorders,[84] a discussion about the symptoms that prompted use may identify opportunities to use other treatments with existing safety data in pregnancy.

These examples also are an important reminder that all pregnant patients should be asked about herbal remedies and over-the-counter supplements, including names, frequency of use, and what happens if use is stopped abruptly.

Ketamine

Much attention has recently focused on the use of ketamine, with heightened media coverage of adverse outcomes after exposure. Ketamine is a general anesthetic and NMDA receptor antagonist with hallucinogenic properties. Although ketamine was first reported for human use in the 1960s,[85] its use has recently surged outside of anesthetic use due to therapeutic applications for depressive symptoms in adults with major depressive disorder.[86] Ketamine is currently a Schedule III controlled substance in the United States, with significant potential for abuse and increasing reports of adverse effects from nonmedical ketamine use in the United States.[87]

Increased use in medical and nontherapeutic settings also increase the risk of ketamine exposure during pregnancy, with limited data available for guidance. A recent study that investigated policies at outpatient ketamine clinics reported that fewer than half of clinics discussed risks of ketamine use in pregnancy, and only 20% of clinics performed pregnancy tests before ketamine treatment.[88] Therefore, it is important that reproductive health care professionals inquire about potential ketamine exposure during pregnancy.

Little is known about the perinatal effects of ketamine exposure. Transplacental transfer is well documented in human studies,[89] with preferential fetal brain distribution and potential neurotoxicity identified in animal studies.[90,91] There are no published data regarding the effects of ketamine exposure on maternal or neonatal outcomes, or on potential excretion in breast milk. Given this lack of data and the ongoing maturation of the fetal brain throughout pregnancy,[92] it is important to collaborate with patients in identifying the reasons behind ketamine use. Through the use of brief intervention techniques,[93] obstetric professionals can identify changes that might help reduce or resolve ketamine exposure during pregnancy, especially for nonmedical use. In patients using ketamine for treatment-resistant depression or suicidal ideation, this may require significant collaboration with mental health specialists to identify other potential treatment options.

CONCLUSION

Emerging substances are a dynamic component of perinatal exposures. It is important that obstetric professionals are aware of new trends in potential exposures. Resources such as the National Drug Early Warning System (ndews.org) can be beneficial in the introduction of novel or reemergent substances that may be an issue for birthing populations.[94] It also is critical that prenatal care intake includes a review of patient medications, supplements, and herbal remedies to identify areas for harm reduction and offer safe alternate medical therapies for identified symptoms or conditions. This also must include a discussion of the increased risk of overdose in the postpartum period even if substance use has been minimized during the pregnancy, due to the risk of a return to nonprescribed substance use.[95] Although universal urine drug testing to identify potential exposures might be considered to identify all substance exposures, this tool has significant limitations, especially in the obstetric setting.[96] Patient education is an important component of reducing exposure and includes an in-depth discussion about the unknowns of continued substance exposure and the best approach for optimizing pregnancy outcomes.

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