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***In Utero* Xylazine Exposure Associated with Feeding Difficulties in Infants with Neonatal Opioid Exposure**

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IRB Determination: Per institutional review board (IRB) guidelines, this is a case study, a medical/educational activity that does not have to be reviewed by the IRB.

***In Utero* Xylazine Exposure Associated with Feeding Difficulties in Infants with Neonatal Opioid Exposure**

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Introduction

Xylazine is an increasingly prevalent illicit opioid adulterant used in veterinary medicine as a sedative, muscle relaxant, and analgesic. It is an alpha-2 agonist and central nervous system depressant and was deemed unsuitable for human use due to significant sedation. Effects include poisoning, sedation, and dermatologic wounds. (Leconte & Sethi, 2023) Xylazine-related overdose deaths increased by greater than 100% across all 4 major US census regions from 2020-2021, with the highest prevalence of xylazine in the Northeast. (DEA, 2022b)

While transfer into fetal tissue has been demonstrated via umbilical cord testing, there have been no human studies characterizing gestational exposure or withdrawal. (Midthun et al., 2023) Bovine and rodent studies suggest that gestational xylazine use is associated with decreases in maternal pulse rate, uterine and fetal blood flow, organ perfusion, and fetal growth. (Hodgson et al., 2002; Samir et al., 2024; Waldvogel & Bleul, 2014) (Thaete et al., 2013)

Neonatal Opioid Withdrawal Syndrome (NOWS) is a clinical diagnosis of withdrawal from opioids to which an infant was exposed in utero. The Finnegan scoring system, or the more recently developed Eat, Sleep Console (ESC) approach guide management with non-pharmacological and/or pharmacological treatment. (Young et al., 2023)

University of Vermont Medical Center (UVMCC) houses UVM Children's Hospital (UVMCH) and the state's only NICU. Opioid overdose is a significant public health concern in

Vermont, as is xylazine. From 2019-2022, Vermont had the highest rates of xylazine-related overdose deaths out of 43 states. (Cano et al., 2024) In the first three quarters of 2024, 89-100% of fentanyl samples contained xylazine according to StreetCheck, a community drug-checking initiative. (StreetCheck, 2024)

We reviewed cases of gestational xylazine exposure at UVMCH to characterize associated symptomatology.

Methods

A case review was conducted of infants born at >35 weeks gestational age and monitored for NOWS between August 2022 to October 2024 at UVMCH NICU. Xylazine exposure was identified by drug testing or parental report. Data related to growth, ESC assessments, speech language pathology (SLP), and feeding were collected.

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UVMCH and surrounding centers use ESC for management of NOWS. All infants receiving pharmacological treatment are transferred to UVMCH NICU where methadone is used first line and clonidine second.

Results

13% of infants with opioid exposure also had known xylazine exposure. Xylazine-exposed infants more consistently had difficulty feeding on ESC assessment than those without known exposure (Table 1). 5 of the 7 exposed infants were treated with methadone; 2 infants received methadone and clonidine. None showed improvement in feeding symptoms following

treatment. Infants who required NG feeds took an average of 12 days to reach full ad lib oral feeds (range 6-22 days). One infant did not require gavage feeding but later required g-tube placement due to poor oral intake. One infant had only early pregnancy exposure and no feeding difficulty. Exposed infants were noted by SLP to have oral greater than pharyngeal stage difficulties characterized by reduced latch, ineffective nutritive suck pattern and difficulty with suck-swallow-breathe organization. All exposed infants required increased caregiver support and compensatory strategies to promote developmentally appropriate oral feeds, reduce risk of feeding-induced cardiorespiratory events, and improve feeding quality (Table 2).

Infants >35 weeks GA with prenatal opioid exposure	Infants with any symptoms on ESC assessments	Assessments positive for any symptoms	Positive assessments with eating difficulty	Positive assessments with sleeping difficulty	Positive assessments with consoling difficulty
No xylazine exposure (n=45)	22 (49%)	157	96 (61%)	76 (48%)	34 (22%)
With xylazine exposure (n=7)	7 (100%)	107	93 (87%)	19 (18%)	12 (11%)

Table 1. Symptoms as noted on Eat Sleep Console (ESC) assessments for infants with opioid exposure with and without xylazine exposure. For all positive assessments in each group, reasons for positive assessment (non-exclusive) were combined across infants and compared between groups. GA= gestational age.

Case	BW z-score (WHO)	Birth HC z-score (WHO)	Day of initial oral feeding cues	Day of start of NG feeds	Day of life of first PO ad lib	Other treatment details	Feeding difficulty per SLP evaluation
1	0.01	0.03	1	2	13	Methadone and clonidine	Habituation to nipple; excessive sucking with poor milk transfer; SSB disorganization
2	-1.54	-2.43	1	6	1	G-tube placed for poor feeding	Reduced latch and oral containment resulting in oral loss; disorganized vs dysfunctional oral stage skills
3	0.11	0.95	1	2	10	Methadone	Reduced root, reduced NNS; chomping pattern vs NS; difficulty maintaining suck; disorganized SSB
4	-1.68	-2.72	1	2	22	Methadone	Reduced tongue cupping and jaw excursions; reduced NNS and NS; excessive gagging; concern for oral defensiveness
5	1.35	0.38	1	3	11	Methadone	Reduced latch, decreased NS, short NS burst pattern
6	-0.24	-0.76	1	N/A	1	Only early pregnancy exposure	NA – not evaluated by SLP
7	-0.41	-3.27	1	2	6	Methadone and clonidine	Reduced milk transfer, difficulty maintaining suck, chomping pattern, oral loss, disorganized SSB
Mean	0.17	-0.78	-	-	12	-	-

Table 2. Growth demographics, timing of feeding progress, treatment characteristics, and details of Speech Language Pathologist (SLP) evaluation for each infant with xylazine exposure in utero. BW = birthweight; NG = nasal gastric tube; DOL = day of life; PO = per os/by mouth, SSB = suck, swallow, breathe, NS = nutritive suck, NNS = non-nutritive suck.

Discussion

Without data regarding gestational xylazine in humans, and data demonstrating serious implications in animals, there is need for research to determine the impact of xylazine on neonates. Though veterinary data raises concern for impact on growth, growth parameters within our cases were within expected ranges. Xylazine-exposed infants had more significant and prolonged feeding difficulties than typically observed for infants with prenatal opioid exposure at our hospital. We did not observe improvement in feeding in response to methadone or clonidine in xylazine-exposed infants. One limitation of our case report is the possibility that more infants than were identified were exposed to xylazine. Furthermore, ESC assessments may not be an appropriate assessment of xylazine-related symptoms. Symptomatology could be associated with xylazine withdrawal or to developmental effects of xylazine exposure, or other causes.

More robust data of the effects of xylazine on fetuses and infants may guide prenatal and neonatal care as well as public health approaches and community harm reduction strategies.

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