Prolonged detection of urine norfentanyl in individuals enrolled in a medication for opioid use disorder in pregnancy and postpartum program: a case series

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BACKGROUND: Although urine drug testing can have vast legal and social ramifications, its interpretation during pregnancy and after birth remains not well understood. Fentanyl metabolism is altered by an individual's genetics, history of opioid use, and liver function. However, little is known about the clearance of fentanyl or its primary metabolite, norfentanyl, in the peripartum period.

OBJECTIVE: We sought to identify and describe cases of delayed urine norfentanyl clearance in the pregnancy and postpartum period within our institution.

STUDY DESIGN: This study described 3 cases of delayed urine norfentanyl clearance in pregnant and postpartum individuals in a colocated obstetrics, postpartum, and addiction medicine program. This program included prescriptions for medication for opioid use disorder and weekly urine drug testing with fentanyl immunoassay with reflex confirmation testing with liquid chromatography-tandem mass spectrometry for positive results with a limit of detection of 2.5 ng/mL.

RESULTS: Low levels of norfentanyl (<16.3 ng/mL) were detected in urine 294 days, 126 days, and 231 days after the last fentanyl use. Patient self-reported abstinence was supported by consistently negative urine fentanyl levels throughout the collection period, compliant weekly urine drug tests that were otherwise only positive for buprenorphine, and negative fentanyl and norfentanyl in umbilical cord toxicology.

CONCLUSION: Despite compliance in a medication for opioid use disorder program, the presence of norfentanyl in urine has significant consequences on the maternal-child dyad in the postpartum period. Caution should be used when using low levels of norfentanyl to determine an individual's abstinence, as it can lead to further discrimination against women in medication for opioid use disorder programs.

Key words: clearance, fentanyl, norfentanyl, opioid, pregnancy

Introduction

Positive urine drug test results have devastating legal and social ramifications, including separation of the maternal-child dyad, which limits the bonding that has known benefits to both the neonate and the mother.[1] In 2020, the National Center on Substance Abuse and Child Welfare reported that, in the United States, more than 22,000 children under the age of 1 year were removed from their home because of alcohol and drug abuse and the rate of removal for this indication has nearly doubled over the last 2 decades. Of these cases, heroin and opioid abuse accounted for 35% of displaced children.[2] The stakes for accurate interpretation of drug testing, especially in the peripartum period, are high and, if misinterpreted, can lead to tragic consequences for thousands of children. Despite this, the interpretation of urine drug levels of both fentanyl and norfentanyl during pregnancy and after birth is poorly understood, specifically the length of time norfentanyl can be detected in urine after the last use of fentanyl. Fentanyl is lipophilic and converted in the liver to norfentanyl[3,4]. Fentanyl not stored in adipocytes is cleared rapidly within 4 days; however, norfentanyl is a longer-lasting metabolite and, therefore, is often used to assess abstinence. Metabolism of fentanyl can be delayed with liver dysfunction, obesity, genetic polymorphisms, and chronic opioid use.[5–7] Furthermore, there are limited data on how clearance parameters may be altered in the peripartum period. Thus, this study aimed to describe 3 cases of persistently low levels of urine norfentanyl (up to 294 days) in pregnant and postpartum individuals with self-reported abstinence from fentanyl and compliant in a weekly medication for opioid use disorder (MOUD) program.

Materials and Methods

This was a case series of 3 patients with prolonged urine norfentanyl detection at a hospital-associated MOUD in

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Why was this study conducted?

Little is known about the normal clearance rate of urine fentanyl and norfentanyl in pregnancy and after birth. However, any positive urine drug test has devastating effects on the maternal-child dyad.

Key findings

Low levels of norfentanyl were detected in urine up to 294 days after the last fentanyl use in 3 women in a medication for opioid use disorder (MOUD) program during pregnancy and postpartum.

What does this add to what is known?

This study adds to the limited data on delayed urine norfentanyl clearance during pregnancy and after birth. Caution should be used when using low levels of norfentanyl to determine an individual's abstinence, as it leads to biased consequences for the maternal-child dyad and increases discrimination against women compliant in MOUD programs.

pregnancy, after delivery, and addiction medicine program between October 2021 and February 2023. This program includes weekly urine drug testing with fentanyl immunoassay (ARK Diagnostics Inc, Fremont, CA) with a cutoff of 1 ng/mL and reflex confirmation testing with liquid chromatography-tandem mass spectrometry (LC-MS/MS) for positive results. This study received institutional ethics approval (identification number: 2020H0058), and written consent was obtained.

Fentanyl or norfentanyl confirmation was performed using LC-MS/MS, Agilent Infinity I 1190/6420 triple quadrupole analyzer, MRM analysis with Poroshell EC-C18 column, fentanyl-d5 (Cerilliant Corp, Round Rock, TX), and norfentanyl-d5 (Cerilliant Corporation, Round Rock, TX) internal standards and quantified using a 6-point calibration curve using weighted least squares regression. The transitions used were 337.2>105.1 (quantifier) and 188.1 (qualifier) for fentanyl, 342.3>188.1 for fentanyl-d5, 233.2>84.1 (quantifier) and 55.2 (qualifier) for norfentanyl, and 238.2>84.1 for norfentanyl-d5. This is a laboratory-developed test with a limited detection of 2.5 ng/mL for both fentanyl and norfentanyl. Internal standards are met by confirmation with both ion ratios and retention times. All specimens for urine drug testing that are positive for fentanyl via immunoassay are reflexed to norfentanyl and fentanyl testing with LC-MS/MS. Data are presented as a concentration of nanogram per milligram for both fentanyl and norfentanyl levels. Data presented as <2.5 ng/mL indicate that the immunoassay for fentanyl is positive. However, the result obtained using LC-MS/MS was below the limit of detection. Secondarily, positive fentanyl and norfentanyl results on LC-MS/MS were normalized to urine creatinine (nanogram per milligram) for comparison.[8] Urine creatinine concentration was measured on a Beckman Coulter DxC700AU (Brea, CA) using a modified kinetic Jaffe reaction. Umbilical cord tissue was analyzed as previously described.[9]

Results

We reported data on 3 patients in our MOUD program with prolonged detection of urine norfentanyl after the last fentanyl use by self-report (Figure). For all 3 patients, medical problems were noncontributory, and there was no common prescription medication. Creatinine and liver transaminase levels were normal, and body mass indices were normal (case 1) and class 1 obesity (cases 2 and 3). In all cases, patients were compliant with weekly drug tests and did not miss a single drug test during the study period. Aside from the positive norfentanyl levels and expected buprenorphine, no other illicit substance was positive on any of the weekly drug tests after medical stabilization and transition to the MOUD program. Cases 1 and 2 received neuraxial anesthesia (with fentanyl infusion) but did not have elevated urine fentanyl or norfentanyl levels on subsequent urine drug tests (Table). Referral to child protective services was made in all cases because of the detection of low levels of urine norfentanyl, despite negative cord toxicology in cases 1 and 2. At the time of this reporting, all 3 patients were still enrolled in our MOUD program.

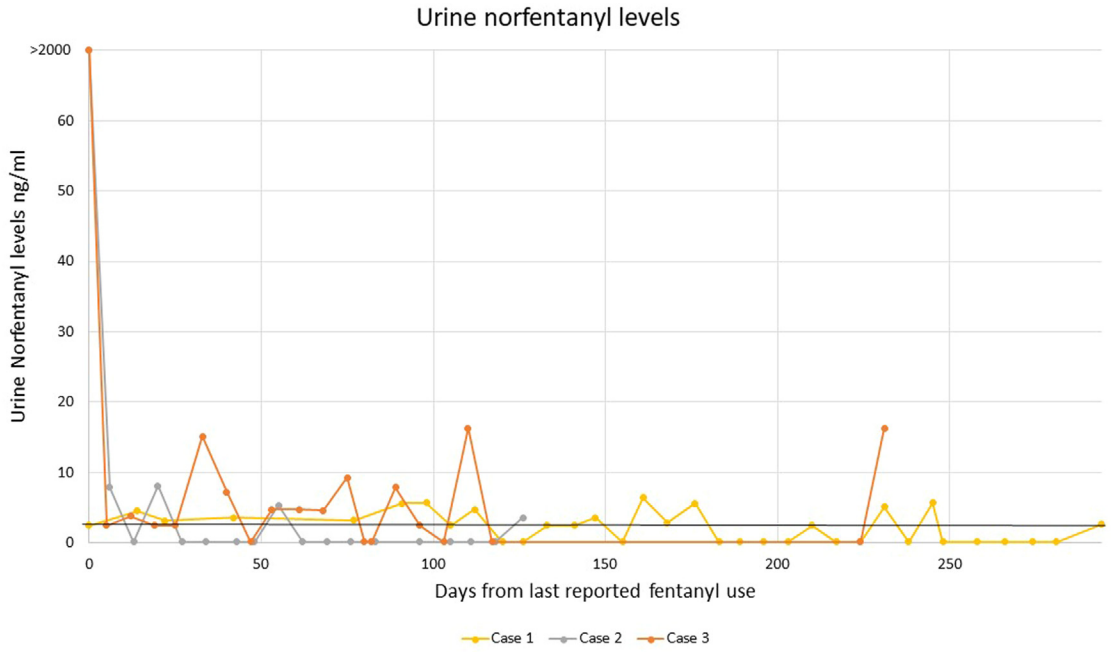
Case 1

This was a 31-year-old G4P3003 patient who initiated care in our weekly MOUD program at 4 weeks of gestation. The patient's last illicit substance use was 6 months before care by self-report, at which time the patient was transitioned to buprenorphine or naloxone with an outside clinic. The patient underwent vaginal delivery under epidural anesthesia at 39 weeks of gestation. Throughout pregnancy and after birth, the patient was compliant with weekly visits, and the patient's urine drug tests were consistent with compliance in the MOUD program. Low levels of urine norfentanyl (range, <2.5 to 6.4 ng/mL) were detectable in urine 294 days after entrance to care, despite negative fentanyl levels on all drug tests. When quantifiable norfentanyl results were normalized to urine creatinine, the peak norfentanyl level was similar (7.1 ng/mg). Cord toxicology results were positive for naloxone, buprenorphine-norbuprenorphine and negative for norfentanyl and fentanyl.

Case 2

This was a 38-year-old G6P5005 patient, who initiated care in our weekly MOUD program at 26 weeks of gestation. The patient's last fentanyl use was 1 day before establishing care, and the patient was successfully transitioned to buprenorphine or naloxone at 26 weeks of gestation. The patient underwent repeat cesarean delivery at 39 weeks of gestation under spinal anesthesia. Throughout pregnancy and after birth,

FIGURE
Urine norfentanyl levels and duration from last fentanyl use



Urine norfentanyl levels on day 1 for case 2 (2293 ng/mL) and case 3 (15,234 ng/mL) are presented as axis maximum (>2000) for visibility of low level norfentanyl variability. Values at 2.5 ng/mL, marked by the horizontal line, represent values that were positive on fentanyl immunoassay. However, both fentanyl and norfentanyl were not quantifiable by liquid chromatography-tandem mass spectrometry. Values at 0 ng/mL reflect urine drug tests that were negative by fentanyl immunoassay.

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the patient was compliant with weekly visits, and the patient's urine drug tests were consistent with compliance in the MOUD program. The initial norfentanyl urine level was 2293 ng/mL (1169 ng/mg normalized to urine creatinine). Low levels of urine norfentanyl (<2.5 to 8.1 ng/mL) were detectable in urine 126 days after last use, despite negative fentanyl levels on all subsequent drug tests. When quantifiable norfentanyl results were normalized to urine creatinine, the peak norfentanyl level was similar (12.3 ng/mg). Cord toxicology results were positive for buprenorphine and norbuprenorphine and negative for norfentanyl and fentanyl.

Case 3

This was a 20-year-old G1P0 patient who initiated care on labor and delivery at 38 weeks of gestation. The patient's last fentanyl use was 1 day before admission. The patient was initiated on buprenorphine while admitted for labor. The patient underwent vaginal delivery at 38 weeks of gestation. Throughout the patient's postpartum care, the patient was compliant with weekly visits, and the patient's urine drug tests were consistent with compliance in the MOUD program. The initial norfentanyl urine level was 15,234 ng/mL (6045 ng/mg normalized to urine creatinine). In the postpartum period, low levels of urine norfentanyl (<2.5 to 10.2 ng/mg) were detectable 231 days after last use, despite negative fentanyl levels on all subsequent drug tests. When quantifiable norfentanyl results were normalized to urine creatinine, the peak norfentanyl level was similar (16.3 ng/mg). Cord toxicology results were positive for norfentanyl, fentanyl, and cocaine.

Discussion

Normal clearance parameters for urine drug toxicology in individuals in MOUD programs during pregnancy and after birth are poorly understood and can have significant consequences on the maternal-child dyad. We describe 3 individuals with low levels of urine norfentanyl detection up to 294 days after last self-reported fentanyl use. These findings are supported by a previous case report of a pregnant individual with norfentanyl detected 70 days after last use.[10]

There are several explanations for our results. The first is misuse, despite reports of abstinence. Although this cannot be definitively ruled out, all patients demonstrated adherence to buprenorphine therapy, which was supported by weekly laboratory measurements of urine buprenorphine and norbuprenorphine. In addition, urine fentanyl was unquantifiable in all patients during the surveillance period. Although it is conceivable to have timed administration of fentanyl between weekly assessments and still have negative testing, this is not consistent with typical fentanyl use. Furthermore, all 3 patients had urine specimens compliant

TABLE
Urine fentanyl and norfentanyl levels by LC-MS/MS during antepartum and postpartum care

	First urine drug screen			Antepartum care			Neuraxial anesthesia		Postpartum care		Buprenorphine compliance		Duration of norfentanyl
Case	Days from last fentanyl use	Urine fentanyl (ng/mL)[a]	Urine norfentanyl (ng/mL[a] and ng/mg[b])	Urine fentanyl range (ng/mL)[a]	Urine norfentanyl range (ng/mL[a] and ng/mg[b])	Epidural or spinal[b]	Days from epidural or spinal to urine drug screen	Urine norfentanyl (ng/mL)[a]	Urine fentanyl range (ng/mL)[a]	Urine norfentanyl range (ng/mL[a] and ng/mg[b])	Rate of urine drug screens consistent with compliant MOUD	Number of urine drug screens positive on immunoassay for fentanyl during the collection period	Days from last reported use and urine norfentanyl detected
Case 1	180	<2.5	<2.5	<2.5	<2.5 to 6.4 7.1[b]	Yes	9	<2.5	<2.5	<2.5 to 2.6 1.9[b]	100%	14/39	294
Case 2	1	52.8	2293 1169[b]	<2.5	<2.5 to 8.1 12.3[b]	Yes	8	<2.5	<2.5	<2.5 to 3.6 1.9[b]	100%	5/18	126
Case 3	1	358	15,234 6045[b]	—	—	No	—	—	<2.5	<2.5 to 16.3 10.9[b]	100%	11/22	231

LC-MS/MS, liquid chromatography-tandem mass spectrometry; MOUD, medication for opioid use disorder.

[a] Urine fentanyl and norfentanyl levels listed as <2.5 indicate that the immunoassay is positive for fentanyl and the confirmatory LC-MS/MS is below the level of detection (<2.5 ng/mL); [b] Peak quantifiable value for norfentanyl during the attributed collection period when it was normalized to urine creatinine (nanogram per milligram); [c]Neuraxial anesthesia within our institution includes fentanyl infusion.

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with buprenorphine intake and would have experienced symptoms of withdrawal. It is unlikely that these results are because of perfect intermittent fentanyl use.

The second explanation is laboratory imprecision. Although there may be imprecision of quantifiable norfentanyl at these very low levels, the variability within our samples exceeds what is expected on the basis of our laboratory quality control assays. Thus, we suspect this to be a true biologic variation. Our examination of laboratory methods is limited by the fact that this is a retrospective case series of clinical results, and additional confirmation was not sent for any of the specimens as it was not the clinical standard of care at the time. We do not have an explanation for the positive fentanyl immunoassay with such low levels of norfentanyl on LC-MS/MS. The lowest threshold for detection of norfentanyl on immunoassay within our laboratory is 15 ng/mL. The values of quantifiable norfentanyl on LC-MS/MS were far below this threshold. Moreover, we note that because substances on LC-MS/MS do not cross-react with similar analogs, we do not have an explanation for the presence of norfentanyl on LC-MS/MS other than true norfentanyl in low levels within the specimen. Furthermore, although umbilical cord testing was negative in cases 1 and 2, the sensitivity of this test to detect fentanyl varies significantly across studies and has poor positive agreement with other methods of perinatal drug testing.[11-13] However, regardless of the accuracy and precision of laboratory testing, until these test results can be reasonably understood, use in clinical and societal applications, such as legal retribution, child protective service involvement, and rehoming newborns, needs to be addressed.

The third explanation is a not fully understood interplay among the storage, breakdown, and clearance of fentanyl and norfentanyl during pregnancy. Although we know that fentanyl metabolism is affected by individual factors, such as liver dysfunction, obesity, and genetic polymorphisms, it is also altered by frequency of use, with a slower

metabolism in those that use more regularly.[5-7] These individual factors need to be taken into account. Moreover, pregnancy likely adds additional variation. Wanar et al[14] calculated the metabolic ratios (norfentanyl to fentanyl) with LC-MS/MS of 112 individuals during pregnancy with positive fentanyl immunoassays. They discovered that there is faster conversion of fentanyl to norfentanyl indicated by higher ratios in the third trimester of pregnancy with increasing gestational age. This published data aimed to establish normal fentanyl metabolism parameters in pregnancy and stressed the importance of accurate interpretation of drug testing in the peripartum period.

Conclusion

Based on this case series, we caution against the use of quantitative drug results for low levels of norfentanyl to determine an individual's abstinence as it may lead to unintended consequences to the maternal-child dyad. Inaccurate interpretation of drug testing has the potential to falsely disrupt the households of thousands of children across the United States yearly.[2] Moreover, policy regarding perinatal drug testing (both targeted and universal), mandatory reporting of positive perinatal drug tests, and referrals to child protective services are not uniform among hospitals or from state to state, leading to significant bias among those affected.[15-18] Finally, states with punitive reporting policies that consider substance use to be child abuse or neglect have not seen improved neonatal outcomes as measured by rates of neonatal abstinence syndrome.[19,20] Without significant policy change on the hospital, state, and federal levels, acceptance of the misuse hypothesis without further data on normative fentanyl clearance in pregnancy and after birth leads to increased discrimination against women in MOUD programs. ■

CRediT authorship contribution statement

Miranda K. Kiefer: Conceptualization, Formal analysis, Investigation, Methodology, Writing − original draft. **Jamie Cowen:** Data curation, Writing − original draft, Writing − review & editing. **Katherine A. Hinely:** Conceptualization, Data curation, Resources, Writing − review & editing. **Kara M. Rood:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing − review & editing.

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