RESEARCH ARTICLE

Association of Prenatal Fentanyl Exposure With Neonatal Opioid Withdrawal Syndrome Severity

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ABSTRACT

OBJECTIVE: Opioid use disorder (OUD) in pregnancy has increased substantially, with illicit fentanyl now the most common illicit opioid. Limited data exist on the impact of antenatal fentanyl exposure on neonatal opioid withdrawal syndrome (NOWS). We aimed to evaluate whether antenatal fentanyl exposure is associated with increased NOWS severity.

PATIENTS AND METHODS: We conducted a retrospective cohort study of mother–infant dyads with OUD between 2017 and 2024. Fentanyl exposure was determined by urine toxicology during the pregnancy and on admission. Infants were monitored using the Eat, Sleep, Console tool and a standardized NOWS protocol. NOWS hospitalization outcomes were compared between the fentanyl-exposed and nonexposed groups with adjustment for breastfeeding, year of birth, and relevant co-exposures.

RESULTS: Among 504 dyads, 131 (26.0%) had fentanyl exposure. Maternal demographics were similar between groups, but fentanyl was associated with higher rates of polysubstance use. Fentanyl-exposed infants were more likely to receive pharmacologic NOWS treatment (61.1% vs 40.8%, $P < .01$), scheduled methadone dosing, secondary pharmacologic agents (15.4% vs 7.4%, $P = .03$), and feeding tubes (40.0% vs 24.5%, $P < .001$). Hospital length of stay (22.1 vs 13.3 days, $P < .01$) and opioid treatment duration (14.2 vs 9.4 days, $P < .01$) were longer in the fentanyl-exposed cohort. In adjusted regression models, fentanyl exposure remained independently associated with prolonged hospitalization (mean difference 5.1 days [95% CI 1.7–8.5]) and increased odds of pharmacologic treatment (adjusted odds ratio 2.1 [95% CI 1.2–3.8]).

CONCLUSION: Antenatal fentanyl exposure is strongly associated with intensive pharmacologic management and extended hospitalization. These findings are suggestive of more severe NOWS.

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BACKGROUND

In parallel with the rise in opioid use as the opioid epidemic progresses, opioid use in pregnancy has increased significantly in recent years and is the leading cause of maternal morbidity.[1,2] Recently, illicitly manufactured fentanyl has become the most common recreationally used opioid by far with a 300% increase in fentanyl use since 2014.[3] Currently, fentanyl use occurs in up to 50% of pregnancies where the pregnant person is on medications for opioid use disorder (MOUD).[4] In addition to the negative health effects that fentanyl use poses for all individuals, nonprescribed opioid use in pregnancy also has significant potential negative health effects for the fetus. These potential adverse effects include fetal growth restriction and risk for fetal distress and preterm delivery.[5] With all chronic opioid exposures in pregnancy, prescribed or nonprescribed, there is a risk for neonatal opioid withdrawal syndrome (NOWS) after delivery.[6] The increase in opioid use in pregnancy has led to an increase in NOWS diagnoses from 1.5 to 6 cases per 1000 births from 1999 to 2013, and approximately $1.5 billion in associated annual hospitalization charges.[6]

After birth, the abrupt cessation of opioid exposure leads to a sudden decrease in opioid receptor stimulation, resulting in a hyper adrenergic state and the characteristic symptoms of NOWS, including irritability, tremors, high-pitched cry, poor feeding, vomiting, diarrhea, and autonomic instability.[6] The average length of hospital stay for an infant with NOWS is anywhere from 10 to 14 days and is longer for infants who receive pharmacological treatment (approximately 50%), with some infants hospitalized for over a month.[6,7] Additionally, NOWS is associated with an increased risk of feeding difficulties and neurobehavioral dysregulation.[8–11] NOWS is a heterogeneous condition with variable levels of severity with multiple factors contributing.[6,12] Existing research has shown that higher cumulative opioid exposure, co-exposure to other substances during pregnancy, and use of certain psychiatric medications is associated with increased NOWS severity.[6,13] NOWS severity is also influenced by epigenetic and genetic factors as well as maternal factors such as engagement in prenatal care.[6]

Fentanyl—a potent synthetic opioid—readily crosses the placenta and binds to fetal opioid receptors, particularly in the central nervous system and gastrointestinal tract.[13] Fentanyl is 50 to 100 times more potent than morphine, rapidly crosses the blood-brain barrier, and binds potently to the opioid receptors.[14] Fentanyl's high potency and rapid placental transfer may contribute to more severe withdrawal compared with some other opioids. Fentanyl exposure during pregnancy has also been associated with unique infant phenotypes and risk for congenital anomalies that remain poorly understood.[15] In addition, there are likely maternal confounding variables associated with fentanyl use, including use of prenatal care, MOUD duration, and maternal comorbidities that contribute to risk for NOWS. Currently, there are limited data about the effects of antenatal fentanyl exposure on NOWS severity and specifically how this compares with infants exposed to MOUD alone. We hope to fill these gaps in knowledge through this cohort study by evaluating whether antenatal fentanyl exposure is associated with increased NOWS severity in a cohort of opioid-exposed infants.

METHODS

This was a single-center retrospective cohort study between January 2017 and December 2024 comparing outcomes of mother–infant dyads with OUD who were taking nonprescribed fentanyl with those without fentanyl exposure. The study took place in an academic urban safety net hospital with a dedicated prenatal program that provides comprehensive prenatal care and addiction services for those with substance use disorders during pregnancy and the postpartum period. Universal verbal screening for substance use disorders was conducted prenatally and on admission to Labor and Delivery. Urine toxicology testing of all pregnant persons with substance use disorders was performed at each prenatal visit and on admission to Labor and Delivery as part of routine care, which includes quantitative testing for fentanyl and norfentanyl. Infants with antenatal exposure to opioids were monitored with a standardized NOWS protocol. This included a rooming-in model of care on the postpartum unit and/or pediatric inpatient unit with a standardized nonpharmacologic care bundle, promotion of breastfeeding, assessment with the Eat, Sleep, Console (ESC) Care Tool,[16] and treatment with methadone when pharmacologic treatment was indicated. Methadone was given on an as-needed approach, with transition to standing methadone for more severe withdrawal as indicated by need for as-needed medication every 8 hours over the course of 24 to 48 hours with continued indicators per ESC assessments of worsening withdrawal.[16] Infants who required a secondary agent were initiated on phenobarbital or clonidine per a standardized protocol.

Data were collected with use of an internal retrospective database. This study was approved by the local institutional review board. For inclusion in our data analysis, dyads had to have had documented a pregnant person with OUD during the current pregnancy, with date of delivery between January 1, 2017, and December 31, 2024, with a live born infant. Additional exclusion criteria included pregnant individuals treated with naltrexone for MOUD. The data set was then divided into 2 groups: mother–infant dyads exposed to fentanyl during pregnancy and dyads not exposed to fentanyl during pregnancy. Fentanyl use was determined based on electronic medical record review of urine toxicology testing results throughout the pregnancy and on admission to Labor and Delivery. Maternal demographics and pregnancy characteristics collected from the electronic medical record include year of birth, maternal age, self-reported race and ethnicity, type of opioid exposures in pregnancy and pregnancy co-exposures. Available co-exposure data included methadone, buprenorphine, heroin, other prescribed opioids, naltrexone, cocaine, marijuana, alcohol, selective serotonin reuptake inhibitors, benzodiazepines, gabapentin, nicotine, amphetamines. Infant data abstracted included gestational age at birth, birth weight, infant sex, breastfeeding, need for nasal gastric (NG) tube feedings, NICU admission, and details of NOWS treatment, including pharmacologic agents used, length of therapy, and overall

length of infant hospitalization. Indication for placement of an NG tube included not meeting standardized intake volume per kilogram per day based on hospital guidelines for gestational age and day of life.

Demographics of the dyads were compared between the fentanyl-exposed and nonexposed cohorts using *t* test for continuous variables and χ^2 test of independence for categorical variables. For the outcome variables, first bivariate analyses were conducted to look at differences between the fentanyl-exposed and nonexposed cohorts, A subgroup analysis was conducted within the fentanyl-exposed cohort to examine timing of fentanyl exposure and association with NOWS severity measures. Next, the associated linear and/or logistic regression models were used to quantify the association between fentanyl exposure and the odds of each outcomes, adjusting for potential covariates including breastfeeding, year of birth, methadone for MOUD, and co-exposure to benzodiazepines, gabapentin, cocaine, amphetamines, and alcohol based on variables that were statistically different between cohorts and that have a known association with NOWS severity. All statistical analysis was conducted in SAS version 9.4.

RESULTS

Among the 504 mother–infant dyads with prenatal opioid exposure in our cohort, 131 (26.0%) had documented fentanyl exposure. Maternal age, race, and ethnicity did not differ significantly between groups. However, year of birth varied ($P < .01$), with fentanyl-exposed births concentrated in more recent years. Substance use patterns showed distinct differences: mothers who used fentanyl had higher rates of methadone (74.8% vs 48.0%, $P < .01$) and heroin exposure (40.5% vs 11.5%, $P < .01$) but lower rates of buprenorphine (25.2% vs 44.2%, $P < .01$) exposure. Co-exposures including cocaine (69.5% vs 19.6%, $P < .01$), alcohol (12.2% vs 4.6%, $P < .01$), benzodiazepines (35.1% vs 17.7%, $P < .01$), gabapentin (15.3% vs 7.8%, $P = .01$), and amphetamines (16.8% vs 8.0%, $P < .01$) were also significantly more prevalent in the fentanyl group (Table 1).

Infant outcomes differed significantly by exposure. Fentanyl-exposed infants were born earlier (37.2 vs 37.8 weeks, $P = .01$), with lower mean birth weight (2784 g vs 2967 g, $P < .01$). Breastfeeding initiation was markedly lower in the fentanyl cohort (25.2% vs 61.0%, $P < .01$). NICU admission occurred more frequently (56.5% vs 30.8%, $P < .01$) and infants had longer hospital stays (22.1 vs 13.3 days, $P < .01$) in the fentanyl-exposed cohort. Any pharmacologic treatment of NOWS was more common (61.1% vs 40.8%, $P < .01$), with fentanyl-exposed infants more likely to receive scheduled rather than as-needed methadone dosing (58.2% vs 28.7%, $P < .01$) and to require a secondary pharmacologic agent (15.4% vs 7.4%, $P = .03$) for NOWS management (Table 2). Requirement of a feeding tube was significantly higher in the fentanyl-exposed infants (40.0% vs 24.5%, odds ratio [OR] 2.06 [95% CI 1.35–3.14, $P < .001$]). In the subgroup analysis of the fentanyl-exposed cohort, infants with continued fentanyl exposure in the 30 days before delivery were more likely to be born at a lower gestational age with lower birth weight and be admitted to the NICU with a longer length of hospital stay (23.4 vs 18.3 days, $P = .04$) compared with infants exposed to fentanyl earlier in the pregnancy. Other NOWS severity measures did not differ based on timing of fentanyl exposure (Table 3).

TABLE 1. Maternal Demographics and Pregnancy Characteristics

Characteristic	Fentanyl Group (n = 131)	No Fentanyl Group (n = 373)	*P* value
Birth year, n (%)			<0.01
2017	0 (0.0)	98 (26.3)	
2018	1 (0.8)	80 (21.4)	
2019	18 (13.7)	49 (13.1)	
2020	21 (16.0)	37 (9.9)	
2021	20 (15.3)	37 (9.9)	
2022	17 (13.0)	32 (8.6)	
2023	38 (29.0)	25 (6.7)	
2024	16 (12.2)	15 (4.0)	
Fentanyl exposure 1 month before delivery, n (%)	98 (74.8)	N/A	N/A
Maternal age, mean (SD), years	32.5 (4.8)	32.1 (4.7)	0.39
Maternal race, n (%)			0.09
Black or African American	16 (12.2)	36 (9.7)	
White	95 (72.5)	290 (78.0)	
Asian	1 (0.8)	1 (0.3)	
American Indian or Alaska Native	0 (0.0)	1 (0.3)	
Other	10 (7.6)	9 (2.4)	
Unknown	9 (6.9)	35 (9.4)	
Maternal ethnicity, n (%)			0.22
Hispanic	14 (10.8)	23 (6.2)	
Non-Hispanic	111 (85.4)	332 (89.2)	
Unknown	5 (3.8)	17 (4.6)	
Other opioid exposures, n (%)			
Methadone	98 (74.8)	179 (48.0)	<0.01
Buprenorphine	33 (25.2)	165 (44.2)	<0.01
Heroin	53 (40.5)	43 (11.5)	<0.01
Other prescribed opioids	2 (1.5)	8 (2.1)	0.66
Co-exposures, n (%)			
Naltrexone	0 (0.0)	5 (1.3)	0.18
Cocaine	91 (69.5)	73 (19.6)	<0.01
Marijuana	20 (15.3)	39 (10.5)	0.14
Alcohol	16 (12.2)	17 (4.6)	<0.01
Selective serotonin reuptake inhibitor	27 (20.6)	62 (16.6)	0.30
Benzodiazepine	46 (35.1)	66 (17.7)	<0.01
Gabapentin	20 (15.3)	29 (7.8)	0.01
Nicotine	87 (66.4)	214 (57.4)	0.07
Amphetamines	22 (16.8)	30 (8.0)	<0.01
Other	14 (10.7)	46 (12.3)	0.62

TABLE 2. Infant Characteristics and NOWS Outcomes

Characteristic	Fentanyl Group (n = 131)	No Fentanyl Group (n = 373)	*P* value
Gestational age at birth, mean (SD), weeks	37.2 (2.3)	37.8 (2.2)	0.01
Birth weight, mean (SD), grams	2784.3 (597.5)	2967.4 (564.5)	<0.01
Infant sex, n (%)			0.29
Male	60 (45.8)	198 (53.1)	
Female	71 (54.2)	174 (46.6)	
Unknown	0 (0.0)	1 (0.3)	
Breastfeeding initiated, n (%)			<0.01
Yes	33 (25.2)	227 (61.0)	
No	98 (74.8)	145 (39.0)	
NICU admission, n (%)			<0.01
Yes	74 (56.5)	115 (30.8)	
No	57 (43.5)	258 (69.2)	
Infant length of stay, mean (SD), days	22.1 (17.1)	13.3 (10.7)	<0.01
Opioid treatment days, mean (SD), days	14.2 (14.7)	9.4 (11.2)	<0.01
NOWS pharmacologic treatment, n (%)			<0.01
Yes	80 (61.1)	152 (40.8)	
No	50 (38.2)	220 (59.0)	
Unknown	1 (0.8)	1 (0.3)	
Methadone dosing type for NOW, n (%)			
Scheduled	4 (5.1)	3 (2.8)	<0.01
As-needed	29 (36.7)	74 (68.5)	
As-needed then scheduled	46 (58.2)	31 (28.7)	
Secondary agent for NOWS treatment, n (%)			0.03
Yes	20 (15.4)	24 (7.4)	
No	110 (84.6)	300 (92.3)	
What secondary NOWS pharmacologic treatment was used?, n (%)			0.18
Clonidine	0 (90.0)	3 (12.5)	
Phenobarbital	18 (90.0)	15 (62.5)	

Abbreviations: NICU, neonatal intensive care unit; NOWS, neonatal opioid withdrawal syndrome.

After adjustment for breastfeeding, methadone for MOUD, and maternal co-exposures to benzodiazepines, gabapentin, cocaine, amphetamines, and alcohol, fentanyl exposure remained significantly associated with prolonged infant length of hospital stay (adjusted MD 5.1 days [95% CI 1.7–8.5], $P = .004$) and increased odds of pharmacologic treatment of NOWS (adjusted OR 2.1 [95% CI 1.2–3.8], $P = .01$). The associations with opioid treatment duration and secondary agent use were attenuated and no longer statistically significant (Table 4).

TABLE 3. Comparison of NOWS Outcomes Based On Timing of Last Fentanyl Antenatal Exposure

Characteristic	Fentanyl Exposure Within the Month Before Delivery (n = 98)	Fentanyl Exposure Over 1 Month Before Delivery (n = 33)	*P* value
Gestational age at birth, mean (SD), weeks	37.0 (2.5)	38.0 (1.7)	0.03
Birth weight, mean (SD), grams	2717.3 (614.3)	2983.3 (501.8)	0.03
NICU admission, n (%)			0.007
Yes	62 (63.3)	12 (36.4)	
No	36 (36.7)	21 (63.6)	
Infant length of stay, mean (SD), days	23.4 (17.7)	18.3 (14.7)	0.04
Opioid treatment days, mean (SD), days	14.1 (15.6)	14.3 (11.4)	0.61
NOWS pharmacologic treatment, n (%)			0.34
Yes	62 (63.3)	18 (54.5)	
No	36 (36.7)	15 (45.5)	
Secondary agent for NOWS treatment, n (%)			0.97
Yes	15 (15.3)	5 (15.2)	
No	83 (84.7)	28 (84.8)	

Abbreviations: NICU, neonatal intensive care unit; NOWS, neonatal opioid withdrawal syndrome.

DISCUSSION

In this retrospective cohort analysis, fentanyl exposure was strongly associated with more severe NOWS, as evidenced by higher rates of pharmacologic treatment, greater use of scheduled and multiagent regimens, and prolonged neonatal hospitalizations compared with infants exposed to MOUD alone. Even after adjusting for maternal co-exposures, fentanyl remained an independent predictor of increased NOWS severity, specifically hospital length of stay and need for pharmacologic treatment. These findings highlight fentanyl as an emerging key driver of more complex NOWS phenotype requiring more intensive treatment.

These results are in line with a previously published report by Rana et al that examined associations between prenatal fentanyl exposure and NOWS outcomes.[4] This previous report used both self-reports and umbilical cord tissue testing to measure opioid exposure and pharmacologic treatment rates for NOWS as a measure of severity. They found that infants exposed to fentanyl had a 3-fold higher incidence of severe NOWS with longer lengths of hospital stay compared with infants not exposed to fentanyl.[4] Infants exposed to higher concentrations of fentanyl, as measured by umbilical cord testing, required higher doses of morphine during their pharmacologic treatment of NOWS.[4] Our study adds to these findings, demonstrating that infants exposed prenatally to nonprescribed

TABLE 4. Regression Results for NOWS Outcomes

Outcome	Fentanyl (n = 131)	No Fentanyl (n = 373)	MD (95% CI) or OR (95% CI)	*P* value	MD (95% CI) or OR (95% CI)	*P* value
			Unadjusted		Adjusted[a]	
Infant length of stay, mean (SD), days	22.1 (17.1)	13.3 (10.7)	8.9 (6.3 to 11.4)	<0.01	5.1 (1.7 to 8.5)	0.004
Opioid treatment days, mean (SD), days	14.2 (14.7)	9.4 (11.2)	4.8 (1.4 to 8.2)	<0.01	2.8 (−1.7, 7.3)	0.23
NOWS pharmacologic treatment, n (%)	80 (61.1)	152 (40.8)	2.3 (1.6 to 3.4)	<0.01	2.1 (1.2, 3.8)	0.01
Secondary agent NOWS treatment, n (%)	20 (15.4)	24 (7.4)	2.3 (1.2 to 4.3)	0.01	1.4 (0.5, 3.6)	0.53

Abbreviations: CI, confidence interval; OR, odds ratio; MD, mean difference; NOWS, neonatal opioid withdrawal syndrome.
[a] Adjusted for breastfeeding, year of birth, methadone, benzodiazepine, gabapentin, cocaine, amphetamine, and alcohol exposure.

fentanyl had longer lengths of hospital stay and were 2-fold more likely to receive pharmacological treatment. Our study has a larger sample size than the previous report, and includes additional consideration of co-exposures to MOUD, other nonprescribed substances, and psychiatric medications. Together, these findings provide additional evidence of adverse effects on NOWS severity with antenatal fentanyl exposure.

The mechanisms for why antenatal fentanyl exposure is associated with more severe NOWS and poor feeding are currently unknown with multiple potential explanations. First, fentanyl is 100 times more potent than morphine and 50 times more potent than heroin, which could precipitate more severe withdrawal symptoms with neurotoxic effects that might impact infant feeding ability.[17–19] Additionally, regionally in New England, adulterants in the illicit fentanyl are common, such as xylazine, a highly addictive tranquilizer and an alpha-2 adrenergic agonist with its own neurotoxic effects.[20–22] Based on known effects, it is likely that fentanyl leads to significant neurologic dysregulation and agitation in infants with associated poor feeding efficiency. Although we did find an increase in NG tube use in the fentanyl-exposed cohort, data were not available on the duration of NG tube usage or overall infant weight trends during the hospitalization, which can be explored in future studies. Despite our investigation helping to illuminate some of the short-term effects of in-utero fentanyl exposure on infants, the long-term effects are largely unknown. A 2023 study by Wadman et al reported a clinically recognizable "fetal fentanyl syndrome," with microcephaly, congenital malformations, distinctive facial features, and short stature resembling the Smith-Lemli-Opitz syndrome, suggesting that fentanyl exposure may be interfering with cholesterol metabolism and synthesis pathways.[15] However, additional research is needed in both human and animal models to elucidate key mechanisms and biological pathways.

Strengths of this study include that it is one of the first studies to examine the effects of nonprescribed fentanyl exposure on NOWS outcomes in a large cohort of infants. In addition, we were able to look at a range of NOWS outcomes with adjustment for relevant co-exposures. However, our study is limited in that it is a retrospective single-center design with the possibility of not capturing all antenatal exposure data. We were limited in that our urine toxicology testing did not include common adulterants in the illicit drug supply such as xylazine, which could have impacted NOWS outcomes. In addition, infants exposed to fentanyl in our study were also co-exposed to MOUD because we did not have a large enough cohort exposed to fentanyl alone for comparison. Moreover, there are likely unmeasured confounding factors such as maternal psychosocial characteristics, prenatal care use, duration of MOUD treatment, maternal comorbidities, or differences in nonpharmacologic variables that we could not account for in our analyses because of absence of these variables in this retrospective data set. Overall length of hospitalization in our study was longer than reported by NOWS Centers for Excellence,[7] but is similar to other large statewide perinatal collaborative data,[23,24] which could reflect areas for on-going quality improvement at the center. It is possible there could have been changes over time in NOWS care practices, which we have attempted to account for by including year of birth in all regression analyses. Last, we did not examine for incidence of congenital anomalies in this data set that have been associated with antenatal fentanyl exposure.

In conclusion, antenatal illicit fentanyl exposure is associated with more severe NOWS requiring additional pharmacologic treatment. Whether or not NOWS treatment algorithms should be tailored with prenatal fentanyl exposure because of the increased risk for severe withdrawal is currently unknown but could be investigated through future multicentered prospective studies. Mechanisms for neurobehavioral dysregulation, severe withdrawal, and feeding difficulties in fentanyl-exposed infants are currently unknown and in need of investigation. Future studies examining the long-term neurodevelopmental and health outcomes of fentanyl-exposed infants are also warranted.

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