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Maternal Opioid Use Disorder and the Risk of Postneonatal Infant Mortality

Sarah Grossarth, MPH; Sarah S. Osmundson, MD, MS; Andrew D. Wiese, PhD, MPH; Sharon E. Phillips, MSPH; Amelie Pham, MD; Ashley A. Leech, PhD, MS; Stephen W. Patrick, MD, MPH, MS; Andrew J. Spieker, PhD; Carlos G. Grijalva, MD, MPH; Margaret A. Adgent, PhD, MSPH

IMPORTANCE The risk of serious long-term outcomes for infants born to individuals with opioid use disorder (OUD) is not fully characterized, nor is it well understood whether risks are modified by infant diagnosis of neonatal opioid withdrawal syndrome (NOWS).

OBJECTIVE To characterize the risk of postneonatal infant mortality among infants with a NOWS diagnosis or born to individuals with OUD.

DESIGN, SETTING, AND PARTICIPANTS The study team conducted a retrospective cohort study of 390 075 infants born from 2007 through 2018 to mothers who were enrolled in Tennessee Medicaid from 183 days prior to delivery through 28 days post partum (baseline). Maternal and infant baseline characteristics were measured using administrative claims and birth certificates, and infants were followed up from day 29 post partum through day 365 or death. Deaths were identified using linked death certificates through 2019. These data were analyzed from February 10, 2022, through March 3, 2023.

EXPOSURE Infant exposures included birth to an individual with OUD or postnatal diagnosis of NOWS. The study team defined a pregnant individual's OUD status (maternal OUD) as having OUD diagnosis or a maintenance medication prescription fill during baseline; this study defined NOWS as having NOWS diagnosis up to day 28. Groups were categorized by exposures as maternal OUD with NOWS (OUD positive/NOWS positive), maternal OUD without NOWS (OUD positive/NOWS negative), no documented maternal OUD with NOWS (OUD negative/NOWS positive), and no documented maternal OUD or NOWS (OUD negative/NOWS negative, unexposed).

MAIN OUTCOME AND MEASURES The outcome was postneonatal infant death, confirmed by death certificates. Cox proportional hazards models were used, adjusting for baseline maternal and infant characteristics, to estimate adjusted hazard ratios (aHRs) and 95% CIs for the association between maternal OUD or NOWS diagnosis with postneonatal death.

RESULTS Pregnant individuals in the cohort had a mean (SD) age of 24.5 (5.2) years; 51% of infants were male. The study team observed 1317 postneonatal infant deaths and incidence rates of 3.47 (OUD negative/NOWS negative, 375 718), 8.41 (OUD positive/NOWS positive, 4922); 8.95 (OUD positive/NOWS negative, 7196), and 9.25 (OUD negative/NOWS positive, 2239) per 1000 person-years. After adjustment, the risk of postneonatal death was elevated for all groups, relative to the unexposed: OUD positive/NOWS positive (aHR, 1.54; 95% CI, 1.07-2.21), OUD positive/NOWS negative (aHR, 1.62; 95% CI, 1.21-2.17), and OUD negative/NOWS positive (aHR, 1.64; 95% CI, 1.02-2.65).

CONCLUSIONS AND RELEVANCE Infants born to individuals with OUD or with a NOWS diagnosis had an increased risk of postneonatal infant mortality. Future work is necessary to create and evaluate supportive interventions for individuals with OUD during and after pregnancy to reduce adverse outcomes.

Multimedia

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Margaret A. Adgent, PhD, MSPH, Department of Health Policy, Vanderbilt University Medical Center, 2525 West End Ave, 7th Floor, Nashville, TN 37203 (margaret.a.adgent@vumc.org).

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Neonatal opioid withdrawal syndrome (NOWS) is experienced by some newborns exposed to opioids prenatally and is characterized by a range of clinical signs, including high-pitched cry, poor feeding and weight gain, hypertonia, and seizures.[1] From 2010 to 2017, the rate of NOWS increased nationally from 4.0 to 7.3 per 1000 birth hospitalizations, accompanied by an increase in the rate of opioid-related conditions (eg, opioid use disorder [OUD]) in mothers at the time of delivery (from 3.5 to 8.2 per 1000 delivery hospitalizations).[2] The state of Tennessee ranked sixth highest across US states in 2017 for both conditions.[2] Infants with NOWS have significantly longer birth hospitalization stays and greater birth hospitalization costs compared with those without NOWS.[2,3] Perinatal and postnatal factors potentially associated with maternal OUD, such as underuse of preventive care, may also contribute to other adverse infant outcomes, such as increased sick and emergency care visits.[4] However, the long-term risks for serious outcomes, such as infant death, that may occur after the neonatal period remain poorly understood.[5-8]

Infant mortality has been investigated in relation to OUD and NOWS with inconsistent findings.[9-12] In a Canadian population (2002 to 2014), Brogly and colleagues[9] reported an infant mortality rate of approximately 12 per 1000 live births among opioid-dependent women, nearly 3 times the general population. A study of Texas Medicaid (2010 to 2014) reported the risk of death among infants born to women with OUD differed by NOWS diagnosis: infants born to women with OUD but without NOWS had an increased risk of death relative to OUD-unexposed infants but those with NOWS did not, following adjustment for confounders.[13] In contrast, a hospital discharge database study in Washington (1990 to 2008) reported elevated mortality risk in NOWS infants.[10] These studies were conducted prior to substantial upticks in maternal OUD and NOWS that have occurred in more recent years and in areas with lower incidence than highly affected states, such as Tennessee. Additionally, most previous studies did not clearly distinguish between early neonatal deaths, which are often attributed to factors related to preterm delivery and complications of pregnancy, and postneonatal deaths, commonly attributed to sudden unexpected infant death and unintentional injury.[14] To better understand the association between maternal OUD, NOWS, and risks to infants following delivery hospitalization discharge, we investigated the risk of postneonatal (more than 28 days) infant mortality among those exposed to maternal OUD and/or who have a NOWS diagnosis among a vulnerable population with a high incidence of OUD and NOWS.

Key Points

Question What is the risk of postneonatal infant mortality among infants with neonatal opioid withdrawal syndrome (NOWS) diagnosis or born to individuals with opioid use disorder (OUD)?

Findings In this cohort study of 390 075 infants, after adjusting for maternal and infant characteristics, the risk of postneonatal infant mortality was significantly higher for those born to individuals with OUD or diagnosed with NOWS as compared with unexposed infants.

Meaning In this study, maternal OUD and NOWS diagnosis were associated with an increased risk of postneonatal infant mortality.

Methods

Population and Study Design

We conducted a retrospective cohort study of infants born to pregnant individuals enrolled in TennCare, the state of Tennessee's Medicaid program. TennCare provides health insurance to Tennessee residents who qualify for Medicaid and covers approximately half of Tennessee births annually. TennCare data include enrollment information, administrative claims (patient encounters, diagnoses, and procedures), and outpatient pharmacy files (filled prescription medications). These data were supplemented with birth and death certificates and data from the Tennessee Hospital Discharge Data System, an all-payers statewide registry of all hospital-based encounters in the state. This linked-data platform has been used widely in previous pharmacoepidemiology studies of pregnant individuals and children.[15-18]

This study included infants born in Tennessee hospitals from 2007 through 2018 to individuals 15 to 44 years old with continuous TennCare enrollment (no gaps for more than 30 days) from 183 days prior to birth through 28 days postbirth (baseline period). To mitigate the influence of extreme prematurity on our assessment, we excluded infants outside the range of 28 to 42 weeks' gestation or with birth weight less than 1500 g.[19] Our cohort comprised infants who were alive at day 29 postbirth (cohort entry, t0) (eFigure in Supplement 1). We initiated follow-up at day 29 to coincide with the standard definition of postneonatal infant mortality[20] and to allow for study infants to be discharged from their birth hospitalization (mean length of stay for infants with NOWS, 16 days[3]). Beginning at t0, we followed up infants until death or day 365 after birth. This study involved retrospective analysis of existing data and was approved with a waiver of consent by institutional review boards of Vanderbilt University Medical Center and the Tennessee Department of Health, and by the Division of TennCare. This report is consistent with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Primary Exposure

The primary exposure was infant exposure to maternal OUD or NOWS diagnosis. We anticipated that not all infants with NOWS would have documented maternal OUD during pregnancy due to poor documentation, unrecognized OUD, or alternative indications for opioid use during pregnancy (eg, pain management associated with sickle cell disease or cancer). Therefore, we defined 4 mutually exclusive exposure groups for all infants: maternal OUD with NOWS (OUD positive/NOWS positive), maternal OUD without NOWS (OUD positive/NOWS negative), NOWS without documented maternal OUD (OUD negative/NOWS positive), and a reference group of unexposed infants (OUD negative/NOWS negative). We defined

maternal OUD as having 1 coded OUD diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* or *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM];* eTable 1 in Supplement 1) from a hospitalization, 23-hour stay or emergency visit, or 2 coded OUD diagnoses on separate dates from outpatient encounters or professional claims during the baseline period, or any (1 or more) prescription fill of maintenance therapy medications (buprenorphine, buprenorphine-naloxone, naltrexone, or methadone) recorded in pharmacy fill records during the baseline period. We defined NOWS as 779.5 (*ICD-9-CM*) or P96.1 (*ICD-10-CM*) recorded from birth through the 28th day postbirth in the maternal or infant record.[21]

Outcome

The primary outcome was postneonatal infant mortality, defined as death occurring from day 29 after birth through day 365 after birth. We verified date and cause of death using linked death certificates from 2007 through 2019. For descriptive purposes, we categorized cause of death according to broad *ICD-10-CM*–based classifications (eg, R codes, ill-defined or unknown causes; V through Y codes, external causes; Q codes, congenital malformations or chromosomal abnormalities; P codes, conditions originating in perinatal period;[22] and others). We collapsed or suppressed categories as needed to conceal small cell counts (10 or fewer observations).

Covariates

Covariates were measured during the baseline period. Covariates obtained from linked birth certificates included maternal age, race, ethnicity, education level, marital status, parity, smoking during pregnancy, receipt of prenatal care, birth year, neonatal intensive care unit admission, birth weight, obstetric estimate of gestational age, and delivery route. We included race and ethnicity due to reported disparities in infant mortality across racial and ethnic groups.[23] We defined severe maternal morbidity using an established US Centers for Disease Control and Prevention algorithm.[24] We measured maternal mental health diagnoses (depression, anxiety, bipolar and related disorders, schizophrenia, and other psychotic disorders) and substance use disorders (alcohol, amphetamines, cannabis, cocaine) using *ICD-9-CM* and *ICD-10-CM*–coded diagnoses during the baseline period. We also characterized prenatal maternal medication use (antidepressants, stimulants/attention deficit hyperactivity disorder medications, benzodiazepines, and antipsychotics). We defined a separate binary covariate for each medication type, corresponding to 1 or more or no prescription fills in the 183 days prior to delivery using pharmacy dispensing records.

Analysis

We calculated descriptive statistics for patient characteristics across exposures (OUD positive/NOWS positive, OUD positive/NOWS negative, OUD negative/NOWS positive, OUD negative/NOWS negative) and calculated incidence of postneonatal infant mortality (deaths per 1000 person-years). We generated Kaplan-Meier curves to compare the survival distributions across exposures.

For our primary analysis, we used Cox proportional hazards regression to estimate adjusted hazard ratios (aHR) and 95% CIs. We used cluster-robust standard errors to account for mothers who had multiple infants during the study period. We selected covariates as potential confounders if they were plausibly associated with the exposure and outcome. The primary model adjusted for potential confounders in 2 steps. First, a partially adjusted model accounted only for maternal and demographic characteristics. These covariates included maternal age, race, Hispanic origin, educational level, marital status, parity, smoking during pregnancy, receipt of prenatal care, birth year, maternal mental health diagnoses, maternal medications, maternal substance use disorders, and severe maternal morbidity. Then, in a fully adjusted model, we accounted for infant and birth characteristics. These additional covariates, obtained from birth certificates, included delivery method, multiple gestation, infant sex, gestational age, birth weight, and congenital anomalies. We calculated risk differences (RD) from logit models with cluster-robust standard errors.[25]

Sensitivity Analyses

Some serious neonatal conditions may require management with opioids and lead to iatrogenic neonatal abstinence syndrome (NAS).[3,21,26] Therefore, we conducted a sensitivity analysis that excluded possible cases of iatrogenic NAS, defined as *ICD-10-CM* code P96.2 (withdrawal symptoms from therapeutic use of drugs in newborn) or as infants who had *ICD-9-CM* codes for the following conditions: intraventricular hemorrhage (code 772.1x), periventricular leukomalacia (code 779.7), necrotizing enterocolitis (code 777.5x), spontaneous intestinal perforation (code 777.6), or bronchopulmonary dysplasia (code 770.7).[3,21,26] We conducted a second sensitivity analysis excluding infants who were still hospitalized at the start of follow-up (day 29), as we expect these infants may have severe underlying risks for mortality potentially unrelated to OUD or NOWS.

Statistical testing was 2-sided, with $P < .05$ considered statistically significant. We conducted all analyses using Stata version 17 (StataCorp), R version 4.1.2, and R Studio 2021.09.2 build 382 (The R Project).

Results

The primary analysis included 390 075 maternal-infant dyads, of which 14 357 were exposed to maternal OUD or had a NOWS diagnosis (any OUD/NOWS) (3.6%) and 375 718 that were unexposed (OUD negative/NOWS negative) (96.3%). Among the dyads with any OUD/NOWS, the study team identified 4922 as OUD positive/NOWS positive (1.3%), 7196 as OUD positive/NOWS negative (1.8%), and 2239 as OUD negative/NOWS positive (0.6%) (**Table 1**). Among mothers meeting this study's definition for OUD positive, 4860 had qualifying OUD *ICD* diagnosis codes only (40.1%), 2602 had qualifying medication fills only (21.5%), and 4656 had both (38.4%).

Overall, most infants were born to mothers who were unmarried (68.7%) and identified as White (66.7%). Most moth-

Table 1. Maternal and Infant Characteristics (Tennessee Medicaid, 2007 to 2018)

Characteristic	OUD+/NOWS+ (n = 4922)	OUD+/NOWS- (n = 7196)	OUD-/NOWS+ (n = 2239)	OUD-/NOWS- (n = 375 718)
Maternal age, mean (SD), y	27.4 (4.7)	26.8 (4.8)	27.1 (5.2)	24.5 (5.3)
Maternal race, No. (%)[a]				
Black/African American	126 (2.6)	412 (5.7)	218 (9.7)	122 655 (32.6)
White	4758 (96.7)	6707 (93.2)	1999 (89.3)	246 763 (65.7)
Other[b]	20 (0.4)	36 (0.5)	12 (0.5)	5145 (1.4)
Maternal ethnicity, No. (%)[a]				
Non-Hispanic	4856 (98.7)	7115 (98.9)	2203 (98.4)	361 298 (96.2)
Hispanic	48 (1.0)	69 (1.0)	28 (1.3)	13 966 (3.7)
Maternal education, No. (%)[c]				
Less than high school	1222 (24.8)	1807 (25.1)	600 (26.8)	83 935 (22.3)
High school/GED	2252 (45.8)	3321 (46.2)	998 (44.6)	161 466 (43.0)
More than high school	1420 (28.9)	2047 (28.4)	631 (28.2)	129 322 (34.4)
Married, No. (%)	1329 (27.0)	2088 (29.0)	610 (27.2)	117 809 (31.4)
Parity, No. (%)[c]				
0	1016 (20.6)	1534 (21.3)	496 (22.2)	138 301 (36.8)
1	1583 (32.2)	2371 (32.9)	730 (32.6)	114 696 (30.5)
2	1190 (24.2)	1779 (24.7)	536 (23.9)	66 893 (17.8)
3	655 (13.3)	834 (11.6)	268 (12.0)	30 041 (8.0)
>4	438 (8.9)	608 (8.4)	186 (8.3)	22 554 (6.0)
Prenatal smoking, No. (%)[c]	3724 (75.7)	5081 (70.6)	1533 (68.5)	95 161 (25.3)
Mental illness, No. (%)				
Depression	704 (14.3)	961 (13.4)	229 (10.2)	12 134 (3.2)
Anxiety	782 (15.9)	950 (13.2)	230 (10.3)	10 522 (2.8)
Bipolar	412 (8.4)	563 (7.8)	128 (5.7)	6370 (1.7)
Psychosis	27 (0.5)	39 (0.5)	14 (0.6)	899 (0.2)
Any prenatal care, No. (%)[c]	4660 (94.7)	6921 (96.2)	2039 (91.1)	365 210 (97.2)
Delivery method, No. (%)[c]				
Vaginal	3167 (64.3)	4752 (66.0)	1394 (62.3)	257 408 (68.5)
Cesarean	1755 (35.7)	2444 (34.0)	845 (37.7)	118 299 (31.5)
Plurality, No. (%)[c]				
Single gestation	4803 (97.6)	7002 (97.3)	2165 (96.7)	366 391 (97.5)
Multiple gestation	119 (2.4)	194 (2.7)	73 (3.3)	9322 (2.5)
Infant sex, No. (%)[c]				
Female	2238 (45.5)	3618 (50.3)	1024 (45.7)	184 242 (49.0)
Male	2684 (54.5)	3578 (49.7)	1215 (54.3)	191 474 (51.0)
Gestational age, mean (SD), wk	38.2 (1.7)	38.1 (1.8)	38.0 (1.8)	38.4 (1.6)
Preterm birth, No. (%)				
Mod/late (32 to <37 wk)	676 (13.7)	1063 (14.8)	377 (16.8)	36 132 (9.6)
Very (28 to <32 wk)	12 (0.2)	50 (0.7)	14 (0.6)	1276 (0.3)
Birth weight, mean (SD), g	2953.10 (504.82)	2977.68 (516.57)	2964.44 (535.62)	3211.99 (519.22)
NICU admission, No. (%)	909 (18.5)	642 (8.9)	475 (21.2)	21 135 (5.6)
Congenital anomalies, No. (%)	18 (0.4)	36 (0.5)	18 (0.8)	1015 (0.3)

Abbreviations: OUD, opioid use disorder; Mod, moderate; NOWS, neonatal opioid withdrawal syndrome; GED, general educational development; NICU, neonatal intensive care unit.

[a] Race and ethnicity were as reported on the birth certificate.

[b] Other race includes American Indian or Native Alaskan, Asian, and Native Hawaiian or Pacific Islander.

[c] Missing data: maternal race, 1224 (0.3%); maternal ethnicity, 492 (0.1%); maternal education level, 1054 (0.3%); marital status, 201 (0.1%); parity, 3366 (0.9%); smoking during pregnancy, 2017 (0.5%); receipt of prenatal care, 3088 (0.8%); delivery method, (less than 1%); plurality, 6 (less than 1%); infant sex, 2 (less than 1%).

ers contributed 1 birth to the cohort (66.2%). Mothers in dyads with any OUD/NOWS were more likely to be older, have lower educational attainment, and identify as White compared with OUD negative/NOWS negative mothers (Table 1). In addition, mothers in dyads with any OUD/NOWS were more likely to have received no prenatal care and were also more likely to have other substance use disorders, mental health diagnoses, and severe maternal morbidities compared with

Table 2. Causes of Postneonatal Infant Death, Overall and by Maternal Opioid Use Disorder (OUD) and Infant Neonatal Opioid Withdrawal Syndrome (NOWS), Tennessee Medicaid 2007 Through 2019

ICD-10-CM underlying cause of death category, leading codes within category, No.[a]	No. (%)		
	Total	Any OUD/NOWS[b]	OUD-/NOWS-
All causes	1317	116	1201
Ill-defined (R codes)	568 (43.1)	54 (46.6)	514 (42.8)
R99, other ill-defined or unspecified cause	372	35	337
R95, sudden infant death syndrome	187	19	168
External (V-Y codes)	363 (27.6)	39 (33.6)	324 (27.0)
W75, accidental suffocation and strangulation in bed	171	21	150
W84, unspecified threat to breathing	68	NA[b]	NA[b]
Congenital malformations, chromosomal abnormalities (Q codes)	182 (13.8)	NA[b]	NA[b]
Q24.9, congenital malformation of heart, unspecified	42	NA[b]	NA[b]
Q23.4, hypoplastic left heart syndrome	20	NA[b]	NA[b]
All other[c]	204 (15.5)	NA[b]	NA[b]
All other and Q codes (summed)[c]	386 (29.3)	23 (19.8)	363 (30.2)

Abbreviations: *ICD-10-CM*, *International Classification of Diseases, Tenth Revision, Clinical Modification*; NA, not applicable.

[a] May not sum to category total; only codes represented at the highest proportion within category are displayed.

[b] Exposure groups are combined and cell values are suppressed to conceal cell sizes that are 10 or less.

[c] Other includes the following code categories: n (% of all-cause total); J codes (upper respiratory causes) 58 (4.4%); I codes (diseases of circulatory system) 31 (2.4%); G codes (diseases of nervous system) 28 (2.1%); P codes (perinatal causes) 25 (1.9%); A, B codes (infections) 21 (1.6%); C, D1 through D4 codes (neoplasms) 12 (0.9%); K codes (diseases of digestive system) 12 (0.9%); and others suppressed due to small counts (10 or less).

mothers in OUD negative/NOWS negative dyads (Table 1; eTable 2 in Supplement 1). Infants in dyads with any OUD/NOWS were more likely to be born preterm (less than 37 weeks) and to be admitted to the neonatal intensive care unit than infants in OUD negative/NOWS negative dyads (Table 1).

Postneonatal Infant Mortality

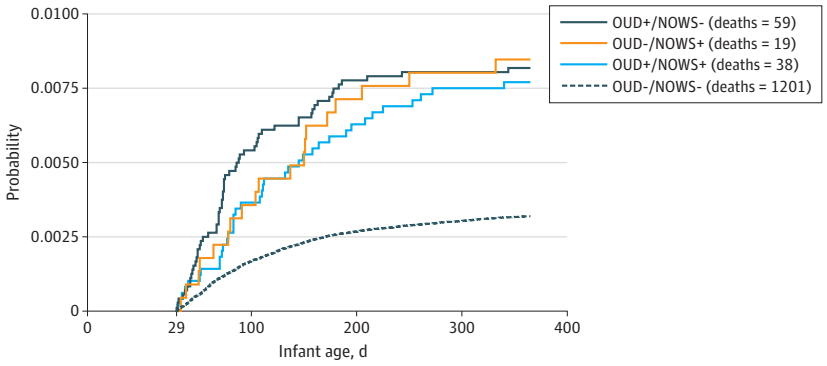
The study team observed 1317 postneonatal deaths corresponding to 3.67 deaths per 1000 person-years (95% CI, 3.48-3.87). The incidence of postneonatal infant mortality was higher in those with any OUD/NOWS compared with OUD negative/NOWS negative (deaths per 1000 person-years: OUD positive/NOWS positive, 8.41; 95% CI, 6.12-11.56; OUD positive/NOWS negative, 8.95; 95% CI, 6.93-11.54; OUD positive/NOWS positive, 9.25; 95% CI, 5.90-14.50 vs OUD negative/NOWS negative, 3.47; 95% CI, 3.28-3.67). Most deaths were due to ill-defined or unknown causes (R codes [43.1%]), followed by external causes (V through Y codes [27.6%]), and congenital malformations/chromosomal abnormalities (Q codes [13.8%]). Relative to deaths in OUD negative/NOWS negative infants (1201), infant deaths with any OUD/NOWS (116) had a higher proportion of deaths attributed to ill-defined causes (54 [46.6%] vs 514 [42.8%]) and external causes (39 [33.6%] vs 324 [27.0%]), including accidental suffocation or strangulation in bed (W75) (21 [18.1%] vs 150 [12.5%]) and were less likely to have deaths attributed to congenital malformations or other causes combined (23 [19.8%] vs 363 [30.2%]) (**Table 2**).

Maternal OUD, NOWS, and Postneonatal Infant Mortality

Survival curves (**Figure**) demonstrate higher risk of postneonatal death among infants with any OUD/NOWS relative to OUD negative/NOWS negative. In the multivariable Cox regression model that adjusted for maternal characteristics (model 1), infants in the OUD positive/NOWS positive, OUD positive/NOWS negative, and OUD negative/NOWS positive groups all had greater risk of mortality, compared with OUD negative/NOWS negative infants. These associations remained significant after additional adjustment for infant and birth characteristics (model 2) (**Table 3**), showing a 54% to 64% increased risk of mortality across exposure groups in this fully adjusted model. Similarly, infants with any OUD/NOWS experienced 4.7 to 5.5 more deaths per 1000 person-years (estimated as RD) relative to OUD negative/NOWS negative infants. The estimated number of excess deaths decreased on adjustment for model 1 covariates (2.5 to 3.6 per 1000 person-years) and model 2 covariates (1.8 to 2.2 per 1000 person-years). In the fully adjusted model (model 2), only the RD for OUD positive/NOWS negative remained statistically significant (Table 3).

The study team excluded 852 infants with probable iatrogenic NAS in a sensitivity analysis. This exclusion did not substantially change the results (eTable 3 in Supplement 1). In a second sensitivity analysis, the study team excluded 3617 infants who were still hospitalized at the start of follow-up. Compared with discharged infants, those with prolonged hospitalization had higher frequencies of high-risk characteristics, including lower mean birth weight (2516 [SD, 750] g vs 3209 [SD, 514]) g, higher proportions of preterm birth (53.1% vs 9.7%), and congenital anomalies (6.9% vs 0.2%). These infants were also more likely to be NOWS positive (29% vs 1.5% in the discharged group). Associations were modestly strengthened for OUD positive/NOWS positive and OUD positive/NOWS negative groups, while associations decreased in the OUD negative/NOWS positive group after exclusions (eTable 4 in Supplement 1). Ill-defined causes and external causes remained as leading causes of death; deaths attributed

Figure. Kaplan-Meier Curve for Probability of Postneonatal Infant Mortality, Tennessee Medicaid 2007 Through 2019, by Maternal Opioid Use Disorder (OUD) and Infant Neonatal Opioid Withdrawal Syndrome (NOWS) Diagnosis



No. at risk

OUD+/NOWS+	4922	0	4904	4891	4885	0
OUD+/NOWS-	7196	0	7157	7140	7138	0
OUD-/NOWS+	2239	0	2231	2223	2221	0
OUD-/NOWS-	375 718	0	375 090	374 712	374 578	0

Postneonatal deaths were defined as those occurring on days 29 to 365 postbirth, identified by Tennessee birth certificates.

Table 3. Characteristics of Postneonatal Infant Death (Tennessee Medicaid, 2007 Through 2019)

Characteristic	OUD+/NOWS+ (n = 4922)	OUD+/NOWS- (n = 7196)	OUD-/NOWS+ (n = 2239)	OUD-/NOWS- (n = 375 718)	Total (N = 390 075)
Deaths, No. (%)	38 (0.77)	59 (0.82)	19 (0.85)	1201 (0.32)	1317 (0.34)
Deaths/1000 person-years (95% CI)	8.41 (6.12-11.56)	8.95 (6.93-11.54)	9.25 (5.90-14.51)	3.47 (3.28-3.67)	3.67 (3.48-3.87)
Unadjusted					
HR (95% CI)	2.42 (1.75-3.34)	2.57 (1.98-3.34)	2.66 (1.69-4.18)	1 [Reference]	NA
RD[a] (95% CI)	4.7 (2.2-7.2)	5.1 (3.0-7.3)	5.5 (1.6-9.5)	0 [Reference]	NA
Model 1[b]					
HR (95% CI)	1.74 (1.21-2.50)	1.86 (1.39-2.50)	2.08 (1.31-3.30)	1 [Reference]	NA
RD[a] (95% CI)	2.5 (0.4-4.5)	2.8 (1.1-4.6)	3.6 (0.4-6.8)	0 [Reference]	NA
Model 2[c]					
HR (95% CI)	1.54 (1.07-2.21)	1.62 (1.21-2.17)	1.64 (1.02-2.65)	1 [Reference]	NA
RD[a] (95% CI)	1.8 (0-3.6)	2.1 (0.5-3.6)	2.2 (−0.5 to 4.8)	0 [Reference]	NA

Abbreviations: HR, hazard ratio; NA, not applicable; NOWS, neonatal opioid withdrawal syndrome; OUD, opioid use disorder; RD, risk difference.

[a] Presented as deaths per 1000 person-years.

[b] Model 1, partial adjustment. Adjusted for maternal age (years), maternal race, mother's Hispanic origin, educational level, marital status, parity, smoking during pregnancy, receipt of prenatal care, birth year, maternal mental health diagnoses (depressive disorders, anxiety disorders, bipolar and related disorders, schizophrenia spectrum and other psychotic disorders), maternal medications, maternal substance use disorders (alcohol, amphetamines, cannabis, cocaine), severe maternal morbidity index.

[c] Model 2, full adjustment. Adjusted for covariates from model 1, as well as delivery method, multiple gestation, infant sex, gestational age, birth weight, and congenital anomalies, obtained from the birth certificate.

to congenital anomalies decreased substantially after exclusions (not shown).

Discussion

Long-term outcomes of infants born to individuals with OUD or diagnosed with NOWS have not been well characterized. In this large retrospective cohort study, we observed that infants with maternal OUD or NOWS diagnosis had a higher risk of postneonatal infant mortality compared with infants without such exposures. These findings underscore the urgent need to diagnose, treat, and support pregnant individuals with OUD prenatally and postnatally, as well as their infants, to prevent devastating outcomes.

Prior literature has suggested that maternal opioid exposure during pregnancy may be associated with an increased risk of infant mortality,[9,10] with some evidence that an infant diagnosis of NOWS may reduce these risks, potentially due to increased availability of surveillance and resources for NOWS infants.[13] Our study focused specifically on postneonatal infant mortality and observed that infants exposed to either maternal OUD or NOWS diagnosis, with or without documented maternal OUD, had an increased risk of death compared with infants without any of those exposures. Postneonatal infant mortality was rare overall and we observed low absolute risk

across all exposure groups, particularly after confounding adjustment. The 3 leading causes of postneonatal infant deaths were ill-defined causes, external causes, and congenital anomalies, similar to previous reports.[14,20] The relatively small number of OUD/NOWS exposed deaths precluded a more in-depth analysis related to cause of death or other related factors. We observed that OUD and NOWS do not occur in isolation, but rather commonly with other medical conditions (eg, depression), additional exposures (eg, tobacco), and social risks (eg, lower educational attainment). We did not assess whether an infant remained in the care of their mother or entered foster care. Furthermore, we cannot rule out a possible mechanism in which prenatal opioid exposure influences developmental or biological processes that may lead to outcomes, such as sudden unexpected infant death.[27,28] Elucidating the underlying mechanism of the observed association is beyond the scope of this assessment and subsequent studies specifically designed to address these new hypotheses would be informative.

Previous research on health outcomes in maternal OUD or NOWS-exposed infants has largely focused on health care utilization. Some studies have reported that infants with NOWS diagnoses are more likely to have readmission after delivery hospitalization discharge than infants without NOWS, often requiring more intensive levels of care.[29] In addition, the proportion of infants with NOWS attending all 6 recommended well-child visits in the first 15 months of life ranged from 39.3% to 62.5% between 2015 and 2017,[30] lower than the US Medicaid median of 65.6%.[31] Our study complements these previous assessments, but also highlights that NOWS did not enhance the risk for infant mortality above what was observed in OUD-only exposed pregnancies. NOWS is a temporary treatable condition that may be the outcome of successful pharmacotherapeutic treatment for OUD.[32] Investigation into the association between maternal use of medications for OUD and infant outcomes was beyond the scope of our study.

The findings of our study and others illustrate a need for policies and resources that facilitate access to treatment for substance use disorders and other supportive services. Pregnant individuals are highly motivated to seek treatment to protect the health of their children and improve their own quality of life, but face numerous barriers.[33-35] Pregnant individuals are less likely to engage in prenatal care or treatment in environments where substance use during pregnancy is criminalized, largely out of fear of losing custody of their children, making such laws counterproductive to supporting maternal and child health. Emerging comprehensive care facilities and services for pregnant individuals and new mothers offer a promising option, promoting nonfragmented access to substance use disorder treatment, pharmacological therapy, pediatric care, and case management with safeguards against discrimination.[33] Our study did not capture the policies or care options available to women over the course of our study period. Additional research is needed to understand how much of our observed association may be attributed to historical policies and whether current trends toward supportive care practices will yield improved outcomes.

Strengths and Limitations

As a strength of our study, we defined OUD by using an algorithm that combined diagnosis codes and maintenance therapy medication prescription fills. Diagnosis codes have demonstrated a high positive predictive value for the identification of NOWS[36]; however, we acknowledge some potential for exposure misclassification related to maternal OUD status. Individuals with opioid dependence due to persistent prescription medication use or illicit opioid use may not have documented evidence of OUD diagnosis or treatment. These individuals would be characterized as OUD unexposed in our study. Additionally, it is possible that some infants that we classified as NOWS positive may have been exposed to nonopioid medications: our NOWS definition includes *ICD-9-CM* code for NAS,[37] which could be caused by medications other than opioids, such as antidepressants or sleeping aids. Many of these individuals will be captured in our OUD negative/NOWS positive exposure group. The misclassification of OUD-exposed individuals into OUD negative/NOWS negative exposure group is also possible, which would likely bias our results toward the null. We also recognize that some maintenance medications used in our exposure definition, such as buprenorphine or naltrexone, could be used for pain management or alcohol addictions in addition to opioid drug use; we expect the number of individuals using these medications for non-OUD indications to be small. Additionally, certain covariates included in our fully adjusted regression model (model 2) could have a mediating role if we were to consider prenatal OUD alone as our primary exposure (eg, gestational age). However, since birth characteristics occurred prior to NOWS assessment, this should temper concerns about a plausible mediating pathway in the context of our combined OUD/NOWS exposure definition.

Unlike some prior studies, our study was designed to examine the risk of postneonatal mortality and included an extended baseline period encompassing the infant's first 28 days. This design ensured adequate time for an infant to receive a NOWS diagnosis and to avoid potential immortal time bias that may occur if follow-up started at birth, prior to the time when a NOWS diagnosis can be made, as noted in previous studies.[13] Additionally, by focusing on postneonatal mortality, we highlight the unique susceptibility of infants later in infancy, where factors such as sudden unexpected infant death and unintentional injuries are leading causes of death.[14,20] Other features of our study include the use of linked death certificates, allowing comprehensive follow-up and outcome assessment irrespective of TennCare enrollment in the year after birth, and the application of a lengthy prenatal baseline enrollment period, allowing ascertainment of important maternal exposures and covariates during pregnancy. Our findings would be directly generalizable to TennCare recipients with enrollment during pregnancy (excluding Medicaid-eligible women who enroll late in pregnancy or not at all) but less so to other populations. However, Medicaid covers approximately 50% of Tennessee births annually and a similar fraction of all births in the US. Our findings are also not directly generalizable to extremely preterm and very low-birth-weight infants.

Conclusion

In this retrospective cohort study, infants born to individuals with OUD and infants with NOWS diagnosis had a higher risk of postneonatal infant mortality compared with infants without such exposures. Expanding diagnosis, treatment, and support for individuals with OUD prenatally and postnatally, as well as their infants, may be beneficial to prevent devastating outcomes in this vulnerable population.

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Author Affiliations: Department of Health Policy, Vanderbilt University Medical Center, Nashville, Tennessee (Grossarth, Wiese, Leech, Patrick, Grijalva, Adgent); Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, Tennessee (Osmundson, Pham); Vanderbilt Center for Child Health Policy, Vanderbilt University Medical Center, Nashville, Tennessee (Wiese, Leech, Patrick); Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee (Phillips, Spieker); Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee (Patrick); Mildred Stahlman Division of Neonatology, Vanderbilt University Medical Center, Nashville, Tennessee (Patrick); Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, Tennessee (Grijalva); Veterans' Health Administration Tennessee Valley Healthcare System, Geriatric Research Education and Clinical Center (GRECC), Nashville (Grijalva).

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Concept and design: Grossarth, Osmundson, Wiese, Pham, Leech, Grijalva, Adgent.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Grossarth, Leech.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Grossarth, Wiese, Phillips, Leech, Spieker, Adgent.
Administrative, technical, or material support: Osmundson, Wiese, Patrick, Spieker, Grijalva.
Supervision: Osmundson, Pham, Spieker, Grijalva, Adgent.

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