Risk of Neonatal Abstinence Syndrome Following Maternal Exposure to either Buprenorphine or Methadone Opioid Maintenance Therapy

Elizabeth Howard, Ben Martin, Xiao Xu, Brian Christman, Linying Zhang

Ochsner Health, Johns Hopkins University, Columbia University, University of Mississippi Medical Center, Washington University School of Medicine

Background

Women are at most risk for substance use during their reproductive years. Recent US national studies show that one in five women filled at least one opioid prescription during their pregnancy.[1] Similarly, the incidence of neonatal abstinence syndrome (NAS) has increased nationally from 3.4 to 5.8 per 1000 hospital births with an increase in aggregate hospital charges from $732 million to $1.5 billion from 2009 to 2012.[2] While there is no clear consensus on the long-term effects on neurodevelopment in neonates exposed to opioids, one study showed that children exposed to opioids had a higher percentage of conduct disorder/emotional disturbance and ADHD.[3] To reduce the risk of poor maternal and child health outcomes, maintenance therapy with either methadone or buprenorphine during pregnancy is encouraged due to the risk of relapse and overdose, despite the risk of neonatal abstinence syndrome (NAS).[4] Literature suggests that buprenorphine carries less risk of NAS than methadone for opioid maintenance therapy.[5,6] However, ensuring the effects of unmeasured confounders have been controlled in observational studies comparing the two medications has been difficult.

This study aims to demonstrate the utility of OHDSI data, methods, and tools for describing neonatal abstinence syndrome (NAS) related to maternal opioid maintenance therapy with buprenorphine or methadone at the population level using the Johns Hopkins University (JHU) OMOP CDM containing JHU patient records.

Primary Objective

To describe the demographic and clinical characteristics of patients prescribed buprenorphine versus methadone for opioid maintenance therapy during pregnancy.

Secondary Objective

To describe the risk of neonatal abstinence syndrome in infants following delivery and up to one week postpartum.

Methods

The study will utilize the aggressively de-identified Johns Hopkins OMOP CDM, which includes patient data from approximately 2.1 million patients seen at Johns Hopkins since July 2016. The process for maternal-infant data linkage was completed using the fact_relationship table (Figure 1).

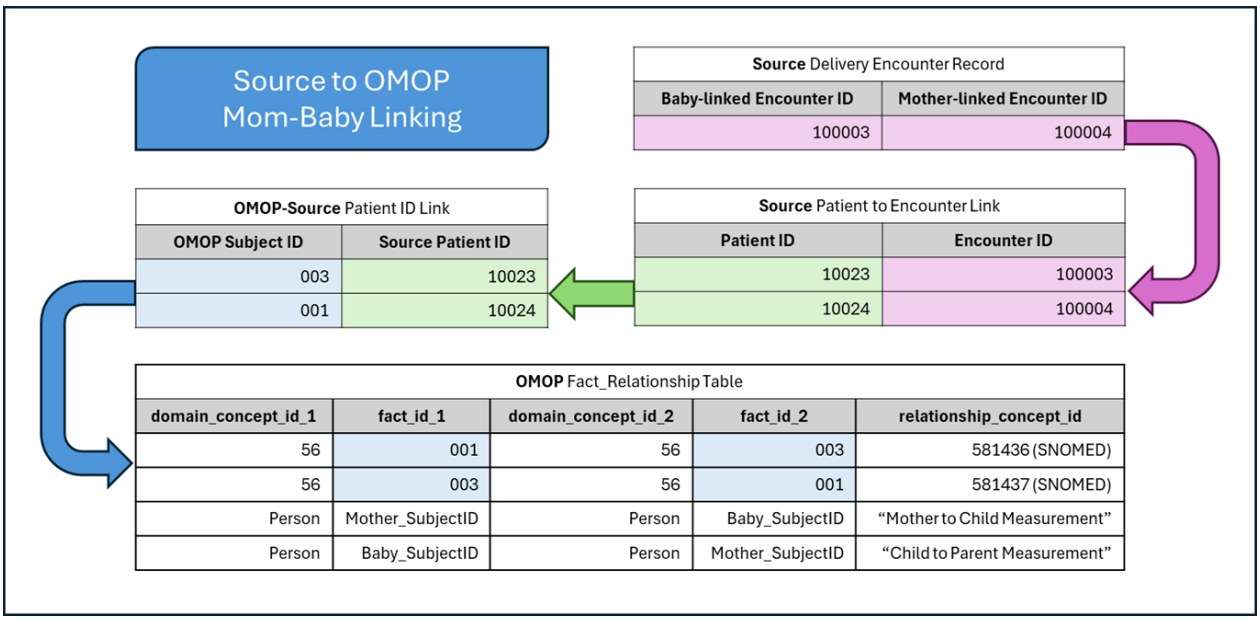

Figure 1. Process for OMOP mother-infant linkage.

All adult pregnant patients 12-55 years old resulting in a singleton live birth who met the inclusion criteria for each exposure cohort were included. The methadone and buprenorphine exposure groups were mutually exclusive with at least one occurrence of methadone or buprenorphine, respectively, for OUD as a procedure or drug exposure where the event starts between 0 and 180 days before the index start date (live birth).

The outcome of interest is neonatal abstinence syndrome (NAS), defined as a singleton live birth resulting in an infant having a diagnosis of NAS between delivery and 7 days after delivery. The phenotype was evaluated by comparing the prevalence of common medications and conditions associated with NAS in both the NAS and non-NAS groups. Data characterization was used to describe and compare differences between methadone and buprenorphine exposed mothers and infants.

Results

Among pregnant patients (N=56,988), 178 buprenorphine exposed mothers and 228 methadone exposed mothers were identified compared to 56,582 unexposed mothers delivering singleton live

infants (Table 1). Maternal age was similar across the cohorts and both the buprenorphine and methadone maintenance therapy cohorts were much more likely to be White and non-Hispanic than the all patients cohort. The maternal opioid use disorder (OUD) maintenance cohorts were also more likely to have both depression and anxiety diagnoses and any pregnancy complication. As for delivery outcomes associated with OUD, severe maternal morbidity was more common in both OUD maintenance therapy cohorts (~10%) and 25% of the methadone cohort experienced preterm birth. Maternal mortality, while rare, proportionally was more common in the methadone cohort.

Table 1. Characteristics of maternal study patients at Johns Hopkins (N=56,988)

	Treated Maternal OUD Singleton Live Births		**All Singleton Live Births**
	Buprenorphine N=178 n(%)	Methadone N=228 n(%)	**N=56,582** n(%)
Age			
15-19	-	-	1244(2.2)
20-24	14(7.9)	25(11.0)	4752(8.4)
25-29	51(28.7)	51(22.4)	9478(16.8)
30-34	65(36.5)	94(41.2)	20,607(36.4)
35-39	39(21.9)	46(20.2)	15,712(27.8)
40-44	9(5.1)	11(4.8)	4283(7.6)
Race*			
White	128(71.9)	173(75.9)	27,619(48.8)
Black	40(22.5)	43(18.9)	13,461(23.8)
American Indian/Alaska Native	4(2.2)	2(0.9)	165(0.3)
Asian	-	-	2380(4.2)
Asian Indian	-	-	1001(1.8)
Ethnicity*			
Hispanic/Latina	3(1.7)	3(1.3)	4283(7.6)
Not Hispanic/Latina	170(95.5)	210(92.1)	45,758(80.9)
Maternal Health			
Depression or Anxiety	16(9.0)	22(9.6)	1282(2.3)
Pregnancy Complication	173(97.2)	226(99.1)	36,268(64.1)
Delivery Outcomes			
Labor & Delivery Complication	164(92.1)	213(93.4)	48,395(85.5)
Preterm Birth	14(7.9)	57(25.0)	2177(3.8)
Severe Maternal Morbidity	19(10.7)	22(9.6)	1724(3.0)
30-day Mortality	0	0	3(0.005)
Total Mortality	2(0.05)	2(0.88)	28(0.05)
Timing of Medication Exposure			Total MOUD Rx
Medication use in ONLY the last 30 days prior to delivery	77(43.3)	122(53.5)	199(49.0)

Medication use ONLY 30-180 days prior to delivery	42(23.6	36(15.8)	78(19.2)

*Categories do not total 100%; the remainder have no matching concept for the covariate. Patients may have more than one maternal health condition or delivery outcome.

The most common maternal conditions documented in the OUD maintenance therapy cohorts were substance dependence, mental health disorders, anemia, and depression, but 21.3% of the all live births cohort also noted mental disorders during pregnancy and 20.5% experienced anemia (Table 2). The most common procedures during pregnancy were drug tests and immunizations (even in the singleton live birth cohort), substance use therapy in the buprenorphine (25.8%) and methadone (51.8%) cohorts, and psychiatric evaluation in the methadone group (26.8%).

Table 2. Most common maternal conditions by maternal opioid maintence therapy cohort.

Buprenorphine Cohort Conditions	#	%
1. Substance dependence in mother complicating pregnancy, childbirth and/or puerperium	156	87.6
2. Mental disorders during pregnancy, childbirth and the puerperium	133	74.7
3. Labor and delivery complicated by fetal heart rate anomaly	76	42.7
4. Major depression, single episode	75	42.1
5. Anemia of pregnancy	74	41.6
Methadone Cohort Conditions	**#**	**%**
1. Substance dependence in mother complicating pregnancy, childbirth and/or puerperium	222	97.4
2. Mental disorders during pregnancy, childbirth and the puerperium	170	74.6
3. Anemia of pregnancy	99	43.4
4. Major depression, single episode	93	40.8
5. Disease of the digestive system complicating pregnancy, childbirth and/or the puerperium	81	35.5
Singleton Live Births Cohort Conditions	**#**	**%**
1. Suspected fetal abnormality affecting management of mother	14240	25.2
2. Second degree perineal laceration	14185	25.1
3. Mental disorders during pregnancy, childbirth and the puerperium	12047	21.3
4. Group B streptococcus infection in mother complicating childbirth	11724	20.7
5. Anemia in mother complicating childbirth	11578	20.5

Of the infant study patients at John Hopkins, 762 infants were diagnosed with NAS (Table 3). The infants were more often White and non-Hispanic. The most common procedures in the NAS cohort were chest

x-ray (24.4%), assistance with respiratory ventilation (11.8%), and vaccination (6.0%).

Table 3. Characteristics of infant study patients at Johns Hopkins (N=39,354)

	NAS N=762 n(%)	Infants w/o NAS N=38,592 n(%)
Race*		
White	489(64.2)	15,943(41.3)
Black	197(25.9)	10,903(28.3)
American Indian/Alaska Native	12(1.6)	129(0.3)
Asian	2(0.3)	1168(3.0)
Asian Indian	0	1576(1.5)
Ethnicity*		
Hispanic/Latina	10(1.3)	1986(5.1)
Not Hispanic/Latina	640(84.0)	27,419(71.0)
Gender		
Male	407(53.4)	20,407(52.9)
Female	355(46.6)	18,185(47.1)
Most Common Procedures		
Radiologic examination, chest	186(24.4)	3227(8.4)
Assistance with Respiratory Ventilation	90(11.8)	2226(5.8)
Introduction of Serum, Toxoid and Vaccine into Muscle	46(6.0)	2815(7.3)
Mortality		
30-day Mortality	0	57(0.1)
Total Mortality	5(0.7)	164(0.4)
Evaluation of the Phenotype		
Pharmaceuticals used for withdrawal	602(75.2)	5322(11.5)
Neonatal jaundice	511(63.8)	24,492(53.1)
Fetal disorder caused by chemicals	347(43.3)	225(0.5)
Respiratory problems	605(75.5)	27,037(58.6)
Low birth weight	341(42.6)	7898(17.1)
Feeding problems	484(60.4)	6966(15.1)
Fever/temperature regulation issues	276(34.5)	13,183(28.6)
Vomiting	224(28.0)	7392(16.0)
Seizures	35(4.4)	1454(3.2)

Note: Categories may not total 100%; the remainder have no matching concept for the covariate. Patients may have more than one maternal health condition or delivery outcome.

The prevalence of eight covariates (seven conditions and one medication) that are commonly associated with NAS infants were compared in each infant cohort, NAS and no-NAS. All the covariates were more common in the NAS group than the non-NAS group. The evaluation suggests the NAS phenotype is adequate (Figure 2).

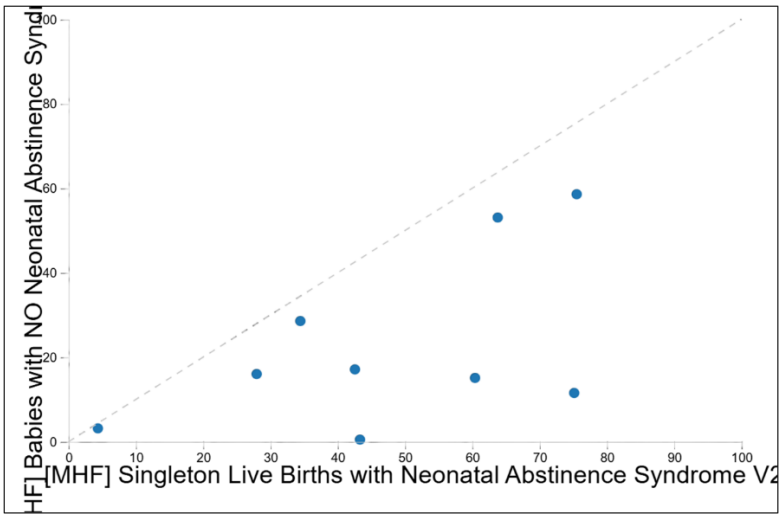

Figure 2. Evaluation of the NAS phenotype by 8 covariates commonly associated with NAS diagnosis.

The proportion of NAS diagnoses in this population of maternal patients treated with either buprenorphine or methadone for their opioid use disorder was 71.4%. Pregnant patients treated with buprenorphine delivered an infant with a NAS diagnosis much less often than patients treated with methadone (55.6% vs 83.8%, respectively).

Conclusion

Linkage of mother and infant health data through the OMOP CDM fact_relationship table helps facilitate perinatal research. By leveraging OMOP CDM and ATLAS, this study provides valuable insights on a comparison of two common maternal opioid maintenance therapy medications and risk of NAS in the infant in this population. Extending this analysis to an OHDSI network study would inform clinical decision-making prescribing habits for opioid maintenance therapy to treat maternal opioid use disorder in order to minimize neonatal abstinence syndrome.

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