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Mental Health of Mothers of Infants with Neonatal Abstinence Syndrome and Prenatal Opioid Exposure

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Abstract

Background The prevalence of opioid use during pregnancy is increasing. Two downstream effects are neonatal abstinence syndrome (NAS), a postnatal withdrawal syndrome, and long-term prenatal opioid exposure (LTPOE) without documented withdrawal symptoms in the infant. Mental health characteristics of mothers of infants with NAS and LTPOE have not been described.

Methods Using linked maternal and infant Medicaid claims and birth certificate data, we analyzed 15,571 infants born to Medicaid-insured women 15–24 years old in a mid-Atlantic city from 2007 to 2010. Pairwise comparisons with multinomial logistic regression, adjusting for maternal and infant covariates, were performed. We compared four mental health conditions among mothers of infants with NAS, infants with LTPOE without NAS, and controls: depression, anxiety, bipolar disorder, and schizophrenia.

Results The prevalence of depression among mothers of infants with NAS, infants with LTPOE, and controls was 26, 21.1, and 5.5% respectively. Similar results were found for anxiety. In multivariable analysis, mothers of infants with NAS and LTPOE had approximately twice the depression risk as controls, while mothers of infants with LTPOE had 2.2 times the bipolar disorder risk and 4.6 times the schizophrenia risk as controls. The overall risk of mental health conditions in mothers of infants with NAS and LTPOE was similar.

Discussion Mothers of infants with LTPOE who did not develop NAS are at similarly high risk for mental health conditions as mothers of infants with NAS, and both are at higher risk than controls. Therefore, those mothers of infants who did not develop symptoms of NAS despite LTPOE may be a vulnerable population that needs additional mental health support in the post-partum period.

Keywords Neonatal abstinence syndrome · Mental health · Opioid use

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Significance

What is known on this subject Pregnant women with opioid use have a high prevalence of mental health conditions, which negatively impacts substance use treatment and pregnancy outcomes.

What this study adds Mothers of infants with LTPOE who did not develop NAS are at similarly high risk for mental health conditions as mothers of infants with NAS, and both are at higher risk than controls. Therefore, those mothers of infants who did not develop symptoms of NAS despite LTPOE may be a vulnerable population that needs additional mental health support in the post-partum period.

Introduction

In the midst of a national opioid crisis, the prevalence of opioid use during pregnancy is also on the rise (Krans and Patrick 2016; Bateman et al. 2014; Desai et al. 2014; Epstein et al. 2013; Cabrera et al. 2008). Studies show that up to a third of pregnant women are prescribed an opioid (Desai et al. 2014; Epstein et al. 2013; Patrick et al. 2015a). This concerning trend has fueled a concomitant increase in neonatal abstinence syndrome, (NAS), a postnatal drug withdrawal syndrome that represents a growing public health problem. The incidence of NAS has increased three-fold from 2000 to 2009 (Patrick et al. 2012) and the rate of neonatal intensive care admissions has increased four-fold from 2004 to 2013 (Tolia et al. 2015).

The interplay between substance use disorders and mental health conditions in pregnancy is bidirectional and complex. Research from the 1980s and 1990s demonstrated that pregnant women with opioid dependence have a high prevalence of mental health diagnoses, ranging from 56 to 73% (Burns et al. 1985; Haller et al. 1993; Unger et al. 2010). Studies from the early 2000s suggested the prevalence of depression or anxiety to be between 5 and 18% (Kissin et al. 2001; Dryden et al. 2009). More recent data show that the odds of opioid use during pregnancy among women reporting depressive or anxiety disorders were almost double the odds for women without these diagnoses (Smith et al. 2015), but there is little research on the relationship between long-term prenatal opioid use (LTPOE, that is, more than occasional or limited use of an opioid medication) and mental health conditions. Importantly, maternal mental health conditions have demonstrated lasting negative consequences for the child (Tronick and Reck 2009; Pearson et al. 2013). However, the prevalence of maternal mental health conditions in general, and the distribution of specific diagnoses, is not known for the current opioid epidemic.

Another important challenge is the changing epidemiology of opioid use in pregnancy. In recent years, there has been an increasing use of illicit and licit prescription opioids. These changes may be associated with differences in the downstream infant outcomes of prenatal opioid exposure, as well as different comorbid conditions among women who use opioids in pregnancy. For example, the infant exposed to heroin typically manifests withdrawal symptoms soon after birth, often in the first 24 h, with near 100% risk of withdrawal. In contrast, withdrawal symptoms after exposure to methadone, buprenorphine or other prescription opioids may not manifest until 3 to 5 days of life or later, and only occur in a subset of infants with prenatal opioid exposure, with estimates ranging from 55 to 94% (Kocherlakota 2014; Hudak and Tan 2012).

Given the epidemiology of the opioid epidemic, a rising proportion of infants may have LTPOE without clinical symptoms of NAS during their initial birth hospitalization. Therefore, there is a need to identify these infants and better understand and address the unique psychosocial stressors present for the maternal half of the mother-infant dyad, whose mental health status is at risk of being overlooked. The aim of this study was to describe the prevalence of four mental health conditions (depression, anxiety, bipolar disorder, and schizophrenia) in mothers in our cohort, and compare these conditions among three groups: mothers of infants with NAS, mothers of infants with LTPOE but without NAS, and controls.

Methods

Study Design, Data Source, and Patient Population

This retrospective cohort study analyzed a dataset assembled for another study (Matone et al. 2016) by linking (1) Medicaid claims data for mothers and infants meeting inclusion criteria, (2) infant birth certificates, and (3) infant death certificates. Maternal mental health diagnoses and psychotropic medication exposure and infant NAS, opioid exposure, and other clinical characteristics were obtained from Medicaid claims. Psychotropic prescriptions include the following classes identified using hierarchical ingredient classifications of National Drug Codes: antipsychotics, antidepressants, mood stabilizers, and anxiolytics. Birth certificate files established infant date of birth and birth weight and maternal demographic characteristics, prenatal clinical characteristics and tobacco use.

Mothers were included in the cohort if they (1) delivered at least one infant between January 1, 2007 and December 31, 2010 in a large mid-Atlantic city; (2) were between the ages of 15 and 24 years at the time of the birth; (3) received Medicaid for at least 10 of 12 months in the year prior to

the estimated date of conception; and (4) were successfully linked to the Medicaid claims of their infant following birth. Infants were included if they (1) were born to a mother meeting criteria 1–4 above; and (2) were successfully linked to the Medicaid claims of their mothers.

Appropriate data use agreements were obtained from the vital statistics office and Commonwealth of Pennsylvania Office of Medical Assistance Programs. As this was a secondary analysis of previously de-identified data assembled for another study, the Children's Hospital of Philadelphia's Institutional Review Board exempted this study from review and waived the requirement for consent. This research was conducted in accord with prevailing ethical principles.

Data Linkage Procedures

Mothers and infants were first identified within birth certificates and then linked to Medicaid claims data using a sequential process that used social security numbers (if available) and unique identifiers constructed from the mother's name, mother's date of birth, and infant's date of birth. Eighty-nine percent of infants meeting the infant inclusion criterion (1) above were successfully linked to their mothers. For the final analytic cohort, all personal identifiers were removed from the data.

Outcomes, Exposures, and Covariates

Using International Classification of Disease-Ninth Revision (ICD-9) codes in the mothers' Medicaid claims data, the outcome of interest was a diagnosis of any of the following four mental health conditions: depression, anxiety, schizophrenia, and bipolar disorder, in the prenatal period for any of the mother's pregnancies,

The main exposure was inclusion in one of three non-overlapping comparison groups at the level of the infant: (1) NAS, (2) LTPOE without NAS, and (3) controls. Infants were considered to have NAS if they had an ICD-9 code of 779.5 in their claims. As in other studies (Patrick et al. 2012), we excluded infants with gestational ages <23 weeks and >44 weeks, with birthweight <400 or >8000 g, or if the birth weight was more than five standard deviations from the mean birth weight for the recorded gestational age in the cohort, to account for potential recording errors in either variable on birth certificates (Parker and Schoendorf 2002). Next, we further excluded presumed iatrogenic NAS, that is, infants with birthweight of <1500 g, or who had diagnoses of chronic lung disease (770.7), any intraventricular hemorrhage (772.1x) or periventricular leukomalacia (779.7, 854.x), necrotizing enterocolitis (777.5x) or spontaneous bowel perforation (777.6), bronchopulmonary dysplasia (770.7), any congenital anomalies (Phibbs et al. 2007), or required mechanical ventilation, any surgery or extracorporeal membrane oxygenation (Patrick et al. 2012, 2014, 2015b).

Infants were categorized as having long-term prenatal opioid exposure if born to mothers (a) in a methadone program (identified by procedure code H0020, as this medication is provided outside the regular clinical setting), (b) who were prescribed buprenorphine at any point in pregnancy, or (c) who had an ICD-9 code consistent with opioid use during pregnancy: 304.0x, 304.7x (opioid dependence); 305.5x (opioid abuse); or V58.69 (use of long-term methadone or other opiate analgesic).

Controls met neither of these criteria. We focused on prenatal opioid exposure as the main cause of NAS and as a focus for recent policy attention. Of note, if a mother was prescribed any opioid during pregnancy, and did not have an infant with NAS or an ICD-9 code consistent with long-term opioid use, she was included in the control group, and a sensitivity analysis was performed after excluding these mothers. These comparison groups were chosen to distinguish, to the extent possible in the data, infant opioid exposure due to medication-assisted therapy with methadone or buprenorphine (opioid-replacement therapy) from exposure due to a maternal prescription opioid (Table 2).

Key covariates included in the models were maternal race, age, education, clinical conditions (gestational diabetes, hypertension, and obesity), income quartile of the zip code of residence, and smoking status; and infant birthweight. Additionally, as psychotropic medication use is associated with having a mental health condition, and is one of the causes of NAS either independently or in combination with opioids (Kocherlakota 2014; Hudak and Tan 2012), we controlled for it in our models.

Statistical Analysis

Descriptive statistics, such as Chi square tests for categorical variables and t-tests for continuous variables, were used to characterize the demographic and clinical characteristics of the mothers (at the level of the infant) and infants between the three comparison groups. Multinomial logistic regression was performed to investigate differences in maternal mental health outcomes between the three comparison groups, after clustering by mother to account for multiple births, and adjusting for the covariates listed above.

Analyses were conducted using STATA Version 13.0 (College Station, TX).

Table 1 Characteristics of the Cohort at the Level of the Infant

	NAS N (%) N = 77	LTPOE N (%) N = 266	Controls N (%) N = 15,228	p value
Maternal characteristics				
Age (mean, median)	22.4, 23.0	20.6, 21.0	20.0, 20.0	**< 0.001**
Race/ethnicity				**< 0.001**
White	58 (75.3)	62 (23.3)	1436 (9.4)	
Black	7 (9.1)	145 (54.5)	10,145 (66.6)	
Other	8 (10.4)	15 (5.6)	1283 (8.4)	
Hispanic	4 (5.12)	44 (16.5)	2364 (15.5)	
Educational level				**< 0.001**
Less than high school	30 (39.0)	158 (59.4)	6268 (41.2)	
High school	46 (59.7)	101 (38.0)	8700 (57.1)	
Unknown	1 (1.3)	7 (2.6)	260 (1.7)	
Income quartile of zip code				**0.009**
1 (lowest)	27 (35.1)	126 (47.4)	8114 (53.3)	
2	42 (54.6)	(38.7)	5546 (36.4)	
3	7 (9.1)	32 (12.0)	1344 (8.8)	
4 (highest)	1 (1.3)	5 (1.9)	224 (1.5)	
Clinical comorbidities				
Obesity (BMI > 30)	10 (13.0)	36 (13.5)	3042 (20.0)	**0.011**
Gestational diabetes	0 (0)	0 (0)	28 (0.2)	0.729
Gestational hypertension	1 (1.3)	3 (1.1)	112 (0.7)	0.649
Psychotropic prescription[a]	30 (39.0)	57 (21.4)	657 (4.3)	**< 0.001**
Mental health conditions				
Depression	20 (26.0)	56 (21.1)	837 (5.5)	**< 0.001**
Anxiety	7 (9.1)	9 (3.4)	209 (1.4)	**< 0.001**
Bipolar disorder	7 (9.1)	44 (16.5)	458 (3.0)	**< 0.001**
Schizophrenia	3 (3.9)	13 (4.9)	44 (0.3)	**< 0.001**
Smoking status (yes)				
1st trimester	64 (83.1)	135 (51.8)	2,313 (15.2)	**< 0.001**
2nd trimester	63 (81.8)	118 (44.4)	1997 (13.1)	**< 0.001**
3rd trimester	63 (81.8)	118 (44.4)	1997 (13.1)	**< 0.001**
Infant characteristics				
Gestational age (mean)	38.6	38.8	38.8	0.314
Birth weight (mean, median)	2816, 2902	3034, 3064	3171, 3181	**< 0.001**
Low birth weight < 2500 g	16 (20.8)	35 (13.2)	1,245 (8.2)	**< 0.001**
Seizure	2 (2.6)	1 (0.4)	21 (0.2)	**0.009**
Respiratory distress	18 (23.4)	24 (9.0)	829 (7.4)	**< 0.001**
Feeding difficulty	1 (1.3)	5 (1.9)	399 (3.6)	0.248
Mean length of stay (days)	29.7	3.9	3.2	**< 0.001**

Bold values indicate statistical significance at $p < 0.05$

BMI body mass index

[a]Psychotropic prescriptions include the following classes identified using hierarchical ingredient classifications of National Drug Codes: antipsychotics, antidepressants, mood stabilizers, and anxiolytics

Results

Characteristics of the Cohort

In the cohort, there were 77 infants with NAS, 266 meeting criteria for LTPOE without NAS, and over 15,000 controls (Table 1). The mothers of infants with NAS were slightly older (mean age 22.4 years compared to 20.6 years for those with LTPOE and 20.0 for controls, $p < 0.001$), more likely to be white, have completed high school, and live in a higher income quartile zip code. Fewer mothers of infants with NAS and LTPOE were obese compared to controls (13.0, 13.5, and 20.0 respectively, $p = 0.011$), but more mothers of infants with NAS smoked in all three trimesters of pregnancy. Finally, 30.9% of mothers of infants with NAS and 21.4% of mothers of infants with LTPOE were prescribed a psychotropic medication in pregnancy, compared to 4.3% of control mothers. (Table 1).

There was no significant difference in gestational age among the three comparison groups of infants, but infants with NAS had significantly lower birthweight; and a higher prevalence of known NAS complications: small for gestational age, seizure, and respiratory distress (Kocherlakota 2014). There were no differences in feeding difficulties, and the mean length of stay was 29.7 days for infants with NAS, 3.9 days for infants with LTPOE, and 3.2 days for controls ($p < 0.001$) (Table 1).

The source of maternal opioid exposure for infants in the three comparison groups is shown in Table 2. Almost half of mothers of infants with NAS (46.8%), 29.3% of mothers of infants with LTPOE, and 26.7% of controls received a prescription for a narcotic during pregnancy. There was only one mother who received buprenorphine, but over 60% of the mothers of an infant with NAS received methadone compared to 5.3% of the mothers of infants with LTPOE.

Table 2 Sources of opioid exposure during pregnancy

	NAS N (%) N = 77	LTPOE N (%) N = 266	Controls N (%) N = 15,228
Methadone	50 (64.9)	14 (5.3)	0 (0)
Buprenorphine prescription	0 (0)	1 (0.4)	0 (0)
Prescription for an opioid	36 (46.8)	78 (29.3)	4066 (26.7)
ICD-9 code for long-term opioid use	55 (71.4)	266 (100.0)	0 (0)

Totals exceed 100% as mothers may have more than one code

Prevalence of Maternal Mental Health Conditions

The prevalence of depression among mothers of infants with NAS was 26, 21.1% among mothers of infants with LTPOE, and 5.5% of the control mothers (Table 1, $p < 0.001$). A similar pattern was found for anxiety. There were higher proportions of bipolar disorder and schizophrenia in the LTPOE group (16.5 and 4.9% respectively) compared to mothers of infants with NAS (9.1 and 3.9%) and controls (3.0 and 0.3%) (Table 1, $p < 0.001$).

Multivariable Comparisons

In multivariable analysis, compared to controls, mothers of infants with NAS had 2.5 times the risk of depression (95% confidence interval [CI] 1.3–5.0), no differences in the risk of anxiety or bipolar disorder, and 6.3 times the risk of schizophrenia (95% CI 1.3–30.0) (Table 3). Compared to controls, mothers of infants with LTPOE who did not develop NAS had 1.8 times the risk of depression (95% CI 1.2–2.7), no increased risk of anxiety, 2.2 times the risk of bipolar disorder, (95% CI 1.4–3.4) and 4.6 times the risk of schizophrenia (95% CI 2.0–10.7). Finally, comparing mothers of infants with NAS compared to those with LTPOE, mothers with infants with NAS had a lower risk of bipolar disorder but there were no differences in the other mental health conditions.

Our sensitivity analysis, which excluded mothers from the control group if they were prescribed an opioid during pregnancy but did not have an infant with NAS or an ICD-9 code consistent with long-term opioid use, yielded the same results. Since these mothers demographically and clinically resembled the other controls, they remained in that group and were assumed to have short-term use of opioids.

Discussion

This study of over 15,000 mother-infant dyads sheds light on the maternal half of the mother-infant dyad in the context of a growing nationwide policy focus on opioid abuse and NAS. It takes the unique perspective of examining mental health characteristics of mothers with long-term opioid use during pregnancy and comparing these characteristics to a subset of mothers whose infants were diagnosed with NAS. We found that the risks of having four mental health conditions for both mothers of infants with NAS and mothers with LTPOE whose infants did not develop NAS were similar and significantly higher than for controls. Our results align with findings from a small retrospective chart review of women enrolled in a comprehensive substance abuse treatment program, in which approximately 30% of women screened positive for moderate to severe depression in the prenatal period (Holbrook and Kaltenbach 2012). However, to our knowledge, there have not been prior descriptions in

Table 3 Pairwise Comparisons Among Three Comparison Groups, for Maternal Mental Health Conditions

Condition	NAS v control RR (95% CI)	p value	LTPOE v control RR (95% CI)	p value	NAS v LTPOE RR (95% CI)	p value
Depression	2.5 (1.3–5.0)	**0.009**	1.8 (1.2–2.7)	**< 0.001**	1.4 (0.6–3.4)	0.41
Anxiety	1.8 (0.7–4.8)	0.21	1.0 (0.5–2.2)	0.90	1.8 (0.5–6.4)	0.34
Bipolar disorder	0.6 (0.2–1.6)	0.33	2.2 (1.4–3.4)	**< 0.001**	0.3 (0.1–0.8)	**0.014**
Schizophrenia	6.3 (1.3–30.0)	**0.02**	4.6 (2.0–10.7)	**< 0.001**	1.4 (0.3–5.8)	0.68

Bold values indicate statistical significance at $p < 0.05$

Multivariable models controlled for race, maternal age, maternal education, median income quartile, birthweight category, receipt of a psychotropic prescription during pregnancy, smoking status, and each of the other three mental health conditions (for example, the comparison yielding the risk ratio for depression controls for anxiety, bipolar disorder, and schizophrenia)

the literature on NAS of the other mental health conditions examined in this study nor comparisons to mothers of infants with LTPOE.

This analysis was motivated by two overarching questions about the rise in opioid use during pregnancy as well as the changing picture of NAS. First, is an NAS diagnosis just the tip of the iceberg for the true burden of subclinical withdrawal in the neonatal population? In this study, there were almost four times as many infants with LTPOE as with an NAS diagnosis. Anywhere from 20 to 90% of substance-exposed infants develop symptoms of NAS, and withdrawal symptoms typically appear earlier in the infant with heroin exposure than other opioids (Kocherlakota 2014) The standard of care is for healthy, full term infants without known prenatal opioid exposure to be discharged from the hospital between days two and four of life, while infants with a maternal history or laboratory findings consistent with opioid exposure are monitored for signs of withdrawal for approximately five to seven days, depending on hospital policy (Kocherlakota 2014; Hudak and Tan 2012). Those infants requiring pharmacologic management often have prolonged birth hospitalizations, during which time many of the supportive services for maternal-infant dyads affected by NAS, including maternal mental health support, are put into place. Therefore, it is important to consider the impact of missing NAS diagnoses if the mother is not known or suspected to be using substances during pregnancy, the infant goes home at two to four days of life to a complex social environment, and then develops poor feeding and growth, severe irritability, or other problems at home.

We have an incomplete understanding of why some infants develop NAS symptoms and others do not (Kocherlakota 2014; Desai et al. 2015) The high-risk group of infants who are exposed to substances prenatally but do not develop clinical signs and symptoms of withdrawal during the initial, and usually brief, birth hospitalization is a population that is difficult to identify, monitor, and study given the current care models for mothers and their infants. The labor-intensive process of linking several data sources for mothers and infants to form the dyads for this analysis illustrates the challenges of breaking down siloes in clinical care and in data collection. This approach is critical, however, to ensure that the mother and infant are cared for as a unit and clinically relevant details that affect both are not overlooked.

The second motivating question is: might we also be missing critical opportunities to recognize and address maternal substance use and mental health conditions in the perinatal and interconception periods if the opioid-exposed infant does not ever develop NAS symptoms or develops them once home from the hospital? One of the priorities during the often-prolonged birth hospitalization for NAS is to connect mothers with appropriate services for their substance use (if not already receiving treatment), resources to care for themselves and their infant, and relevant to this study, mental health support (Kocherlakota 2014). However, the mean length of stay for the infants with LTPOE was only 3.9 days, and the prevalence of mental health conditions in their mothers was strikingly similar to the mothers of infants identified as having NAS. In fact, these mothers had higher proportions of bipolar disorder and schizophrenia than mothers of infants with NAS, yet their length of stay was much shorter than the mean length of stay for maternal-infant dyads affected by NAS (29.7 days). The shorter length of stay means that these dyads have less engagement with the healthcare system and their needs may be less visible to their care teams in the postpartum period.

Of course, to optimize care for these higher-risk women, mental health disorders ideally would be recognized and treated early in the pregnancy. The January 2016 United States Preventive Services Task Force recommendation that all pregnant women receive screening and appropriate treatment for perinatal depression represents progress but only partially addresses the complex challenge of recognizing women with dual diagnoses of a mental health condition and substance use (Siu et al. 2016). Thus, mothers with significant mental health diagnoses whose infants do not show signs of withdrawal in the immediate post-partum period may not receive the wrap-around support and close monitoring that families affected by NAS ideally receive during the long birth hospitalization.

These potential missed opportunities to recognize unaddressed maternal substance use and mental health conditions during the birth hospitalization have long-term implications for the mother-infant dyad. For pregnant women, regardless of substance use, mental health conditions have harmful effects across the entire perinatal continuum, from prenatal care adherence, to birth outcomes, to maternal-infant attachment (Holbrook and Kaltenbach 2012; Kelly et al. 2012, 2000). Specifically, pregnant women in methadone treatment who have comorbid mental health conditions have an increased risk of relapse and treatment drop out (Fitzsimons et al. 2007). Recent research shows that infants with NAS have a significantly increased risk of hospitalization from maltreatment or trauma, which occurred significantly earlier (generally in the first four months of life) than in infants without NAS (Uebel et al. 2015). Therefore, it is conceivable, although more data are needed, that infants with subclinical withdrawal or symptoms that develop after discharge may also be at higher risk of maltreatment, given the demands of caring for an infant that may be extremely irritable, have increased caloric needs but uncoordinated feeding, and/or be experiencing frequent loose stools.

Our study findings suggest opportunities to improve the intergenerational care of these dyads affected by prenatal opioid use. There are many clinicians involved in providing care along the perinatal continuum: prenatal care providers, obstetricians or midwives at the delivery, pediatricians or neonatologists in the newborn period, and outpatient primary care pediatricians and allied health professionals. "Warm hand-offs" of information among these clinicians, the early and seamless involvement of social work and mental health colleagues, and optimization of the electronic health record to improve the confidential communication of key information such as maternal substance use or mental health history, are just a few suggestions to address the complex interplay of substance use and mental health in the perinatal period.

This analysis had the following limitations. First, with Medicaid claims data, misclassification was possible, especially false negatives for NAS in infants and substance use in mothers, which would bias our results towards the null. Second, these data did not include detailed information about opioid prescriptions filled during pregnancy, such as dose and duration, nor about facility-specific assessment and treatment protocols for NAS. Third, our small sample size of infants with NAS and LTPOE has two potential explanations: the aforementioned misclassification (although the NAS ICD-9 code has been shown to have a high sensitivity and specificity) (Patrick et al. 2012), or that the dataset, which was created for a separate study, included young, urban mothers in a single city, both limiting generalizability and not capturing rural mothers, who are known to have a higher prevalence of opioid misuse and abuse. However, this dataset offered a unique opportunity to investigate the mental health conditions of mothers with substance use in pregnancy whose infants did not develop NAS.

In summary, in the context of a concerning increase in the prevalence of opioid use during pregnancy, mothers of infants with LTPOE who did not develop NAS are at similarly high risk for mental health conditions as those whose infants were identified as having NAS. The former represent a population of high-risk mother-infant dyads that have the potential to be sub-optimally connected to mental health resources and social services, if the clinicians during the birth hospitalization (both obstetric and pediatric) are operating in siloes, separate from each other and from the mother's prenatal care records. Future work should use a larger sample to study the following subgroups: women with illicit versus licit opioid use, women with polysubstance use, and those with pharmacologically vs. non-pharmacologically-managed mental health conditions. With the increasing use of psychotropic medications during pregnancy to adequately treat maternal mental health conditions, continued research on the downstream effects on the infant is indicated.

As long-term outcomes for infants with prenatal substance exposure are so dependent on maternal functioning and a supportive and stimulating home environment (Kern et al. 2004; Lean et al. 2013; Logan et al. 2013), this study highlights the pressing need to ensure that maternal mental health conditions and substance use are identified and addressed as part of holistic care (Jones et al. 2014) for the mother and infant across the perinatal continuum.

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