



One-Year Postpartum Mental Health Outcomes of Mothers of Infants with Neonatal Abstinence Syndrome

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Abstract

Introduction Women with substance use disorders have high incidences of psychiatric and mood disorders, which may affect their ability to cope with an infant with neonatal abstinence syndrome (NAS), particularly one with a protracted NICU course, exacerbating symptoms of mental health disorders. We examined the incidence of mental health diagnoses in the first 12 postpartum months in mothers of an NAS infant compared to mothers of an infant without NAS.

Methods In this retrospective, cohort study, data were extracted from MarketScan[®] database (2005–2013). NAS newborns were identified using ICD-9 codes. Each mother of an NAS newborn was matched to a mother of a newborn without NAS on age at delivery, birth year, gestational age, NICU stay and maternal mental health diagnoses in the 9 months prior to delivery. Primary outcomes were claims for major depression, postpartum depression, anxiety, adjustment reaction, post-traumatic stress disorder, and suicidal ideation.

Results 338 mother-infant pairs met all inclusion/exclusion criteria and were matched 1-to-1 with controls. 245 (73%) of the NAS infants had a NICU admission. Median length of stay for these infants was 10 days compared to 3 days for infants with no NICU admission ($p < 0.001$). Mothers of NAS infants were more likely to have claims for major depression (33% vs. 15%, $p < 0.01$), postpartum depression (7% vs. 3%, $p = 0.04$), and anxiety (27% vs. 13%, $p < 0.01$).

Conclusion Mothers of infants with NAS have a higher incidence of mental health diagnoses in the first 12 months postpartum compared to mothers of infants without NAS.

Keywords Addiction and pregnancy · Maternal mental health · Maternal substance abuse · Neonatal abstinence syndrome · Neonatal withdrawal syndrome · Opioid use and pregnancy · Postpartum depression · Substance use disorder

Significance

What is known? Women with a history of substance use disorders have a high incidence of coexisting psychiatric and mood disorders and difficulty managing adversity. The postpartum period can be a particularly vulnerable time for mental health exacerbations. *What this study adds?* Mothers of infants with NAS have a higher incidence of mental health diagnoses in the first postpartum year compared to mothers of infants without NAS, and this incidence increases with time. This information suggests that new mothers affected by substance use disorders may warrant careful, repeated mental health screenings over the course of the 1st year postpartum.

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Introduction

Opioid use and abuse in the United States (U.S.) has reached epidemic proportions and has affected individuals of all socioeconomic classes, gender, race and age, including women in their reproductive years (Epstein et al. 2013; Krans et al. 2015; Stover and Davis 2015). Between 2000 and 2009, the incidence of maternal opioid use during pregnancy increased from 1.19 to 5.77 per 1000 hospital live births per year (Patrick et al. 2012). Opioid use disorders (OUD) among women of child-bearing age are due to both legal consumption through provider prescription for pain control (Ailes et al. 2015; Warren et al. 2015; Yazdy et al. 2015) as well as illegal use of prescription drugs such as oxycodone and illicit drugs such as heroin (Cicero et al. 2015; Gomes and Juurlink 2016). Nationally, the centers for disease control and prevention (CDC) reported that approximately one-third of U.S. women of reproductive age filled a prescription for opioids in the years 2008–2012 (Ailes et al. 2015). In the U.S., the increase in OUD in pregnancy has also led to a notable rise in the incidence of a withdrawal condition in the opioid-exposed newborn known as neonatal abstinence syndrome (NAS), reflecting trends seen around the world (Corr and Hollenbeak 2017; Kocherlakota 2014; Patrick et al. 2012, 2015b; Tolia et al. 2015). While NAS most frequently results from maternal opioid use during pregnancy, neonatal withdrawal can occur following prenatal exposure to a variety of substances, including benzodiazepines, barbiturates and alcohol. (Hudak and Tan 2012).

NAS has become a growing cause for neonatal intensive care unit (NICU) admission in the U.S. with 4% of NICU days attributable to NAS in 2013, an increase from just 0.6% a decade prior (Tolia et al. 2015). Infants affected by NAS are characteristically irritable and display a number of symptoms and behaviors related to neurologic excitability and gastrointestinal dysfunction (Hudak and Tan 2012). While non-pharmacologic measures are first-line treatment, medication administration is often indicated to prevent complications related to moderate and severe symptoms (Hudak and Tan 2012). Opioid therapy is standard of care for opioid withdrawal with supplementary medications such as barbiturates for especially difficult cases or occurrences of multidrug exposure (O'Grady et al. 2009). The administration of these controlled substances has traditionally been done in the hospital setting and can result in a protracted NICU course (Corr and Hollenbeak 2017; Patrick et al. 2012; Tolia et al. 2015). Additionally, infants with in utero drug exposure are at greater risk for premature birth (Hudak and Tan 2012; Patrick et al. 2015c; Whiteman et al. 2014), increasing the likelihood of a prolonged birth admission. These lengthy hospital stays may create additional stressors for susceptible mothers.

Pregnant women with a substance use disorders have high rates of co-existing mental illnesses and often receive treatment for a mental health disorder (Kissin et al. 2001). Gravid women who use opioids are also more likely to meet diagnostic criteria for depression, anxiety, post-traumatic stress disorder (PTSD), and panic disorder (Smith et al. 2015). Because stress can both exacerbate mental health symptoms and be a challenge for individuals with mental health and substance use disorders, a new mother with a history of substance use may have unique difficulties coping with the strain of a newborn, particularly one with withdrawal symptoms and a prolonged hospitalization, and she may be at risk for worsening of mental health conditions. Therefore, we sought to evaluate the incidence of six mental health disorders (major depression, postpartum depression, anxiety, adjustment reaction, PTSD, and suicidal ideation) in the 12 months postpartum in mothers of an infant with NAS. We compare these incident rates to matched controls.

Methods

Design

This retrospective, cohort study was designed to determine the incidence of 6 mental health disorders in the 12 months after delivery for mothers of newborns with a diagnosis of NAS compared to mothers of newborns without NAS.

Data

Data were collected from the MarketScan® Commercial Claims and Encounters database for the years 2005–2013. Institutional IRB exemption status was obtained. MarketScan® is a national database that consists of reimbursed healthcare claims. Individuals included are covered by private insurance plans across the U.S. with claims information from > 130 payers describing healthcare use and expenditures for approximately 50-million employees and family members per year. Individuals are assigned a unique enrollee identifier, and the database contains information on inpatient, outpatient and prescription drug service use as well as patient age, sex, geographic location, and type of health insurance plan. The medical claims contain International Classification of Disease: 9th Revision (ICD-9) diagnoses and procedure codes and Current Procedural Terminology, 4th edition (CPT-4) procedure codes.

Study Cohort

We examined all inpatient admissions in the years 2005–2013 with an admission type coded as “Maternity and Newborn”, age of 0, and relationship to primary beneficiary

listed as child. For these admissions, newborns with a diagnosis of NAS were identified using the ICD-9 diagnosis code 779.5 (drug withdrawal syndrome in the newborn). To ensure that the inpatient admission indicated a birth, we required that at least one ICD-9 diagnosis code for delivery (V30.00, V30.01, V31.00, V31.01, V32.00, V33.01, V34.01), gestational age (765.2x, 766.21, 766.22), or other perinatal code (764.xx, 765.0x, 765.1x) was included. Additional inclusion criteria included gestational age of 35 weeks or greater (ICD-9 diagnosis codes of 765.28, 765.29, 766.21, 766.22) or missing, which were assumed to be full term; no ICD-9 diagnosis code indicating extreme immaturity (765.0x) or other preterm delivery (765.1x); known final discharge status (not missing) and survived to discharge; and linked to mother's records. Maternal inclusion criteria included an inpatient claim indicating delivery (ICD-9 diagnosis codes: 650, 651.xx—659.xx, V27.0—V27.9, 644.2x, 646.xx, 648.xx, 649.xx; ICD-9 procedure codes: 72.x—74.x) during the dates of the newborn birth hospitalization; and continuous enrollment in a health insurance plan from 9 months prior to and 1 year after delivery. For mothers with 2 children at different ages (not twins), only the first child was included.

Outcomes

The primary study outcomes were the following mental health diagnoses, all of which were determined using ICD-9 diagnosis codes from inpatient and outpatient encounters: major depression (296.x, 296.3x, 311, postpartum depression (648.4x), anxiety (300.0x, 308.xx), adjustment reaction (309.xx, excluding 309.22 & 309.81), PTSD (309.81), and suicidal ideation (V62.84) in the 12 months postpartum. The total number of post-delivery mental health diagnoses was calculated. These mental health diagnoses were also determined during the 9-month period prior to delivery (except postpartum depression).

Matching

Mothers of an infant with a diagnosis of NAS during the birth hospitalization were matched to mothers of an infant with no diagnosis of NAS. To form a set of potential matches, the same inclusion/exclusion criteria were used for birth hospitalizations in which no ICD-9 diagnosis code for NAS was found. In an effort to evaluate only mothers of infants who were presumably healthy at the time of birth discharge, newborns who had medical problems that were expected to require ongoing or recurrent post-discharge treatment or care (e.g. encephalopathy, spina bifida, multiple congenital anomalies, etc.) beyond the initial birth hospitalization were also excluded. These diagnoses were identified by analyzing ICD-9 codes after matching, and then

excluding codes and re-matching as necessary. Authors may be contacted for a list of ICD-9 diagnoses codes that were excluded.

A total of 547,477 mothers met all inclusion/exclusion criteria and formed the set of potential matches. We used a greedy matching algorithm (Bergstralh 1995) to match each mother of an infant with a diagnosis of NAS to 1 mother of an infant without a diagnosis of NAS on the basis of the following variables: maternal age at delivery (± 5 years), birth year (± 1 year), gestational age of newborn (35–36 weeks, 37–40 weeks [or missing], ≥ 41 weeks; exact match), NICU stay (exact match), and mental health diagnoses observed for the mother within 9 months prior to delivery (exact match).

Statistical Analysis

Postpartum mental health diagnoses were compared by matched groups using conditional logistic regression. For the number of postpartum health diagnoses, a Cochran-Mantel-Haenszel test was used to compare matched groups. The method of Kaplan-and-Meier (Kaplan 1958) was used to create cumulative incidence curves with the logrank test used to test for differences between curves. Patients who had not yet had a diagnosis for a given mental health outcome at 365 days postpartum were censored at that time point. All statistical tests were two-sided with $p < 0.05$ considered statistically significant.

Results

Among 2012 newborns who were diagnosed with NAS in the database, 338 were part of a mother-infant pair that met all inclusion and exclusion criteria. The majority of newborns diagnosed with NAS had a NICU admission (72.5%), with median hospital lengths of stay of 10 days and 3 days for those with and without a NICU admission, respectively ($p < 0.001$). Compared to matched controls, infants with a diagnosis of NAS had significantly longer birth admissions with a median length of stay of 7 days for those infants with NAS and 3 days for infants without a diagnosis of NAS ($p < 0.001$) (Table 1). Infants with a diagnosis of NAS were also much more likely to be transferred to another hospital during their birth admission (NAS: 8.0% vs non-NAS: 1.5%; $p < 0.001$). The most common antepartum mental health diagnosis in mothers who delivered a child with NAS was major depression (22.5%) followed by anxiety (15.4%), adjustment reaction (6.2%), and PTSD (2.7%) (Table 1).

Compared to matched controls, mothers of an infant with a diagnosis of NAS had significantly higher rates of major depression (32.8% vs. 14.5%; $p < 0.001$), postpartum depression (6.8% vs 3.3%; $p = 0.044$), and anxiety (26.6% vs. 12.7%; $p < 0.001$) in the 12 months following delivery

Table 1 Demographic and birth characteristics of mothers of an infant with neonatal abstinence syndrome and matched controls

Variable	Mothers of an infant with NAS (N = 338)	Matched mothers (N = 338)	P value
Maternal age ^a			
Median (Interquartile range)	31.0 (28.0–35.0)	31.0 (28.0–35.0)	
Infant gestational age ^a			
35–36 weeks	3 (0.9%)	3 (0.9%)	
37–40 weeks	332 (98.2%)	332 (98.2%)	
≥ 41 weeks	3 (0.9%)	3 (0.9%)	
NICU stay ^a	245 (72.5%)	245 (72.5%)	
Antepartum mental health diagnoses ^a			
Major depression	76 (22.5%)	76 (22.5%)	
Anxiety	52 (15.4%)	52 (15.4%)	
Adjustment reaction	21 (6.2%)	21 (6.2%)	
PTSD	9 (2.7%)	9 (2.7%)	
Suicidal ideation	0	0	
Type of delivery			0.166
Vaginal	168 (50%)	187 (55.3%)	
Cesarean	168 (50%)	151 (44.7%)	
Infant transferred	27 (8.0%)	5 (1.5%)	< 0.001
Infant length of stay (days)			
Median (Interquartile range)	7.0 (4.0–16.0)	3.0 (2.0–4.0)	< 0.001
Maternal length of stay			
Median (Interquartile range)	3.0 (2.0–4.0)	3.0 (2.0–3.0)	0.078

NAS neonatal abstinence syndrome, NICU neonatal intensive care unit, PTSD post-traumatic stress disorder

^aMatched characteristic

(Table 2). Figure 1 shows cumulative incidence curves of these mental health diagnoses. New diagnoses were less common across the study time frame for mothers of child without an NAS diagnosis, and mothers of an infant with NAS continued to see increased incidences of new mental health diagnoses across the study time frame, particularly for major depression and anxiety ($p < 0.001$).

When determining the set of potential controls, we excluded mothers of infants with diagnoses that were expected to require significant ongoing treatment following birth discharge, but these exclusions were not used for mothers of NAS infants. Therefore, in order to ensure differences in outcomes were not secondary to a sicker population contained within the NAS cohort, we performed a subgroup analysis in which we excluded 55 mothers (16%) of an infant with NAS who had ICD-9 diagnosis codes that were expected to require significant post-discharge management. For the remaining 283 mothers (and matched controls), results were largely the same with significantly greater incidence of major depression (32.2% vs. 13.8%; $p < 0.001$), postpartum depression (6.7% vs. 2.5%; $p = 0.024$), and anxiety (26.9% vs. 12.0%; $p < 0.001$) in mothers of an infant with NAS compared to matched controls (Table 3).

Table 2 Mental health diagnoses in the 12 months after delivery of mothers of a child with neonatal abstinence syndrome and matched controls

Variable	Mothers of an infant with NAS (N = 338)	Matched mothers (N = 338)	P value
Major depression	111 (32.8%)	49 (14.5%)	< 0.001
Postpartum depression	23 (6.8%)	11 (3.3%)	0.044
Anxiety	90 (26.6%)	43 (12.7%)	< 0.001
Adjustment reaction	29 (8.6%)	24 (7.1%)	0.399
PTSD	11 (3.3%)	14 (4.1%)	0.142
Suicidal ideation	2 (0.6%)	2 (0.6%)	1.000
Number of mental health diagnoses			< 0.001
0	178 (52.7%)	247 (73.1%)	
1	79 (23.4%)	58 (17.2%)	
2	61 (18%)	26 (7.7%)	
3	16 (4.7%)	4 (1.2%)	
4	3 (0.9%)	1 (0.3%)	
5	1 (0.3%)	2 (0.6%)	

NAS neonatal abstinence syndrome, PTSD post-traumatic stress disorder

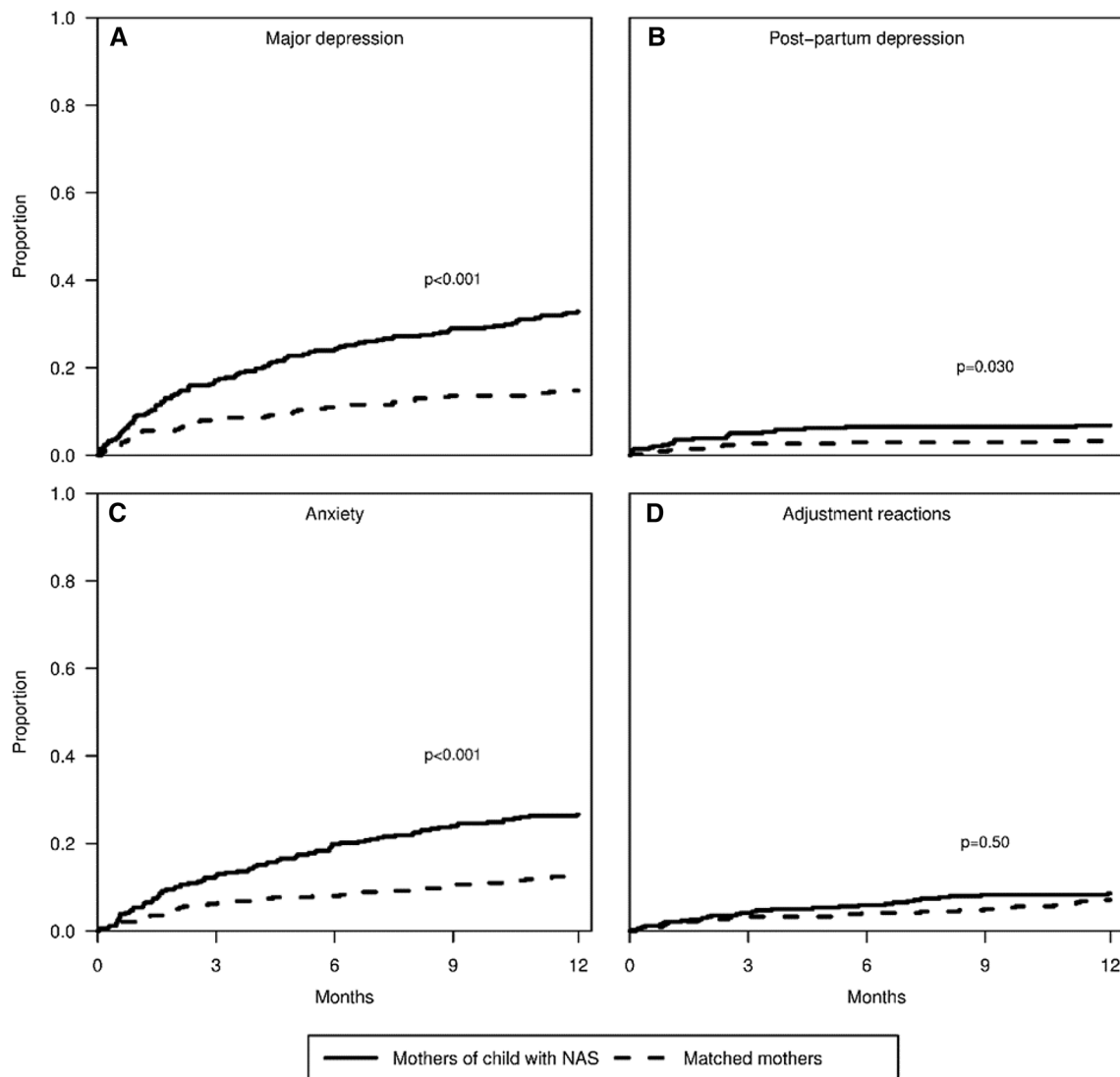


Fig. 1 Cumulative incidence curves of post-delivery mental health diagnoses for mothers of a child with neonatal abstinence syndrome (NAS) and matched controls for **a** major depression, **b** post-partum depression, **c** anxiety, and **d** adjustment reaction

Discussion

This retrospective, cohort study using a national sample of privately-insured individuals demonstrated significantly-increased incidences of depression, postpartum depression, and anxiety in the first 12 months postpartum in mothers of a child with NAS compared to mothers of a child without NAS who were similar with respect to key variables. The cumulative incidence of these mental health diagnoses increased significantly over time in mothers of an infant with a history of NAS compared to mothers of an infant without such a history.

Mental health and mood disorders are observed at high rates among pregnant women with substance use disorders and are associated with increased medical, social, and

psychological impairment (Benningfield et al. 2010; Kissin et al. 2001; Schempf and Strobino 2009; Smith et al. 2015). In one study, nearly two-thirds of opioid-dependent pregnant women affirmed the presence of symptoms that supported a diagnosis of a psychiatric disorder including anxiety, depression, and suicidal thoughts (Benningfield et al. 2010). The current study supports such findings, with a prenatal diagnosis of major depression noted in 22.5% of mothers with a history of substance use and anxiety diagnosed in 15.4% within the 9 months prior to delivery.

Mental health disorders are complex and caused by a mixture of biological, psychological and environmental factors. Life stress as a contributor to mental health disorders is a concept that has been studied for decades (Berkman 1971; Kraines 1964; Langner and Michael 1963). Our

Table 3 Subgroup analysis of 12-month post-delivery mental health diagnoses of mothers of infants with neonatal abstinence syndrome without serious medical diagnoses and matched controls

Variable	Mothers of child with NAS (N = 285)	Matched mothers (N = 285)	P value
Major depression	91 (32.2%)	39 (13.8%)	< 0.001
Postpartum depression	19 (6.7%)	7 (2.5%)	0.024
Anxiety	76 (26.9%)	34 (12.0%)	< 0.001
Adjustment reaction	24 (8.5%)	20 (7.1%)	0.481
PTSD	7 (2.5%)	5 (1.8%)	0.424
Suicidal ideation	2 (0.7%)	1 (0.4%)	0.571
Number of mental health diagnoses			< 0.001
0	148 (52.3%)	210 (74.2%)	
1	69 (24.4%)	48 (17.0%)	
2	51 (18.0%)	20 (7.1%)	
3	13 (4.6%)	3 (1.1%)	
4	1 (0.4%)	1 (0.4%)	
5	1 (0.4%)	1 (0.4%)	

NAS neonatal abstinence syndrome, PTSD post-traumatic stress disorder

findings suggest that mothers of a child with NAS may have innate difficulty in coping with this stress in the 1st year postpartum leading to a higher frequency of four distinct mood disorders. This noted difference may be due to a number of factors.

Women with substance use diagnoses are disproportionately affected by concurrent depressive and anxiety disorders and may be more likely to use drugs to manage a negative affect (McHugh et al. 2014). This difficulty in managing mood may have profound implications as women enter the postpartum period. Newborns with NAS are characteristically irritable and difficult to soothe (Hudak and Tan 2012; Kocherlakota 2014). They may exhibit symptoms of regurgitation and vomiting, poor feeding and loose stools. These displays of withdrawal require intense participation of the caretaker to effectively manage symptoms (Grossman et al. 2017, 2018). In moderate to severe cases, when symptoms of neonatal drug dependence do not respond to non-pharmacologic interventions, administration of medications such as opioids and barbiturates may be required to manage withdrawal, resulting in a lengthy NICU course (Corr and Hollenbeak 2017; Patrick et al. 2012; Tolia et al. 2015). For the predisposed mother with a history of substance use and possibly a psychiatric disorder, the culmination of these stressors may result in difficulty coping in this newly-created family unit. Indeed, pregnant women with substance use disorders who reported the presence of psychiatric symptoms were more likely to have deficits in family and social functioning as well as overall psychological functioning

(Benningfield et al. 2010), and it is reasonable to presume these deficits continue into the postnatal period.

The neurologic manifestations of NAS can extend well beyond discharge, and the ongoing exposure to an irritable, difficult-to-console infant may also begin to wear on the mother who may have a limited social support network (Sutter et al. 2017). Newborns exposed to opioids in utero are at increased risk for adverse cognitive, psychomotor, and behavioral outcomes as toddlers and preschoolers (Baldacchino et al. 2014, 2015; Hunt et al. 2008), and some of these difficulties may begin to emerge during the infant period, creating ongoing challenges for a mother who is likely continuing to manage her own mental health and substance use disorders. In addition, admission rates for children during the first 30 days to 5 years are higher for those with a history of NAS compared to unexposed controls suggesting that these children have persistent and lasting health disparities that may create additional stressors for the mother (Hwang et al. 2017; Patrick et al. 2015a; Witt et al. 2017). These various, aforementioned challenges encountered by the mother of an infant with a history of NAS may intensify symptoms of dysfunctional coping and lead to exacerbation of mental health disorders.

The possibility exists that these differences in coping may be unrelated to caring for a child with NAS. Simply having a child who was exposed to long-term prenatal opioids, in the absence of the development of NAS, has been shown to be associated with increases in depression, bipolar disorder, and schizophrenia in mothers with a substance use disorder compared to controls (Faherty et al. 2018). Alternatively, postnatal symptoms of withdrawal occur on a spectrum, and it is possible the infants in this cited study did not display severe enough symptoms to be diagnosed with NAS but did display some of the characteristic, ongoing irritability following hospital discharge, which may affect a susceptible mother.

The results of our study are concerning for a variety of reasons. Research demonstrates that children of mothers with a history of mental health illnesses are at increased risk of adverse health and psychological outcomes including inadequate parent-child bonding (Dietz et al. 2007) and child abuse and neglect (Brockington et al. 2011; Lewin and Abdrbo 2009; Mullick et al. 2001). In particular, the child of a parent with a mental health disorder may be exposed to emotional unavailability, anger, disturbed behaviors, parental preoccupation and deprivation (Brockington et al. 2011). Therefore, it is crucial that comprehensive programs that address the needs of the mother-infant dyad are put in place prior to birth hospitalization discharge. Support for mothers includes ensuring she is established with medication-replacement therapy; providing mental health support including substance use counseling; assigning a case manager to address issues

with housing and transportation as well as Women, Infants and Children (WIC) and Medicaid access; and establishing primary care for both mother and infant with provisions of parenting support (Sutter et al. 2017). Programs that embrace such a comprehensive approach have shown improved outcomes, including continued abstinence from substance use and increased frequency of mothers maintaining custody of their children (Buckley et al. 2013). In addition, integrated outpatient programs that care for these mothers and their offspring through the 1st years of the child's life lead to positive maternal and child health outcomes and hinder relapse in the mother (Ordean and Kahan 2011).

There are several limitations to this study. The use of a national database for study investigation relies on input of accurate ICD-9 codes. Incorrect coding can result in under- or over-reporting of a true diagnosis of NAS and improper categorization in this study. Moreover, diagnosing maternal substance use based on infant diagnosis of NAS allows for the potential to mislabel a woman with a substance use disorder as having none if her infant does not experience withdrawal. However, as this miscategorization would bias the study towards the null hypothesis, our findings remain concerning. This study is also limited by the fact that it does not investigate the type of maternal drug use (i.e. illicit substance use or medication-assisted therapy), whether the mother receives substance use or mental health counseling, whether she is on any psychotropic medications, whether she retained custody of her child, and what her social network and family support system resembles. All of these factors can have a profound effect on a mother's ability to cope with stress. Finally, due to the nature of the database used, this study only examined women covered by private insurance. We know that > 75% of children with NAS, beneficiaries of their mother's insurance, have Medicaid insurance coverage at the time of birth (Corr and Hollenbeak 2017; Patrick et al. 2012). Because Medicaid is a proxy for low socioeconomic status (Rosenbaum 2002), our findings are even more concerning as the affected mothers in our study, who presumably have greater access to resources and relative wealth than those with Medicaid coverage, have a significantly greater incidence of mental health diagnoses over the 1st year of their infant's life.

Despite these limitations, this study reveals additional concern for a vulnerable population working to maintain sobriety while taking on the challenges of parenting. Our study suggests that more intense mental health screening should be provided for mothers with substance use disorders, not only at the initial postpartum check, but at least through the 1st year after delivery.

Conclusion

Mothers of infants with NAS have a higher incidence of mental health diagnoses in the first 12 months postpartum compared to mothers of infants without NAS, and this incidence increases with time. For new mothers affected by substance use disorders, careful, repeated mental health screenings over the course of the 1st year postpartum may be beneficial to both the mother and her infant.

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