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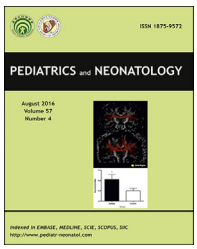

Original Article

Neonatal outcomes of preterm infants with in-utero exposure to drugs of substance use: US national data

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Key Words
hospitalization costs;
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outcomes;
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prenatal

Background: Infants exposed prenatally to drugs of substance use are at increased risk for seizures, strabismus, feeding difficulty, and neurodevelopmental delays. Exposed preterm infants may have additional morbidities related to prematurity. There is limited literature on national outcomes of preterm infants exposed to drugs of substance use. We aimed to evaluate the trends and neonatal outcomes of preterm infants born in the USA who were exposed in-utero to drugs of substance use.
Methods: Retrospective cohort study of preterm live born (<37 weeks gestation) exposed in-utero to opioids, hallucinogens, or cocaine in the Healthcare Cost and Utilization Project database from 2002 to 2017. Neonatal outcomes were identified using international classification of diseases 9&10 codes.
Results: Of the 54,469,720 live-born infants, 7.7% (4,194,816) were preterm, and 58 679 (1.4%) were exposed in-utero to maternal opioids/hallucinogens (n = 39,335) or cocaine (n = 19,344). There was a trend for increased exposure to opioids/hallucinogens (Z score = 76.14, $p < 0.001$) during the study period. Exposed preterm infants had significantly more neurological anomalies, intra-ventricular hemorrhage and periventricular leukomalacia ($p < 0.001$).
Conclusions: There was a trend for increased in-utero exposure to opioids and hallucinogens in the preterm infants in the USA. Exposed preterm infants had more neurological morbidities.

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1. Introduction

The rapid rise of substance use disorders has created an unprecedented public health crisis in the USA.[1] In the last two decades, increased incidence of substance use in women of reproductive years has exposed a greater number of fetuses to these drugs in-utero and consequently has resulted in higher incidence of neonatal abstinence syndrome (NAS).[2–6] During the same period, improving survival of premature infants has placed more preterm infants at risk for exposure.[3,4] Of note, the trend for increased in-utero exposure to drugs has been reported in term infants, but there is no specific study looking at the trends of exposure in the preterm population.[5]

Preterm infants are at a higher risk for sub-optimal neuro-developmental outcomes due to multiple perinatal and postnatal insults on their immature brain.[6,7] It is logical to speculate that in-utero exposure to substances used during pregnancy, illicit or prescribed, may enhance this risk on a developing brain. Associated exposure to nicotine and alcohol may also contribute to adverse outcomes in this high-risk population.

Using national database sets, previous studies on term infants have demonstrated an increase in the incidence of NAS and associated hospital costs for Medicaid insurance.[5,8] However, there is a significant knowledge gap about trends in drug exposure rates and their impact on neonatal outcomes in prematurity.

We aimed to describe the frequency trends and outcomes for a large cohort of preterm infants born in the USA who were exposed prenatally to drugs of use, using the Healthcare Cost and Utilization Project (HCUP) database. We hypothesized that in utero exposure of preterm infants to drugs of substance use would enhance the risk for adverse neonatal outcomes.

2. Methods

2.1. Data source and analysis

Agency for Healthcare Research and Quality produces de-identified HCUP data compiled from more than seven million cases from hospitals across the USA.[9] Among the hundreds of variables included for each patient, HCUP datasets include information about patient age, sex, race, admission and payment source, disposition at discharge, up to twenty-five different diagnoses, and up to fifteen different procedures. HCUP produces the National Inpatient Sample (NIS) dataset annually, which includes 20% of the HCUP samples. The pediatric version, KID, is produced every three years. The KID dataset was used for the years 2003, 2006, 2009, 2012, and 2015 in this analysis. NIS dataset was used for the years 2002, 2004, 2005, 2007, 2008, 2010, 2011, 2013, 2014, 2016 and 2017. Clinical diagnoses and procedures are coded using the International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9&10-CM). We combined data sets from the years 2002–2017 for the analysis in this study.

2.2. Study design and population

All live-born premature neonates born from 2002 to 2017 in the combined dataset were included. Live-born infants included in the study were identified by ICD-9 & 10 codes of V3x and Z38x. Gestational age (GA) $<$ 37 weeks was identified by the codes 765.21–765.28, P07.21–P07.26, and P07.31–P07.39. For in-utero exposure to opioids or hallucinogens (methamphetamine), we used the codes 760.72, 760.73 and P04.49. ICD codes 760.75 and P04.41 were used for cocaine exposure. Demographic characteristics of the infants like GA, birth weight (BW), race, sex, geographic region, length of stay, cost of hospitalization and type of insurance utilized were identified.

Infants were classified into three GA sub-groups $\leq$ 28 weeks, 29–32 weeks and 33–37 weeks. In these cohorts, the frequency trends for in-utero exposure to drugs in the study sample over the study period were assessed. The demographic characteristics and neonatal outcomes were compared between the infants who were exposed and not exposed in-utero to drugs of substance use. Congenital anomalies were compared under four major categories: neurological, cardiac, gastrointestinal and genitourinary systems. Neonatal morbidities like respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), seizures, hypotension, persistent pulmonary hypertension of newborn (PPHN), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), neonatal jaundice and infections were also identified using appropriate ICD-9 & 10 codes. 'Died during hospitalization' is a variable defined in the NIS dataset and was used to assess mortality.

2.3. Statistical analysis

Demographic characteristics of the study sample were produced using the frequency procedure. Cochran-Armitage trend test (Z scores) was used to assess for the frequency trends in the occurrence of opioids/hallucinogens and cocaine over the years of study. Group comparisons were done using Mann–Whitney U test for continuous variables and Chi-square/Fischer exact tests for categorical variables. P-values less than 0.05 were considered statistically significant. We used SPSS version 25 (Chicago, IL) for statistical analysis.

3. Results

A total of 54,469,719 live-born neonatal records were reviewed. Of them, 4,194,815 (7.7%) were preterm infants and 58 679 (1.4%) of these infants were exposed in-utero to maternal opioids, hallucinogens, or cocaine (Fig. 1). Among the preterm infants who were exposed, 8.6% developed NAS symptoms. There was a trend for increased frequency of exposure to opioids/hallucinogens (Z score = 76.14, $p < 0.001$) and decreased exposure to cocaine (Z score = 76.14, $p < 0.001$) over the years (Fig. 2). A higher number of moderate and late preterm infants were exposed

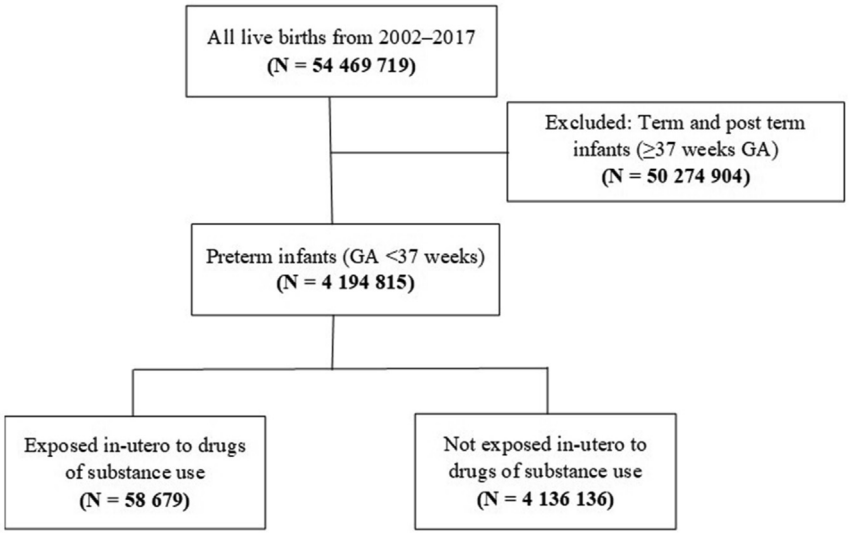

Figure 1 Study population flow chart.

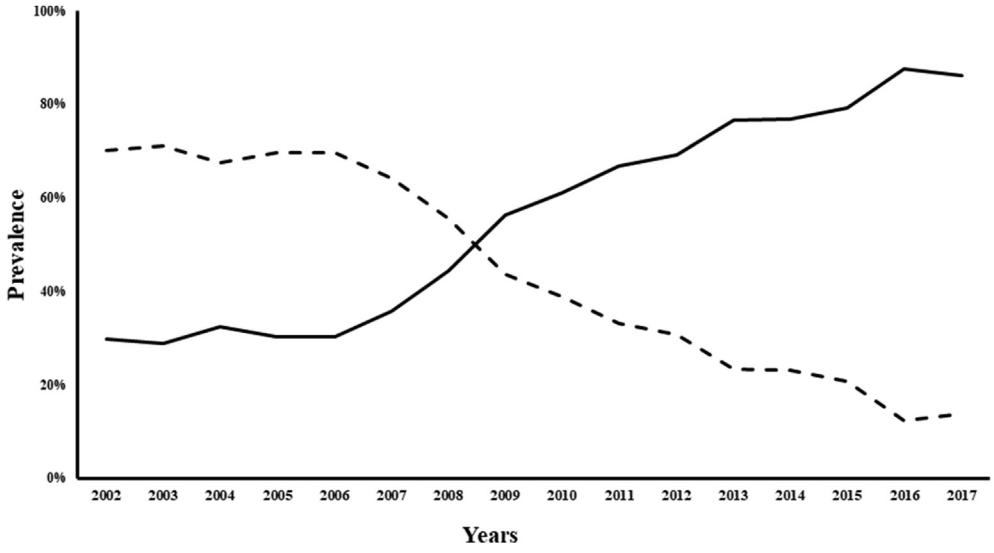

Figure 2 Frequency trends for the prevalence of in-utero exposure. Solid line indicates Opioid/Hallucinogen exposure; dotted line indicates Cocaine exposure. There is a statistically significant ($p < 0.001$) trend towards increased exposure to Opioid/Hallucinogens and statistically significant ($p < 0.001$) trend towards decreased exposure to Cocaine; p value calculated using Cochrane—Armitage test for trends.

to drugs of use (Fig. 3). The proportion of drug-exposed infants increased significantly with increasing gestational age ($p < 0.001$, Table 1). The drug exposure rates were [gestational age (percentage)] $\leq$ 24 weeks (0.54%); 25—26 weeks (1.23%); 27—28 weeks (1.41%); 29—30 weeks (1.57%); 31—32 weeks (1.71%); 33—34 weeks (1.65%) and 35—36 weeks (1.31%).

There was a disproportionately higher number of African-American infants in the exposed group (Table 1). Associated exposure to alcohol was higher in the drug exposed group (2.1% vs. 0.1%, $p < 0.001$). Preterm infants who were exposed had significantly longer duration of hospital stay (10 days [IQR 4—21] vs. 5 days [IQR 2—16], $p < 0.001$) and higher cost of hospital charges (33837$ [IQR 8288$—94195$] vs. 16271$ [IQR 3768$—68193$], $p < 0.001$). Exposed preterm infants had significantly higher rates of utilization of Medicaid insurance compared to the non-exposed infants (80.4% vs. 45.1%, $p < 0.001$).

Table 2 describes neonatal morbidities and mortality in this cohort. Exposed preterm infants were significantly smaller for gestational age (SGA) and had intrauterine growth restriction (IUGR) at birth. Neurological anomalies were significantly higher in exposed group (1.6% vs. 0.9%, $p < 0.001$). Preterm infants who were exposed had significantly higher RDS, IVH, PVL seizures, ROP, chorioamnionitis and sepsis ($p < 0.001$). However, they had significantly less BPD, hypotension, PPHN and jaundice. The overall mortality rate for the exposed infants was 1.1%. For exposed

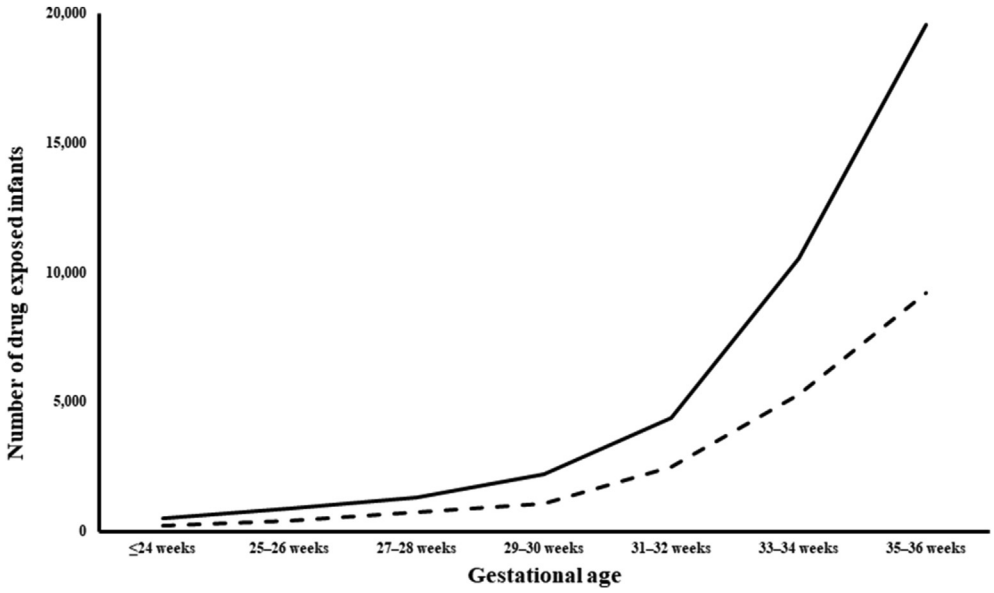

Figure 3 In-utero drug exposure by gestational age. Solid line indicates Opioid/Hallucinogen exposure; dotted line indicates Cocaine exposure. The proportion of drug-exposed infants increased significantly with increasing gestational age. ($p < 0.001$).

infants who survived greater than three days, the mortality rate was 0.5%. On subgroup analysis, there was no significant difference in mortality rate after excluding infants who died after three days across GA 29—32 weeks and 33—37 weeks. Subgroup GA<28 weeks had decreased mortality in the exposed group.

4. Discussion

This study on a large cohort of preterm infants born in the USA demonstrated an increasing trend for in-utero drug exposure over the 16 years of the study period. Opioid/hallucinogen exposure increased significantly in the years 2008—2017. In-utero exposure to drugs is disproportionately higher in African-American infants. Exposed preterm infants were associated with increased duration and costs of hospitalization. Medicaid insurance utilization was higher among these infants. They had significantly more neurological anomalies, IVH, PVL, seizures, RDS, ROP, and sepsis. Mortality rates after three days were not significantly different in the moderate and late preterm infants.

Previous studies on outcomes for in-utero drug-exposed infants have focused mainly on term neonates.[8,10] However, preterm infants are at substantial risk for adverse neurodevelopmental outcomes due to neurological immaturity.[11] Outcomes for preterm infants exposed to drugs have not been well-described outside of single-center studies.[12]

This study demonstrated that there is a trend for increased exposure to drugs of use for opioids and hallucinogens. Over the years, opioid use has increased drastically, surpassing cocaine as the most common drug of use. This rapid rise has been fueled by the opioid epidemic of this decade which has resulted in more fetuses being exposed to them.[13] Cocaine is now the second most common drug of use in this population. Opiates cross the placenta readily and achieve equilibrium between the mother and fetus. Opiates have been shown to decrease brain growth and neuronal development in animal studies; however, results regarding their effects on opioid receptors and neurotransmitters have been mixed in human studies.[14] Cocaine interferes with neurotrophic role of the monoaminergic transmitters during brain development. This can significantly affect cortical neuronal development before homeostatic regulatory mechanisms are fully developed, and it may lead to morphologic abnormalities in several brain structures, including the frontal cingulate cortex. Methamphetamines also alter monoaminergic neurotransmitter systems in the developing fetal brain and brain morphogenesis.[14]

In this study, disproportionately more African-American preterm infants were exposed to in-utero drugs of substance use. There is evidence to suggest that there is a racial difference in access to prenatal care and substance use programs for African-American and Hispanic women.[15,16] Racial disparity, lower socioeconomic status, and level of parental education are all well-recognized risk factors for adverse neurodevelopmental outcomes in preterm infants.[17] Exposure to drugs would put them at the highest risk for these adverse outcomes.

Although some studies have shown that drug-exposed preterm infants have less severe withdrawal symptoms and need for treatment for NAS,[12] the higher morbidity might contribute to their longer hospitalization and added additional health care costs. Not only was the duration of hospitalization increased in our study, but the economic burden also doubled in the exposed group. A retrospective study estimated that annual costs of NAS newborn admissions in the United States increased from $60 million in 2003 to around $315 million in 2012.[8] The study further demonstrated that NAS was more common in infants born in lower income families and that around 77% of the patients diagnosed with NAS were insured by Medicaid.[8] Another study that used national data from 2004 to 2014 found that the incidence of NAS increased five-fold in infants covered

Table 1 Characteristics of the study population.

	Exposed to drugs in-utero (N = 58 679)	Not exposed to drugs in-utero (N = 4 136 136)	*p*-value
Gestational age			<0.001
≤24 completed weeks	706 (1.2)	129,714 (3.1)	
25–26 completed weeks	1285 (2.2)	104,457 (2.5)	
27–28 completed weeks	2019 (3.4)	143,581 (3.5)	
29–30 completed weeks	3286 (5.6)	209,579 (5.1)	
31–32 completed weeks	6843 (11.7)	400,178 (9.7)	
33–34 completed weeks	15,790 (26.9)	953,458 (23.1)	
35–36 completed weeks	28,750 (49.0)	2,195,170 (53.1)	
Birth weight			<0.001
<1500 g	7998 (13.6)	630,194 (15.2)	
1500–2500 g	41,171 (70.2)	2,328,403 (56.3)	
>2500 g	9510 (16.2)	1,177,540 (28.5)	
Sex			<0.001
Male	30,369 (51.8)	2,190,652 (53.0)	
Female	28,281 (48.2)	1,942,988 (47.0)	
Race			<0.001
Caucasian	25,648 (43.7)	1,708,269 (41.3)	
African-American	14,337 (24.4)	623,168 (15.1)	
Hispanic	6500 (11.1)	592,934 (14.3)	
Asian or Pacific Islander	513 (0.9)	165,780 (4.0)	
Native American	810 (1.4)	28,319 (0.7)	
Other	2020 (3.4)	200,407 (4.8)	
Unclassified	8851 (15.1)	817,260 (19.8)	
Exposure to Alcohol	1236 (2.1)	2175 (0.1)	<0.001
Duration of Hospitalization (days): Median (IQR)*	10 (4–21)	5 (2–16)	<0.001
Cost of hospitalization (dollars): Median (IQR)*	33,837 (8288–94 195)	16,271 (3768–68 193)	<0.001
Disposition of patient			<0.001
Routine discharge	46,293 (79.0)	3,257,952 (78.7)	
Transfer to Short-term hospital	5043 (8.6)	366,256 (8.9)	
Home Health Care	5284 (9.0)	332,396 (8.0)	
Primary payer			<0.001
Medicaid	47,104 (80.4)	1,864,007 (45.1)	
Private insurance	5193 (8.9)	1,965,344 (47.6)	
Self-pay	4446 (7.6)	153,704 (3.7)	
Other	1834 (3.1)	145,734 (3.5)	
Region			<0.001
Northeast	7294 (12.4)	584,662 (14.1)	
Midwest	12,374 (21.1)	865,327 (20.9)	
South	20,059 (34.2)	1,241,916 (30.0)	
West	14,161 (24.1)	903,656 (21.8)	
Unclassified	4792 (8.2)	540,575 (13.1)	

Data are expressed in frequency (%); Chi-square or Fisher's exact tests were used for analysis except for data * that is expressed in median (interquartile range) for which Mann–Whitney U test was used.

under Medicaid.[5] Our study also found that there was an increased use of public insurance in infants exposed to drugs of substance use. This reiterates that the maternal population in lower socio-economic status is more prone for substance use and must be targeted for treatment and counseling during prenatal care.

In-utero growth parameters and infant size at birth are important determinants of outcomes for neonates. The study demonstrated higher rates of IUGR (3.9% vs. 3.3%) and SGA (5.2% vs. 3.8%) in the exposed preterm infants. In a study on term infants, cocaine exposure was estimated to be associated with a decrease in birth weight, length and, most importantly, head circumference.[18] Poly-drug use in mothers has also been shown to affect growth parameters in full-term gestation pregnancy. Infants born to mothers with any history of cocaine, opiate, alcohol, tobacco, or marijuana use during pregnancy were significantly smaller at birth.[19] Maternal smoking, which is an independent risk factor, might be also contribute to growth restriction in these drug-exposed infants.

In our study, there was a higher prevalence of neurological anomalies in the exposed group. Fetal teratogenicity from exposure to drugs has been difficult to elicit. Compared to fetal alcohol syndrome, no characteristic

Table 2 Neonatal outcomes in the study population.

	Exposed to drugs in-utero (n = 58 679) N (%)	Not exposed to drugs in-utero (n = 4 136 136) N (%)	OR (95% CI)	*p*-value
Size of the infant:				
SGA	3916 (6.7)	207,270 (5.0)	1.36 (1.31–1.40)	<0.001
LGA	490 (0.8)	64,528 (1.6)	0.53 (0.49–0.58)	<0.001
IUGR	1495 (2.5)	34,935 (0.8)	3.07 (2.91–3.23)	<0.001
Congenital anomalies:				
Nervous system	915 (1.6)	38,499 (0.9)	1.69 (1.58–1.80)	<0.001
Cardiac system	5709 (9.7)	402 463 (9.7)	1.00 (0.97–1.03)	0.991
Digestive system	709 (1.2)	56,389 (1.4)	0.89 (0.82–0.95)	0.001
Genitourinary system	501 (0.9)	39,530 (1.0)	0.89 (0.82–0.98)	0.012
Neonatal Morbidities:				
Respiratory:				
Respiratory distress syndrome	14,143 (24.1)	932,627 (22.5)	1.09 (1.07–1.11)	<0.001
Bronchopulmonary dysplasia	942 (1.6)	92,346 (2.2)	0.71 (0.67–0.76)	<0.001
Neurology:				
Intraventricular hemorrhage	2024 (3.4)	130,480 (3.2)	1.10 (1.05–1.15)	<0.001
Periventricular leukomalacia	170 (0.3)	9776 (0.2)	1.22 (1.05–1.43)	0.009
Seizures	19 (0)	747 (0)	1.79 (1.14–2.83)	0.019
Cardiac:				
Hypotension	949 (1.6)	81,374 (2.0)	0.82 (0.77–0.87)	<0.001
PPHN	315 (0.5)	29,997 (0.7)	0.74 (0.66–0.83)	<0.001
Infections:				
Chorioamnionitis	680 (1.2)	24,586 (0.6)	1.96 (1.82–2.12)	<0.001
Sepsis	5024 (8.6)	251,047 (6.1)	1.45 (1.41–1.49)	<0.001
Meningitis	163 (0.3)	7286 (0.2)	1.58 (1.35–1.84)	<0.001
Necrotizing enterocolitis	625 (1.1)	43,341 (1.0)	1.02 (0.94–1.10)	0.685
Retinopathy of prematurity	1696 (2.9)	108,475 (2.6)	1.11 (1.05–1.16)	<0.001
Hemolytic jaundice and perinatal jaundice	30,081 (51.3)	2,220,660 (53.7)	0.91 (0.89–0.92)	<0.001
Mortality	642 (1.1)	124,835 (3.0)	0.36 (0.33–0.39)	<0.001
Mortality after excluding infants died in the first 3 days of life				
≤28 completed weeks	189 (5.0)	18,821 (6.4)	0.77 (0.66–0.89)	<0.001
29–32 completed weeks	40 (0.4)	3067 (0.5)	0.78 (0.57–1.07)	0.140
33–36 completed weeks	40 (0.1)	2808 (0.1)	1.01 (0.74–1.38)	0.947

Data are expressed in frequency (%); Chi-square or Fisher's exact tests were used for analysis.

pattern of malformation has been described for these drug-exposed infants. There are case reports suggesting limb reduction defects associated with cocaine exposure.[20] However, a single-center study on prenatally identified cocaine users did not show a difference in the number or type of congenital anomalies.[10] Animal and human studies have suggested an association with opioid exposure with neural tube defects, oral cleft, and atrial or ventricular septal defect.[21,22] Cocaine exposure to developing nervous system might result in permanent changes in brain structure and function and produce altered responsiveness to environmental or pharmacologic challenges later.[23] However, association with characteristic anomalies with either opioids or cocaine is lacking, which is possibly due to confounders like the use of additional drugs, alcohol, and the small sample size of studies.

Preterm infants have been described as being at lower risk of drug withdrawal symptoms with a less severe and shorter course of stay. A study on infants born at less than 35 weeks' gestation whose mothers received methadone maintenance had significantly lower total abstinence scores than did term infants of mothers receiving similar methadone dosages.[24] Lower gestational age has correlated with a lower risk of neonatal withdrawal.[25] Similar to previous studies, only 8.6% of exposed preterm infants were diagnosed with NAS. The apparent decreased severity of signs in preterm infants may relate to developmental immaturity of the CNS that minimizes expression of motor signs, differences in total drug exposure, or lower fat depots of drugs. Alternatively, the clinical evaluation of the severity of abstinence may be more difficult in preterm infants because scoring tools to describe withdrawal were largely developed in term or late preterm infants.[26]

IVH and PVL are major neurological risk factors for adverse long-term neurodevelopmental outcomes in preterm infants. In our study, the exposed preterm infants had significantly more IVH, PVL, and seizures. In the setting of prematurity, neonatal seizure is also an independent risk factor for unfavorable outcomes, including cerebral palsy, epilepsy, and intellectual disability, and microcephaly.[27,28] Need for long-term neuro-monitoring and anti-epileptic medications will add to the neuro-morbidities and health

care costs. Some studies on term NAS infants have also shown that they are at risk for strabismus in childhood[29,30] and behavioral issues later in life.[31]

In our study, a higher number of infants were diagnosed with RDS in the exposed group. Previous studies have also reported higher RDS in the drug-exposed infants.[32] We should interpret such difference (24% vs. 22%) with caution as, although statistically significant ($p < 0.001$), clinically it may not be impactful. Possible explanations could include lack of adequate prenatal care, less antenatal steroid administration, increased risk of preterm delivery, suboptimal monitoring, and higher risk of chorioamnionitis in these mothers. Contrasting results from another study that included small number of infants born between 32 and 37 weeks' gestation showed the risk of RDS may be less in preterm infants born to heroin-addicted mothers.[33] The BPD rates were lower in exposed infants despite high RDS incidence in this study. A uniform definition of BPD is lacking and variation in coding practices might have contributed to this finding. ICD diagnosis of BPD should include either oxygen requirement at 36 weeks' GA or use other standardized definitions.[34,35] This data set did not have sufficient information to delineate the association. The lower rates of PPHN and hypotension in the exposed infants are interesting. The regulatory problems of prenatally drug-exposed infants are manifested in dysfunctional vagal regulation of autonomic processes.[36] Neonatal abstinence syndrome is associated with agitation and hypertension in the term infants during the withdrawal phase. It is also plausible that the drug exposure could up-regulate the end organ secretion of nitric oxide. Opioids are also used during the management of PPHN.

In our study, sepsis and meningitis were more prevalent in the exposed preterm infants. In addition to the higher susceptibility to infection from being premature, lack of prenatal care, decreased intra-partum prophylaxis for group B streptococcus, delivery complications, and prolonged hospital course are all contributors to the higher infection rates noted in this group. Similarly higher sepsis rates have also been reported in drug-exposed infants.[32] Complications from infections are a major burden for increased mortality and morbidity in preterm infants and contribute to adverse long-term neurodevelopmental outcomes.[37]

Neonatal jaundice prevalence was lower in the exposed preterm infants. Potential mechanisms may include accelerated liver maturation due to in-utero stress and higher SGA status in this group. This interesting finding may need to be explored further with prospective studies.

Mortality rate was lower in the exposed infants $\leq$28 weeks' gestation after excluding infants who died $<$3 days of life. There is a higher reported incidence of stillborn infants for mothers with prenatal exposure to drugs.[38] The current data set based on infants' ICD diagnoses does not include stillborn data, which might be missing for this gestational age group.

5. Strengths and limitations

This large study, involving more than 7 million infants, has the strength of being inclusive to the entire nation without selection bias and having the ability to follow trends over years. To the best of our knowledge, this is the only study to report outcomes of premature infants exposed in-utero to drugs of substance use. However, it has some limitations. While short-term outcomes are important, there is no data available on long-term neurodevelopmental outcomes for these infants from the database. Classification bias is inherent to using administrative databases like HCUP, which is compiled from hospital discharge information using ICD 9 & 10 diagnostic codes. There could also be bias from underreporting, changes in policy, practices, or education during this wide time frame. The dose—response relationship for the effects of drugs of substance use is hard to establish in this database. Such a relationship was not reported in maternal opioid use in previous studies on mothers in treatment programs.[39] Despite these limitations, there is a clear trend in increased exposure to opioids/hallucinogens and increased neurological morbidities of the preterm infants during the study period.

In conclusion, there is a trend towards an increased in-utero exposure to opioids and hallucinogens and a decrease in cocaine exposure in preterm infants in the USA during the study period. In-utero exposure to drugs is disproportionately higher in African-American infants. Moderate and late preterm infants, who constituted most of the exposed infants, had higher cost and duration of hospitalization with more utilization of public insurance. These infants had significantly more neurological, respiratory and infectious morbidities. Improved understanding of the adverse outcomes for preterm infants with in-utero exposure to drugs of use will help in the identification of risk factors to mitigate long-term adverse outcomes. Future long-term prospective studies on fetal drug exposure and neonatal abstinence syndrome should also include preterm infants with the ultimate goal of optimizing their health and neurodevelopmental outcomes.

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Authors have no financial relationships relevant to this article to disclose.

Data availability

The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest to disclose.

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