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Original Article

Pregnancy outcome among women with drug dependence: A population-based cohort study of 14 million births

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ABSTRACT

Objective: Drug dependence is on the rise worldwide. The purpose of this study is to examine the association between drug dependency in pregnancy (DDP) and maternal and newborn outcomes.
Methods: We carried out a population-based retrospective cohort study evaluating DDP using the Healthcare Cost and Utilization Project Nationwide Inpatient Sample from 1999 to 2014. DDP was identified using ICD-9 coding. The associations between DDP and maternal and newborn outcomes were estimated using multivariate logistic regression analyses to estimate adjusted odds ratios and 95 % confidence intervals.
Results: Among 14,513,587 deliveries, 50,570 were to mothers with DDP for an overall prevalence of 35 cases/10,000 deliveries. The rate of pregnancies to drug-dependent women increased during the 15-year study period, from approximately 25/10,000 in 1999 to 69/10,000 in 2014. Women with DDP were younger in age, users of tobacco, and in lower income quartiles with more pre-existing health conditions, such as diabetes and hypertension. DDP was associated with greater risk of venous thromboembolism (OR 1.60; 95 % CI, 1.45–1.76), sepsis (OR 2.94; 95 % CI, 2.48–3.49), and maternal death (OR 2.77; 95 % CI, 1.88–4.08). Neonates born to mothers with drug dependence were at higher risk of prematurity (OR 1.37; 95 % CI, 1.33–1.41), intrauterine growth restriction (OR 1.60; 95 % CI, 1.54–1.67), and intrauterine fetal death (OR 1.27; 95 % CI, 1.16–1.40).
Conclusion: DDP is increasing in frequency and it is associated with maternal and newborn deaths and adverse events. Further research and public health initiatives should be undertaken to address prevention, screening, and treatment.

Introduction

In the United States (US), substance abuse in women is most prevalent during the reproductive years, particularly between 18 and 29 years of age [1]. In fact, an estimated 5% of women have reported to using illicit drugs while pregnant [2]. Alcohol is the most predominantly used drug during pregnancy, followed in prevalence by nicotine, marijuana and cocaine [3,4], with poly-substance use being common [3,5]. Drug use in pregnancy is on the rise and it will likely continue to grow in the future. For example, between 2000 and 2009, a five-fold increase in opiate use in pregnancy was observed in the US [6,7]. Likewise, it is predicted that the use of marijuana will increase substantially in the next few years, given the growing trend of its legalization in many states [8].

Drug use in pregnancy is a major obstetrical and public health problem as it can have deleterious effects on the health of both the mother and her developing fetus. Several studies have found various illicit drugs to be associated with adverse obstetrical and perinatal outcomes, such as preterm birth [9,10], small for gestational age [9,11], low birth weight [9,11–13], placental abruption [10,14], and intrauterine fetal death [10]. However, little information is available on the effect of, specifically, drug dependence on pregnancy complications.

Drug dependence refers to a compulsive and continuous consumption of medicinally active substance(s), which has led to a physiological need for the substance(s) (15). Further, people who are drug dependent often require a higher dose of substance use, due to the diminished effects of the substance(s) in maintaining their physical, emotional and psychological effects [16]. Therefore, drug dependence is often associated with more severe drug-related manifestation. Our study objective is to

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evaluate the association between drug-dependency in pregnancy (DDP) and obstetrical and neonatal outcomes.

Materials and methods

We conducted a retrospective population-based cohort study composed of 14 million delivery admissions in the United States that resulted in either a delivery or a maternal death between 1999–2014 in the Healthcare Cost and Utilization Project, Nationwide Inpatient Sample (HCUP-NIS) [17]. In brief, the HCUP-NIS is a healthcare database consisting of upwards of 7 million inpatient stays occurring annually in the United States. It includes discharges from community hospitals in the United States. This data allows for the estimation of nationally applicable rates of inpatient outcomes, utilization, charges, and quality [18]. Using structured quality control procedures, HCUP regularly examines the NIS database for quality, validity, internal consistency, and consistency with established norms [19].

The study cohort was created by using the following International Classification of Diseases, ninth edition, Clinical Modification (ICD-9CM) procedural and diagnostic codes to identify all delivery-related discharges between 1999 and 2014: 72.x, 73.x, 74.0–74.99 or diagnosis 650.xx, 677.xx, or 651.xx to 676.xx where the fifth digit is 0, 1 or 2. Of note, only delivery-related codes were used so that patients who had multiple hospital admissions for a given pregnancy would only be included once for that pregnancy. Subsequently, we defined the women with DDP group using the ICD-9CM code 304.x. The list of drugs includes opioids, sedatives, hypnotics, anxiolytics, cocaine, cannabis, amphetamine, psychostimulants, hallucinogens, and other specified and unspecified drugs. The remaining pregnant women who delivered or were deceased composed the comparison group. The HCUP-NIS and ICD-9CM codes were used to identify the following maternal demographic characteristics: age, race, median household income quartile, insurance type, hospital location/teaching status, smoking status, weight, pre-existing diabetes, hypertension, previous cesarean section, and multiparity. The maternal outcomes examined included preeclampsia, gestational diabetes, antepartum hemorrhage, preterm labor, preterm premature rupture of membranes (PPROM), chorioamnionitis, mode of delivery, postpartum hemorrhage, maternal death, postpartum depression, hospital length of stay, sepsis, venous thromboembolism (VTE), and liver disorders. Neonatal outcomes of interest were congenital malformation, preterm birth, intrauterine growth restriction (IUGR), and intrauterine fetal death (IUFD).

Three sets of analyses were done in this study. First, we examined the prevalence of DDP during the study period. We further stratified the prevalence in three different age groups (less than 25 years old, 25−34 years old and older than 34 years old). Second, we compared the demographic and clinical characteristics of women with DDP to women without DDP. Third, separate multivariate logistic regression models were used to study the association between DDP and each maternal and neonatal obstetrical outcome through the estimation of odd ratios (OR) and 95 % confidence intervals (CI). Each regression model was adjusted for the potential confounding effects of the maternal baseline characteristics shown in Table 1. For instances where data were missing for variables, they were coded as a missing category and included in the analyses.

SAS Enterprise Guide software (version 6.1) was used for all analyses. P values < 0.05 were considered to be statistically significant. According to the Tri-Council Policy statement (2010), this study is exempt from institutional review board approval, as it is based solely on publicly available data.

Results

Between 1999 and 2014, a total of 14,513,587 deliveries were recorded. Among these, 50,570 (0.35 %) deliveries were to women with DDP, which represent a prevalence of 35 cases per 10,000

Table 1
Baseline Characteristics by Drug Dependence Group.

Characteristic		No Drug Dependence N = 14,463,017 (%)	Drug Dependence N = 50,570 (%)	P-Value (Chi-Sq)
Age	<25	34.63	29.27	<.0001
	25−34	51.00	56.96	
	35+	14.37	13.77	
Race	Caucasian	41.93	55.17	<.0001
	African American	11.51	13.66	
	Hispanic	18.23	8.31	
	Other	8.18	3.30	
	Missing	20.15	19.56	
Income Quartile	Q1	20.34	30.36	<.0001
	Q2	18.53	21.38	
	Q3	17.90	17.92	
	Q4	16.63	10.95	
	Missing	26.60	19.39	
Insurance Type	Medicare	0.61	3.41	<.0001
	Medicaid	40.95	71.77	
	Private	51.99	14.62	
	Other	6.24	9.97	
	Missing	0.21	0.23	
Hospital Location/Teaching	Rural	11.60	9.77	<.0001
	Urban Non-Teaching	41.15	28.62	
	Urban Teaching	46.89	60.99	
	Missing	0.37	0.62	
Smoker		5.04	41.34	<.0001
Obesity	Obese	1.65	1.81	<0.01
	Morbidly obese	0.92	0.83	
	Neither	97.43	97.43	
Pre-existing diabetes		1.17	1.63	<.0001
Hypertension		0.80	1.25	<.0001
Previous Cesarean section		14.03	12.93	<.0001
Multiparity		0.34	0.24	<0.001

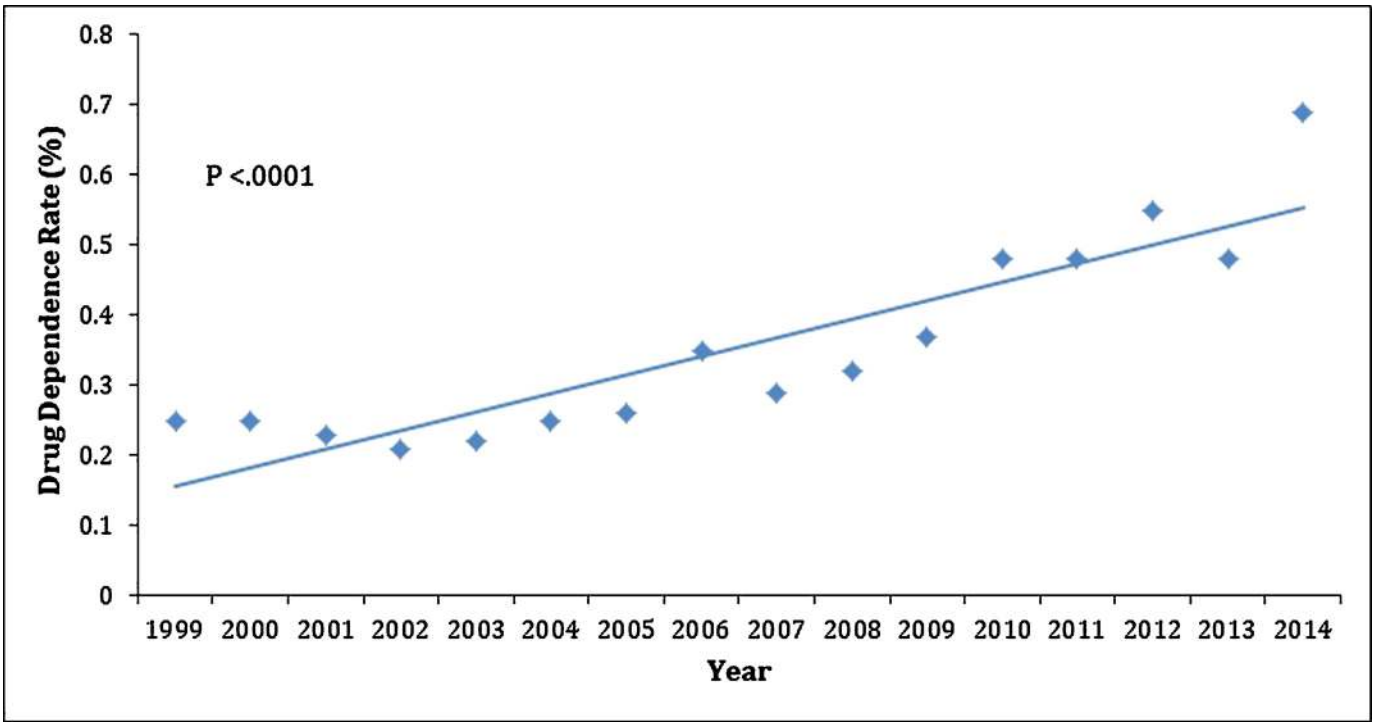

Fig. 1. Rate of drug dependence among pregnant women who gave birth between 1999 and 2014.

deliveries. More importantly, and as shown in Fig. 1, the percentage of deliveries with mention of DDP increased almost three-fold from 25 admissions per 10,000 deliveries in 1999 to 69 in 2014. Among women with DDP, those between the ages of 25–34 were the predominant group during the study period (Fig. 2). This age group also experienced the steepest growth in terms of pregnancies over the study, rising from a rate of 15 per 10,000 deliveries in 1999 to almost 45 in 2014.

The baseline maternal demographic and clinical characteristics of the cohort are displayed in Table 1. Women with DDP were more likely to be between the ages of 25 and 34, belong to a lower income quartile and possess Medicaid insurance. They were less likely to be of Hispanic ethnicity. In addition, women with DDP more commonly had pre-existing diabetes mellitus, obesity and hypertension. They were also more likely to report smoking as compared to women without DDP.

The frequency of specific drug dependence is listed in Table 2. The majority of women with DDP were dependent on opioids, followed by cocaine and cannabis. Many women with DDP were dependent on multiple drugs.

Tables 3 and 4 show the association between drug dependence and maternal and neonatal outcomes, respectively. We found a significant increase in both maternal and fetal mortality amongst women with DDP compared with their non-DDP cohort counterparts. Women with DDP were also found to have higher rates of pregnancy-related complications, including preterm premature rupture of membranes (PPROM), preterm labor, hemorrhage, sepsis, liver disorder and venous thromboembolism (VTE). Postnatally, women with DDP were more likely to have postpartum depression (PPD) and stayed in hospital for a longer period of time, compared with women without DDP. Newborns of women with DDP were at greater risk for intrauterine growth restriction (IUGR) and preterm birth. Women with DDP were found to be less likely to have preeclampsia, gestational diabetes (GDM), postpartum hemorrhage and chorioamnionitis. They also had lower rates of requiring operative deliveries.

Discussion

With the rising trend of drug use worldwide, especially opioid and cannabis use, we sought to understand the maternal and neonatal outcomes among women with DDP. Our large population-based administrative database from the United States showed an increase in prevalence of DDP over the 15-year period,

Table 2
Frequency of specific drug dependence among pregnant women (N = 50,570).

Drug name	Number of pregnant women with drug dependence	Percentage of drug dependence
Opioids	33,285	65.82
Cocaine	10,539	20.84
Cannabis	7244	14.32
Amphetamine	3327	6.58
Barbiturates	1832	3.62
Hallucinogens	48	0.09
Antidepressants	10	0.02
Multiple drugs (>1)	8244	16.30

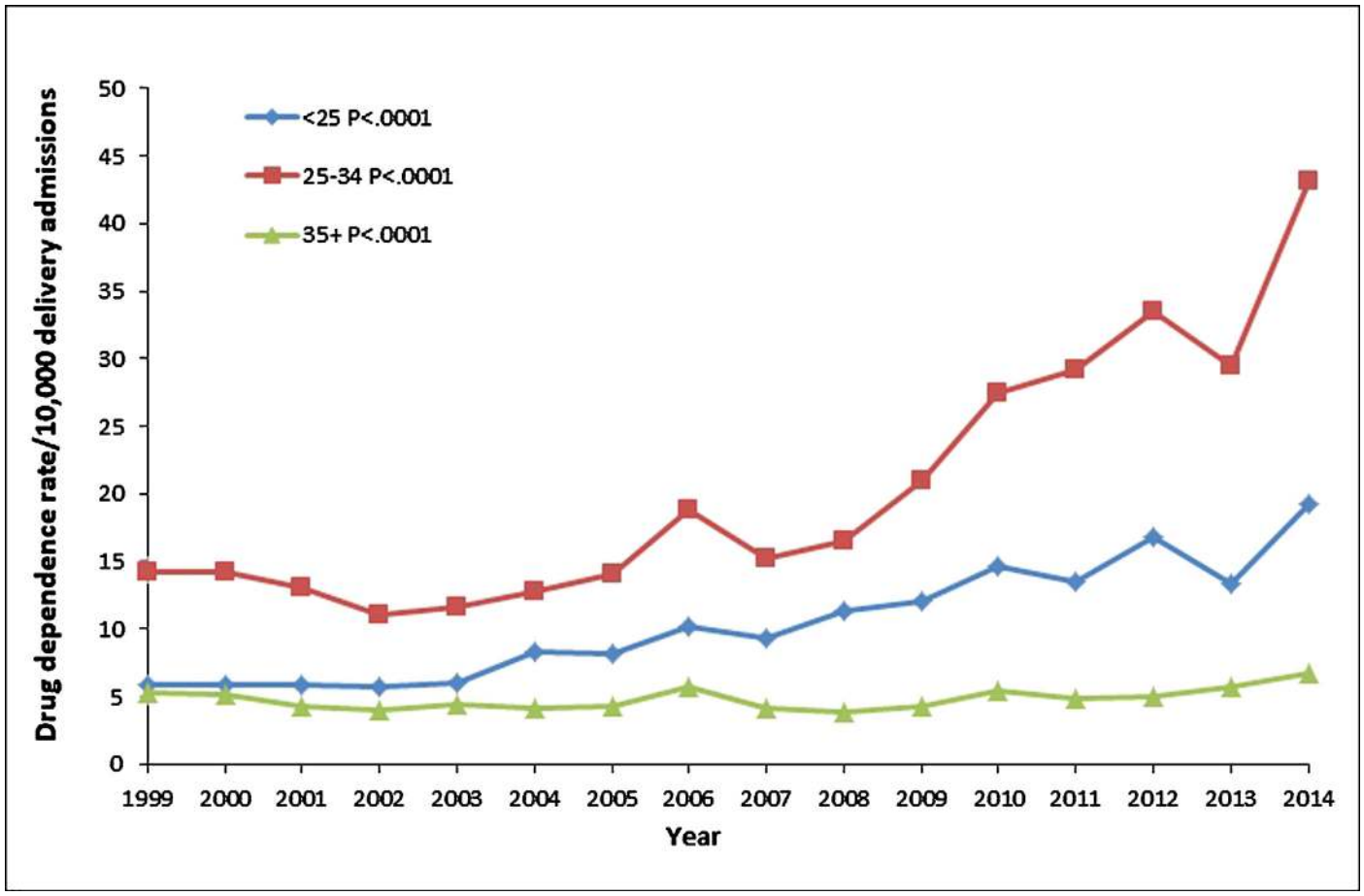

Fig. 2. Rate of drug dependence, by age, among pregnant women who gave birth between 1999 and 2014.

Table 3
Maternal Outcomes by Drug Dependence Group.

Outcomes	No Drug Dependence N = 14,463,017 (%)	Drug Dependence N = 50,570 (%)	Crude OR (95 % CI)	Adjusted OR* (95% CI)	Adjusted* P-Value
Antepartum					
Preeclampsia	3.93	3.02	0.76 (0.72–0.80)	0.71 (0.67–0.75)	<.0001
Gestational diabetes	5.17	1.95	0.37 (0.34–0.39)	0.33 (0.31–0.36)	<.0001
Antepartum hemorrhage	1.69	3.32	2.00 (1.91–2.10)	1.50 (1.43–1.57)	<.0001
Intrapartum					
Preterm Labor	2.00	2.43	1.22 (1.15–1.29)	1.08 (1.02–1.14)	0.01
PPROM	0.56	0.82	1.48 (1.34–1.63)	1.15 (1.04–1.26)	0.01
Chorioamnionitis	1.65	1.20	0.72 (0.67–0.78)	0.73 (0.67–0.79)	<.0001
Mode of Delivery:					
Spontaneous vaginal delivery	66.91	76.07	1.0 (Ref)	1.0 (Ref)	
Cesarean section	27.47	21.24	0.68 (0.67–0.70)	0.69 (0.68–0.71)	<.0001
Forceps vaginal delivery	1.12	0.50	0.40 (0.35–0.45)	0.51 (0.45–0.57)	<.0001
Vacuum vaginal delivery	4.50	2.18	0.43 (0.40–0.45)	0.56 (0.53–0.60)	<.0001
Postpartum					
Postpartum hemorrhage	2.59	2.11	0.81 (0.76–0.86)	0.80 (0.75–0.85)	<.0001
Postpartum depression	0.14	1.94	13.68 (12.82–14.60)	4.63 (4.33–4.96)	<.0001
Length of Stay					
0–2 days	60.04	44.23	1.0 (Ref)	1.0 (Ref)	–
3–6 days	37.92	43.70	1.56 (1.54–1.59)	1.65 (1.62–1.68)	<.0001
≥7 days	2.04	12.07	8.01 (7.79–8.24)	6.14 (5.95–6.33)	<.0001
Other Outcomes					
Sepsis	0.06	0.28	4.90 (4.16–5.78)	2.94 (2.48–3.49)	<.0001
VTE	0.31	0.84	2.68 (2.44–2.95)	1.60 (1.45–1.76)	<.0001
Liver disorder	0.17	2.31	14.21 (13.39–15.08)	8.03 (7.54–8.56)	<.0001
Maternal Death	0.01	0.05	4.18 (2.86–6.11)	2.77 (1.88–4.08)	<.0001

Abbreviations: PPROM, preterm premature rupture of membranes; VTE, venous thromboembolism.
* All models are adjusted for the variables shown in Table 1.

Table 4
Neonatal Outcomes by Drug Dependence Group.

Outcomes	No Drug Dependence N = 14,463,017 (%)	Drug Dependence N = 50,570 (%)	Crude OR (95 % CI)	Adjusted OR* (95% CI)	Adjusted* P-Value
Congenital malformation	0.43	0.57	1.33 (1.19–1.50)	1.01 (0.90–1.14)	-NS
Preterm birth	6.52	10.56	1.69 (1.65–1.74)	1.37 (1.33–1.41)	<.0001
IUGR	1.87	4.56	2.50 (2.40–2.61)	1.60 (1.54–1.67)	<.0001
IUFD	0.58	0.89	1.53 (1.40–1.68)	1.27 (1.16–1.40)	<.0001

Abbreviations: IUGR, Intrauterine growth restriction; IUFD, Intrauterine fetal death; NS, not statistically signficant.
* Adjusted for variables shown in Table 1.

especially in the last five years. In addition, the steepest growth in DDP was among women of ages 25–34, with a near three-fold increase from 2007 to 2014. The most common drug of dependence in our cohort were opioids, followed by cocaine. DDP was found to be associated with greater risk of mortality for both mother and fetus. Further, VTE, sepsis, and post-partum depression were also more common among women with drug-dependency. Their newborns were more likely to suffer from IUGR and to be born preterm.

The temporal increase in drug-dependency during pregnancy observed in our study is in agreement with other studies. For instance, previous studies showed a five-fold increase in opiate use in pregnancy between 2000 and 2009 [6,7,20]. In addition, marijuana use in pregnant women increased from 4.2%–7.1% between 2009 and 2016 [21], partly due to the legalization of cannabis in many states. Polysubstance use is as high as 50 % [3,5]. We anticipate that the rate of drug users will continue to rise within the next few years; therefore, it is essential for healthcare providers to understand the characteristics of drug users and the adverse effects of substance use on pregnancy outcomes.

In our study, women with DDP were more likely to be 25−34 years old, Caucasian, smokers, belonging to lower income quartiles, and receiving Medicaid insurance. Moreover, these women possessed greater pre-existing health conditions, such as diabetes, hypertensive disorders and obesity. Many of these characteristics, independent of dug-use, are associated with poorer pregnancy outcomes. However, even though we controlled for these variables within our analyses, our study found significant increased risks in both maternal and neonatal complications among women with DDP, including substantial risk of mortality for both mothers and fetus.

In our study, women with, DDP had higher rates of mortality and intrauterine fetal demise (IUFD). A meta-analysis of 57 studies found that any active maternal smoking was associated with increased risk of stillbirth [22]. In our study, women with DDP were at significantly higher risk of having an IUFD, even after adjustment for smoking history and other comorbid illnesses. Multiple factors may explain these adverse events, including maternal complications during pregnancy, poor nutritional status and inadequate antenatal care [22–24]. The association of increased maternal and fetal mortality in drug-dependent women emphasizes the importance of identifying these women and providing them with appropriate interventions.

Women with DDP had higher risks of sepsis compared with their non-drug dependent counterparts. In agreement with our findings, Knapp and colleagues also reported an increased risk of maternal sepsis in women with DDP, specifically, with opioid dependence [25]. Maternal sepsis is known to be associated with maternal death and premature birth [26,27]. We speculate that the high risk of infections among women with DDP to be among the common etiologies. The most common pathogens are *Escherichia coli* and Group B *Streptococcus* [27]. Hepatitis C, hepatitis B, chlamydia and HIV were also found to be common in pregnant women with drug use disorder [28,29].

Our study demonstrated an alarming 8-fold greater risk of liver disorders among women with DDP. To our knowledge, this is the second report on the increased risk of liver disorder among women with DDP [29]. While the mechanism of drug use on liver toxicity is not known, several correlations can be drawn. First, women with DDP are at higher risk for heavy alcohol use [30,31]. Furthermore, they also have an increased risk of Hepatitis C and B [28,29]. Interestingly, the recent meta-analysis by Huang et al. suggested a strong association between maternal Hepatitis C infection and increased risk of preterm birth [32]. This may potentially explain the greater likelihood of preterm birth among DDP observed in our study.

Our results suggest that women with DDP have a 1.6 times higher risk of VTE compared with women without DDP. While the underlying pathophysiology for this association is unclear, it may be associated with an increased risk of infection and overall, a higher rate of comorbid illnesses. In light of this association, we propose that it may be beneficial for women with DDP to receive anticoagulation therapy during the immediate postpartum period. Of course, this association must be replicated in further studies before any practice recommendations can be made.

We found that women with DDP had an increased risk of antepartum hemorrhage. The association of cocaine use and increased risk of placental abruption has been well established [14,33,34]. Recently, opioid use in pregnancy was reported to correlate with greater risk of third trimester bleeding [35].

In our study, we also observed that women with DDP had a higher likelihood for preterm labor, PPROM and preterm birth. The increased risks of preterm labor and preterm birth among drug users have been observed in many studies [6,23,31,36]. Quesada et al. reported cocaine and opiate use to be most predictive of preterm birth [37]. In addition, a recent population-based study showed an increased risk of preterm birth in pregnant women with cannabis use disorder [24].

Our study showed an increased likelihood of PPD among women with DDP. This is in keeping with the observation by Whiteman et al. in 2014 [31]. It is noted that the majority of women with DDP earned less income and had lower tiers of insurance, which could make them, in general, more vulnerable to experiencing depression. This greater tendency for experiencing depression prior to pregnancy may be associated with the higher likelihood of PPD observed in our study [38].

The increased risk of IUGR has been reported for pregnant women with substance use, which was further confirmed in our study [30,39]. Social factors and nutritional status among DDP women play an important role. In addition, it is well known that drugs like cocaine can cause uteroplacental insufficiency that results in acidosis and fetal hypoxia [40]. While the placenta appears to limit fetal exposure to marijuana, studies have - provided evidence for the harmful effects of marijuana on developing biological systems, altered uterine blood flow and altered maternal behavior [41].

Our study revealed a lower likelihood of chorioamnionitis among women with DDP, despite their higher risks of PPROM and

preterm labor. Regrettably, our lack of access to the detailed diagnosis of chorioamnionitis limited the data analysis. As clinical chorioamnionitis is diagnosed solely based on clinical signs, misdiagnosis could be a potential source of error. More importantly, subclinical chorioamnionitis does not present with the typical clinical signs, but rather manifests as preterm labor or even more commonly as PPROM, the two conditions that were more likely to occur among women with DDP in our study [42,43].

We observed lower rates of GDM and preeclampsia among women with DDP in spite of the higher prevalence of preexisting diabetes and obesity. This finding is consistent with the recent study by Knapp et al. on opioid dependence in pregnancy [25]. It is possible that the lower rate of GDM in DDP women might be due to the lower rate of non-white ethnicity in this group. In addition, we do not have access to information regarding prenatal care and diet, which could play an important role in GDM. As for preeclampsia, it is unclear why these rates are lower; however, it may be due to an increased rate of prematurity as a competing outcome, as well as the increased prevalence of smoking and possibly an increased risk of miscarriage pregnancies that would otherwise have been destined to develop preeclampsia. Previous studies reported inconsistent results regarding the effects of maternal drug use on preeclampsia [29,30,36,44–46].

We observed that women with DDP had a significantly lower rate of operative deliveries. This finding agrees with the studies by Phupong et al. and Neves et al. [46,47]. The higher rate of vaginal delivery -may be due to higher incidences of preterm birth, as well as lower rates of GDM, and greater rates of growth restriction. Neves et al. proposed that psychological factors and lower socioeconomic status might delay the receipt of medical care during labor among women with DDP. Interestingly, privately insured mothers were reported to receive more cesareans than mothers who are not privately insured [48].

We acknowledge some limitations of our study. First, the retrospective nature of the study can lead to misclassification and reporting errors. There is the possibility that the prevalence of drug dependence may be subject to underreporting. Hence, drug dependence prevalence during pregnancy may in fact be higher than we report. We chose to examine the pregnancy outcomes for women with DDP, rather than simply drug use, as the patients in the former group present with much more severe manifestations and it is likely to provide the most accurate representation of drug use. In addition, although it is likely that the prevalence of DDP is underreported, we believe that compared with the past, women may now be increasingly open to reporting drug use and health care providers may be more observant of drug use in their patients; hence, the rise in DDP prevalence over time may also, to a minor degree, represent this greater reporting of drug use.

Another limitation of our study was a lack of information on prenatal care follow-up, as well as postnatal care and treatment. These data would provide important information on the level of care these high-risk pregnancies received prior to birth and how they were followed post hospital discharge. Further, there is the possibility that the frequency of variables related to the longer-term postpartum period, such as postpartum depression, may be underestimated as these events may take place after hospital discharge. Likewise, there is the possibility of underestimation of antepartum conditions as they may be tested on an outpatient basis and hence, not recorded in the HCUP-NIS database. However, we feel confident that the reporting of the maternal and neonatal outcomes is complete and any misclassification is negligible as the outcomes included in our study are all common and serious adverse conditions that may occur in pregnancy and hence, if they were diagnosed they would be reported. Also, we did observe that the prevalence of obesity appears to be under-reported in our study. This is in agreement with studies that have found that obesity is generally not captured well in administrative databases [49,50]. This under-reporting of obesity has been attributed to obesity not being explicitly noted in physician or nursing notes and also coders simply not coding obesity due to time constraints. However, it has also been found that once obesity is captured, it is coded accurately [49,50] Lastly, we lacked information on neonatal intensive care admissions that could allow us to better assess the effects of heavy drug use on neonates.

In spite of the limitations of our study, it also has some strengths. The large sample size of the study (50,570 deliveries to drug dependent pregnant women out of a total of 14,513,587 deliveries) provided it with sufficient power to examine the maternal and neonatal outcomes for pregnant women with drug dependence. Moreover, the study was population-based, which allows for generalization of the study results to the greater American population.

Conclusion

Our study observed a rising trend of drug dependence in pregnant women, with increasing rates within the last recent years. We also demonstrated a strong association of drug dependence and increased risk of adverse maternal and neonatal outcomes, including serious consequences of maternal and fetal mortalities. Overall, in light of the increasing prevalence and the important effects of drug dependence in pregnancy, we suggest further research and targeted public health initiatives to be undertaken to address prevention, screening, and treatment of DDP.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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