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TRENDS IN OPIOID USE DISORDER AMONG PREGNANT WOMEN AND OPIOID USE DURING VAGINAL DELIVERY HOSPITALIZATION

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TRENDS IN OPIOID USE DISORDER AMONG PREGNANT WOMEN AND OPIOID USE DURING VAGINAL DELIVERY HOSPITALIZATION

BY

AYOOLUWATOMIWA DEBORAH ADEKUNLE, MBCHB

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR MASTER OF PUBLIC HEALTH DEGREE AT THE UNIVERSITY OF KENTUCKY

COMMITTEE:

CHAIR- DR. KATHLEEN WINTER

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APRIL 2019

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ABSTRACT

Background: The prevalence of opioid use in pregnancy has increased sharply in recent years. Kentucky is one of the hardest hits states and has seen many babies born with withdrawal symptoms over the past decade. Recent years have seen an increase in efforts to decrease opioid use in both inpatient and outpatient settings. However, Kentucky continues to have high rates of opioid prescription. This study aims at looking at trends in Opioid Use Disorder (OUD) in pregnancy, Neonatal Opioid Withdrawal Syndrome(NOWS) and the use of opioids during delivery hospitalization at a Kentucky tertiary institution.

Methods- Data on all deliveries between Jan 1st, 2013 and December 31st, 2017 were obtained from University of Kentucky Health Care. Information on a total of 8,999 individual deliveries were included in the dataset. Using Cochrane-Armitage tests first and then logistic regression, the data were analyzed for trends in OUD, NOWS and the administration of opioids during delivery hospitalization.

Results- An increase in prevalence of OUD in pregnancy ($p<0.0001$) and NOWS($p=0.007$) was observed over the study period. No significant trend was observed in the use of opioids during vaginal delivery hospitalizations($p=0.07$). Among women who delivered vaginally, advancing maternal age was associated with slightly lower odds of inpatient opioid administration while tobacco use (OR=1.33, CI=1.04, 1.69), lower county income quartile (OR= 1.90, CI=1.09, 3.29) and unmarried status (OR=1.40, CI=1.16, 1.69) were significantly associated with higher odds of inpatient opioid administration.

Conclusion- The findings of significant increases in NOWS over the years highlight the need for better family planning services targeted towards people of reproductive age with opioid use disorder. Better opioid stewardship is required to substantially reduce therapeutic opioid use.

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BACKGROUND INFORMATION

Burden of the opioid epidemic

Opioid Use Disorder (OUD) is described by the DSM-5 as a problematic pattern of opioid use leading to clinically significant impairment or distress.[1] It is characterized by cravings, tolerance and a powerlessness to self-regulate use. [2] Despite its associated ramifications, prevalence of the disorder has continued to soar in recent years; with the United States recording a 3-fold increase in the rates of drug overdose deaths involving opioids between 2000 and 2016.[3,4] In the year 2017, over 65% of the 70,200 drug overdose deaths that occurred in the U.S. involved an opioid. It is estimated that approximately, 130 Americans die daily from opioid related overdoses. [5] In 2016 alone, the Commonwealth of Kentucky recorded 1404 overdose deaths, up from 1248 reported in 2015.[6]

The disorder has steadily grown into one of epidemic proportions, presenting a major public health challenge. [7]

Opioid use is associated with not just mortality, but also significant rates of morbidity. Injection drug use puts individuals at a higher risk of cellulitis, bacteremia, osteomyelitis, endocarditis, abscesses, injection site ulcers, amongst other problem.[8] A study in California found just under a third of the intravenous drug using population to have at some point experienced skin and soft tissue infections. [9] Another study conducted in England found a 36% prevalence of self-reported bacterial infection symptoms among People who inject drugs, PWIDs. [10] Yet another study, conducted in Baltimore found a 34.9% prevalence of any type of current wound among PWIDs.[11] The sharing of needles predisposes PWID to HIV and Hepatitis C(HCV). The sharing of snorting straws and other drug equipment further increases the risk of HCV in this population and research from the Centers for Disease Control and Prevention (CDC)

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shows that the surge in the number of acute HCV infections observed in recent years has been driven by the opioid crisis.[12]

The burden on the healthcare system has been tremendous. A study examining 394 drug-related bacterial infection hospitalizations, over a 12- month period found 17 resultant deaths and a cumulative cost to the health care system of over 11 million USD. Another study conducted between 2012 and 2015 found that compared to matched non-opioid using patients opioid abusing patients within the population incurred 14,810 USD more in health care utilization costs.[8,13] It was estimated that in 2013 alone, prescription opioids misuse, abuse and dependence cost the United States around 78.5 billion USD and this amount does not include costs incurred from illegal opioid use.[14] Research shows that the cost of the opioid epidemic to the United States economy between 2001 and 2017 was around 1 trillion USD. This cost is expected to increase by 500 billion USD between 2018 and the year 2020.[15]

Prior to 2010, most drug overdose deaths occurred in the 5th decade of life and were mostly cocaine related. However, prescription and synthetic opioids have slowly caught up, with synthetic opioids taking over as the leading culprits.[16] Synthetic opioids have been responsible for overdose mortality mostly among young Non-Hispanic White males, living in urban areas and aged between 20 and 40 years.[16] Prescription opioids on the other hand have been found to cause overdose mortality mostly among Non-Hispanic White females, living in rural areas and aged between 40 and 60 years. Overall, Non- Hispanic Whites appear to be more affected than Blacks and males more than females.[16,17] In a retrospective study spanning a ten-year period, opioid overdosing was also found to be significantly associated with unmarried, unemployed status while adverse outcomes due to overdosing were correlated with use of psychotropic

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medications, comorbid physical and mental conditions as well as an increased level of prescription opioid usage.[18]

The overall epidemic has mainly affected Non-Hispanic Whites of lower socio-economic status. Studies have found that patients admitted for IVDU related causes were more likely to be uninsured or beneficiaries of publicly funded insurance schemes such as Medicaid. [8,19] Although, historically, heroin abuse was considered an urban inner-city problem, there has been a shift in trends with one study finding only 25% of users to be dwellers in large urban areas. The same study also observed that almost 90% of those initiating opioid use within the past ten years were Non- Hispanic Whites with a mean age of 22.9 years.[16] This represents a deviation from older patterns in which opioid abuse began at a much younger age and was mostly a problem of minorities.[16]

Opioid abuse in pregnancy

Concomitant with the increase in OUD prevalence in the overall population, vulnerable subpopulations including the pregnant and parenting have also seen an increase in OUD prevalence. Evidence shows a greater than four-fold increase in prevalence of OUD at delivery hospitalization over the 5-year period between 1999 and 2014.[19,20] OUD in pregnancy increases risk of pregnancy associated deaths and has been associated with adverse maternal outcomes.[21] Additionally, the incidence of neonatal opioid withdrawal syndrome(NOWS); a myriad of symptoms resulting from opioid withdrawal in babies born to opioid using mothers; is also reported to have increased by greater than 400% between 2004 and 2014. NOWS treatment is reported to have cost over half a billion USD in the year 2014 alone. Over 80% of that cost was covered by Medicaid, emphasizing the fact that the epidemic affects mostly people of lower socioeconomic status.[3,19]

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NOWS, sometimes referred to as Neonatal Abstinence Syndrome(NAS), is often attended by nervous and gastrointestinal system hyperactivity and often results in higher rates of complications such as seizures, feeding difficulties, meconium aspiration syndrome, etc., increased hospitalization costs and longer length of stay. [22-25] It has been recognized for a long time as developing from the termination, after delivery, of the maternofetal transfer of morphine.[22-24] Although its management has improved over the years, factors that predict its occurrence in exposed babies are still not well established. [22,26] It is thought that volume of maternal opioid use, timing of last use and genetics play a role.[22,26,27]

Some tools currently exist for screening newborns; however, the overall approach is not standardized.[22,28,29] Given the fact that NOWS can occur as late as 7 days of life, after the neonate would usually have been discharged, it is important to identify more factors that could help predict its occurrence and severity. [30,31] Identifying these factors could potentially help clinicians with improving surveillance for and identification of NOWS.

Infants born to women who use opioids have multiple layers of vulnerability. Opioids are able to cross the placenta and have been associated with an increased risk of adverse outcomes such as preterm delivery, some birth defects, poor fetal growth and still births. [32,33] In addition to these, mothers with OUD often have other factors that further contribute to maternal and infantile risk. These factors include intimate partner violence, concurrent use of other drugs and comorbid psychiatric disorders and in some cases inadequate health care.[22,34-36] Although some researchers have questioned the role of confounding in the adverse pregnancy outcomes observed in OUD, the general consensus is that OUD in pregnancy is a serious condition with potentially severe outcomes.[20,35,37-39]

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From over-prescription to opioid crisis

Excessive therapeutic use of opioids has primarily been blamed for the epidemic. The increasing prevalence of uncontrolled chronic pain, over the past three decades, coupled with cardiovascular and toxicity concerns surrounding non-opioid alternatives, led key players to seek out analgesic alternatives that were effective yet devoid of aforementioned concerns. Fueled by the assurance of minimal addiction potential provided by pharmaceutical companies, the practice of excessive and uncurtailed opioid prescription steadily became more prevalent. This effectively created an increasingly opioid dependent population and laid the foundation for the current crisis. [40-43]

Although, beginning with prescription opioids, the current crisis has become more complicated over the years. The increasing awareness about the addiction potential coupled with the introduction of stricter regulatory measures and difficult to crush formulations resulted in a decreased availability of prescription opioids to a dependent population. The effect of this was an increasing propensity towards acquisition of opioids from alternative sources. These sources being illegal and unregulated, were more readily available and provided cheaper and often times more potent alternatives to prescription opioids. Initially limited to mostly heroin, the spectrum of illicit drugs has now broadened to include illegally manufactured fentanyl and its analogs. [42,44,45]

Even though the crisis has shifted to mostly illicitly obtained opioids, multiple studies have shown that most users have their first contact within opioids in a therapeutic context. Consequently, the need for minimal administration of opioids, while employing alternative methods of effective pain relief in settings of acute pain cannot be overemphasized. Recent studies have shown that there is an increasing awareness of this and although pain is often the

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primary reason for presentation in the ER, many ER providers are now cutting back on opioid administration.[46-48]

Opioid use in obstetric pain management

Pain is a commonly reported symptom within the obstetric setting, especially in the early post-partum period. Suboptimal pain control has the ability to increase risk of opioid use, result in post-partum depression, decrease a mother's ability to care for her infant and to evolve into chronic pain. [37,49] Consequently, it is important to ensure that peri-partum pain is adequately controlled. Because of the risk of persistent opioid use after obstetric exposure in opioid naïve patients, American College of Obstetrics and Gynecology recommends a cautious, individualized approach to pain management that is stepwise, multimodal and maximizes other methods of pain management before resorting to opioids. [49] While complete avoidance of opioids is not the end goal, recent advocacy efforts are being targeted towards ensuring that opioids are only used when absolutely necessary. Currents recommendations encourage clinicians to consider non-pharmacological methods of pain management such as sitz baths, cold, heat, etc., maximum acceptable doses of acetaminophen and NSAIDS and in appropriate situations, ultrasound guided nerve blocks and other analgesia techniques that could help avoid unnecessary opioid use. It is recommended that, in the event that opioids are required, they should be used in combination with other pain relief modalities, be limited, as much as possible to the short acting formulations and their duration of usage should be limited to the shortest possible effective duration.[48-51]

Although studies have looked at trends in the use of opioids for acute pain management in the ER setting, not many have looked at such trends in the setting of peri-partum pain management. [47,52] One study did find that hospitals in the South are more likely to administer opioids during delivery hospitalization.[53] Kentucky providers continue to prescribe high rates of

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opioids with an opioid prescription rate of 97 per 100 persons in the year 2015.[54] Considering that a large study found 0.3% of women who had never been previously exposed to opioids becoming persistent users within one year of undergoing cesarean sections, it is important to examine how much opioids are being used for management of peri-partum pain. [51] This study aims to examine trends in maternal opioid use disorder, neonatal withdrawal syndrome and opioid administration during delivery hospitalization at a tertiary institution in Central Kentucky.

METHODS

Data for the current study were obtained from the University of Kentucky Center for Clinical and Translational Science (UK CCTS). UK CCTS keeps data on all patients seen at UK Healthcare. De-identified maternal and infant data from all delivery hospitalizations between 2013 and 2017 were requested. The initial dataset contained information on 8,999 unique deliveries. Information present within the dataset included hospitalization details such as length of stay, discharge disposition, payer, APR diagnostic groups, APR risk of mortality and APR severity of illness scores, diagnostic codes, medications administered and procedures performed. Demographic information including age, race, marital status, and county of residence were also present within the dataset.

Using ICD-9 and ICD 10 CM codes (see appendix), data on OUD, diabetes mellitus, hypertension, renal disease, amphetamine abuse, cocaine abuse, tobacco use, cannabis use, HIV status, Hepatitis C status, mode of delivery, complications of delivery, thrombocytopenia, comorbid psychiatric conditions and Neonatal withdrawal symptoms were extracted from the data. Inferential procedures were performed for all predictors and outcomes of interests, and differences between the OUD and non-OUD groups were assessed using chi square analyses for categorical variables and t-tests for continuous variables. Results for this are presented in Table

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1. To examine temporal trends, Cochrane-Armitage test for trends were initially performed using year and the outcome of interest (OUD status, NOWS status and opioid use status). And then, to further explore the trends while controlling for possible confounding, a logistic regression model was fitted. The logistic regression model for OUD in pregnancy was fitted using time (years), age (years), payer (Private, Bluecross /Blueshield, Medicaid, other), county income quartile (calculated using average county per capita personal income between 2015 and 2017 for every county represented in the data set. County per capita personal income data was obtained from The United States Bureau of Economic analyses, BEA. Available here: https://www.bea.gov/data/income-saving/personal-income-county-metro-and-other-areas), comorbidity count (calculated by assigning one point to each of the following risk factors: diabetes mellitus, renal disease, obesity and hypertension present in the individual record) and race (assigned as "White" versus "Other"). Race was initially included as a variable with multiple levels but due to quasi complete separation of data points, it was then recoded as "White" versus "Non-White", to allow for convergence of the model.

For opioid administration during delivery hospitalization, only vaginal deliveries were considered. Cesarean sections are often associated with more severe pain than vaginal deliveries and the pain is often managed using co-analgesia[55]. Consequently, they were left out of the analyses. Patients with bleeding disorders and renal disease, in whom NSAIDs may be contraindicated were excluded from the analyses because opioids may have been indicated in these patients.[56] A total of 4562 records of women who had vaginal deliveries and met the inclusion criteria were included in the analyses. The adjustment variables were similar to those in the OUD model with the only differences being that, race was included as a 5-level variable (White, African American, Asian, Hispanic, other) and OUD (Yes versus No) and mode of

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delivery (operative vaginal i.e. forceps/vacuum vs vaginal) were added as additional adjustment variables. Opioid was defined as the presence of any opioid administered to a patient who delivered vaginally, during delivery hospitalization.

Due to the fact that methadone and buprenorphine are indicated for treatment of OUD in pregnancy, their use in women with OUD was not considered in-hospital opioid administration for the purposes of this study[34].

Information about NOWS was extracted, using all-encompassing ICD 9 CM and ICD 10 codes that cover all maternal drugs of addiction. These codes represented withdrawal symptoms in infant due to any maternal drug of addiction in use and was not specific to just opioids. A child was considered to have NOWS if those codes were present and the mother also had OUD. The logistic regression model was fitted with year of birth, maternal age, tobacco use, comorbid psychiatric conditions, marital status, county income quartile, substance use score (obtained by giving 1 point for each of the following substances in use: Cocaine, amphetamines and cannabis) and alcohol. Because NOWS only occurs in babies exposed to opioids in-utero, the odds ratios were calculated using only babies born to mothers with OUD. Race was excluded from the model due to quasi complete separation of data points (resulting from the fact that majority of the mothers with OUD were White).

All adjustment variables were selected a priori based on a review of literature. No variables were added on.

RESULTS

The overall prevalence of OUD in the population was 5.2% (n=465). Although significantly higher in the OUD than in the Non-OUD group, the overall prevalence of amphetamine abuse was negligible (0.06%). Prevalence of comorbid psychiatric disorders, cannabis use, cocaine use,

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tobacco use, was also significantly higher in the OUD group compared to the non-OUD group. More than 50% of the OUD population came from counties with per capita personal incomes in the lowest quartile, compared to only 23% of those in the non-OUD group (p value <.0001). HIV was rare within the population with only 0.1% having a diagnosis of HIV. Compared to the non-OUD group, a significantly lower proportion of women with OUD were currently in a marriage relationship. (52.4% vs 15.3%). Overall prevalence of any kind of withdrawal symptoms in the study population was 4%. Neonatal opioid withdrawal symptoms specifically occurred in about 3% of the overall population and half of the babies born to mothers with OUD. *Table 1.*

The prevalence of opioid use and NAS significantly increased over the 5-year period. No significant trend was observed in in-hospital administration of opioids for peri-partum pain management. See Figure 1.

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DESCRIPTIVE STATISTICS FOR THE STUDY POPULATION PRESENTED BY OUD STATUS.

Maternal Characteristics	Level	Non-OUD n=8,534	OUD n=476	p-value
Age	-	28.62 (5.88) - (0.00,49.00)	29.02 (4.82) - (17.00,47.00)	0.0594
Amphetamines abuse	Yes	2 (0.0%)	3 (0.6%)	<.0001
	No	8521 (100.0%)	473 (99.4%)	
Cannabis use	Yes	147 (1.7%)	28 (5.9%)	0001
	No	8376 (98.3%)	448 (94.1%)	
Cocaine Use	Yes	56 (0.7%)	22 (4.6%)	<.0001
	No	8467 (99.3%)	454 (95.4%)	
Comorbid Psychiatric disorder	Yes	647 (7.6%)	154 (32.4%)	0001
	No	7876 (92.4%)	322 (67.6%)	
Comorbidity count		0.08 (0.30) - (0.00, 3.00)	0.05 (0.22) - (0.00, 2.00)	0.0132
HIV	Yes	10 (0.1%)	0 (0.0%)	0.4546
	No	8513 (99.9%)	476 (100.0%)	
Hepatitis C	Yes	139 (1.6%)	217 (45.6%)	<.0001
	No	8384 (98.4%)	259 (54.4%)	
Cesarean section	Yes	3308 (38.8%)	229 (48.1%)	<.0001
	No	5215 (61.2%)	247 (51.9%)	
Income Quartile	Q1	1959 (23.0%)	276 (58.0%)	<.0001
	Q2-Q3	6272 (73.6%)	191 (40.1%)	
	Q4	279 (3.3%)	8 (1.7%)	
	Missing	13 (0.2%)	1 (0.2%)	
Length of Stay*		2 (1.00, 338.00)	11 (1.00, 250.00)	<.0001
Marital Status	Married	4442 (52.1%)	72 (15.1%)	<.0001
	Unmarried	4081 (47.9%)	404 (84.9%)	
Neonatal Substance Withdrawal	Yes	93 (1.1%)	238 (50.0%)	<.0001
	No	8430 (98.9%)	238 (50.0%)	
Payer	BlueCross/ Blueshield	1145 (13.4%)	11 (2.3%)	<.0001
	Medicaid	4971 (58.3%)	440 (92.4%)	
	Private	625 (7.3%)	6 (1.3%)	
	Other	1782 (20.9%)	19 (4.0%)	

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Peri-partum opioid	Yes	1070 (12.6%)	54 (11.3%)	p-value=0.5568
	No	7453 (87.4%)	422 (88.7%)	
Race	African American	1050 (12.3%)	8 (1.7%)	p-value=<.0001
	Asian	459 (5.4%)	0 (0.0%)	
	Hispanic	94 (1.1%)	0 (0.0%)	
	Other	166 (1.9%)	1 (0.2%)	
	White	6754 (79.2%)	467 (98.1%)	
Tobacco Use	Yes	917 (10.8%)	351 (73.7%)	p-value=<.0001
	No	7606 (89.2%)	125 (26.3%)	
Significance level is set at 0.05. Please note that if cells counts are less than 5, the Chi-Square test p-value is unreliable. Percentages may not add up to 100 due to rounding *Median values were presented due to skewness of data, p value was estimated using Kruskal wallis test				
For continuous variables, the mean (standard error) - (minimum, maximum) is displayed in each cell				

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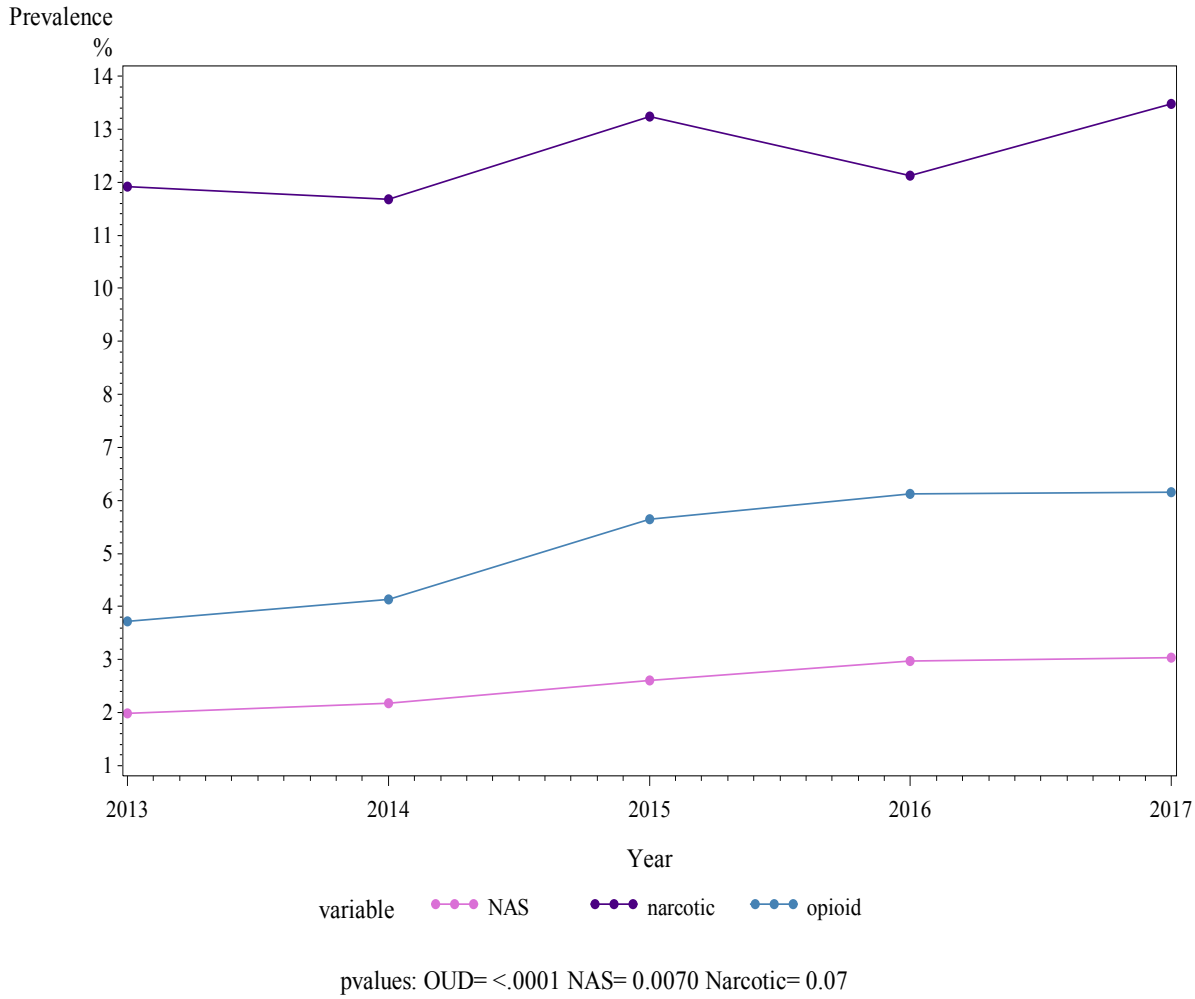

Figure 1- S*howing trends in OUD NAS and opioid administration during delivery hospitalization between 2013 and 2017.*

The odds of a pregnant woman presenting with OUD increased by 18% per year, on average. For every year increase in age, the odds of OUD increased by 8%, on average. Compared to non-smokers, smokers had greater than 10 times the odds of having OUD. Women from counties whose incomes fell in the lowest quartile had a 2.28 fold odds of OUD compared to those from the counties within the highest income quartile See *table 2.*

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TABLE 2: LOGISTIC REGRESSION OUTCOMES FOR OUD (n=8,709)

Maternal Characteristic	Opioid Use Disorder
Year, OR(CI)	
+1	**1.20 (1.11, 1.30)**
Age, OR (CI)	
+1	**1.09 (1.07, 1.11)**
Tobacco use, OR(CI)	
Yes vs No	**10.30 (8.07, 13.15)**
Comorbid Psychiatric Condition, OR (CI)	
Yes vs No	**2.48 (1.91, 3.23)**
Marital Status, OR (CI)	
Unmarried vs Married	**2.75 (2.03, 3.72)**
Payer, OR (CI)	
Medicaid vs Private	**5.91 (2.11, 16.56)**
Bluecross/ Blueshield vs Private	1.31 (0.40, 4.31)
Other vs Private	1.48 (0.48, 4.58)
County Income Quartile, OR (CI)	
Q1 vs Q4	**2.67 (1.16, 6.10)**
Q2-3 vs Q4	1.04 (0.45, 2.37)
Comorbidity Count, OR (CI)	
+1	**0.38 (0.24, 0.61)**
Race, OR(CI)	
White vs non-White	**7.93 (4.01, 15.70)**

Maternal age, smoking status, marital status, payer, county income and substance count did not significantly affect the occurrence of Neonatal withdrawal. See Table 3.

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TABLE 3: LOGISTIC REGRESSION OUTCOMES FOR NEONATAL OPIOID WITHDRAWAL SYNDROME (NOWS)

Maternal Characteristic	Neonatal withdrawal (n=238)
Year, OR(CI)	
+1	0.94 (0.82,1.06)
Race	
White vs other	0.48 (0.11.2.12)
Age, OR (CI)	
+1	1.02 (0.98,1.06)
Smoking, OR (CI)	
Yes vs No	1.09 (0.71,1.66)
Marital status, (CI)	
Unmarried vs Married	1.67 (0.99, 2.8)
County income quartile	
Q1 vs Q4	1.24 (0.27,5.67)
Q2-3 vs Q4	1.54 (0.33, 7.09)
Substance score	1.30 (0.76,2.23)

On average, the odds of receiving an opioid during a vaginal delivery hospitalization remained constant over the 5 year period. Increasing maternal age was significantly protective against inpatient opioid administration. Race, comorbidity count, mode of delivery and payer were not significantly associated with inpatient opioid administration.

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TABLE 4: SHOWING LOGISTIC REGRESSION RESULTS FOR OPIOID ADMINISTRATION DURING VAGINAL DELIVERY HOSPITALIZATION N=4562

Maternal Characteristic	Opioid administration
Year, OR(CI)	
+1	1.03 (0.97, 1.08)
Age, OR (CI)	
+1	**0.97 (0.95, 0.98)**
Tobacco, OR(CI)	
Yes vs No	**1.33 (1.04, 1.69)**
Comorbid Psychiatric condition, OR(CI)	
Yes vs No	1.30 (0.90, 1.87)
Marital status, OR (CI)	
Unmarried vs Married	**1.40 (1.16, 1.69)**
Payer, OR (CI)	
Medicaid vs Private	0.88 (0.62, 1.24)
Bluecross/ Blueshield vs Private	0.96 (0.65, 1.41)
Other vs Private	0.77 (0.52, 1.14)
County income quartile, OR (CI)	
Q1 vs Q4	**1.90 (1.09, 3.29)**
Q2-3 vs Q4	1.47 (0.86, 2.48)
Comorbidity Count, OR (CI)	
+1	1.30 (0.90, 1.87)
Mode of delivery, OR (CI)	
Operative vaginal vs vaginal	1.07 (0.36, 3.16)
Laceration, OR (CI)	
Yes vs No	0.99 (0.83,1.19)
Race, OR (CI)	
African American vs Asian	1.16 (0.75, 1.81)
Hispanic vs Asian	1.32 (0.62, 2.84)
White vs Asian	1.07 (0.72, 1.57)
Other vs Asian	1.02 (0.52, 2.01)
OUD, OR (CI)	
+1	0. 77 (0.52, 1.14)
LOS	1.01 (1.00,1.01)

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DISCUSSION

The current study looked at trends in and predictors of OUD in pregnancy, NOWS and opioid use during delivery hospitalization. Significant increases were observed in OUD and NOWS over time, but no significant changes were observed in overall inpatient opioid use. This study builds on existing literature by examining the maternal sociodemographic characteristics associated with NOWS as well as those looking at factors associated with peri-partum opioid use within the inpatient setting.

The current findings confirm the previously documented association of White race, lower socioeconomic status, smoking, comorbid psychiatric conditions and increasing maternal age with OUD in pregnancy as well as the well documented increase in prevalence of OUD in pregnancy over the years. [2,19,20,57]

The observed increase in prevalence of NAS over the years highlights a need for family planning counselling and services to women of reproductive age in Kentucky, who have OUD. People with OUD are more likely to engage in risky sexual behavior and it is estimated that over 80% of pregnancies occurring in this population are unplanned.[58,59] Guidelines issued by the Unites States Substance use and Mental Health Services Administration (SAMHSA), recommend that health care providers discuss family planning methods with women with OUD prior to discharge; as a means of reducing the occurrence of NAS. [56] The scaling up of family planning services at harm reduction centers could also help reduce the risk of unplanned pregnancies in women with OUD. In the face of a worsening opioid epidemic, action in this direction would be immensely beneficial.

This study deviates from findings of higher odds of OUD in patients with cardiovascular comorbidities.[35] Although individual comorbidities were not examined, comorbidity count;

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reflective of overall burden of cardiovascular disease was not significantly associated with OUD. Important to note is that obesity itself, as a stand-alone diagnosis, has been found to be associated with lower odds of OUD. [35,60]

None of the factors included in the model was significantly associated with NOWS. The occurrence of NOWS in infants of mothers with OUD has generally been considered difficult to predict. Factors such as genetics, maternal physiology and genetic polymorphisms which are thought to affect its expression are not routinely measured in the clinical setting.[22,28,30,31] Additionally, lack of information on timing of last use, quantity of use and poor-quality of information on gestational age was a limitation of this study. Although, the ability to predict which infants would get OUD would be ideal, in the absence of validated prediction tools, clinical astuteness is necessary. [31] Because the onset of NOWS can occur as late as greater than 72 hours after delivery, a neonatal monitoring period of at least 5 days is recommended.[30,31] A tool commonly used for clinical assessment is the modified Finnegan Score, however, this tool has been criticized as focusing on a number rather than a person.[28,61] Effort need to be put into creating a valid, widely accepted tool that is simple to use and serves the purpose of improving clinical outcomes.[31]

The prevalence of opioid administration among patients who delivered vaginally was about 17.5%. This is higher than findings of a 12% prevalence in a nationwide study of opioid prescriptions following vaginal deliveries. [62] Despite the fact that there has been a push for less opioid use in the management of pain, the use of opioids did not significantly change with the passage of time. This suggests that there could be room for improving opioid stewardship. [48-50]

Because the perception of pain control has been shown to impact patient satisfaction, providers might feel dis-incentivized to try other analgesic methods. [63] However, this can be

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navigated by discussing patients' expectations regarding pain; developing realistic pain management goals and developing an individualized plan along with the patient for managing perinatal pain. This should ideally be done during the antenatal period. [64]

Clinicians should employ a holistic approach to pain that could include psychological methods, if needed. Research has shown that pain management culture is more strongly correlated with patient satisfaction than actual perception of pain control. [63] Some centers have been able to cut back by as much as 40%; achieved by implementing multimodal pain therapy, individualized, goal directed therapeutic planning and more objective methods of measuring pain. [65] Similar methods could be employed at other tertiary institutions in an effort to bring about reductions in therapeutic opioid use.

Concomitant with findings in a previous study, lacerations during vaginal deliveries were not significantly associated with opioid use.[62]

OUD did not significantly impact the odds of in hospital opioid administration among the study population. Although, it might be tempting to think that in-hospital opioid use should be lower among people with OUD, it is important to note that opioids, although not encouraged, are not contraindicated in this population. [66-68] Because concerns have arisen about inadequate peri-partum analgesia in women with OUD, clinical judgement is required when managing peri-partum pain in this population.[69] As with all cases, management should be individualized to ensure that pain management goals are achieved, while minimizing opioid use.

Tobacco use was associated with higher odds of receiving an opioid. This is similar to findings from another study in which tobacco use was associated with a slight increase in odds of filling an opioid prescription within 5 days of vaginal delivery.[62] Studies in post-operative settings have also found tobacco use to be associated with higher analgesic; particularly opioid

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requirement.[70-72] It is thought that chronic use of nicotine results in tolerance to nicotine induced analgesia and that in such people, subsequent abstinence from nicotine e.g. in the post-partum period increases perception of pain.[72] However, the mechanisms are not fully understood. More research is needed in this area[72]

Lower socioeconomic status and unmarried status were positively associated with opioid administration. This is supported by findings from a study which showed that single women were more likely to perceive a higher pain intensity in the postoperative setting compared to their married counterparts. [73] Evidence has also shown socioeconomic status to be inversely related to perceived pain intensity. [74] The perception of pain is complex and multi-faceted and thought to be affected by psychological, social and environmental factors surrounding the perceiver. [75] These factors could by extension affect in-hospital opioid requirements. Further studies that explore this are required. In order to achieve a reduction in unnecessary opioid use, providers would need to address patients' needs holistically, employing pharmacological and non-pharmacological techniques to achieve adequate pain control.

Limitations of the current study include the fact that it depended on a previously existing dataset. Problems that could arise from this include exposure or outcome misclassification due to wrong coding and inadequate documentation. However, if there was exposure misclassification, the resultant bias is most likely to have been non-differential. There is likely to be underreporting of NOWS, because physicians are thought to be reluctant to diagnose NAS in instances where there was no morphine requirement. [76] Taking this into consideration, it can be concluded that NAS estimates obtained from this study are at best modest.

Another limitation of this study was the fact that there was no data on what specific opioids were in use, how long they were in use and in what quantities they were used among the

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women who had OUD. Further studies should include a breakdown of drug use and quantities used.

The dataset did not contain any information on pain intensity and provider characteristics, consequently, these variables could not be adjusted for when analyzing in-hospital opioid administration. Although, absence of this information does not eliminate the validity of findings from this study, these factors should be taken into consideration in future studies.

Although this study looked at inpatient opioid use, it did not examine, nor does it predict post discharge prescription of opioids. Further studies that examine these two issues as a continuum are required. Insight into what proportion of patients who receive an inpatient opioid prescription go on to receive an outpatient prescription could help inform provider practices. In the face of the worsening opioid epidemic, cautious, evidence based use of opioids is highly warranted.

CONCLUSIONS

The current study demonstrates an increase in prevalence of OUD in pregnancy and Neonatal Opioid Withdrawal Syndrome among Central Kentucky women between 2013 and 2017. It also demonstrates a constant prevalence of opioid administration during vaginal delivery hospitalization over the same period. It is the first study of its kind to examine inpatient opioid use in women delivering at a tertiary institution in Kentucky.

Strengths of the current study include the fact that it used a large dataset and was consequently sufficiently powered to detect effects of the exposures examined. The racial distribution within this study is comparable to that within the state of Kentucky suggesting that the racial distribution of the study population was representative of that of Kentucky. [77] Although opioid usage policies could differ by institutions, it is expected that results from this

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study would stimulate conversations about opioid usage within in-patient settings. It is also hoped that findings from this study would set the stage for quality improvement efforts; aimed particularly at reducing opioid use in the management of acute pain.

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APPENDIX

ICD codes for comorbid psychiatric disorders:

"648.41" "296.8" "F41.0" "F41.1" "F43.0" "F60.3" "O99.344" "F41.9" "295.9" "311" "295.9" "300.01" "309.81"

ICD codes for HIV:

'042' '043' '044' 'Z21' 'B20.0' 'B20.1' 'B20.2' 'B20.3' 'B20.4' 'B20.5' 'B20.6' 'B20.7' 'B20.8' 'B20.9' 'B21.0' 'B21.1' 'B21.2' 'B21.3' 'B21.7' 'B21.8' 'B21.9' 'B23.0' 'B23.1' 'B23.2' 'B23.8' 'B24' 'B22.0' 'B22.1' 'B22.2' 'B22.7' 'B21.0'

ICD codes for hypertension:

'401.0' '401.1' '401.9' '402.00' '402.01' '402.10' '402.11' '402.90' '402.91' '403.00' '403.01' '403.10' '403.11' '403.90' '403.91' '404.00' '404.01' '404.02' '404.03' '404.10' '404.11' '404.12' '404.13' '404.90' '404.91' '404.92' '404.93' '405.01' '405.09' '405.11' '405.19' '405.91' '405.99' 'I10' 'I11.0' 'I11.9'

ICD codes for Diabetes Mellitus:

'250.00' '250.01' '250.02' '250.03' '250.1' '250.2' '250.3' '250.4' '250.5' '250.6' '250.7' '250.8' '250.9' 'E11.9' 'E13' 'E10' 'Z79.84' 'Z79.4'

ICD codes for Renal Disease:

'N18.1' 'N18.2' 'N18.3' 'N18.4' 'N18.5' 'N18.6' 'N18.9' '585.9' '585.6' '585.1' '585.2' '585.3' '585.4' '585.5' '583.81' '403.9' '586' '583.89'

ICD codes for tobacco use:

'F17.210' 'O99.334' 'F17.200' 'O99.333' '649.01'

ICD codes for Obese:

'278.00' 'Z68.30' 'Z68.31' 'Z68.32' 'Z68.33' 'Z68.34' 'Z68.35' 'Z68.36' '278.01' '278.03' '793.91' '649.11' 'V85.30' 'Z68.37' 'Z68.38' ' Z68.39' 'Z68.41' ' Z68.42' ' Z68.43' ' Z68.44' ' Z68.45' 'V85.31' 'V85.32' 'V85.33' 'V85.34' 'V85.35' 'V85.36' 'V85.37' ' V85.38' 'V85.39' 'V85.4' 'V85.41' ' V85.42' '793.91' 'V85.43' 'V85.44' ' V85.45' 'V85.54' 'E66.0' 'E66.01' 'E66.2' 'E66.8' 'E66.9' 'O99.214' '278'

ICD codes for Cannabis:

'F12.90' '305.2' '305.21' 'F12.10' 'F12.99' 'F12' 'F12.1' 'F12.2' 'F12.20' '304.30' '304.31' '304.32'

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ICD codes for Cocaine:

'305.6' 'F14.10' '304.21' '305.61' 'F14.90' 'F14.129' '304.2' 'F14.20'

ICD codes for Alcohol:

'F10.10' 'F10.20' '291.81' '291.0' '291.1' '291.2' '291.3' '291.4' '291.5' '291.8' '291.82' '291.89' '291.9' 'O99.314' '303.91' 'O99.310' '305'

ICD codes for

ICD codes for Bleeding disorders:

'N17.0' '584.5' 'N17.1' 'N17.2' 'N17.8' 'N17.9' '584.6' '584.7'

ICD codes for HCV:

'V02.62' '070.54' '70.70' '070.44' '70.7' '70.54' '70.44' '70.71' '070.70' '070.71' 'B18.2' 'B18.20' 'B19.20' 'B19.2' 'B17.1'

ICD codes forCcesarean section:

'O82' 'O82.0' 'O82.1' 'O82.2' 'O82.8' 'O82.9' '669.70' '669.7' '669.71' '649.8'

ICD codes for 3rd degree laceration:

'664.31' 'O70.3'

ICD codes for 4th degree laceration:

'664.21' 'O70.2' 'O70.20' 'O70.21'

ICD codes for NAS:

'P96.1' '779.5'

ICD codes for Opioid use:

'304.71' '304.72' 'E935.0' 'E850.0' 'E935.2' '305.50' '305.51' '305.52' '305.53' 'F11.20' 'F11.90' '305.5' '304' '304.00' '304.01' '304.02' '304.70' 'F11.10' 'F11' 'E850.2' '965.00' 'F11.23' '304.7'

ICD codes for Operational Vaginal delivery:

'669.51' '669.5' ' 669.50 ' 'O66.5' '660.71' 'P03.3' '763.3'

ICD codes for Amphetamines:

'305.7' '304.41' 'F15.10'

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