Published in final edited form as:

Drug Alcohol Depend. 2020 November 01; 216: 108236. doi:10.1016/j.drugalcdep.2020.108236.

Substance use disorders and risk of severe maternal morbidity in the United States

Marian Jarlenski¹, Elizabeth E Krans², Qingwen Chen¹, Scott D Rothenberger³, Abigail Cartus⁵, Kara Zivin⁴, Lisa M Bodnar^{2,5}

¹Dept of Health Policy and Management, University of Pittsburgh, 130 DeSoto Street Pittsburgh, PA 15261, USA

²Magee-Womens Research Institute and Dept of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh, 3380 Boulevard of the Allies, Pittsburgh, PA 15213, USA

³Dept of General Internal Medicine, University of Pittsburgh, 200 Meyran Ave, Suite 300, Pittsburgh, PA 15213, USA

⁴Dept of Psychiatry, University of Michigan, 2800 Plymouth Road, Building 16, Room 228W, Ann Arbor, MI 48109, USA

⁵Dept of Epidemiology, University of Pittsburgh, 130 DeSoto Street, Pittsburgh, PA 15261 USA

Abstract

Background: The contribution of substance use disorders to the burden of severe maternal morbidity in the United States is poorly understood. The objective was to estimate the independent association between substance use disorders during pregnancy and risk of severe maternal morbidity.

Methods: Retrospective analysis of a weighted 53.4 million delivery hospitalizations from 2003–2016 among females aged >18 in the National Inpatient Sample. We constructed measures of substance use disorders using diagnostic codes for cannabis, opioids, and stimulants (amphetamines or cocaine) abuse or dependence during pregnancy. The outcome was the presence of any of the 21 CDC indicators of severe maternal morbidity. Using weighted multivariable logistic regression, we estimated the association between substance use disorders and adjusted risk

Corresponding Author: Marian Jarlenski, PhD, MPH (she/her), Associate Professor of Health Policy and Management, University of Pittsburgh Graduate School of Public Health, 130 DeSoto St, A619, Pittsburgh, PA 15261 USA, +1 412 383 5363, marian.jarlenski@pitt.edu.

Author contributions

Jarlenski, Krans: Study conception and design, acquisition of and interpretation of data, obtained funding.

Jarlenski: Drafting of the work

Chen, Rothenberger: Study design, analysis and interpretation of data.

Cartus, Zivin, Bodnar: Study conception and design and interpretation of data.

All authors: Revising work critically, final approval of the version to be published, agreement to be accountable for all aspects of the work.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest

No conflicts declared.

of severe maternal morbidity. Because older age at delivery is predictive of severe maternal morbidity, we tested for effect modification between substance use and maternal age by age group (18–34 y vs >34 y).

Results: Pregnant women with an opioid use disorder had an increased risk of severe maternal morbidity compared with women without an opioid use disorder (18–34 years: aOR: 1.51; 95% CI: 1.41,1.61, >34 years: aOR: 1.17; 95% CI: 1.00,1.38). Compared with their counterparts without stimulant use disorders, pregnant women with a stimulant use disorder (amphetamines, cocaine) had an increased risk of severe maternal morbidity (18–34 years: aOR: 1.92; 95% CI: 1.80,2.0, >34 years: aOR: 1.85; 95% CI: 1.66,2.06). Cannabis use disorders were not associated with an increased risk of severe maternal morbidity.

Conclusion: Substance use disorders during pregnancy, particularly opioids, amphetamines, and cocaine use disorders, may contribute to severe maternal morbidity in the United States.

Keywords

Pregnancy; opioid use disorder; cannabis use disorder; stimulant use disorder; severe maternal morbidity

1. INTRODUCTION

The United States has a higher rate of maternal mortality than any other high-resource nation (Alkema et al., 2016). Closely related to maternal mortality, severe maternal morbidity encompasses a series of acute adverse events during pregnancy, delivery, or postpartum and provides a population measure of “near miss” events (Creanga et al., 2014; Say et al., 2009). During the past two decades, the United States has experienced a 45% increase in the rate of severe maternal morbidity (Fingar, 2018; Kuklina et al., 2009).

Prior research has suggested that a number of factors may explain the increase in the rate of severe maternal morbidity, including older maternal age at delivery (Aoyama et al., 2019; Lisonkova et al., 2017), racial and geographic disparities in the receipt of life-saving interventions (Janevic et al., 2020; Kozhimannil et al., 2019), and an increasing burden of chronic health conditions in pregnancy (Admon et al., 2017; Kuklina and Callaghan, 2011; Kuklina and Callaghan, 2010). Little is known about the contribution of substance use disorders to the increase in severe maternal morbidity. Over the past decade, marked increases in amphetamine, opioid, and cannabis use have led to a rise in number of pregnant women who develop a substance use disorder (Admon et al., 2018a; Haight et al., 2018; Jarlenski, 2020; Young-Wolff et al., 2017), which may affect the risk of severe maternal morbidity through both biological mechanisms, such as increased risk of infectious disease and poor nutrition (Behnke et al., 2013; Centers for Disease and Prevention, 2012), and through social mechanisms, such as stigma and poverty (Jenkins and Gordon, 2015; Terplan et al., 2015). Opioid use disorder is associated with cardiovascular risks that could increase risk of severe maternal morbidity with potentially greater risk at older ages (Andersson and Vasan, 2018). Stimulant use disorders may be associated with increased risk of hemorrhage and preeclampsia (Atkinson et al., 2015; Cohen et al., 2017), which could increase risk of severe maternal morbidity. Cannabis use in pregnancy is common, yet the association

between cannabis use disorders and severe maternal morbidity is unknown. While some prior research has suggested increased risk of severe maternal morbidity among patients with any substance use disorders (Admon et al., 2018a; Admon et al., 2018b), prior research has not considered the range of commonly used substances in pregnancy or the potential for effect modification with greater maternal age.

Despite the co-occurring temporal increases in the prevalence of substance use disorders during pregnancy and maternal morbidity, the independent contribution of substance use disorders to maternal morbidity remains unclear. Therefore, our objective was to estimate the independent association between substance use disorders and the risk of severe maternal morbidity in the United States.

2. METHODS AND MATERIALS

2.1 Data

We obtained the National Inpatient Sample (NIS) data from 2003–2016. The NIS is an annual, nationally representative sample of U.S. hospital discharges administered by the U.S. Agency for Healthcare Research and Quality. Specifically, the NIS comprises a 20% stratified sample of data elements collected from hospital discharges across the country, excluding rehabilitation and long-term care hospitals. Data include information on patient demographic characteristics, diagnosis and procedure codes, diagnosis related groups, and patient severity and comorbidities. The University of Pittsburgh Institutional Review Board determined this study was exempt because the data were fully de-identified.

We identified hospital stays for obstetric delivery from 2003 to 2016 using a validated algorithm including Diagnosis Related Groups (DRGs) and ICD-9-CM diagnosis codes (Kuklina et al., 2008), and we then cross-walked the ICD-9-CM codes to ICD-10-CM codes to identify delivery hospitalizations that occurred after Oct 1, 2015. The weighted and unweighted counts of delivery hospitalizations identified before and after the ICD-9 to ICD-10 transition were highly consistent (Supplementary Material Table S1). We included delivery hospitalizations for females aged 18 years and older. Those younger than age 18 were excluded because substance use disorder treatment guidelines are different for adolescents (National Institute on Drug Abuse, 2020). The final analytic sample included pooled cross-sectional data, including a weighted 53.4 million (unweighted N=11.1 million) delivery hospitalizations.

2.2 Exposure Measurement

For each delivery hospitalization, we constructed non-mutually exclusive, binary measures for 7 different substances defined as ICD-9-CM and ICD-10-CM diagnosis codes for the abuse or dependence of alcohol, amphetamines, cannabis, cocaine, opioids, or tobacco (Supplementary Material Table S2). Next, we created binary indicators for 3 broad categories of substance use disorders identified at the delivery hospitalization: cannabis, opioid, and stimulant (amphetamine or cocaine) use disorders.

2.3 Outcomes

Our primary outcome was a binary measure of severe maternal morbidity, defined according to the algorithm published by the Centers for Disease Control and Prevention (CDC (Centers for Disease Control and Prevention, 2015). The CDC algorithm identifies the presence of any of 21 indicator conditions for severe maternal morbidity. Taken together, the presence of any of these indicators represents an adverse outcome that is a ‘near miss’ with maternal death. We also constructed a secondary binary measure of severe maternal morbidity, exCIuding blood transfusion from the definition. Although the gold standard measurement is transfusion of 4 or more units of packed red blood cells (Main et al., 2015), the NIS data lack information on the amount of blood that was transfused. Therefore, we present results for severe maternal morbidity with and without blood transfusion (Kuklina et al., 2009).

2.4 Confounders

Covariates inCIuded age group (18–34 years, >34 years); race/ethnicity (White, Black, Hispanic/Latina, Asian/Pacific Islander, Other race); insurance type (Medicaid, private insurance, other insurance, or self-pay/no charge); quartiles of household income at the zip-code level; and urban/rural county of patient residence (Ingram and Franco, 2014). We also inCIuded indicators for CIinical comorbidities associated with both substance use disorders and severe maternal morbidity inCIuding any additional substance use, HIV or HCV infection, mental health conditions, renal disease, cardiovascular disease, pre-existing or gestational diabetes, hypertension, asthma, and anemia (Supplementary Table S2 inCIudes ICD-9-CM and ICD-10-CM diagnosis codes used).

Because of a large amount of missing data for race/ethnicity in early years of the NIS (~20%), we used a full conditional specification approach to conduct multivariate imputation of race (Healthcare Cost and Utilization Project, 2015). Using a discriminant function, imputed race/ethnicity was modeled on patient age, an indicator for in-hospital death, patient location, NIS stratum, insurance type, ZIP code-based income quintile, an indicator for severe maternal morbidity, and indicators for CIinical comorbidities. All analyses presented inCIude imputed race/ethnicity. Observations with other variables with missing data (insurance type, zip code income, patient urban/rural county of residence) were exCIuded; all had missingness of <3%.

2.5 Statistical Analysis

We employed multivariable logistic regression to estimate the association between each substance use category and risk of severe maternal morbidity. All analyses incorporated survey weights to produce nationally representative results (Healthcare Cost and Utilization Project, 2019). Because maternal age of 35 years or greater is a well-established risk factor for severe maternal morbidity, we were interested in examining whether the association of substance use with severe maternal morbidity might increase with age. Therefore, we inCIuded a statistical interaction term between age groups and substance use disorders in all models.

We fit one model for each substance use disorder or category of disorders. All models inCIuded age group indicators, an interaction between age group and the primary substance

use disorder, an indicator of any other substance use disorders, and Clinical and demographic confounders. The equation shown below demonstrates our modeling of cannabis use disorder and risk of severe maternal morbidity:

$$\text{Logit}[\text{Pr}(SMM = 1)] = \beta_0 + \beta_1 CAN_i + \beta_2 AgeGrp_i + \beta_3 SUD_i * AgeGrp_i + \beta_4 TOB_i + \beta_5 AgeGrp * TOB_i + \beta_6 OtherSUB_i + \beta_7 X_i$$

Where *SMM* is severe maternal morbidity; *CAN* represents the diagnosis of cannabis use disorder, *AgeGrp* signifies whether age at delivery is >34 years (vs 18–34), *TOB* indicates the presence of tobacco use, *OtherSUD* indicates the presence of any additional substance use disorders, and *X* includes a vector of demographic and Clinical confounders for each delivery hospitalization *i*. From this model, we calculated the linear combination of the effects of age group, cannabis use disorder, and their interaction terms (i.e., $\beta_0 + \beta_1 + \beta_2 + \beta_3$ represents the adjusted association between cannabis use disorder and SMM among women aged >34), controlling for other substance use and demographic and Clinical confounders. We replicated this model and linear combination for each substance use disorder category (i.e. cannabis, opioid, stimulant use disorders). We present the adjusted association and related 95% CI between each substance use disorder category and severe maternal morbidity within each age group. Because severe maternal morbidity is a rare outcome, odds ratios approximate risk ratios.

2.6 Sensitivity Analyses

We conducted sensitivity analyses to examine the robustness of our estimates. To examine the consistency of our estimates given a different specification of substance use disorders, we conducted a multivariable regression where we included indicators for each of 7 specific substance use disorder diagnoses (alcohol, amphetamines, cannabis, cocaine, opioids, tobacco, and sedatives/hallucinogens), and their interactions with age group. To examine results had we not imputed race, we conducted a complete-case analysis in which those observations with missing race were excluded.

3. RESULTS

Weighted descriptive characteristics of the study population, overall and stratified by the diagnosis of any substance use disorder at delivery hospitalization, are shown in Table 1. The diagnosis of a substance use disorder during pregnancy was more common among women who were younger, had non-Hispanic white race, and who resided in rural counties. Medicaid was the primary insurance coverage for 70% of pregnant women with a substance use disorder, compared with 40% of pregnant women without a substance use disorder. All Clinical comorbidities, with the exception of gestational diabetes, were markedly higher among pregnant women diagnosed with any substance use disorder relative to those not diagnosed with a substance use disorder. Notably, the prevalence of a mental health condition diagnosis at delivery was 13% among those with a substance use disorder, compared to 2.7% among those without a substance use disorder.

The weighted prevalence of cannabis, opioid, and stimulant use disorders among pregnant women aged 18–34 were 0.75, 0.40, and 0.41, respectively (Table 2). The comparable

weighted prevalences among women aged >34 were 0.26, 0.27, and 0.43, respectively. Table 2 also shows that the unadjusted associations between cannabis, opioid, and stimulant use disorders and the rate of severe maternal morbidity, with and without blood transfusion, by age group. The rates of severe maternal morbidity were significantly greater among women with cannabis, opioid, or stimulant use disorders. The unadjusted associations between cannabis, opioid, or stimulant use disorders were markedly greater among women aged >34 years, relative to those aged 18–34 years. Results were consistent across both definitions of severe maternal morbidity, with and without blood transfusion. (See Appendix Table 3 for the rates of each specific severe maternal morbidity indicator, by age group and substance use disorder status).

Figure 1 shows the weighted adjusted association between cannabis, opioid, and stimulant use categories and the risk of severe maternal morbidity, according to age group. Results can be interpreted as the association between each category of substance use disorder and severe maternal morbidity, adjusting for all other substance use disorders and demographic and Clinical confounders. After adjusting for demographic characteristics and Clinical comorbidities, cannabis use disorder was associated with a small reduction in the risk of severe maternal morbidity either in those aged 18–34 (aOR: 0.95; 95% CI: 0.87,1.01) and was not associated with risk of severe maternal morbidity in those aged >34 (aOR: 0.91; 95% CI: 0.78,1.06). Compared with women without opioid use disorder, women with an opioid use disorder had a 50% increased risk (aOR: 1.51 95% CI: 1.41,1.61) of severe maternal morbidity among those aged 18–34. By comparison, among women aged >34, having an opioid use disorder was associated with a smaller increased risk of severe maternal morbidity (aOR: 1.17; 95% CI: 1.00,1.38). Stimulant use disorders were associated with a substantially increased risk of severe maternal morbidity among those aged 18–34 (aOR: 1.92, 95% CI: 1.80,2.04) compared with women without a stimulant use disorder, with a similar increased risk observed among those aged >34 (aOR: 1.85, 95% CI: 1.66,2.06). Results from the multivariable models were consistent in terms of magnitude, direction, and 95% confidence intervals when examining the association between substance use disorders and risk of severe maternal morbidity, excluding blood transfusions.

3.1 Sensitivity Analyses

Results from a model including indicators for specific substances were highly consistent with the primary results (Supplementary Material Table S4). There were no meaningful differences in our results when we included only women with complete data for race and ethnicity (Supplementary Material Table S5).

4. DISCUSSION

In this nationally representative study, we found that pregnant women with either an opioid or stimulant use disorder have a significantly increased risk of severe maternal morbidity compared with women who did not have these disorders, and that cannabis use was not associated with an increased risk of severe maternal morbidity. The magnitude and direction of associations we observed were consistent across maternal age groups and were consistent when considering severe maternal morbidity with and without including blood transfusions.

These findings indicate that the rise in the prevalence of substance use disorders among pregnant women may accompany other chronic conditions such as hypertension and diabetes as a contributing factor to the rise in severe maternal morbidity in the United States.

We did not observe an independent association between cannabis use disorders and increased risk of severe maternal morbidity, after controlling for other substance use including tobacco. Although smoked cannabis is associated with an increased risk of low birthweight, (El Marroun et al., 2009; National Academy of Medicine Committee on the Health Effects of Marijuana, 2017) evidence is mixed on whether and how cannabis is associated other adverse pregnancy outcomes (Metz et al., 2017). Notably, cannabis acts differently from other substances of abuse, such as narcotics or alcohol, in that it does not act on the central nervous system but rather through the endocannabinoid system (Behnke et al., 2013; Metz and Stickrath, 2015). A potential explanation for our current finding may be that cannabis use is not associated with injection drug use and overdose, which can precipitate sequelae such as sepsis, endocarditis, cardiovascular and pulmonary failure which are on the causal pathway to severe maternal morbidity (Smid et al., 2019).

Opioid and stimulant use disorders were independently associated with substantial increases in the risk of severe maternal morbidity. Opioid use disorders were associated with a moderate (17%–50%) increased risk of severe maternal morbidity. However, the risks associated with opioid use disorder are mitigated by treatment with buprenorphine or methadone (Jones et al., 2012; Zedler et al., 2016). Because the NIS data do not allow us to observe medication treatment for opioid use disorder, the risks we observed represent the average association among women with and without medication treatment (Krans et al., 2019). Stimulant use disorders, including amphetamine or cocaine use disorders, were associated with nearly double the risk of severe maternal morbidity. This is consistent with past research linking these substances to increased risk of mortality in the post-delivery period (Hser et al., 2012; Wolfe et al., 2005). Surprisingly, in adjusted analyses, we did not identify a stronger association between substance use disorders and severe maternal morbidity among those in the older age group. Substance use or abuse often develops at younger ages with progression to dependence over time, and women may progress to dependence at a faster rate than men (Hernandez-Avila et al., 2004). Additionally, a lack of effect modification by age might reflect that older women may be more likely to receive treatment for substance use disorders in pregnancy relative to younger women (Krans et al., 2019).

4.1 Limitations

This study has limitations. First, we relied on diagnosis codes to identify substance use disorders, which may introduce exposure misclassification. Because of the lack of validation studies of diagnostic codes for identifying substance use in pregnancy (McGrew et al., 2020), it is unclear how such exposure misclassification would bias results (Lash, 2007). We note that characteristics of our exposed group are highly consistent with prior research of women with substance use disorders (Substance Abuse and Mental Health Services Administration, 2014). Second, the NIS data do not allow for us to accurately distinguish between substance use and substance use disorders. For instance, a woman who

with substance use or a substance use disorder may be more likely to receive a diagnosis of substance use disorder because of increased screening or urine testing pregnancy. Third, the data lacked information on treatment for substance use disorders in pregnancy, which we would expect to be an important effect modifier. The associations in our study therefore represent average associations among women with and without treatment. Fourth, the data did not allow us to follow the same individuals over time, precluding our ability to assess the progression of substance use disorders within the same person. Fifth, the CDC algorithm to identify severe maternal morbidity in hospital discharge data is limited and has been shown to result in false positive cases (Himes and Bodnar, 2020; Main et al., 2016). To address this limitation, we assessed severe maternal morbidity with and without blood transfusion in the definition and our results were consistent. Finally, we cannot rule out possible bias from unmeasured confounding. Although we included a broad range of demographic and clinical comorbidities available in the NIS, we were unable to measure social-environmental factors, such as neighborhood context, that affect both substance use disorders and risk of severe maternal morbidity (Wang et al., 2020).

4.2 Conclusion

Substance use, particularly the use of opioids, amphetamines, or cocaine, may contribute to severe maternal morbidity in the United States. Our findings highlight the need for universal delivery of evidence-based screening and treatment of substance use disorders in pregnancy. Further investigation is needed to elucidate the complex causal pathways by which specific substance use disorders or polysubstance use may influence the risk of severe maternal morbidities and how substance use treatment may mitigate the risk of severe maternal morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Role of Funding Source

This study was supported by the National Institute on Drug Abuse (award number R01DA045675). The funder had no role in the collection, analysis, and interpretation of the data; or the decision to approve publication of the finished manuscript.

REFERENCES

- Admon LK, Bart G, Kozhimannil KB, Richardson CR, Dalton VK, Winkelman TNA, 2018a Amphetamine- and Opioid-Affected Births: Incidence, Outcomes, and Costs, United States, 2004–2015. *Am. J. Public Health*, e1–e7.
- Admon LK, Winkelman TNA, Moniz MH, Davis MM, Heisler M, Dalton VK, 2017 Disparities in Chronic Conditions Among Women Hospitalized for Delivery in the United States, 2005–2014. *Obstet. Gynecol* 130, 1319–1326. [PubMed: 29112666]
- Admon LK, Winkelman TNA, Zivin K, Terplan M, Mhyre JM, Dalton VK, 2018b Racial and Ethnic Disparities in the Incidence of Severe Maternal Morbidity in the United States, 2012–2015. *Obstet. Gynecol* 132, 1158–1166. [PubMed: 30303912]
- Alkema L, Chou D, Hogan D, Zhang S, Moller AB, Gemmill A, Fat DM, Boerma T, Temmerman M, Mathers C, Say L, United Nations Maternal Mortality Estimation Inter-Agency Group, c., technical advisory, g., 2016 Global, regional, and national levels and trends in maternal mortality between

- 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. *Lancet* 387, 462–474. [PubMed: 26584737]
- Andersson C, Vasan RS, 2018 Epidemiology of cardiovascular disease in young individuals. *Nat. Rev. Cardiol* 15, 230–240. [PubMed: 29022571]
- Aoyama K, Pinto R, Ray JG, Hill AD, Scales DC, Lapinsky SE, Hladunewich MA, Seaward GR, Fowler RA, 2019 Association of Maternal Age With Severe Maternal Morbidity and Mortality in Canada. *JAMA Netw. Open* 2, e199875. [PubMed: 31441937]
- Atkinson AL, Santolaya-Forgas J, Blitzer DN, Santolaya JL, Matta P, Canterino J, Oyelese Y, 2015 Risk factors for perinatal mortality in patients admitted to the hospital with the diagnosis of placental abruption. *J. Matern. Fetal. Neonatal. Med* 28, 594–597. [PubMed: 24888498]
- Behnke M, Smith VC, Committee on Substance Abuse, Committee on Fetus and Newborn, 2013 Prenatal substance abuse: short- and long-term effects on the exposed fetus. *Pediatrics* 131, e1009–1024. [PubMed: 23439891]
- Centers for Disease, C., Prevention, 2012 Integrated prevention services for HIV infection, viral hepatitis, sexually transmitted diseases, and tuberculosis for persons who use drugs illicitly: summary guidance from CDC and the U.S. Department of Health and Human Services. *MMWR Recomm. Rep* 61, 1–40.
- Centers for Disease Control and Prevention, 2015 Severe Maternal Morbidity in the United States. <http://www.cdc.gov/reproductivehealth/maternalinfanthealth/severematernalmorbidity.html>. (Accessed May 21 2016).
- Cohen JM, Hernandez-Diaz S, Bateman BT, Park Y, Desai RJ, Gray KJ, Paterno E, Mogun H, Huybrechts KF, 2017 Placental Complications Associated With Psychostimulant Use in Pregnancy. *Obstet. Gynecol* 130, 1192–1201. [PubMed: 29112657]
- Creanga AA, Berg CJ, Ko JY, Farr SL, Tong VT, Bruce FC, Callaghan WM, 2014 Maternal mortality and morbidity in the United States: where are we now? *J. Womens Health (Larchmt)* 23, 3–9. [PubMed: 24383493]
- El Marroun H, Tiemeier H, Steegers EA, Jaddoe VW, Hofman A, Verhulst FC, van den Brink W, Huizink AC, 2009 Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. *J. Am. Acad. Child. Adolesc. Psychiatry* 48, 1173–1181. [PubMed: 19858757]
- Fingar K, Hambrick MM, Heslin KC, Moore JE, 2018 Trends and Disparities in Delivery Hospitalizations Involving Severe Maternal Morbidity, 2006–2015, in: *Agency for Healthcare Research and Quality (Ed.). Rockville, MD*
- Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM, 2018 Opioid Use Disorder Documented at Delivery Hospitalization - United States, 1999–2014. *MMWR Morb. Mortal. Wkly. Rep* 67, 845–849. [PubMed: 30091969]
- Healthcare Cost and Utilization Project, 2015 HCUP Methods Series: Missing data methods for the NIS and the SID, in: *Healthcare Cost and Utilization Project (Ed.).*
- Cost Healthcare and Project Utilization, 2019 Trend weights for HCUP NIS data. <https://www.hcup-us.ahrq.gov/db/nation/nis/trendwghts.jsp>. (Accessed December 28 2019).
- Hernandez-Avila CA, Rounsaville BJ, Kranzler HR, 2004 Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. *Drug Alcohol. Depend* 74, 265–272. [PubMed: 15194204]
- Himes KP, Bodnar LM, 2020 Validation of criteria to identify severe maternal morbidity. *Paediatr. Perinat. Epidemiol*
- Hser YI, Kagihara J, Huang D, Evans E, Messina N, 2012 Mortality among substance-using mothers in California: a 10-year prospective study. *Addiction* 107, 215–222. [PubMed: 21831178]
- Ingram DD, Franco SJ, 2014 2013 NCHS Urban-Rural Classification Scheme for Counties. *Vital Health Stat* 2, 1–73.
- Janevic T, Zeitlin J, Egorova N, Hebert PL, Balbierz A, Howell EA, 2020 Neighborhood Racial And Economic Polarization, Hospital Of Delivery, And Severe Maternal Morbidity. *Health Aff. (Millwood)* 39, 768–776. [PubMed: 32364858]
- Jarlenski M, Paul NC, Krans EE, 2020 Polysubstance use among pregnant women with opioid use disorder in the United States, 2007–2016. *Obstet. Gynecol.* epub ahead of print

- Jenkins JA, Gordon AJ, 2015 Substance use disorder prevention and treatment in stigmatized patient populations: ripe for innovation. *Subst. Abuse* 36, 1–2. [PubMed: 25607933]
- Jones HE, Fischer G, Heil SH, Kaltenbach K, Martin PR, Coyle MG, Selby P, Stine SM, O'Grady KE, Arria AM, 2012 Maternal Opioid Treatment: Human Experimental Research (MOTHER)--approach, issues and lessons learned. *Addiction* 107 Suppl 1, 28–35. [PubMed: 23106924]
- Kozhimannil KB, Interrante JD, Henning-Smith C, Admon LK, 2019 Rural-Urban Differences In Severe Maternal Morbidity And Mortality In The US, 2007–15. *Health Aff. (Millwood)* 38, 2077–2085. [PubMed: 31794322]
- Krans EE, Kim JY, James AE 3rd, Kelley D, Jarlenski MP, 2019 Medication-Assisted Treatment Use Among Pregnant Women With Opioid Use Disorder. *Obstet. Gynecol* 133, 943–951. [PubMed: 30969219]
- Kuklina E, Callaghan W, 2011 Chronic heart disease and severe obstetric morbidity among hospitalisations for pregnancy in the USA: 1995–2006. *BJOG* 118, 345–352. [PubMed: 21091604]
- Kuklina EV, Callaghan WM, 2010 Cardiomyopathy and other myocardial disorders among hospitalizations for pregnancy in the United States: 2004–2006. *Obstet. Gynecol* 115, 93–100. [PubMed: 20027040]
- Kuklina EV, Meikle SF, Jamieson DJ, Whiteman MK, Barfield WD, Hillis SD, Posner SF, 2009 Severe obstetric morbidity in the United States: 1998–2005. *Obstet. Gynecol* 113, 293–299. [PubMed: 19155897]
- Kuklina EV, Whiteman MK, Hillis SD, Jamieson DJ, Meikle SF, Posner SF, Marchbanks PA, 2008 An enhanced method for identifying obstetric deliveries: implications for estimating maternal morbidity. *Matern. Child Health. J* 12, 469–477. [PubMed: 17690963]
- Lash TL, 2007 Heuristic thinking and inference from observational epidemiology. *Epidemiology* 18, 67–72. [PubMed: 17149141]
- Lisonkova S, Potts J, Muraca GM, Razaz N, Sabr Y, Chan WS, Kramer MS, 2017 Maternal age and severe maternal morbidity: A population-based retrospective cohort study. *PLoS Med* 14, e1002307. [PubMed: 28558024]
- Main EK, Abreo A, McNulty J, Gilbert W, McNally C, Poeltler D, Lanner-Cusin K, Fenton D, Gipps T, Melsop K, Greene N, Gould JB, Kilpatrick S, 2016 Measuring severe maternal morbidity: validation of potential measures. *Am. J. Obstet. Gynecol* 214, 643 e641–643 e610. [PubMed: 26582168]
- Main EK, Goffman D, Scavone BM, Low LK, Bingham D, Fontaine PL, Gorlin JB, Lagrew DC, Levy BS, National Partnership for Maternal, S., Council for Patient Safety in Women's Health, C., 2015 National Partnership for Maternal Safety: consensus bundle on obstetric hemorrhage. *Anesth. Analg* 121, 142–148. [PubMed: 26091046]
- McGrew KM, Homco JB, Garwe T, Dao HD, Williams MB, Drevets DA, Jafarzadeh SR, Zhao YD, Carabin H, 2020 Validity of International Classification of Diseases codes in identifying illicit drug use target conditions using medical record data as a reference standard: A systematic review. *Drug Alcohol. Depend* 208, 107825. [PubMed: 31982637]
- Metz TD, Allshouse AA, Hogue CJ, Goldenberg RL, Dudley DJ, Varner MW, Conway DL, Saade GR, Silver RM, 2017 Maternal marijuana use, adverse pregnancy outcomes, and neonatal morbidity. *Am. J. Obstet. Gynecol*
- Metz TD, Stickrath EH, 2015 Marijuana use in pregnancy and lactation: a review of the evidence. *Am. J. Obstet. Gynecol* 213, 761–778. [PubMed: 25986032]
- National Academy of Medicine Committee on the Health Effects of Marijuana, 2017 The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. The National Academies Press, Washington, DC.
- National Institute on Drug Abuse, 2020 Evidence-based approaches to treating adolescent substance use disorders. <https://www.drugabuse.gov/publications/principles-adolescent-substance-use-disorder-treatment-research-based-guide/evidence-based-approaches-to-treating-adolescent-substance-use-disorders>. (Accessed June 22 2020).
- Say L, Souza JP, Pattinson RC, et al., 2009 Maternal near miss--towards a standard tool for monitoring quality of maternal health care. *Best Pract. Res. Clin. Obstet. Gynaecol* 23, 287–296.

- Smid MC, Metz TD, Gordon AJ, 2019 Stimulant Use in Pregnancy: An Under-recognized Epidemic Among Pregnant Women. *Clin. Obstet. Gynecol* 62, 168–184.
- Abuse Substance and Mental Health Services Administration, 2014 Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series Rockville, MD
- Terplan M, Kennedy-Hendricks A, Chisolm MS, 2015 Prenatal Substance Use: Exploring Assumptions of Maternal Unfitness. *Subst. Abuse* 9, 1–4.
- Wang E, Glazer KB, Howell EA, Janevic TM, 2020 Social Determinants of Pregnancy-Related Mortality and Morbidity in the United States: A Systematic Review. *Obstet. Gynecol* 135, 896–915. [PubMed: 32168209]
- Wolfe EL, Davis T, Guydish J, Delucchi KL, 2005 Mortality risk associated with perinatal drug and alcohol use in California. *J. Perinatol* 25, 93–100. [PubMed: 15496968]
- Young-Wolff KC, Tucker LY, Alexeeff S, Armstrong MA, Conway A, Weisner C, Goler N, 2017 Trends in Self-reported and Biochemically Tested Marijuana Use Among Pregnant Females in California From 2009–2016. *JAMA* 318, 2490–2491. [PubMed: 29279917]
- Zedler BK, Mann AL, Kim MM, Amick HR, Joyce AR, Murrelle EL, Jones HE, 2016 Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. *Addiction* 111, 2115–2128. [PubMed: 27223595]

HIGHLIGHTS

- Severe maternal morbidity is increasing in the United States
- The contribution of substance use disorders to severe maternal morbidity is unclear
- Opioid and stimulant use disorders were associated with risk of severe maternal morbidity
- Cannabis use disorder was not associated with increased risk of severe maternal morbidity

Figure 1. Weighted adjusted association between substance use disorders in pregnancy and severe maternal morbidity among females ages 18 and older in the US.

Adjusted odds ratios represent the linear combination of age group, substance use disorders, and their interaction terms. Models control for age, race/ethnicity, patient insurance, rural/urban residence, and all Clinical comorbidities (HIV, HCV, mental health conditions, renal or cardiovascular disease in pregnancy, diabetes or gestational diabetes, hypertension, anemia, asthma, and thyroid disease). Models also control for use of tobacco, alcohol, or any substance use other than the primary substance.

Table 1.

Weighted descriptive characteristics of delivery hospitalizations among females ages 18 and older in the United States, overall and by substance use disorder status

	Overall, Weighted N=53,405,672	No substance use disorder, Weighted N=50,384,176	Any substance use disorder, Weighted N=3,021,496
Age group, % (95% CI)			
<i>18 – 34 years</i>	84.6 (84.3,84.8)	84.2 (83.9,84.6)	90.3 (90.2,90.5)
<i>> 34 years</i>	15.4 (15.1,15.7)	15.8 (15.5,16.1)	9.7 (9.6,9.9)
Race/Ethnicity[*], % (95% CI)			
<i>White</i>	54.0 (53.1,55.0)	53.1 (52.1,54.1)	69.9 (68.9,70.9)
<i>Black</i>	13.3 (12.8,13.8)	13.2 (12.7,13.7)	15.7 (15.0,16.4)
<i>Hispanic</i>	21.3 (20.3,22.3)	22.1 (21.1,23.1)	8.3 (7.8,8.8)
<i>Other</i>	11.3 (10.9,11.8)	11.6 (11.2,12.1)	6.1 (5.6,6.6)
Insurance Type[†], % (95% CI)			
<i>Medicaid</i>	41.6 (40.1,42.5)	39.8 (38.9,40.8)	70.1 (69.4,70.8)
<i>Private Insurance</i>	51.9 (50.8,53.0)	53.7 (52.6,54.8)	22.8 (22.2,23.4)
<i>Other / Medicare</i>	3.3 (3.2,3.5)	3.3 (3.1,3.5)	4.1 (3.9,4.4)
<i>Self-pay / No-charge</i>	3.2 (3.0,3.5)	3.2 (3.0,3.5)	3.0 (2.9,3.2)
Clinical Comorbidities[‡], % (95% CI)			
<i>HIV</i>	0.11 (0.10,0.12)	0.10 (0.09,0.11)	0.30 (0.27,0.33)
<i>HCV</i>	0.25 (0.24,0.26)	0.11 (0.11,0.12)	2.6 (2.4,2.7)
<i>Mental Health condition[§]</i>	3.3 (3.2,3.3)	2.7 (2.6,2.8)	12.5 (12.3,12.8)
<i>Renal disease in pregnancy</i>	0.19 (0.19,0.20)	0.19 (0.18,0.19)	0.29 (0.27,0.30)
<i>Heart disease in pregnancy</i>	0.71 (0.68,0.74)	0.71 (0.68,0.74)	0.81 (0.77,0.86)
<i>Gestational diabetes</i>	6.8 (6.7,6.9)	6.9 (6.8,7.0)	6.2 (6.1,6.3)
<i>Hypertension</i>	4.9 (4.8,5.0)	4.9 (4.8,5.0)	5.5 (5.4,5.6)
<i>Anemia</i>	9.3 (9.0,9.5)	9.0 (8.8,9.3)	13.2 (12.8,13.5)
<i>Asthma</i>	3.2 (3.1,3.2)	2.9 (2.8,3.0)	7.6 (7.4,7.8)
<i>Thyroid disorder</i>	2.7 (2.6,2.7)	2.7 (2.7,2.8)	2.0 (1.9,2.0)
County of Residence, % (95% CI)			
<i>Urban</i>	85.6 (85.1,86.3)	86.3 (85.7,86.9)	74.8 (73.7,75.9)
<i>Rural</i>	14.4 (13.7,15.0)	13.7 (13.1,14.3)	25.2 (24.1,26.3)

Note: Substance use disorder defined as at least one of any of the following diagnoses: alcohol, amphetamine, cannabis, cocaine, opioid, sedative or tobacco use disorders.

^{*} Missing race/ethnicity data were imputed using a full conditional specification approach based on observed patient characteristics.

[†] Other insurance includes Veterans Administration and military health plans.

[‡] See Appendix for full description of conditions and ICD-9 and ICD-10 diagnostic codes

[§] Mental health conditions include depressive disorders, anxiety, bipolar disorder, schizophrenia, suicidal ideation, and suicide attempt

// Urban/rural county of residence based on the National Center for Health Statistics Urban-Rural Classification scheme.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Weighted unadjusted association between substance use disorders and severe maternal morbidity among delivery hospitalizations among females ages 18 and older in the United States

Table 2.

	Substance use disorder prevalence, %	Severe maternal morbidity per 100,000	Unadjusted Odds Ratio [†]	Unadjusted Odds Ratio (95% CI)	Severe maternal morbidity per 100,000 excl. blood transfusion	Unadjusted Odds Ratio (95% CI) [‡]
Age 18–34						
Cannabis Use Disorder	0.75	-	-	-	-	-
No	-	1,397		ref	456	ref
Yes	-	2,235		1.61 (1.52, 1.72)	654	1.44 (1.31, 1.58)
Opioid Use Disorder	0.40	-	-	-	-	-
No	-	1,397		ref	455	ref
Yes	-	2,962		2.16 (2.02, 2.30)	1,038	2.29 (2.07, 2.54)
Stimulant Use Disorders [*]	0.41	-	-	-	-	-
No	-	1,394		ref	455	ref
Yes	-	3,709		2.73 (2.57, 2.89)	1,098	2.43 (2.20, 2.69)
Age >34						
Cannabis Use Disorder	0.26	-	-	-	-	-
No	-	2,066		ref	719	ref
Yes	-	4,660		2.32 (2.01, 2.67)	1,457	2.041 (1.588, 2.623)
Opioid Use Disorder	0.27	-	-	-	-	-
No	-	2,065		ref	718	ref
Yes	-	5,000		2.50 (2.17, 2.87)	1,818	2.560 (2.027, 3.231)
Stimulant Use Disorders [*]	0.43	-	-	-	-	-
No	-	2,052		ref	715	ref
Yes	-	6,955		3.57 (3.25, 3.92)	2,237	3.18 (2.71, 3.72)

^{*} Includes amphetamines and cocaine use disorders

[†] From a univariate logistic regression of each substance use disorder on severe maternal morbidity, stratified by maternal age group

[‡] From a univariate logistic regression of each substance use disorder on severe maternal morbidity excluding blood transfusions, stratified by maternal age group