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Severity of neonatal opioid withdrawal syndrome with prenatal exposure to serotonin reuptake inhibitors

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Abstract

OBJECTIVE: To evaluate the severity of neonatal opioid withdrawal syndrome (NOWS) in infants prenatally exposed to medications for opioid use disorder (MOUD) and serotonin reuptake inhibitors (SRI).

METHODS: A prospective cohort included 148 maternal–infant pairs categorized into MOUD (n = 127) and MOUD + SRI (n = 27) groups. NOWS severity was operationalized as the infant's need for pharmacologic treatment with opioids, duration of hospitalization, and duration

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AUTHOR CONTRIBUTIONS

All authors have met the *Pediatric Research* authorship requirements. L.N.B. and A.S. conceptualized the research idea and study design, provided the overall guidance and oversight, and made substantial contributions to interpretation of data. L.N.B. also contributed to the funding acquisition and acquisition of the data, and drafted the initial version of the manuscript. L.H. contributed to the research methodology and conducted data analyses. A.S., M.H., and M.A. contributed to the data acquisition and data curation, quality control/quality assurance efforts, and interpretation of data. All authors provided revisions for important intellectual content and approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Written informed consent was obtained from all participants.

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of treatment. The association between prenatal SRI exposure and the need for pharmacologic treatment (logistic regression), time-to-discharge, and time-to-treatment discontinuation (Cox proportional hazards modeling) was examined after adjusting for the type of maternal MOUD, use of hydroxyzine, other opioids, benzodiazepines/sedatives, alcohol, tobacco, marijuana, gestational age, and breastfeeding.

RESULTS: Infants in the MOUD + SRI group were more likely to receive pharmacologic treatment for NOWS (OR = 3.58; 95% CI: 1.31; 9.76) and had a longer hospitalization (median: 11 vs. 6 days; HR = 0.54; 95% CI: 0.33; 0.89) compared to the MOUD group. With respect to time-to-treatment discontinuation, no association was observed in infants who received treatment (HR = 0.59; 95% CI: 0.26, 1.32); however, significant differences were observed in the entire sample (HR = 0.55; 95% CI: 0.34, 0.89).

CONCLUSIONS: Use of SRIs among pregnant women on MOUD might be associated with more severe NOWS.

INTRODUCTION

Over-prescription of opioid analgesics in the United States during the last few decades resulted in escalating prevalence of prescription opioid misuse. Opioid use disorder (OUD) has become a national crisis affecting over two million Americans.[1] Pregnant women and newborn children are among the most vulnerable populations being impacted. In 2019, 6.5% of pregnant women self-reported use of prescription opioids,[2] while earlier estimates, based on the Medicaid claims data, suggested that as many as 22.8%[3] to 28%[4] of women filled at least one opioid prescription during pregnancy. The prevalence of OUD reported at the time of infant delivery quadrupled between 1999 and 2014[5]. Opioids, including medications for opioid use disorder (MOUD), cross the placental barrier into fetal circulation.[6,7] Decreasing levels of opioid in the newborn after delivery precipitate the onset of signs and symptoms of physiologic and/or behavioral dysregulation (grouped into four key domains: state control/attention, motor and tone control, sensory processing, and autonomic control)[8] collectively labeled neonatal opioid withdrawal syndrome (NOWS) or neonatal abstinence syndrome (NAS).[9,10] During the last decade, NOWS incidence increased three- to five-fold,[11,12] and might be as high as 14.4 per 1000 births in some subgroups.[12] While the term NOWS was developed to describe withdrawal symptoms attributed specifically to opioids, most of these infants have polysubstance exposure. There is currently no “gold standard” definition of NOWS and various scoring tools are used to determine severity and guide treatment.[13,14] Recent evidence suggests a number of factors that might increase NOWS severity, including polysubstance use, male sex, more advanced gestational age at birth, and use of more than one psychotropic medication during gestation.[15–17]

Use of psychotropic medications is recommended in pregnancy for most psychiatric disorders of at least moderate intensity with functional impairment.[18] An estimated 25–45% of pregnant women with OUD have additional psychiatric co-morbidities, with anxiety and depression being the most common.[16] Selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI; SRIs collectively) are the most commonly prescribed medications in pregnancy for the treatment of depression and anxiety with maternal prescription rates estimated at 5.5% in the United States and 3.01%

globally.[19] Gestational SRI exposure is associated with adverse signs of the neurological, gastrointestinal, and respiratory systems in about 30% of exposed newborns.[20] However, these signs do not follow the same course as opioid-related withdrawal symptoms,[21] may not be attributed to decreasing levels of medication in the neonate,[22] and appear to be related to the degree of platelet serotonin suppression in the neonate.[23,24] The signs of NOWS have not been reliably differentiated from non-opioid neonatal adverse signs; therefore, it is difficult to determine which agents are contributing the most in infants with polysubstance exposure.[9] The primary objective of this study is to compare the severity of NOWS, defined as the need for pharmacologic treatment with opioids, duration of hospitalization, and duration of treatment, in neonates exposed prenatally to MOUD with and without concurrent co-exposure with SRIs.

METHODS

Study design and eligibility criteria

This study utilizes data collected in a prospective cohort—Ethanol, Neurodevelopment, Infant and Child Health (ENRICH-1), at the University of New Mexico (UNM).[25] The study was approved by the UNM Human Research Review Committee; all participants were recruited through UNM prenatal care clinics and signed the informed consent. The ENRICH cohort included four study visits: prenatal, delivery-attended visit, and infant evaluations at 6 and 20 months. The following eligibility criteria were applied: (1) ≥18 years; (2) singleton pregnancy; (3) Albuquerque metro area resident; (4) ability to participate in informed consent process in English; (5) no more than occasional stimulant use (defined as less than monthly use of cocaine, methamphetamine, or MDMA in the first trimester and no use in second and third trimester); and (6) no major fetal anomalies per ultrasound examination. Two primary exposures of interest included MOUD and alcohol use resulting in four study groups: MOUD (receiving MOUD in pregnancy with no concurrent alcohol use); Alcohol (≥3 drinks per week or ≥2 binge drinking episodes in periconceptional period and alcohol use during pregnancy (either per self-report or positive biomarkers) and no use of MOUD); (c) MOUD + Alcohol; (d) Controls (lifetime abstainers of illicit drugs and tobacco, abstinent from alcohol during pregnancy, and reported no more than minimal alcohol use in periconceptional period). For purposes of this analysis, the sample size was limited to subjects in MOUD and MOUD + Alcohol groups, which were combined, and the effect of alcohol was examined as a potential confounder. Then the combined MOUD group was stratified by SRI exposure in the third trimester (any vs. none). The following additional eligibility criteria were utilized for this analysis: (1) exposure to MOUD during the third trimester of pregnancy (5 participants who discontinued MOUD use before the third trimester were excluded); (2) completion of study Visits 1 and 2; (3) live birth and survival during the first month of life (1 infant demise shortly after birth was excluded); and (4) gestational age at delivery ≥32 weeks (2 very preterm infants were excluded). The final sample size included 148 maternal–infant pairs: 121 in the MOUD group and 27 in MOUD + SRI.

Maternal mental health disorders, use of psychotropic medications, and NOWS severity

Exposure of interest was defined as the third trimester use of SRI, which was abstracted from inpatient and outpatient progress notes, external medication history provided by community pharmacy refill and pharmacy benefits manager records, medication reconciliation, and other clinical documentation in electronic medical records (EMR). The use of other common psychotropic medications (i.e., hydroxyzine) were also obtained. Additionally, diagnoses of maternal mental health disorders during pregnancy were abstracted from the EMR and ICD-10 codes. According to the UNM hospital guidelines adopted by all neonatal units, pharmacological treatment of NOWS is initiated if an infant scored ≥8 on the Finnegan Neonatal Abstinence Scoring Tool[26] on three consecutive assessments, if the mean of three scores is ≥8, or if two consecutive scores are ≥12[27]. All infants with confirmed or suspected prenatal opioid exposure remain inpatient for a minimum of 96 h. EMR administration records were reviewed to obtain frequency and dosing of methadone or morphine administration during the infant's hospitalization. Severity of NOWS symptoms was operationalized as: (1) proportion of infants with NOWS requiring pharmacologic treatment; (2) length of hospitalization; (3) length of pharmacologic treatment. These measures have been extensively used in other clinical studies.[14,27–30] Length of treatment (number of days) was considered in the entire cohort (infants who were not treated experienced the "event" of treatment discontinuation at day 0) and after restricting to those pharmacologically treated.

Other prenatal and perinatal risk and resilience factors

Based on the existing literature,[31,32] information on the type of maternal MOUD (methadone vs. buprenorphine), use of other psychotropic medications during the third trimester (i.e., hydroxyzine), gestational age at delivery, initiation of breastfeeding in the hospital,[31] infant rooming-in with the mother during the hospital stay (exclusive, partial, no/limited rooming-in), and prenatal substance use were collected. Alcohol use was ascertained by the Timeline Follow back (TLFB) interviews[32] which captured alcohol use in (a) the periconceptional period; (b) 30 days before enrollment; and (c) 30 days before delivery. Reported quantity and frequency of alcohol use was converted to absolute alcohol (AA) using multipliers proposed by Bowman et al.[33] averaged across three TLFB calendars, and categorized as no exposure, 0–0.5 AA per day, and >0.5 AA per day. Substance use was ascertained by both a structured questionnaire, based on the National Survey on Drug use and Health,[34] and a urine drug screen panel 7 (UDS-7: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, PCP, cannabinoids/THC). UDS-7 samples were analyzed at the U.S. Drug Testing Laboratory (Des Plaines, IL). For analysis purposes, substance use was dichotomized and reflected the self-reported use between Visit 1 and Visit 2 and results of UDS-7 administered at Visit 2, which, in combination, approximate use in the third trimester.

Statistical analyses

Differences in demographic, medical, and substance use among study groups were compared using Fisher's exact test and a two-sample *t*-test with unequal variances for categorical and continuous variables, respectively. The NOWS continuous outcomes were

summarized using medians and interquartile ranges (Q1, Q3). In unadjusted analyses, the association between SRI exposure and these outcomes was evaluated using a log-rank test. The multivariable analyses used Cox proportional hazards modeling; statistical significance was evaluated using a Wald test, and effect sizes were measured using hazard ratios (HR) and corresponding 95% Wald confidence intervals (95% CI). The HR was defined as the ratio of the instantaneous event rate between the groups. Since the "event" in this case is either leaving the hospital or discontinuing treatment, it marks a positive outcome. Therefore, a *HR < 1 indicates that SRI use has an adverse effect* relative to the no SRI group. For example, when the event is hospital discharge, a HR < 1 indicates that infants in the SRI group tend to leave the hospital later than infants in the no SRI group. The association between prenatal SRI exposure and the proportion of infants requiring pharmacologic treatment was examined by the Fisher's exact test and logistic regression in univariate and multivariable analyses, respectively.

Type of maternal MOUD was examined as a potential effect modifier, using the same regression models as above, but with an interaction term added. Given increasing recognition that gestational age at delivery and breastfeeding are not traditional confounders, but might instead be along the causal pathway,[35] analyses were conducted with and without adjusting for these variables. Thus, Model 1 was adjusted for the type of maternal MOUD, hydroxyzine, heroin/misuse of opioid analgesics, benzodiazepines/sedatives, alcohol use, tobacco, and marijuana; Model 2 included preterm delivery and initiation of breastfeeding in a hospital in addition to covariates in Model 1. Additionally, sensitivity analyses were conducted after addition of the three most common maternal mental health disorders (depression, anxiety, posttraumatic stress disorder) and rooming-in variables (no/limited vs. partial vs. exclusive) in all models.

RESULTS

The mean (±SD) maternal age at enrollment was 28.1 ± 5.4 years, and a sample included a large proportion of Hispanic/Latina patients (72.1%) and almost a third (27.9%) of participants with less than high school education. The mean gestational age at enrollment was 22.3 ± 7.1 weeks. Among the two study groups (MOUD vs. MOUD + SRI), no significant differences were observed in maternal age or gestational age at enrollment, ethnicity, race, marital status, education, employment status, gravidity, or parity (Table 1). No significant differences in key infant or postpartum characteristics were observed (all p's > 0.05).

In the entire sample, 42.6% of participants were on methadone and 57.4% on buprenorphine as the latest type of MOUD before delivery. No significant differences in the type of MOUD between the groups were observed ($p = 0.20$; Table 2). The most prevalent co-exposures were tobacco (51.7%) and marijuana (20.3%). Significantly higher proportion of subjects in the MOUD + SRI group (38.5%) had used heroin or reported misuse of opioid analgesics compared to the MOUD group (16.5%; $p = 0.02$). Almost half of women in the MOUD + SRI group reported alcohol use, with 15.4% in the MOUD + SRI and 7.4% in the MOUD group reporting >0.5 AA/day (equivalent to >7 standard drinks per week). There was no evidence of any other differences in substance use between the groups (all p's >0.05). The

most prevalent SRI medication in the MOUD + SRI group was sertraline (44.4%) followed by fluoxetine (40.7%) and duloxetine (37.0%). Concurrent use of hydroxyzine was prevalent in both groups (38.0% in MOUD and 37.0% in the MOUD + SRI; $p = 1.00$). Women in the MOUD + SRI group had a significantly higher prevalence of depression/depressive symptoms (85.7% vs. 36.9%) and anxiety (75.0% vs. 41.8%) compared to the MOUD group ($p < 0.01$).

In univariate analysis, a higher proportion of infants in the MOUD + SRI group required pharmacologic treatment for NOWS (59.3%) compared to the MOUD group (38.0%, $p = 0.053$; Table 3). These differences became significant after adjusting for the type of maternal MOUD, use of hydroxyzine, heroin/misuse of opioid analgesics, benzodiazepines/sedatives, alcohol, tobacco, and marijuana. In the entire sample, the mean duration of hospitalization was 12.7 ± 11.0 days (median: 6 days; Q1: 5, Q3: 18). Infants in the MOUD + SRI group had prolonged hospitalization (median 11 days; Q1: 5, Q3: 20.5) compared to the MOUD group (median 6 days; Q1: 5, Q3: 18; $p = 0.16$ in unadjusted analysis; $p < .05$ after adjusting for confounders). Among infants who received pharmacologic treatment for NOWS, duration of treatment was similar in both groups (median 12 days; Q1: 9, 18 days in the MOUD vs. median 10.5; Q1: 6; Q3: 14.5; $p > 0.05$ in both unadjusted and adjusted analyses).

Table 4 shows results of multivariable modeling (logistic regression for binary outcome and survival analysis for time-to-event outcomes). Infants in the MOUD + SRI group were more likely to require pharmacologic treatment for NOWS in both Model 1 (OR = 3.58; 95% CI: 1.31; 9.76) and Model 2 (OR = 3.90; 95% CI: 1.40; 10.89). Other statistically significant predictors included maternal use of hydroxyzine (Model 1: OR = 2.62; 95% CI: 1.18, 5.83; Model 2: OR = 2.37; 95% CI: 1.05; 5.35) and the maternal use of methadone vs. buprenorphine (Model 1: OR = 5.43; 95% CI: 2.43, 12.11; Model 2: OR = 4.78; 95% CI: 2.10; 10.85; Supplemental Table 1). There was no statistically significant evidence of an interaction between the type of MOUD and SRI use with respect to the need for pharmacologic treatment ($p = 0.14$). The effect size was larger and statistically significant only in those prenatally exposed to buprenorphine though (Model 1: OR = 5.68, 95% CI: 1.70, 19.04), while association was non-significant in the methadone subgroup (OR = 1.22, 95% CI 0.22, 6.78). Results were similar between Model 1 and Model 2 (data not shown).

Cumulative incidence curves and HRs for the entire sample and after stratification by the type of maternal MOUD are presented for the following outcomes: (a) time-to-discharge (Supplementary Fig. 1A–C); (b) time-to-discontinuation of NOWS treatment in the entire sample (Supplementary Fig. 2A–C); (c) time-to-discontinuation of NOWS treatment in a subset of infants who received pharmacologic treatment (Supplementary Fig. 3A–C). There was no evidence of an interaction between the type of MOUD and SRI use with respect to the duration of hospitalization ($p = 0.34$) or duration of treatment ($p = 0.64$), though the magnitude of the effect was larger in the buprenorphine subgroup (see Supplementary Figs. 1–3 for unadjusted and adjusted effect sizes). Infants in the MOUD + SRI group were discharged later then infants in the MOUD group (Model 1: HR = 0.54; Model 2: HR = 0.51; both p's<0.05). With respect to the length of treatment, no evidence of a difference between the two groups was observed when in analyses restricted to those who received

pharmacologic treatment (Model 1: HR = 0.59; Model 2: HR = 0.54; both p's > 0.05). However, in the entire sample of treated and untreated infants, the MOUD + SRI group completed treatment for NOWS later than the MOUD group (Model 1: HR = 0.55; Model 2: HR = 0.53; both p's < 0.05). Other significant predictors included the type of maternal MOUD and initiation of breastfeeding in a hospital (Supplementary Table 1).

Results of sensitivity analyses (inclusion of three most common maternal mental health conditions and infant rooming-in) did not substantially change the magnitude or significance of the association between SRI exposure with NOWS outcomes (data not shown); however, we acknowledge that due to a very strong collinearity between SSRI use and maternal mental health conditions interpretation of these results is challenging. As expected, limited/no rooming-in with the mother was associated with worse NOWS outcomes; however, causal inferences cannot be drawn from these results given that the infant placement in a higher-level nursery is driven by severity of the symptoms. Additionally, we examined results from the reduced models by applying stepwise regression using AIC as a criterion. Most covariates were removed from the models in the stepwise procedure; however, the overall results remained largely the same indicating that overparameterization was not present in fully saturated models.

DISCUSSION

Results of this study indicate that use of SRIs in the third trimester among women on MOUD is associated with more severe NOWS. Specifically, infants in the MOUD + SRI group had significantly higher odds of the need for pharmacologic treatment of NOWS (3.6–3.9 times higher in the MOUD + SRI group, depending on the statistical model). Additionally, the likelihood of being discharged sooner was lower in the MOUD + SRI group comparted to the MOUD group. Results were inconclusive for the length of treatment.

Among three retrospective cohort studies, which relied on the information available in EMR, only one focused on the SSRI co-exposure with MOUD,[36] while the other two focused on antidepressants in general.[37–39] A study by Bhatt-Mehta et al.[36] demonstrated a higher incidence of NOWS requiring pharmacologic treatment, longer length of treatment, and longer length of stay in the SSRI + MOUD group compared to MOUD only; however, none of the differences reached statistical significance. O'Connor et al.[39] demonstrated that maternal use of buprenorphine and antidepressants was associated with the longer "time to the onset of NAS resolution" (defined as the number of hours from birth until the last time the peak NAS score is reached) compared to the buprenorphine only group. In a retrospective cohort of women on methadone treatment, concurrent antidepressant use was not a significant predictor of NOWS outcomes.[37] A study by Wachman et al.[38] found that maternal use of methadone and SSRIs was associated with prolonged infant hospitalization. A report from the only randomized clinical trial in the field to examine the relative effectiveness of buprenorphine vs. methadone for OUD reported that concurrent SSRI and MOUD (not stratified by methadone or buprenorphine) use was associated with higher peak NAS score and higher total dose of medication required to treat NAS.[16]

It should be noted that none of the prior studies examined the impact by the type of maternal MOUD in the same study population when examined as a co-exposure with psychotropic medications. In our study, the effect of SRIs was more pronounced after adjusting for the type of MOUD. The interaction between SRI and the type of MOUD was not statistically significant, possibly due to the limited statistical power. However, given a priori knowledge about a strong association between the type of MOUD on NOWS outcomes (maternal buprenorphine use being associated with less severe NOWS),[31,40] we were compelled to examine the stratified results, which demonstrated larger effect sizes in the buprenorphine group. Results of survival analysis were significant only in the buprenorphine subgroup; however, we acknowledge that it had a larger sample size compared to the methadone subgroup. Future studies should examine the interaction between SRI use and the type of MOUD further.

In terms of potential biological mechanisms underpinning the association between SRI and NOWS outcome, one might hypothesize that serotonin toxicity in the neonate may increase the severity of neonatal withdrawal through a potential drug–drug interaction between SRIs and opioid medications that inhibit the reuptake of serotonin. In March 2016, the FDA issued a Drug Safety Communication concerning the association of the entire class of opioid pain medicines with serotonin toxicity.[41] Methadone, fentanyl, tramadol, and meperidine are known to inhibit serotonin transporter (SERT) activity, and methadone and meperidine are known to increase serotonin release in the neural synapses.[41] Additionally, certain antidepressants (i.e., fluoxetine, paroxetine, citalopram, and bupropion) are potent inhibitors of CYP2D6 and may decrease neonatal metabolism of CYP2D6 substrates.[42] Serotonin toxicity in the neonate may manifest as signs similar to NOWS including irritability, hypertonia, restlessness, and tremors.[43] To date, we are not aware of any clinical or scientific reports describing serotonin toxicity in pregnant women on MOUD or infants exposed to opioids and SSRIs; thus, the impact of these interactions in the neonate is unknown at this time and requires further investigation.

As expected, the prevalence of mental health conditions was much higher in the MOUD + SRI group compared to the MOUD group in our sample. Despite this difference, the MOUD group had substantial psychiatric comorbidity with 70% of the women having a diagnosed mental health condition and 37% a depressive disorder. Due to multicollinearity between SRI and psychiatric diagnosis, we could not adjust for the underlying condition, thus confounding by indication cannot be ruled out. The 2015–2017 National Survey on Drug Use and Health data indicate that among adults with OUD, more than 64% reported past-year mental illness.[44] In our study, the MOUD + SRI group also had a substantially higher use of illicit opioids—35% compared to 13% in the MOUD group. The prevalence of alcohol use was also higher in the MOUD + SRI group; however, differences did not reach statistical significance. Our earlier study reported that prenatal alcohol exposure was not associated with NOWS severity; however, one infant diagnosed with Fetal Alcohol Syndrome had very severe NOWS.[30] The effect of alcohol co-exposure, especially heavy chronic alcohol use (not a focus of ENRICH cohort), requires further investigation. It should be noted that concurrent use of illicit opioids, alcohol, and other substances was controlled for in multivariable analysis in this study.

The study findings should be examined in light of its limitations. First, we acknowledge that while the hypothesis of a potential synergistic effect of SRIs and opioids is based on emerging clinical observations and suggested biological mechanisms, a robust theoretical framework to differentiate infant physiologic and/or behavioral dysregulation attributable to a specific class of medications versus polysubstance exposure is currently lacking in the field. While both prenatal (polysubstance use, type of MOUD) and early postpartum factors (rooming-in, breastfeeding) are known to influence NOWS severity, it is difficult to conceptualize complex interplay and temporal relationship between these variables. Limited rooming-in, while associated with NOWS severity in previous reports, might be a consequence rather than a predictor of severe NOWS (i.e., infants with more severe NOWS symptomatology are placed in higher level nurseries with limited rooming-in options). Additionally, gestational age at delivery is gaining recognition as a 'collider' rather than a confounder.[43,45,46] Thus, we presented two statistical models: first with adjustment for known prenatal confounders and second with addition of gestational age and breastfeeding. We also recognize that this report excluded two very preterm infants (<32 weeks gestation) due to a known strong effect of such early gestational age on prolonged hospitalization. Second, we recognize that a sample size of the MOUD + SRI group is modest, which might have limited statistical power in examination of interactions and stratified analyses. Third, this report could not examine more nuanced effects of specific SSRI and SNRI medications, SRI dose (including dose–response patterns), or frequency/quantity of co-exposures; thus, we acknowledge the possibility of residual confounding. Fourth, we recognize that this report relied on medical diagnoses and indications for medication use abstracted from medical records. While prescription information was supplemented by review of inpatient and outpatient progress notes, external prescription history provided by community pharmacy refill and pharmacy benefits manager records, medication reconciliation, and other clinical documentation, we acknowledge potential misclassification of SRI exposure (both under- and over-estimation of true exposure in some patients). Differential misclassification (that is, more accurate SRI information in one study group vs. another), however, is highly unlikely, due to prospective nature of the study. Additionally, we could not examine the effect of underlying severity of maternal mental health symptoms, measured on a continuous scale, on NOWS outcomes. The prevalence of psychiatric comorbidity in our study, however, is similar to prior reports,[47] and the results of sensitivity analyses after addition of three most common maternal mental conditions as covariates did not substantially change the results (although collinearity between maternal mental health conditions and SRI use make results difficult to interpret).

The study had a number of unique strengths. First, a prospective cohort design minimized potential information bias. Maternal prenatal substance use, including MOUD, illicit drugs, tobacco, and alcohol, was carefully characterized by prospective repeated questionnaires and biomarker panels. Second, the sample included racially and ethnically diverse group of patients underrepresented in research. It is important to note that there were no substantive differences in demographic characteristics and co-exposures between the groups, except heroin/illicit opioid use, which was controlled in multivariable analyses. Third, rigorous eligibility criteria helped to ensure higher internal validity and minimize effect of confounding factors (e.g., any potential effects of stimulant co-exposures were effectively

controlled for by restriction). Fourth, UNM hospital utilizes consistent protocol-driven approach to both pharmacologic and non-pharmacologic treatment of NOWS, including a standardized NOWS scoring system, consistent methadone and morphine dosing, and deescalation of treatment affecting the length of therapy. Finally, the study carefully examined the potential effect modification by the type of maternal MOUD, which had not been previously examined, and the effect of other common psychotronic medications (e.g., hydroxyzine).

The American College of Obstetrics and Gynecology (ACOG) recognizes the importance of adequate screening and treatment of OUD in pregnancy and postpartum follow up.[48] ACOG recommends universal screening not only for opioid use but also polysubstance use and comorbid mental health disorders that often impact this population.[49] Disentangling the effect of underlying mental health conditions from the effect of psychotropic medications and other exposures known to affect infant dysregulation is challenging. A large database linkage study of Medicaid-covered patients demonstrated that exposure to two or more psychotropic medications increased the risk of and severity of NOWS.[15] Adequate screening and treatment for depression and SUD is paramount during the antepartum and postpartum periods;[50] however, substantial disparities in the availability of the treatment for both depression and SUD in young and racial/ethnically minority women exist.[51] Treatment options which maximize positive outcomes for *both* the mother and fetus in patients with comorbid OUD and mental health disorders are not well established. This study is among the first emerging reports in the field drawing attention to complex interplay between prenatal antidepression treatment, OUD, underlying medical conditions, and other pre/perinatal factors which affect NOWS severity.

Expanding upon this work in larger samples is critical to informing optimal treatment choices for women with OUD and their infants. Recent changes in NOWS assessment and treatment practices include a focus on parent-infant centered care and non-pharmacologic management. However, infants with severe NOWS continue to have heightened short- and long-term risks. A recent report utilizing data from more than 400 healthcare facilities in the U.S. indicate that NOWS is associated with increased unplanned healthcare utilization in infants during the first year of life.[52] The impact of newborn care practices and treatments, both pharmacologic and non-pharmacologic, on long-term child outcomes needs to be evaluated in larger studies of infants with prenatal co-exposure to MOUD and SRI. It will be important to examine the effect of the dose, duration, and potency of both SRIs and maternal mental health conditions on NOWS outcomes. Untangling these complex relationships will provide key information to understand which medications in pregnancy, in isolation and combination, may contribute to better outcomes for women with OUD and their infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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IMPACT:

- A potential drug–drug interaction between maternal SRIs and opioid medications that inhibit the reuptake of serotonin has been hypothesized but not carefully evaluated in clinical studies.
- Results of this prospective cohort indicate that the use of SRIs among pregnant women on MOUD is associated with more severe neonatal opioid withdrawal syndrome.
- This is the first prospective study which carefully examined effect modification between the type of maternal MOUD and SRI use on neonatal outcomes.
- This report lays the foundation for treatment optimization in pregnant women with co-occurring mental health and substance use disorders.

Table 1.

Socio-demographic and medical characteristics of participants by study group.

Characteristics	MOUD (*n* = 121)	MOUD + SRI (*n* = 27)	*P*
Maternal characteristics			
	Mean (SD)	Mean (SD)	
Maternal age (years)	28.1 (5.3)	28.3 (5.6)	0.69
Gestational age at enrollment (weeks)	22.6 (7.1)	20.8 (7.2)	0.23
	N (%)	*N* (%)	
Maternal ethnicity:			0.47
Hispanic/Latina	89 (73.6)	17 (63.0)	
Non-Hispanic	32 (26.4)	9 (33.3)	
Maternal race:			0.06
White	106 (87.6)	21 (77.8)	
African American	4 (3.3)	1 (3.7)	
American Indian	11 (9.1)	2 (7.4)	
Other	–	2 (7.4)	
Marital status:			0.67
Single/separated/divorced	57 (47.1)	11 (40.7)	
Married/cohabitating	63 (52.1)	15 (55.6)	
Maternal education:			0.32
Less than high school	44 (36.4)	6 (22.2)	
High school/some college	34 (28.1)	7 (25.9)	
College/professional degree	43 (35.2)	13 (48.1)	
Currently employed	39 (32.0)	8 (29.6)	1.00
Gravidity: primigravida	21 (17.4)	3(11.1)	0.57
Parity: nulliparous	31 (24.8)	5 (18.5)	0.62
Infant characteristics			
	Mean (SD)	Mean (SD)	
Gestational age at delivery (weeks)	38.5 (1.9)	38.3 (2.4)	0.65
Birth weight (g)	2935 (525.5)	2896 (623.1)	0.89
	N (%)	*N* (%)	
Infant gender: female	59 (48.8)	12 (46.4)	0.83
Breastfeeding initiation in the hospital	58 (47.9)	15 (55.6)	0.52
Rooming-in during the hospital stay[a]			0.48
Exclusive	64 (52.9)	11 (40.7)	
Partial	15 (12.4)	4 (14.8)	
No/limited rooming-in	42 (34.7)	12 (44.4)	

[a]Exclusive rooming-in includes placement in the units, such as Mother Baby Unit (MBU) and OB Special Care where infant stayed in the same room as the mother; no/limited rooming-in included higher level nurseries (NICU, ICN-3, ICN-4); partial included placement in both types of units during birth hospitalization.

Table 2.

Maternal MOUD and substance use patterns by study group.

Characteristics	MOUD (*n* = 121) *n* (%)	MOUD + SRI (*n* = 27) *n* (%)	*P*
MOUD before delivery:			0.20
Methadone	55 (45.5)	8 (29.6)	
Buprenorphine	66 (55.5)	19 (70.4)	
Heroin or misuse of opioid analgesics	20 (16.5)	10 (38.5)	0.02
Sedatives or benzodiazepines	10 (8.3)	3 (11.1)	0.71
Marijuana	24 (19.8)	6 (22.2)	0.79
Tobacco	62 (51.2)	14 (53.8)	0.83
Alcohol use throughout pregnancy:			0.23
No use	84 (69.4)	14 (53.8)	
>0 & <0.5 AA/day	28 (23.1)	8 (30.8)	
>0.5 AA/day	9 (7.4)	4 (15.4)	
SRI medications:			
Fluoxetine	–	11 (40.7)	–
Sertraline	–	12 (44.4)	–
Citalopram	–	2 (7.4)	–
Escitalopram	–	2 (7.4)	–
Duloxetine	–	10 (37.0)	–
Hydroxyzine	46 (38.0)	10 (37.0)	1.00
Psychiatric disorder (any)	75 (70.0)	27 (100.0)	<0.001
Depression	45 (36.9)	23 (85.7)	<0.001
Anxiety	51 (41.8)	20 (75.0)	<0.01
PTSD	19 (16.4)	8 (28.6)	0.10
Bipolar disorder	11 (9.0)	3 (10.7)	0.72
Schizophrenia	2 (1.6)	0 (0.0)	1.00

AA absolute alcohol (oz) averaged across three TLFB calendars.

Table 3.

NOWS severity outcomes by the SSRI/SNIR exposure.

NOWS severity outcomes	MOUD (*n* = 121) *N* (%)	MOUD + SRI (*n* = 27) *N* (%)	Unadjusted *P*	Adjusted *P*[a]
NOWS requiring pharmacologic treatment[b]	46 (38.0)	16 (59.3)	0.053	0.01
Morphine	29 (24.0)	12 (44.4)	–	–
Methadone	25 (20.7)	5 (18.5)	–	–
	Median (Q1, Q3)	Median (Q1, Q3)		
Duration of hospitalization in days	6 (5, 18)	11 (5, 20.5)	0.16	0.02
Duration of treatment in days (all infants)	0 (0, 9)	6 (0, 11)	0.26	0.02
Duration of treatment in days (infants who received pharmacologic treatment)	12 (9, 18)	10.5 (6, 14.5)	0.66	0.20

[a]Adjusted for the type of maternal use of MOUD, hydroxyzine, heroin/misuse of opioid analgesics, benzodiazepines/sedatives, alcohol use, tobacco, marijuana.

[b]Categories are not mutually exclusive as nine infants (eight in MOUD and one in MOUD + SRI groups) were treated with both morphine and methadone during the hospitalization).

Table 4.

Association between SRI prenatal exposure and NOWS severity outcomes.

NOWS severity outcomes	Model 1			Model 2		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Need for pharmacologic treatment of NOWS	3.58	1.31; 9.76	0.01	3.90	1.40; 10.89	0.01
	HR	**95% CI**		**HR**	**95% CI**	
Time to hospital discharge	0.54	0.33, 0.89	0.02	0.51	0.31, 0.84	0.01
Time-to-treatment discontinuation (entire sample)	0.55	0.34, 0.89	0.02	0.53	0.33, 0.86	0.01
Time-to-treatment discontinuation (limited to infants who received pharmacologic treatment)	0.59	0.26, 1.32	0.20	0.54	0.24, 1.23	0.14

Model 1: Adjusted for the type of maternal use of MOUD, hydroxyzine, heroin/misuse of opioid analgesics, benzodiazepines, alcohol use, tobacco, marijuana.

Model 2: Adjusted for all covariates in Model 1 and also preterm delivery and initiation of breastfeeding in a hospital.

Note: Odds ratios (OR) > 1 indicates increased odds of the need for pharmacological treatment of NOWS in SRI vs. No SRI group; thus, indicate negative outcome.

Hazard ratios (HR) indicates the ratio of the instantaneous event rate (hospital discharge or discontinuation of treatment) between SRI and no SRI groups. Thus, HR > 1 indicates positive outcome (higher likelihood of being discharged or discontinue treatment earlier) and HR < 1 indicates negative outcome (lower likelihood of being discharged or discontinue treatment earlier).