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History of postpartum depression as a contributor to the severity of NAS

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HIGHLIGHTS

- Maternal history of Post-Partum Depression correlated to more severe NAS.
- Prenatally exposed male neonates withdrawal more severely.
- Neonate NAS was not altered by most maternal co-occurring psychiatric conditions.

ABSTRACT

Currently, there are no clinical tools available to accurately predict the severity of neonatal withdrawal. Studies of non-exposed neonates suggest that maternal depression and anxiety are predictive of negative short and long-term neonatal outcomes, but research is lacking in the addicted population. We studied of 109 pregnant women in medication-assisted treatment (MAT) and their neonates to determine if psychiatric conditions co-occurring with Substance Use Disorder (SUD) contributed to the severity of neonatal withdrawal. The need for pharmacological intervention, Finnegan scores, length of methadone treatment, and length of hospital stay were used to assess withdrawal severity. Categorical variables were analyzed in Stata14 using Chi Square and continuous variables were analyzed using Wilcoxon Rank Sum. Among the 110 neonates whose outcomes were reviewed, a maternal history of Postpartum Depression (PPD) was found to be correlated with increased severity of withdrawal. The neonates born to mothers with past diagnoses of PPD had more consecutive days of high Finnegan scores (95% confidence interval [CI], $P = 0.003$), longer length of treatment (95% CI, $P = 0.006$), and length of hospital stay (95% CI, $P = 0.014$). There was no apparent relationship between NAS severity and other psychiatric disorders. In a study of pregnant women with SUD and their neonates, we uncovered a relationship between the severity of NAS and maternal history of PPD. Our findings demonstrate that further research into these deleterious outcomes is warranted. Until then, we suggest collection of maternal history of PPD and careful screening for new cases in the SUD population.

1. Introduction

The global epidemic that is the opioid addiction crisis is accompanied by a soaring incidence of Neonatal Abstinence Syndrome (NAS), the symptomology observed in neonates with *in utero* exposure to neuroactive substances. (Kocherlakota, 2014) Our institution reports some of the highest rates of substance use during pregnancy in the United States, with approximately 94.3 per 1000 live births at risk for developing NAS due to *in utero* exposure. About half of those exposed require pharmacological intervention to treat withdrawal symptoms. (Loudin, Werthammer, et al., 2017) NAS depends on a conglomeration of complex genetic and environmental factors, and currently, there are

Abbreviations: NAS, Neonatal Abstinence Syndrome; SUD, Substance Use Disorder; MAT, medication-assisted treatment; CHH, Cabell Huntington Hospital; UDS, Urine Drug Screen; NICU, Neonatal Intensive Care Unit; NTU, Neonatal Therapeutic Unit; PPD, Postpartum Depression

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no clinical tools to accurately predict the incidence and severity of neonatal withdrawal.

Studies in non-exposed neonates suggest that maternal depression and anxiety are predictive of poor neonatal outcomes. (Eastwood et al., 2017; Hoffman, Dunn, & Njoroge, 2017) Many of these adverse outcomes, including risk of preterm labor, low birth weight, delayed pediatric psychomotor skills, and behavioral difficulties have also been correlated with Neonatal Abstinence Syndrome (NAS) (Logan, Brown, & Hayes, 2013), the symptomology observed in neonates with *in utero* exposure to neuroactive substances. (Kocherlakota, 2014) However, research regarding psychiatric conditions is lacking in the Substance Use Disorder (SUD), pregnant population. In a review of the impact of maternal stress and psychological state on fetal development, Kinsella and Monk describe support behind the "fetal origins hypothesis", in which prenatal exposures, including psychological condition of the mother, have a lasting impact. (Kinsella & Monk, 2009).

Individuals with psychiatric disorders, including depression and anxiety, are more than twice as likely to have a SUD. (Quello, Brady, & Sonne, 2005) SUD exacerbates mental illness, leading to cyclical consequences that negatively impact the clinical course and prognosis of patients with these comorbidities. Applying this interpretation to the exclusively taxing experience that is pregnancy, expectant mothers with psychiatric comorbidities and their fetuses are an exceptionally disadvantaged population. It is therefore valuable to dedicate investigative resources to study NAS in the context of the mother neonate dyad, rather than the mother and child as separate entities. Understanding the interaction of SUD and maternal psychiatric diagnosis on neonatal outcomes is essential to guide clinical decision-making in this disadvantaged population.

2. Methods

2.1. Data collection

Data was collected from women enrolled in MAT programs located in Huntington, West Virginia and their neonates from January 2016 to October 2017. The study was limited to women who gave birth at the same hospital, to assure a consistent treatment protocol and was approved by the Marshall University Institutional Review Board. Medical records were extracted from electronic health systems at Marshall Health, Valley Health System, and Cabell Huntington Hospital (CHH) and stored on a secure REDCap database. All births included in data analysis (n = 109, n = 110, respectively) occurred at CHH. MAT programs use buprenorphine (Subutex) and were in compliance with State and Federal guidelines, as well as American Society for Addiction Medicine recommendations. (ASAM, 2015; SAMHSA, 2015; WV-DHHR, 2016) Maternal information including baseline demographics, psychiatric history, medical history, substance use history, previous pregnancy and birth history, medications prescribed during pregnancy, and urine drug screen (UDS) toxicology (supplemental material) results were extracted and verified.

Neonatal data included gender, birth weight, birth length, head circumference, delivery method, hospital length of stay, known *in utero* exposure, umbilical cord toxicology report, Finnegan Scale Scoring System (Finnegan, Connaughton, Kron, & Emich, 1975) results, need and duration of pharmacological treatment for neonatal withdrawal, and discharge plan.

Umbilical cord toxicology was ordered if the mother had a positive UDS at the time of delivery, a known positive screen during pregnancy, or a maternal admission of drug abuse. The results of the umbilical toxicology report (United States Drug Testing Laboratories, Des Plaines, Illinois) (supplemental material) were used in addition to maternal UDS and reported substance use during pregnancy to account for substances of exposure.

The hospital length of stay was a summation of the days spent in the newborn nursery, Neonatal Intensive Care Unit (NICU), Neonatal Therapeutic Unit (NTU), and Lily's Place. (Loudin, Murray, et al., 2017) The clinical staffs at the NICU, NTU, and Lily's Place follow the same NAS clinical and training protocols. Therefore, Finnegan scoring and pharmacological treatment strategies are consistent.

2.2. Neonatal outcomes

The neonatal outcomes included the length of hospital stay, length of methadone treatment, consecutive days with an average Finnegan score greater than or equal to 8, and the pharmacological interventions used to control withdrawal symptoms. We included the length of methadone treatment in concordance with length of hospital stay to report the neonates' time spent exhibiting acute withdrawal symptoms without confounding factors that influence length hospital stay. Circumstances such as medical complications and social placement issues can delay discharge.

Days with high Finnegan scores provided a quantitative description of the severity of withdrawal of the neonate. The number of consecutive days with a Finnegan score greater than or equal to 8 was calculated according to the daily mean Finnegan score, based on scores collected every 3 h. At the time of this study, our institution considered 3 consecutive scores that equaled or exceeded 8 to warrant pharmacological treatment beginning with methadone.

Methadone was the first-line medicine for NAS with clonidine as a second line adjuvant as previously described.(Loudin, Murray, et al., 2017) If treatment with methadone and clonidine failed to control withdrawal symptoms, adjunctive medication was given based on the patient symptomology and *in utero* exposure. Based on the treatment recommendations for neonatal withdrawal, the treatment profile was utilized to further provide description of the severity of withdrawal. Neonates categorized by 1) no pharmacological intervention, 2) methadone, 3) methadone and clonidine, or 4) methadone, clonidine, and adjunctive medication (phenobarbital, lorazepam, and/or gabapentin). Thus, patients receiving adjunctive therapy were considered to have more severe withdrawal.

3. Method of analysis

Descriptive statistics were described in terms of mean, median, and sum. To study the relationship between maternal psychiatric disorders and neonatal outcomes, statistical analyses were performed using Stata14 (StataCorp, 2015). Categorical variables were analyzed using Chi Square and continuous variables were analyzed using Wilcoxon Rank Sum. Neonatal withdrawal treatment category was treated as a categorical variable (0 = no pharmacological intervention, 1 = methadone, 2 = methadone and clonidine, 3 = methadone, clonidine, and adjunctive medication). Consecutive days of high Finnegan score, length of methadone treatment, and length of hospital stay were treated as continuous variables.

Neonates were organized into groups based on maternal psychiatric diagnosis. Each psychiatric diagnosis was treated as a dichotomous variable (0 = no disorder, 1 = disorder) and statistical significance was accepted at $P \leq .05$. In a separate analysis, the psychiatric diagnosis groups were further divided by the presence or absence of treatment with psychotropic medications during the pregnancy to account for the potential confounding variable. Neonates whose mothers were prescribed psychotropic medication at any time during the pregnancy were placed in the "treatment" group and compared to the "no treatment" group. Psychotropic medications included antidepressants, anxiolytics, mood stabilizers, and antipsychotics.

4. Results

4.1. Maternal characteristics

A total of 109 pregnant women were studied. Characteristics of