Can Birth Weight Influence the Development of Neonatal Abstinence Syndrome?

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Can Birth Weight Influence the Development of Neonatal Abstinence Syndrome?

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Introduction & Objective

A constellation of neurologic, respiratory, and gastrointestinal symptomologies, not only have the number of diagnostic cases of NAS risen over the years but so has the cost associated with the treatment and management of this condition. For example, NICU admissions for NAS increased in the United States from 7 per 1,000 admissions in 2004 to 27 per 1,000 admissions in 2012, while the mean hospital charges for babies diagnosed with NAS rose from $39,400 in 2000 to $53,400 in 2009 meanwhile mean hospital charges for all other newborns rose from $6,600 in 2000 to $9,500 in 2009. The state of Tennessee, and in particular, East Tennessee, has one of the highest rates of NAS incidence in the United States, and the number of NAS births each year in this part of the country is almost two to three times higher compared to number of NAS births in the rest of the country.

While multiple research studies have been and are currently being conducted on NAS, one aspect of NAS that seems to baffle yet intrigue most researchers is that why do only 35-40% of opioid exposed pregnancies result in NAS requiring medication while the rest do not. This means that there are definitely some discriminatory factors at play in addition to in utero opioid exposure, and our objective in this study was to shed light on one of those potential discriminatory factors, namely birth weight.

Therefore, our objective in this study was to use a large sample size (N=18,728) to elucidate the relationship between birthweight and NAS diagnosis. That is, can high or low birth weight predict the development of NAS among newborns prenatally exposed to opioids.

Methods

This study is a retrospective analysis of all deliveries within the Mountain States Health Alliance System over a 5 years period (July 1, 2011 to June 30, 2016) at all 5 delivery sites in Northeast Tennessee and Southwestern Virginia, N=18,728. Out of the 18,728 newborns file, 2,392 newborns were identified who had prenatal opioid exposure and were simultaneously full term (37+ weeks based on pregnancy ultrasound). The affiliated university Institutional Review Board (IRB) approved the study. Informed consent was waived as the study included encrypted chart review data and no protected health information (PHI). Study participants were identified, and study variables obtained, via electronic abstraction from the delivery hospital electronic health record systems (EHR). Inclusion criteria for the study were available maternal urine drug screen (UDS) at delivery and any opioid exposure during pregnancy. All delivery hospitals had a policy of admission UDS for pregnant mothers at the time of delivery. Opioid exposure was determined via multiple methods, including self-report, positive UDS at delivery, existing diagnosis of maternal substance use disorder involving opioids (from prenatal records), indication and/or prescription of medication assisted treatment, and infant exposure diagnosis or determination that infant had NAS (based on UDS, cord tissue samples, and Finnegan scoring protocol).

Statistical Analysis & Results

All statistical analyses were conducted using SPSS (version 25). Our question was whether birth weight predicted the development of NAS among newborns prenatally exposed to opioids. The file, which was automatically abstracted from the electronic health record, contained all deliveries within the Mountain States Health Alliance System over a 5 year period (July 1, 2011 – June 30, 2016) at all 5 delivery sites in Northeast Tennessee and Southwest Virginia, N=18,728. When limited to newborns who had prenatal opioid exposure (based on self-report, positive urine drug screen during pregnancy or at delivery, or positive cord blood test) and were full term (37+ weeks dating based on pregnancy ultrasound), the sample contained 2,392 newborns.

Birth weight was grouped at ≤3.5kg and ≥3.5kg, with 1712 and 680 newborns in the respective groups, and with ≤3.5kg being a proxy for low or average birth weight with respect to gestational age thresholds and ≥3.5kg being a proxy for high birth weight with respect to gestational age thresholds

To determine control variables, the two birth weight groups were compared on the variables in Table 1. Chi square or t-test was used as applicable for this analysis; t-test was used for age (continuous variable) and Chi square was used for the other variables (which were categorical in nature). Those variables that were significant were included in the final logistic regression analysis predicting NAS development from grouped birth weight.

Table 1. Sample characteristics by birthweight group

	Birthweight ≤ 3.5kg n=1712	Birthweight ≥ 3.5kg n=680	χ2 or t	p
Maternal age (yrs.)	26.4±5.2	26.6±5.3	1.13	.259
Marital status (% married)	37.8%	49.3%	26.36	<.001
Race (% White)	94.9%	96.9%	4.35	.037
Infant gender (% male)	46.7%	59.0%	29.18	<.001
Pregnancy smoking (%)	59.5%	29.6%	173.09	<.001
Pregnancy benzodiazepine use (%)	5.4%	2.1%	11.32	.001
Pregnancy marijuana use (%)	5.4%	1.3%	18.83	<.001

At this stage, when comparing the two birth weight groups on whether or not NAS developed, without having doing logistic regression or controlling for confounding variables, newborns who weighed ≤3.5kg were significantly more likely to develop NAS (22.7%) compared to newborns who weighed ≥3.5kg (9.3%) ($\chi 2=57.11$, $p<.001$).

To determine whether the relationship between birthweight and the development of NAS was a result of pre-existing differences between the two birth weight groups, logistic regression analyses were then run predicting NAS development from birth weight, while controlling for the significant variables in Table 1. Results are presented in Table 2. As can be seen, even after controlling for background and other prenatal exposure differences, newborns who weighed ≤3.5kg were nearly twice as likely to develop NAS compared to newborns who weighed ≥3.5 kg (aOR of 1.95). Interestingly, we can also see that neonates born through pregnancies which involved smoking, benzodiazepine usage, and marijuana usage, had a significantly higher chance of developing NAS, independent of each other, and birth weight as well as other associated factors.

Table 2. Logistic regression results predicting NAS development

	Unstandardized Regression Coefficient	Adjusted Odds Ratio	95% CI
Marital status	.562	1.75	1.36-2.27
Race	-.449	.64	.33-1.22
Infant gender	.300	1.35	1.07-1.71
Pregnancy smoking	1.49	4.45	3.36-5.91
Pregnancy benzodiazepine use	.849	2.34	1.49-3.68
Pregnancy marijuana use	.343	1.41	.87-2.30
Birth weight	.666	1.95	1.41-2.69

Reference groups: Marital Status—married; Race—white; Gender—female; Smoking—none; Benzodiazepine use—none; Marijuana use—none; Birthweight—≥ 3.5 kg

Discussion & Implications

Our study helps shed some important light on the discriminatory factors for NAS development, with birth weight being a significantly associated clinical factor as we now know. That infants born with low or average birth weight (with respect to gestational age thresholds) have a higher risk or are almost twice as likely to develop NAS compared to infants born with a high birth weight (with respect to gestational age thresholds).

Unfortunately, the mechanism for the transport of opioids across the placenta is complicated, and poorly understood. There may be a higher bioavailability of opioids in low to average birth weight infants with there being more unbound or free opioid compounds and metabolites compared to infants of a higher birth weight who may potentially have a higher lipid binding of opioids and subsequently less bioavailability of the free or unbound compounds and metabolites. However, this is more of a speculation rather than a conclusion to explain the results our study.

Regardless, we believe that our study has positive implications for the clinical diagnosis and management of NAS. Being equipped with this knowledge that opioid exposed neonates of low to average birth weight (with respect to gestational age thresholds) have a higher risk of developing NAS will allow physicians to identify infants with a higher risk for NAS early, and this will subsequently lead to better outcomes and reduced severity in cases of NAS.

Conflicts of Interest & Funding

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