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Head circumference in infants with nonopiate-induced neonatal abstinence syndrome

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Original Research

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Abstract

Background. No relationship has been reported between nonopiate neonatal abstinence syndrome (NAS) and anthropometric indices, including head circumference (HC). The purpose of this study was to determine the relationship between maternal nonopioid drug use and HC at birth in neonates with NAS.

Methods. This retrospective observational study included neonates born between January 1, 2010 and March 31, 2019, whose mothers had been taking antipsychotic, antidepressant, sedative, or anticonvulsant medications. The outcome measures were HCs of NAS infants and controls.

Results. Of 159 infants, 33 (21%) were diagnosed with NAS. There was no maternal opioid use among mothers during pregnancy. The HCs in the NAS group were significantly smaller than those in the control group. The median *z*-scores for HC at birth were −0.20 and 0.29 in the NAS group and the control group, respectively ($P = .011$). The median HCs at birth were 33.0 and 33.5 cm in the NAS group and the control group, respectively. Multivariate analysis revealed that maternal antipsychotic drug use and selective serotonin reuptake inhibitors were independently associated with NAS ($P < .001$ and $P = .004$, respectively). Notably, benzodiazepine use and smoking were not independent risk factors.

Conclusions. The results suggest an association between maternal antipsychotic drug use and NAS, which was further associated with decreased HC. Careful monitoring of maternal drug use should be considered to improve fetal outcomes.

Introduction

Neonatal abstinence syndrome (NAS) occurs in infants of mothers who use opioids, antipsychotics, and antidepressants during pregnancy.[1] The clinical features of NAS range from central and autonomic nervous system deficits to digestive system disturbances. Symptoms include irritability, apnea, involuntary movement, seizure, tachycardia, sweating, vomiting, and diarrhea. Infants are assessed and diagnosed using the Finnegan score.[2]

Maternal opioid use is increasing in several countries, and consequently, the incidence of opioid-induced NAS is equally increasing.[3,4] On the contrary, opioids are not generally used as maternal analgesics in Japan, and illicit drug use during pregnancy is rare. Thus, NAS is seldom occurs due to maternal opioid use; instead, it is commonly triggered by maternal use of antipsychotics, antidepressants, and anticonvulsants.

Several studies have reported that infants with opioid-induced NAS have small head circumferences (HCs) at birth.[5,6] HC is related to brain volume and has a possible impact on neurodevelopment.[7-9] Nevertheless, no relationship has been reported between nonopioid-induced NAS and anthropometric indices, including HC. Therefore, this study aimed to determine the relationship between maternal nonopioid drug use and HC in neonates with NAS at birth.

Methods

This retrospective study included neonates born at Okayama University Hospital between January 1, 2010 and March 31, 2019, whose mothers had been taking antipsychotics, antidepressants, sedatives, or anticonvulsants. Only infants with gestational age ≥36 weeks were included. NAS was diagnosed using the Isobe score (Appendix Table A1), a modified Finnegan score widely used in Japan. The scoring commenced several hours after birth and was measured three times daily until discharge. Diagnosis of NAS was established following the confirmation that the use of medication had been continued before or during pregnancy until just before delivery, and an Isobe score of 1 or more was achieved during hospitalization over more than two

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consecutive observations. Pharmacologic treatment was administered following the attainment of an Isobe score of 8 or more. Treatment was considered when there were complications such as seizures, frequent apnea, or parental difficulty situations (eg, breastfeeding challenges due to irritability of the infant).

Maternal demographics, including a history of psychiatric disease, epilepsy, and diabetes, medical history, and perinatal details, were collected. Medication records were investigated to confirm the use of antipsychotics, selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, anticonvulsants, and nonbenzodiazepine hypnotics. Similarly, information on maternal smoking and a history of alcohol consumption were obtained. Neonatal data, such as gender and anthropometric indicators, including birth weight, length, and HC, were collected.

At birth, midwives measured the HC, length, and weight of all newborns. HC was measured with an unstretchable tape on the line passing through the broadest part of the forehead above the eyebrow and the most prominent part of the back of the head. Microcephaly was defined as a HC less than 10th percentile. As the fetus grows weekly, the HC increases. To compare the standardized HCs, the *z*-scores of HCs were used. Each *z*-score was calculated using the physique index calculation sheet developed by the Japan Society for Neonatal Health and Development.[10] Newborns with low birth weight (<2000 g), congenital malformations, chromosomal abnormalities, congenital heart disease, and respiratory disorders were excluded, and neonatal HC was considered the primary outcome.

In statistical analysis, Fisher's exact test, Mann–Whitney *U* test, and binomial logistic regression analysis were used. *P* values <.05 were considered statistically significant. The R 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

This study was approved by the Ethics Committee of Okayama University (No. 1907-040, approved on August 8, 2019). Informed consent was obtained from the mothers of the infants via the opt-out method. This study was a retrospective observational study, performed using the opt-out method on the hospital website.

Results

Table 1 shows the characteristics and clinical parameters of this cohort. In total, 164 newborns and their mothers were included, and five children met the exclusion criteria. Of the remaining 159 infants, 33 were diagnosed with NAS based on the Isobe score, and the prevalence of NAS was 21%. HCs in the NAS group were significantly smaller than those in the control group (Table 2). In infants with NAS, it was similarly noticed that a significantly higher proportion of primiparous mothers and longer hospital stays of the infants were needed; in addition, Apgar scores Of the NAS group at 5 minutes were lower than those of controls. No significant differences were observed in the maternal body mass index or diabetes.

Z-scores at birth were calculated based on the mean measurement for the relevant gestational age. Infants in the NAS group had significantly smaller *z*-scores for length than those of the control group. Between infants in the NAS group and the control group, the ranges of HC had different *z*-scores; however, the median was equally significantly smaller in the NAS group ($P = .011$).

Maternal drug use included antipsychotics in 64 (40%) mothers, benzodiazepines in 46 (29%), SSRIs in 27 (17%), anticonvulsants in 25 (16%), and nonbenzodiazepine hypnotics in 10 (6%) mothers. Table 3 shows that NAS was significantly associated with maternal use of antipsychotics and SSRIs, maternal use of multiple medications, and maternal smoking; however, it was not associated with maternal use of benzodiazepines or anticonvulsants, or maternal alcohol consumption. Notably, no opioid use was observed in either group.

Table 1. Characteristics of the Study

Clinical Characteristics	Total Number
No.	33
Maternal age (y)	31 (29-36)
Maternal BMI (kg/m^2)	21.6 (19.4-25.0)
Multiparity, n (%)	58 (36)
Mode of delivery: vaginal, n (%)	123 (77)
Gestational age at delivery (wk)	39.0 (38.0-40.0)
Male infant, n (%)	84 (53)
Birth weight (g)	2928 (2639-3106)
Birth weight in *z*-score	0.01 (−0.65 to 0.54)
Neonatal length (cm)	50.0 (48.0-51.0)
Neonatal length in z-score	0.59 (−0.11 to 1.24)
Neonatal HC (cm)	33.5 (32.5-34.0)
Neonatal HC in z-score	0.13 (−0.53 to 0.69)
Apgar score at 1 minute	8 (8-8)
Apgar score at 5 minutes	9 (9-9)
Umbilical artery Ph	7.304 (7.270-7.330)
NICU length of stay (day)	6 (5-8)
Growth restrictive maternal disease, n (%)	18 (11)
Gestational and pregestational diabetes, n (%)	18 (11)

Values are expressed in median (interquartile range [IQR]) or number (ratio).
Abbreviations: BMI, body mass index; HC, head circumference; NICU, neonatal intensive care unit.

Subsequently, a multivariate regression analysis was performed with NAS as the dependent variable. Antipsychotics, benzodiazepines, SSRIs, and smoking were incorporated into the model. Maternal antipsychotic use and SSRIs were significantly associated with NAS (adjusted odds ratio [aOR]: 5.83, 95% confidence interval [CI]: 2.15-17.09; aOR: 5.55, 95% CI: 1.76-18.36, respectively). However, benzodiazepine use and smoking were not independent risk factors (aOR: 0.90, 95% CI: 0.24-2.90).

Discussion

It was observed that the use of antipsychotics and SSRIs during pregnancy may cause NAS in newborns; in addition, infants with NAS had significantly smaller HCs, even in mothers with no history of opioid use.

To our knowledge, this is the first study describing the relationship between NAS and HC at birth and nonopioid substance maternal use. Several studies have suggested that opioid use during pregnancy reduces HC in infants with NAS.[5,6] In this study, because there were no maternal opioid users, the relationship between nonopioid drug use and infant HC was evaluated.

Although reduction in HC among infants was observed in this study, few infants were diagnosed with microcephaly. Studies on opioid-induced NAS have reported relatively higher rates of microcephaly with HCs lower than the 10th percentile.[5] While prenatal

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Table 2. Outcome Parameters for NAS and Control Groups.

Clinical Characteristics	NAS Groups	Control Groups	*P* Value
No.	33	126	–
Maternal age (y)	31 (29-36)	33 (29.3-36)	.401
Maternal BMI (kg/m^2)	22.9 (19.2-27.1)	21.6 (19.5-24.0)	.273
Multiparity, n (%)	17 (52)	41 (33)	.066
Mode of delivery: vaginal, n (%)	26 (79)	97 (77)	1
Gestational age at delivery (wk)	38.9 (38.1-39.7)	39.0 (38.0-40.1)	.865
Male infant, n (%)	16 (48)	68 (54)	.696
Birth weight (g)	2928 (2639-3106)	2920 (2622-3228)	.310
Birth weight in *z*-score	−0.36 (−0.63 to 0.25)	0.13 (−0.68 to 0.69)	.127
Neonatal length (cm)	49.0 (48.0-50.0)	50.0 (48.5-51.5)	.048
Neonatal length in *z*-score	0.23 (−0.43 to 0.85)	0.63 (−0.00 to 1.30)	.030
Neonatal HC (cm)	33.0 (32.0-33.5)	33.5 (32.5-34.0)	.034
Neonatal HC in *z*-score	−0.20 (−0.74 to 0.23)	0.29 (−0.46 to 0.79)	.011
Apgar score at 1 min	8 (8-8)	8 (8-8)	.338
Apgar score at 5 min	9 (8-9)	9 (9-9)	.002
Umbilical artery Ph	7.301 (7.269-7.322)	7.304 (7.270-7.332)	.566
NICU length of stay (d)	9 (5-12)	5 (5-7)	<.001
Growth restrictive maternal disease, n (%)	4 (12)	14 (11)	1
Gestational and pregestational diabetes, n (%)	4 (12)	14 (11)	1

Values are expressed in median (interquartile range [IQR]) or number (ratio).
Abbreviations: BMI, body mass index; HC, head circumference; NAS, neonatal abstinence syndrome; NICU, neonatal intensive care unit.

Table 3. Drug Use by NAS and Control Groups

Clinical Characteristics	NAS Groups	Control Groups	*P* Value
No.	33	126	–
Antipsychotic usage, n (%)	22 (68)	32 (25)	<.001
Benzodiazepine usage, n (%)	14 (42)	32 (25)	.083
Nonbenzodiazepine hypnotic drug usage, n (%)	3 (9)	7 (6)	.434
SSRI usage, n (%)	12 (36)	15 (12)	.003
Antiepileptic usage, n (%)	3 (9)	21 (17)	.414
Smoking, n (%)	8 (31)	8 (7)	.003
Alcohol, n (%)	5 (19)	9 (8)	.145
Multiple drugs, n (%)	17 (52)	20 (16)	<.001

Values are expressed in number (ratio).
Abbreviation: NAS, neonatal abstinence syndrome; SSRI, selective serotonin reuptake inhibitors.

opioid administration was reported to reduce fetal brain volume,[11,12] no association has been reported between nonopioid administration and small HC at birth.[13-15]

Notably, the prevalence of NAS in this study was 21%, lower than the values obtained in previous opioid studies (55%-94%).[16] Nonopioid medication use had less impact on both NAS prevalence and low HC at birth than has been reported in opioid studies. Contrary to previous studies, it was observed that smaller HCs were associated with the onset of NAS. If the fetuses were exposed to an amount of drug sufficient to induce smaller HC, NAS would equally be induced.

Regarding neurodevelopment, catch-up growth in HC could be an indicator of development. Because HC correlates with brain volume,[7-9] poor HC growth would be an indicator of developmental retardation. Veroniki et al[17] reported that exposure of the fetus to valproic acid was associated with poor long-term prognosis; however, HC was not reported in that study. The effects of antidepressants and antipsychotics on infant development are yet to be reported.[18,19] For these reasons, continuous measurement of HC and developmental assessments are important in nonopioid NAS infants to reveal any associations. Further follow-up studies are needed since follow-up data were not obtained in this study.

Concerning maternal substance use and NAS onset, it was observed that benzodiazepine use posed no significant risk on NAS development ($P = .082$). In a previous study, Huybrechts et al[20] reported that antipsychotics, SSRIs, and benzodiazepines were associated with NAS. This may be due to maternal benzodiazepine use in both control and NAS groups in this study.

In this study, the length of hospital stay of the infants was longer in the NAS group, which is consistent with the findings of the American National Cohort study.[3] Compared to a previous study,[5] the length of hospital stay in the NAS group studied was 6 days shorter. This could be because opioid-induced NAS probably necessitates longer hospital stays than nonopioid-induced NAS.

Maternal smoking was not a confounding factor for maternal drug use, NAS onset, and HC at birth. Although no reports have demonstrated a direct relationship between NAS and maternal smoking, several reports have demonstrated an indirect impact of smoking on NAS. Oga et al[21] reported that active smokers used

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more drugs during pregnancy than did nonsmokers (61.9% vs 19.1%). Miyazaki et al[22] reported that in Japan, smoking is associated with maternal mental illness during pregnancy. There have been several studies showing the association between maternal smoking and neonatal HC.[23–25] In Japan, Inoue et al[26] reported a significant reduction in HC at birth by maternal or paternal smoking. Tsuda et al[27] reported that smoking might affect maternal blood levels of psychotropic drugs. Considering these findings, it is highly possible that smoking increases the likelihood of NAS. In this study, the cause of the discrepancy seems to be due to the small sample size of smokers.

There were a few limitations to this study. First, observers could have been more likely to diagnose NAS when they were aware of maternal drug use; therefore, there may have been assessment bias. Nevertheless, in this study, because multiple observers established diagnoses, and the bias was minimized. Second, differences in underlying maternal diseases and stress may have affected birth HC. Nevertheless, in this study, these differences were minimized because there was similarity in maternal medication use between study groups. However, duration and doses of medication in each group were not revealed in this study. We are planning to conduct further study to investigate the relationship between HC and total dose of psychotropic drugs. Third, this study was retrospective, and the sample size was relatively small. Although the association between NAS onset and smoking was not statistically significant in the analysis, the high OR may be clinically important.

Conclusion

In conclusion, reduction in HC at birth is associated with non-opioid induced NAS. The specific nonopioid drugs that were significantly associated with NAS were antipsychotics and SSRIs. Given the long-term issues associated with nonopioid induced NAS, in the event antipsychotics and SSRIs are taken during pregnancy, infants require close monitoring and long-term follow-up.

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Supplementary Materials To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S1092852920001522.

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