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Original Research

Elucidating the Relationship Between Maternal Diabetes and Neonatal Abstinence Syndrome

A 2017-2018 Project WATCH Study in Rural Appalachia

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ABSTRACT

Background: Previous research indicated that diabetes during pregnancy results in a more permeable placenta. Based on this data, we hypothesized that women with maternal diabetes were more likely to have infants who developed neonatal abstinence syndrome (NAS).

Purpose: The purpose of the study was to examine the association between maternal diabetes and NAS in a cohort of women reporting substance use during pregnancy.

Methods: This study used data from a population-based cohort of all newborns born in 2017 and 2018 (N = 36,974) in the state of West Virginia and restricted the analysis to those infants with intrauterine substance exposure (14%, n = 5188). Multiple logistic regression was performed to analyze the adjusted relationship between maternal diabetes and NAS while controlling for maternal and infant covariates.

Results: Just over 28% of women with diabetes had an infant who developed NAS, whereas 34.8% of women without diabetes had an infant who developed NAS. The adjusted odds ratio of infants developing NAS born to women with diabetes was 0.70 (95% confidence interval: 0.51, 0.94) compared with those born to mothers without diabetes after controlling for covariates. Contrary to our hypothesis, the study suggests that maternal diabetes during pregnancy is associated with a decreased risk of an infant developing NAS.

Implications for Practice: Future research generating from this hypothesis may lead to potential implications for practice for infants born to mothers with substance use during pregnancy and diabetes.

Implications for Research: More research should be conducted to investigate the relationship between glucose metabolism and NAS.

Key Words: intrauterine substance exposure, maternal diabetes, neonatal abstinence syndrome, neonatal withdrawal

In West Virginia, 51.3 out of every 1000 infants are born with neonatal abstinence syndrome (NAS),[1] a condition in which infants who are exposed to certain neuroactive substances during pregnancy experience withdrawal symptoms shortly after birth.[2] The incidence rate of NAS in West Virginia is 6 times the national average of 8 per 1000 live births.[3] NAS rates parallel opioid use both nationally and in West Virginia. West Virginia has the highest number of opioid overdoses in the United States at 57.8 out of every 1000 people, after adjusting for age.[4] This is more than double the national average of 21.7 per 1000 people.[5]

In addition to the dramatically high rate of opioid usage, West Virginia also has high rates of chronic health conditions including diabetes. Nearly 15% of West Virginians have diabetes, which is the second highest prevalence nationally.[6] Infants born to mothers with diabetes are susceptible to hypoglycemia at birth due to higher insulin levels in utero.[7] Of note, the symptoms of NAS and hypoglycemia may overlap, with both conditions possibly presenting with altered levels of consciousness, poor feeding, jitteriness, irritability, vomiting, tremors, convulsions, and seizures.[2,8]

Previous research has shown that diabetes during pregnancy may contribute to a more permeable placenta. For instance, Sgarbosa et al[9] found that women with diabetes have higher rates of apoptosis in the placenta, making it more porous. Other studies by Babawale et al[10] and Cvitic et al[11] demonstrated that exposure to diabetic conditions changed the expression of junctional proteins in the placenta, decreasing their effectiveness as a barrier. In addition, a study by Leach and colleagues[12] found that fetoplacental vessels in women with type 1 diabetes had lost over 50% of their protein content, suggesting compromised barrier integrity in the placenta. A more porous placenta could lead to increased exposure to neuroactive substances. This idea is supported in research conducted by Logan et al,[2] which

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suggested that a longer gestational age is associated with NAS development because it allows the fetus to be exposed to substances for a longer period, particularly in the third trimester when the placenta naturally becomes more permeable.[13-15] These studies support the notion that diabetes during pregnancy could affect exposure of the fetus to various substances, including those that are neuroactive.

Therefore, placental permeability may play a key role in the development of NAS. While data show only about half of infants exposed to substances in utero develop NAS, the reason that some infants are affected and some are spared remains elusive.[16] Although the type and amount of substance likely plays a role,[17] there is also an association of NAS development with sociodemographic risk factors such as maternal age, race, and health insurance status.[1,18] Therefore, the origins of NAS are likely due to an intricate interplay of genetic and environmental factors.

Given the potential interplay between maternal diabetes, placental permeability, and potential exposure to substances in utero, we hypothesize that changes in the placenta elicited by maternal diabetes could potentially increase the placental permeability of intrauterine substances. This, in turn, may increase the likelihood of developing NAS. To our knowledge, no previous studies have investigated a possible link between maternal diabetes during pregnancy and NAS development. Due to the high rates of both NAS and diabetes in West Virginia, the purpose of this study was to examine the hypothesis that infants born to mothers with diabetes were more likely to develop NAS compared with infants born to mothers without diabetes in a subsample of women who reported substance use during pregnancy.

What This Study Adds

- Insight into the impact of maternal diabetes in the development of NAS in infants exposed to substances in utero.
- Evidence for the need to train clinicians in differentiating between hypoglycemia and NAS.
- Suggestions of possible treatments of NAS specific to the individual risk factors of the infant that warrant further research.

METHODS

Design

This study utilized data from Project WATCH (Working in Appalachia to identify at-risk infants, Critical congenital heart disease, and Hearing loss), which is an electronic surveillance tool that has been used to collect data on every newborn born in hospital/birthing facility in West Virginia since 1998. The purpose of this surveillance is to identify children at high risk for health and developmental challenges to link these families to appropriate resources.[19] In late 2016, Project WATCH expanded to gather information on maternal substance use and NAS. A standardized NAS definition was developed with input from key state stakeholders (pediatricians, epidemiologists, neonatologists, hospital coders, WVDHHR, and members of the West Virginia Perinatal Partnership and Project WATCH) to be used by the Project WATCH surveillance tool to gather NAS data. NAS was defined as neonatal withdrawal from a neuroactive substance manifesting as clinical symptoms but not limited to those requiring pharmaceutical intervention.[1,20] Using data from Project WATCH, we reviewed de-identified data from a population-based cohort of all newborns born between 2017 and 2018. The total number of births included was 36,974. For the purpose of this analysis, we narrowed our data to only those infants who had intrauterine substance exposure (n = 5188, 14.03%) to examine the association of maternal diabetes and NAS.

Measures

Outcome

The main outcome variable was the diagnosis of NAS (yes/no), which was determined clinically by physicians based on the definition used by Project WATCH. According to this definition, NAS was diagnosed when a fetus is exposed to neuroactive substances in utero that reacts with the nervous system, causing withdrawal symptoms. To diagnose NAS, the infant needs to fulfill 2 criteria: (1) they must have been exposed to a neuroactive substance in utero and (2) have clinical symptoms consistent with NAS. For the Project WATCH surveillance tool, intrauterine substance exposure includes opioids, stimulants, cannabinoids, sedative-hypnotics, gabapentin, and antidepressants. The diagnosis of NAS is ultimately made by the physician, and then nurses at each hospital transcribe this into the Project WATCH form at discharge. Notably, pharmacological treatment is not a necessary criterion for the diagnosis of NAS.[1]

Exposure

Data on maternal diabetes are recorded in Project WATCH by a nurse as one of the following: never diagnosed (n = 4791, 94.98%), type 1 diabetes (n = 12, 0.24%), type 2 diabetes (n = 32, 0.63%), or gestational diabetes (n = 209, 4.14%) and missing data on 144 cases. For the purpose of this study, we categorized diabetes as either yes or no.

Covariates

- *Maternal characteristics*. Sociodemographic variables included age, race, health insurance

status, and education. Maternal age at the time of birth was dichotomized as greater than 19 or less than or equal to 19 years. Race was similarly dichotomized as White and others due to West Virginia's predominately White population (94%).[21] Health insurance status was recorded as private, Medicaid, or no insurance. Several studies have found a significant positive correlation between Medicaid insurance and NAS.[18,22] Education was dichotomized to 10th grade and below, and 11th grade and above. While 30.9% of the US population achieves a bachelor's degree or higher, only 19.9% of West Virginians achieve the same.[21] Education level of mothers could affect both medical knowledge and employment opportunities. Other maternal characteristics that were considered covariates and included in the analysis were breastfeeding preference, smoking during pregnancy, and gestational age. Breastfeeding has been associated with a decreased need of pharmaceutical treatment and shorter hospital stays for infants with NAS and is thus encouraged in women on medication-assisted therapy regardless of the dose.[23] Breastfeeding preference was recorded as a binary variable (yes or no). Studies suggest that smoking during pregnancy in combination with use of opioids may increase the infant's risk of developing NAS.[24] Maternal smoking was recorded as a binary variable (yes/no). Longer gestations are also associated with an increased risk of NAS.[2] Term birth was defined as greater than or equal to 37 weeks of gestation. Term birth was recorded as a binary variable (yes/no).

- *Infant characteristics*. Other potential confounders included neonatal intensive care unit (NICU) admittance and the sex of the infant. Male sex has been associated with an increased risk of NAS.[25] Sex was recorded as a dichotomous variable (male/female). NICU admittance was recorded as a dichotomous variable (yes/no) as well.

Statistical Analysis

We conducted statistical analysis using SAS version 9.4. χ^2 tests were performed to assess for bivariate associations of maternal diabetes and NAS in women who used substances during pregnancy. The magnitude of the association includes the reported odds ratios (ORs) and 95% confidence intervals (CIs). Multiple logistic regression was performed to analyze the adjusted relationship between the exposure (maternal diabetes) and the outcome (NAS) while controlling for the covariates. Nonstatistically significant (eg, $\alpha > .05$) covariates were removed from the model in a stepwise manner.

Due to the higher likelihood of preterm birth observed in women with diabetes,[26] a sensitivity analysis was conducted on the initial results. The purpose was to determine whether the observed relationship was caused by a shorter gestation due to maternal diabetes, resulting in a decreased exposure to substances in utero. Therefore, we stratified the dataset by preterm births (n = 827, 16.96%) and term births (n = 4354, 84.04%) and examined the association between NAS and maternal diabetes using simple and multiple logistic regression analysis in each of the stratified groups.

RESULTS

There were 36,972 infants born in West Virginia who were recorded in Project WATCH in 2017 and 2018. In these 2 years of data, nearly 14% (n = 5188) women reported using substances during pregnancy. Of these 5188 women, 253 (5.02%) also had diabetes. Among these infants who were exposed to substances during pregnancy, more than one-third developed NAS (n = 1814, 34.97%). The population characteristics are given in Table 1.

Among all those infants who developed NAS, 4.14% were born to mothers with diabetes, while of all those infants who did not develop NAS, 5.48% were born to mothers with diabetes. The difference in proportion was statistically significant, χ^2 (1, n = 5044) = 4.32, $P = .0376$. [The unadjusted odds ratio of infants developing NAS when born to mothers with diabetes vs "no diabetes" was 0.74 (95% CI: 0.56, 0.98)].

The results of the multiple logistic regression showed that the adjusted odds ratio of infants developing NAS in mothers with diabetes was 0.70 (95% CI: 0.51, 0.94) compared with those born to mothers with "no diabetes" ($P = .0194$) after adjusting for maternal age, education, race, health insurance status, gestational age, exclusive human milk before hospital discharge, and NICU admission (Table 2).

Sensitivity Analysis

Among the infants with substance exposure, 827 (16%) were born preterm. The prevalence of diabetes in the stratified preterm and term birth groups was 7.19% and 4.61%. The analysis showed that the statistically significant protective effect of maternal diabetes on developing NAS in infants was maintained in infants carried to term birth only (Table 3). The odds of NAS in preterm infants born to substance use women with diabetes versus "no diabetes" was 0.85 (95% CI: 0.48, 1.51), while the odds of developing NAS in substance use women with diabetes versus "no diabetes" was 0.72 (95% CI: 0.52, 0.98) in the term birth group. For the term group infants, the results of the adjusted analysis showed that the odds of developing NAS in diabetes versus "no diabetes" group was 0.67 (95% CI: 0.48, 0.95) after controlling for maternal health insurance status, age, race, exclusive breastfeeding, gestational age, and NICU admission.

TABLE 1. Maternal and Infant Characteristics of Intrauterine Substance-Exposed Group Only (N = 5188) 2017-2018 Project WATCH Data

Population Characteristic	Total IUSE n = 5188 n (%)	NAS n = 1814 n (%)	No NAS n = 3374 n (%)	*P* Value
Breastfeeding[a]				
Yes	882 (17.0)	188 (84.37)	694 (20.57)	<.0001
No	4306 (83.0)	1626 (15.63)	2680 (79.43)	
Diabetes				
Yes	253 (5.02)	72 (4.14)	81 (5.48)	.0382
No	4791 (94.98)	1669 (95.86)	3122 (94.52)	
Missing	144			
Gestational age				
Preterm (<37 wk)	827 (15.96)	282 (15.58)	545 (16.17)	.5839
Full term (≥37 wk)	4354 (84.04)	1528 (84.42)	2826 (83.83)	
Health insurance				
Medicaid	3681 (81.28)	1290 (84.37)	2391 (79.7)	.0001
Non-Medicaid	848 (18.72)	239 (15.63)	609 (20.3)	
Missing	7			
Maternal age				
≤19	335 (6.46)	55 (3.03)	280 (8.3)	<.0001
>19	4853 (93.54)	1759 (96.97)	3094 (91.7)	
Maternal education				
≤10th grade	663 (12.78)	256 (14.11)	407 (12.06)	.0351
>11th grade	4525 (87.22)	1558 (85.89)	2967 (87.94)	
Maternal race				
White	4696 (91.72)	1717 (95.76)	2979 (89.54)	<.0001
Non-White	424 (8.28)	76 (4.24)	348 (10.46)	
Sex of infant				
Male	2650 (51.08)	932 (51.38)	1718 (50.92)	<.0001
Female	2538 (48.92)	882 (48.62)	1656 (49.08)	
Smoking during pregnancy				
Yes	3559 (68.6)	1460 (80.49)	2099 (62.21)	<.0001
No	1629 (31.4)	354 (10.36)	1275 (37.79)	

Abbreviations: IUSE, intrauterine substance exposure; NAS, neonatal abstinence syndrome.
[a]Breastfeeding before hospital discharge.

DISCUSSION

The purpose of our study was to assess the potential association between NAS and presence of maternal diabetes during pregnancy in West Virginia. Overall, the results of the study contradict our initial hypothesis that among mothers using neuroactive substances, women with diabetes would be more likely to give birth to an infant who will develop NAS. This hypothesis was based on prior research that indicated that hyperglycemic conditions as a results of maternal diabetes can change gene expression in the placenta, altering tight junctions, thus making the placenta more permeable to

TABLE 2. Results of the Simple and Multiple Logistic Regression to Predict the Association of NAS (Yes vs No) and Maternal Diabetes (No vs Yes) (IUSE N = 5188)

Simple Logistic Regression	Estimate	Standard Error	Wald χ^2	*P* Value	Odds Ratio (95% CI)
Intercept	−0.9218	0.1393	43.7687	<.0001	
Diabetes (no vs yes)	−0.2955	0.1426	4.2958	.0382	0.744 (0.563, 0.984)
Multiple Logistic Regression	**Estimate**	**Standard Error**	**Wald χ^2**	***P* Value**	**Adjusted Odds Ratio (95% CI)[a]**
Intercept	−4.0848	0.2999	185.5459	<.0001	
Diabetes (no vs yes)[a]	−0.3631	0.1554	5.4623	.0194	0.696 (0.513, 0.943)

Abbreviations: CI, confidence interval; IUSE, intrauterine substance exposure; NAS, neonatal abstinence syndrome.
[a]The adjusted variables include maternal health insurance status, age, education, race, exclusive breastfeeding, gestational age (binary term/preterm), and NICU admission.

TABLE 3. Results of the Simple and Multiple Logistic Regression to Predict the Association of NAS (Yes vs No) and Maternal Diabetes (No vs Yes) in Preterm Versus Full-Term Infants (IUSE N = 5188)[a]

Preterm Group (n = 827)					
Simple Logistic Regression	**Estimate**	**Standard Error**	**Wald χ^2**	***P* Value**	**Odds Ratio (95% CI)**
Intercept	−0.7985	0.2838	7.9152	.0049	
Diabetes (no vs yes)	−0.1668	0.294	0.3219	.5704	0.846 (0.476, 1.506)
Full-Term Infants (n = 4354)					
Simple Logistic Regression	**Estimate**	**Standard Error**	**Wald χ^2**	***P* Value**	**Odds Ratio (95% CI)[b]**
Intercept	−0.9597	0.16	35.9642	<.0001	
Diabetes (no vs yes)[b]	−0.3327	0.1634	4.1458	.0417	0.717 (0.52, 0.988)
Multiple Logistic Regression	**Estimate**	**Standard Error**	**Wald χ^2**	***P* Value**	**Adjusted Odds Ratio (95% CI)[b]**
Intercept	−3.7917	0.3144	145.4729	<.0001	
Diabetes (no vs yes)[b]	−0.3963	0.178	4.9588	.026	0.673 (0.475, 0.954)

Abbreviations: CI, confidence interval; IUSE, intrauterine substance exposure; NAS, neonatal abstinence syndrome.

[a]*Preterm: less than 37 weeks; full-term: more than 37 weeks.*

[b]*The adjusted variables include maternal health insurance status, age, race, exclusive breastfeeding, gestational age (binary term/preterm), and NICU admission.*

substances,[9-12,27] including specific intrauterine substances associated with NAS resulting in higher NAS rates. On the contrary, the results from our study indicated that having diabetes during pregnancy was associated with a lower rate of NAS development in infants. Based on these findings, we postulate several notable factors to consider when interpreting the results of our study.

First, our study did not have information on the onset of maternal diabetes, the duration of glucose intolerance during pregnancy and was not able to differentiate between controlled and uncontrolled diabetes during pregnancy. The severity of diabetes and degree of hyperglycemia could therefore vary greatly between mothers and infants in the diabetes group. Additionally, diabetes during pregnancy is associated with preterm birth[26] and currently NAS scoring tools are not tailored for preterm population,[28] which may have potentially led to misclassification of the outcome (false negative) in the preterm population only. However, classic NAS scoring tools, such as the modified Finnegan score, are routinely administered to preterm infants. Additional analysis from our study (data not shown) also indicated that premature birth is protective against developing NAS [(term birth vs preterm birth OR = 1.49 (95% CI: 1.23, 1.81)]. The result from the post hoc sensitivity analysis examining preterm and term births separately also showed that maternal diabetes during pregnancy was statistically significantly associated with lower odds of NAS in infants carried to term only. This suggests that diabetes during pregnancy is not protective simply because it increases the chances of preterm birth. Moreover, the diagnosis of NAS is subjective and varies by each practitioner regardless of the use of standard definition used by all birthing hospitals in the state. In general, about half of neonates exposed to neuroactive substances develop NAS.[16] Therefore, discrepancies in diagnosis of NAS could potentially exist within the population studied. Lastly, Project WATCH did not distinguish between the types of substances used in utero. The infants may have been exposed to a variety of substances or multiple substances simultaneously.

There are several notable strengths to consider when interpreting the results as well. The study examined this novel hypothesis using a large population-level data for 2 years. The relationship between diabetes and NAS was examined in a noninvasive manner, which posed no risk to the mother or child. West Virginia is one of the few states that collect extensive surveillance data on mothers and infants born within all of its birthing hospitals. This created the unique opportunity to study important mother–infant relationships. To the best of our knowledge, this is the first study to examine the association between maternal diabetes and NAS and provides insight that will serve as a foundation for future research on this topic.

IMPLICATIONS AND FUTURE RECOMMENDATIONS

The incidence of infants diagnosed with NAS remains high in Appalachian states and other areas that are greatly affected by the opioid crisis. Therefore, research regarding additional risk factors associated with infants who develop NAS when prenatally exposed to substances, and potential treatment variations specific to associated risk factors, may

Summary of Recommendations for Practice and Research	
What we know:	• Neonatal abstinence syndrome affects approximately half of all infants exposed to neuroactive substances in utero. • Neonatal abstinence syndrome development depends on an interplay of genetic and environmental factors. • Maternal diabetes can lead to a more permeable placenta. • Maternal diabetes is associated with decreased odds of developing NAS.
What needs to be studied:	• The relationship between glucose metabolism and NAS development. • The mechanism by which maternal diabetes decreases the odds of developing NAS in infants with intrauterine substance exposure. • The effectiveness of current algorithms in distinguishing between NAS and neonatal hypoglycemia. • The possible benefits of glucose as a treatment for infants with NAS.
What we can do today:	• Consider the overlap in symptoms of NAS and neonatal hypoglycemia when diagnosing either condition in a neonate. • Provide standardized training for nurses and physicians responsible for diagnosing NAS, emphasizing the distinction of NAS from conditions that mimic withdrawal symptoms. • Work with multiple disciplines to develop and maintain a standard definition for NAS diagnosis. • Use extra discernment to the care of mothers with diabetes who use substances during pregnancy.

benefit some of the most vulnerable victims of the epidemic. To improve our understanding of these complex mechanisms, there are several areas of future research to expand upon.

First, an effort should be made to uncover the biochemical pathways that may alter intrauterine substance absorption in placenta in the presence of hyperglycemia. Maternal diabetes was found to reduce the chances of infants being born with NAS, which suggests that metabolism of glucose or the effect of glucose on gene expression may have played a role in the development of NAS. A biochemical understanding of these findings may aid in the development of therapies to reduce the number of infants who experience withdrawal symptoms.

Second, when infants are born to mothers with diabetes, they are exposed to higher levels of insulin in utero and are therefore more likely to develop hypoglycemia.[7] NAS and hypoglycemia present with similar symptoms including lethargy, poor feeding, seizures, jitteriness, vomiting, cyanosis, difficulty breathing, and high-pitched cry.[2,8] It is fairly difficult to determine which diagnosis is correct because the symptoms of the 2 conditions overlap, and the definition of NAS used in West Virginia is fairly general. The definition of NAS used to diagnose infants in West Virginia through Project WATCH would tend to favor a labeling of an infant with NAS even if they showed signs of hypoglycemia. Discerning the correct diagnosis ultimately relies on the physician's judgment. However, if a clinician felt that the symptoms were more related to hypoglycemia than NAS, the NAS diagnosis could be changed prior to submitting the Project WATCH form. Further investigation is needed to determine whether the current diagnostic algorithms and techniques are able to accurately distinguish between NAS and hypoglycemia.

Lastly, the decreased chance of developing NAS in infants born to mothers with diabetes during pregnancy necessitates exploration into the potential for glucose to mask the symptoms of NAS. In neonates, glucose is known to have an analgesic effect.[29] It is often used to decrease pain in infants when they are receiving venipunctures or intramuscular injections.[30] When an infant is born to a mother with diabetes, he or she is more likely to experience hypoglycemia in the first 2 days of life. If the infant develops hypoglycemia, he or she is given a bolus of dextrose, which is chemically identical to glucose, followed by IV dextrose.[31] It is plausible that the glucose given to hypoglycemic infants born to mothers with intrauterine substance exposure masks the symptoms of withdrawal. More research should be done to evaluate the potential uses of glucose as an analgesic for NAS infants.

CONCLUSION

This study suggests that maternal diabetes was associated with a decreased chance of an infant developing NAS. The results generate questions about the relationship between glucose metabolism and NAS. Answers to these questions may contain a better understanding of the mechanism and associated risk factors for NAS.

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