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Early Treatment Innovation for Opioid-Dependent Newborns: A Retrospective Comparison of Outcomes, Utilization, Quality, and Safety, 2006–2014

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Background: Few coordinated treatment programs address the needs of infants and families struggling with the effects of substance use. In 2003 a large Southeastern regional hospital launched the Managing Abstinence in Newborns (MAiN) program, providing multidisciplinary, coordinated, community-based care for neonatal abstinence syndrome (NAS). A hypothesis-generating study was conducted to compare the outcomes of MAiN infants to comparable NAS infants receiving traditional care from 2006 through 2014 in South Carolina.

Methods: De-identified sociodemographic and clinical data on MAiN infants, as well as NAS infants not treated with MAiN, were obtained from South Carolina statewide databases. Study measures included medical and safety outcomes, health services utilization, child protective services involvement, emergency services utilization, and inpatient readmissions.

Results: Some 110 infants were identified who received the MAiN intervention and 356 NAS infants, also in South Carolina, who were potentially MAiN eligible. Overall, there were no significant differences in the two groups regarding medical or safety outcomes or child protective services involvement. Traditional care NAS infants were more likely to be treated in a higher-level nursery (68.8% vs. 0%). MAiN infants had $8,204 less per birth in median charges ($p < 0.001$) than the traditional care NAS infants. MAiN infants also had a lower percentage of ED visits ($p = 0.01$) assessed as possibly or likely NAS related compared to traditional care NAS infants.

Conclusion: This study demonstrates the potential value of implementing the MAiN model in eligible NAS infants. With no difference in medical and safety outcomes and a significant reduction in charges, the MAiN model can be considered safe and cost-effective.

Prescription and nonprescription opioid use and dependence is increasing in women of childbearing age and during pregnancy.[1] The Centers for Disease Control and Prevention reports that, from 2008 to 2012, more than one quarter of privately insured and one third of Medicaid-enrolled women of childbearing age filled an opioid prescription written by a health care provider.[2] For pregnant women with opioid use disorders, methadone or buprenorphine maintenance therapy is considered standard of care.[3] Although maintenance therapy improves an opioid-dependent woman's chances for a successful pregnancy, fetal opioid exposure can result in neonatal abstinence syndrome (NAS), a condition that results when a dependent newborn is no longer exposed to substances used by the mother during pregnancy.[4] According to the Tennessee Department of Health's 2015 NAS surveillance report, more than two thirds of NAS cases statewide were attributable to supervised opioid replacement or pain therapy.[5] Earlier sources have estimated that 48% to 94% of neonates exposed to opioids prenatally develop NAS.[6,7]

In recent years, NAS rates have increased rapidly across the United States, increasing from 1.2 per 1,000 hospital births in 2000 to 5.8 per 1,000 hospital births in 2012.[8,9] The NAS epidemic is alarming both because of the severity of the neonate's medical withdrawal experience and because the majority of NAS cases are covered by Medicaid, a publicly provided state health insurance program. In 2012 Medicaid was the primary payer for 81% of NAS cases, with mean hospital charges of $66,700 per infant and $93,400 per pharmacologically treated NAS infant.[9] South Carolina is in a region with one of the highest NAS rates in the country.[9,10]

The majority of birthing centers are not skilled in detecting or treating NAS; observation and treatment protocols vary by institution, state, and country.[11] The conventional approach is to manage affected infants in level II–IV nurseries while withholding pharmacologic treatment until clear objective evidence of NAS is observable, typically two to five days after birth. Full withdrawal usually results in vomiting, diarrhea, skin abrasions, perianal maceration, disorganized suck patterns, irritability and sleeplessness, elevated muscle tone, and significant weight loss.[12] There are few coordinated and collaborative programs to address the broad range of needs for infants and their families struggling with the effects of substance abuse issues during pregnancy,

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hospitalization, and postnatal periods. Medication used to treat NAS varies by hospital. In a study conducted by Patrick et al. of 1,424 NAS infants from 14 children's hospitals, 6 of the hospitals used methadone and 6 used morphine to treat NAS. When compared to NAS infants who had been treated initially with morphine, infants treated with methadone had a shorter length of treatment and shorter length of stay (LOS).[11]

In 2003 a large Southeastern regional hospital launched the Managing Abstinence in Newborns (MAiN) program, which provides multidisciplinary, coordinated, community-based care for infants at high risk for opioid withdrawal and their families within a mother/baby unit. MAiN's three essential elements are early treatment (methadone administered within 48 hours of birth), the option to room in with the mother for the entire hospitalization, and a combined inpatient/outpatient wean. The objective of the current study was to compare MAiN infants to NAS infants who were potentially eligible for MAiN but received traditional care in other South Carolina hospitals between 2006 and 2014. This study fills a gap in the literature by combining supportive care environmental elements described in other studies[12,13] with the concept of anticipatory weaning for managing presumed opioid dependence due to antenatal exposure.[14]

METHODS

MAiN Model for Early Treatment Description

In 2003 a multidisciplinary team developed the MAiN model, an early treatment model for infants at high risk for opioid withdrawal. MAiN is based on the theory that neonates who are chronically exposed to long-acting opioids in late gestation should be considered dependent, as research has demonstrated significant transfer of opioids across the placenta.[15] The team does not presume that all substance-exposed newborns will require or benefit from treatment; only those with "presumed opioid dependence" at birth after high levels of opioid exposure in late gestation. Early methadone treatment (within 48 hours of birth) and subsequent weaning may prevent severe opioid withdrawal and its complications.[16] The pharmacologic approach is similar to the stabilization and weaning process used for neonates with iatrogenic opioid dependence. We conclude that regardless of the source (intravenous or placental transfer), a newborn with chronic continuous opioid exposure may be presumed to be opioid dependent.

The MAiN care protocol is consistent with many elements cited in a Joint Commission *Quick Safety* advisory, which recommends a multidisciplinary treatment approach combined with maternal participation, protocol-based drug weaning, "rooming in" and maternal-dyad care, standard treatment protocols, combined inpatient and outpatient care, and education of staff specific to treatment standards.[17] All substance-exposed infants, including those treated with the MAiN intervention, are cared for in a supportive and low-stimulation environment, which includes rooming in with mother on a 24-hour basis until she is discharged (and for the entire newborn stay when appropriate), low lighting and noise levels, frequent skin-to-skin care and holding, swaddling, breastfeeding (if not contraindicated), pacifier use (if needed), and minimized sleep interruptions (such as exams). All MAiN–treated newborns have continuous monitoring of heart rate and breathing to alert staff to events potentially related to withdrawal, medication side effects, or other safety events (such as maternal overlay). The study hospital is Baby-Friendly designated[18]; for example, mother and baby are together for 23–24 hours per day, and parents are the primary caregivers as long as they are rooming in with the baby.

MAiN eligibility criteria include that a neonate must be at least 35 weeks completed gestation and have no other conditions at birth that require intensive care. In addition, the neonate should be considered high risk for opioid withdrawal, which includes mothers taking at least 20 mg of methadone per day or at least 9 mg of buprenorphine per day for at least two weeks immediately prior to delivery. The early treatment thresholds were established in 2004 and were based on the experience and observations of local newborn hospitalists and pediatric pharmacists, well before NAS was a research focus. In 2012 the American Academy of Pediatrics recommended that each unit establish a threshold for treatment of NAS cases and made recommendations for managing (with an oral wean) newborns with presumed opioid dependence.[14] The two weeks is a rough parallel to the standard that if an infant is exposed to IV fentanyl for nine days or more, he or she is presumed to be dependent and needs to be weaned.[14] Approximately 25% of NAS–diagnosed infants met the MAiN eligibility criteria during the study period (2006–2014).

Neonates eligible for MAiN are admitted to the low-acuity Mother/Baby Unit and are offered early methadone treatment and extended maternal stay for the duration of the birth hospitalization. All neonates receive low-stimulation supportive care and are managed by a pediatrician. Within 6–48 hours of birth, infants exposed to maternal methadone doses of 60 mg or higher are initiated on 0.1 mg/kg/dose every 6 hours; those exposed to buprenorphine or a lower methadone dose receive 0.05 mg/kg/dose every 6 hours. Staff routinely perform urine and meconium drug screening, perform prescription monitoring database queries, and complete a social work evaluation for all families. Continuous apnea and bradycardia monitoring is provided in the mother's room, and modified Finnegan scoring is performed every 4 hours. The Finnegan score is a 31-item scale designed to quantify the severity of NAS and to guide treatment.[19] Breastfeeding is encouraged and supported.

Dosing adjustments are made for signs of poor symptom control or oversedation, if necessary. Over several days, dosing intervals are transitioned from 6 hours to 12 hours. From 2006 to 2014, only 4% of MAiN infants were oversedated,

and 2% needed adjuvant medication.[16] Discharge criteria include no signs of oversedation for 48 hours, abstinence scores consistently below 8 on the Finnegan scale, weight increasing or stable, adequate feeding pattern/milk intake, stable vital signs for at least 24 hours, normal voiding and stooling patterns, social issues related to home disposition are resolved, and an appointment has been established with a medical home. When an infant meets criteria for discharge, a weaning calendar is developed by a pediatric pharmacist. Methadone is dispensed in prefilled oral syringes at an average out-of-pocket cost to the family of $13 per one-month supply. Caregivers are required to fill the prescription prior to discharge, and unit staff reconcile that all necessary syringes have been dispensed and educate the caregivers on how to administer medication.

During the outpatient weaning period, the dosage is reduced approximately 15% every Sunday and Wednesday. Weekly office visits occur at an outpatient pediatric medical home during weaning to evaluate the effect of slow methadone reduction. Outpatient physicians assess signs or symptoms of poor NAS control and have the option to slow the weaning process. A regional health department office provides one or two home visits, and families are educated about signs of uncontrolled withdrawal that should prompt additional visits. All newborns are referred for developmental assessment at 3–4 months of age, as well as to phone-based parenting support and developmental screening services available until the child reaches 8 years of age.

Study Population and Data Sources

This was a retrospective cohort study to compare the NAS infants who were treated with the MAiN model to other similar NAS infants in South Carolina who were treated with traditional care. MAiN infants were identified retrospectively from medical records from the study hospital. The study hospital contains 710 beds and is part of a larger, public not-for-profit academic medical center. From 2006 through 2014, the study hospital experienced average annual births of 5,221 infants.

The comparison group was retrospectively selected from South Carolina statewide databases from the same time frame (2006–2014). De-identified sociodemographic and clinical data on MAiN infants, as well as South Carolina NAS infants not treated with MAiN, were obtained from statewide databases. South Carolina all-payer inpatient hospitalization and emergency department (ED) encounter data were linked with birth certificate and Medicaid claims data by a state-issued identifier. The linked data sets included any inpatient, outpatient, or ED encounters within six months of birth for infants born from 2006 to 2014 and any inpatient, outpatient, or ED visit encounter by the infant's mother from the initial prenatal care visit through delivery. The linked database also contained prescription claims for Medicaid recipients. Institutional Review Board approval was obtained prior to the study.

Within the linked statewide database, NAS infants were first identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 779.5 and/or 760.72 in one of 14 discharge diagnosis fields. The ICD-9-CM code 779.5 is defined as "drug withdrawal syndrome in newborn," and the ICD-9-CM code 760.72 as "narcotics affecting fetus or newborn via placenta or breast milk." The hospitalization related to birth was distinguished using ICD-9-CM codes (V30.00 to V39.01 with the last two digits of "00" or "01") and its inpatient status.

As shown in Figure 1, the comparison group was selected from the statewide databases by ICD-9-CM codes and then by the MAiN eligibility criteria. To determine which of the identified state NAS infants would be potentially eligible for the MAiN model, we considered, according to MAiN model eligibility criteria, infants with at least 35 weeks gestational age and born to a mother diagnosed with opioid dependence (ICD-9-CM codes 304.00, 304.01, 304.02, 304.03) during the pregnancy. Infants characterized by one of the following abnormal conditions were excluded because treatment in a Mother/Baby Unit setting would have been unlikely due to these complications: (1) assisted ventilation (6 hours), (2) surfactant replacement therapy, (3) and/or seizure. Infants born at the study hospital were also excluded from the state NAS sample. Infants treated in neonatal intensive care units (NICUs) were not excluded because treatment protocols vary, and infants treated on the Mother/Baby Unit by MAiN are likely to have been treated in NICUs elsewhere. As previously reported, in the MAiN group 82% of mothers received methadone, and 18% received buprenorphine.[16] Medication information was not available for the comparison group.

Demographic and Clinical Information

Demographic and clinical characteristics of the mothers and infants, such as child's sex, child's gestational age, plurality of birth, mother's race, mother's education level, and mother's age, were obtained from state birth certificate files. Infections during pregnancy included gonorrhea, syphilis, herpes, and chlamydia. Prenatal care usage was measured by the Kotelchuck Adequacy of Prenatal Care Utilization Index, which is a measure of prenatal care that takes into account the timing of prenatal care initiation and services received and combines these dimensions into one single score.[20]

Outcome Measures

The study outcome measures addressed medical and safety outcomes, health services utilization, child protective services involvement, and emergency services utilization. Medical and safety outcomes were identified by the following ICD-9-CM codes: abnormal loss of weight (783.21); adverse effect of other drug, medicinal and biological substance (995.29); cerebral irritability (779.1); convulsions (779.0, 780.3); diaper or napkin rash (691.0); failure to thrive (783.41); feeding

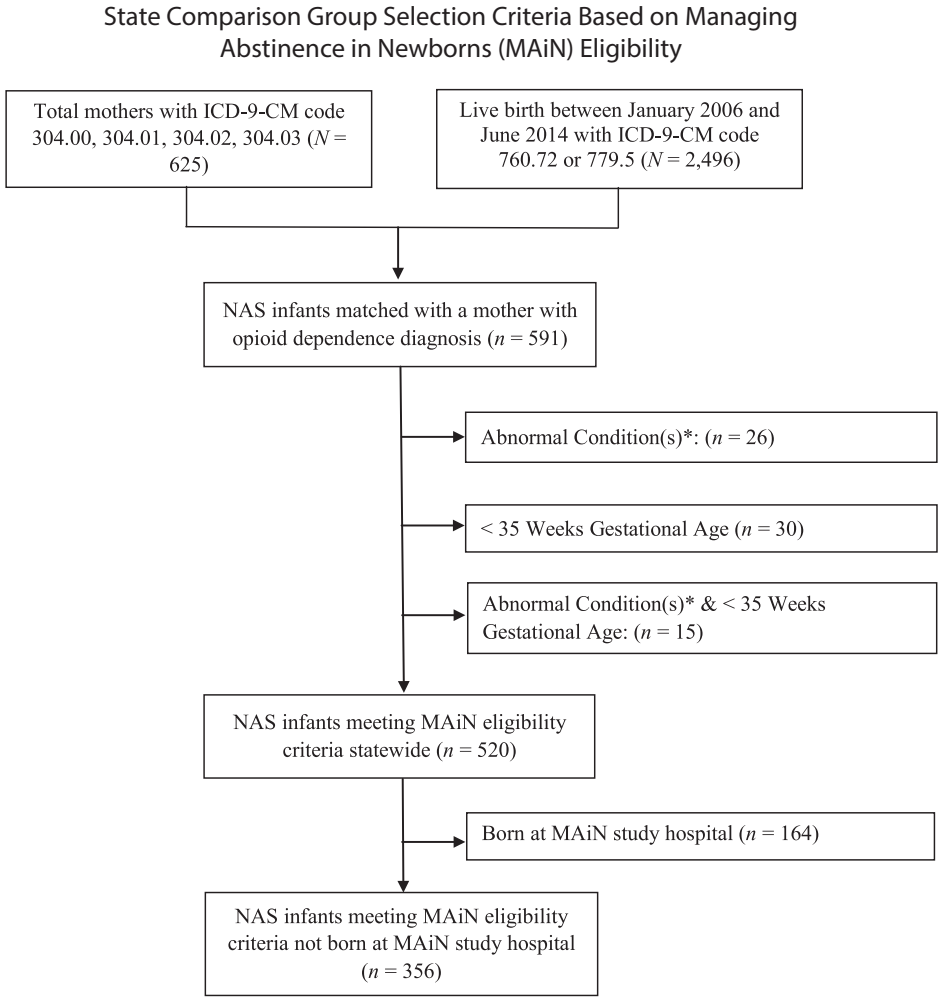

Figure 1: State records were available for 110 infants treated with the MAiN model. Among 2,496 neonatal abstinence syndrome (NAS) infants identified in South Carolina during the study period, 356 were used as the comparison group (traditional care NAS). ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

difficulty (779.3x); suffocation (E913.9); and unspecified fall (E888.9). Health services utilization included length of hospital stay (patient encounter data), total charges (patient encounter data), the level of treatment nursery (patient encounter data), and breastfeeding (state birth certificate data). Information about child protective services involvement was provided by the South Carolina Department of Social Services as the number of intakes per child if a case had been opened.

Emergency services utilization and inpatient readmissions that occurred from day 1 to 60 days after discharge were obtained. Only the month and year of each visit was provided, so for each infant, ED visits and readmissions occurring in the month of discharge from the initial birth hospitalization or the following month were captured and reported. ED visits and inpatient readmissions were classified as likely NAS related, possibly NAS related, or not NAS related based on physician review of the diagnoses associated with each encounter. Visits classified as likely NAS related were identified by at least one of the following ICD-9-CM codes related to effects of narcotics or drug withdrawal/dependence: 292.0, 304.90, 760.72, and 779.5. Visits classified as possibly NAS related were for diagnoses such as diarrhea, feeding problems, vomiting, esophageal reflux, and weight loss in addition to central nervous system symptoms such as involuntary movements, convulsions, epilepsy, myoclonus, fussy baby, and excessive crying.

Statistical Analyses

Results of descriptive analyses were expressed as mean (standard deviation), median (interquartile range [IQR]), or percentage. The differences between the MAiN infants and the state comparison group were examined using either the *t*-test for continuous normally distributed variables, the two-sample Wilcoxon rank-sum test for skewed variables, or the χ^2 test for categorical variables ($\alpha = 0.05$). Multivariate analysis

was not conducted because of the small sample size and highly skewed data. Analysis of outcomes was performed using Stata 14.2 (StataCorp LP, College Station, Texas).

RESULTS

MAiN Model and Comparison Groups

State records were available for 110 infants treated with the MAiN model. Among 2,496 NAS infants identified in South Carolina during the study period, 356 were used as the comparison group (traditional care NAS infants) (Figure 1). The number of state NAS infants identified as MAiN eligible increased dramatically during the study period (Figure 2).

The comparison group for the study was drawn from South Carolina inpatient health facilities with capacity to handle deliveries. As expected, a significant portion (44.9%) (160/356) of state infants classified as potentially MAiN eligible were born at facilities with level III nurseries. Forty-nine percent were delivered at hospitals with level II nurseries. Although size of hospitals in the comparison group varied, birth-related services provided can be expected to be relatively consistent across the institutions.

Demographic and Clinical Characteristics

The demographic and clinical characteristics of NAS infants and their mothers are summarized in Table 1. There was no difference in the MAiN infants and the traditional care NAS infants on the basis of infant's sex (χ^2 [df = 1] = 0.51; $p = 0.48$), race (χ^2 [df = 2] = 0.51; $p = 0.29$), birthweight (t [df = 464] = 0.13; $p = 0.90$), or Medicaid status (χ^2 [df = 1] = 0.01; $p = 0.91$). Infants in the MAiN group had a significantly higher mean gestational age 38.6 (1.6) than infants in the traditional care group 38.2 (1.6) (t [df = 463] = 2.54; $p = 0.01$).

Demographic and clinical characteristics of the mothers were similar between the MAiN infants and traditional care NAS infants for the following aspects: age (t [df = 464] = −0.51; $p = 0.61$), education attained (χ^2 [df = 3] = 6.76; $p = 0.08$), Kotelchuck Adequacy of Prenatal Care Utilization index (χ^2 [df = 3] = 7.82; $p = 0.05$), and Women, Infants, and Children (WIC) recipient status (χ^2 [df = 2] = 4.65; $p = 0.10$). However, the mothers of MAiN infants had higher rates of infections during pregnancy (χ^2 [df = 1] = 11.11; $p < 0.001$), tobacco use during pregnancy (χ^2 [df = 1] = 7.28; $p = 0.007$), and tobacco use prior to pregnancy (χ^2 [df = 1] = 10.76; $p = 0.001$) than mothers of traditional care NAS infants.

Newborn Outcomes

Newborn outcomes are presented in Table 2. There was no significant difference in the proportion infants who were breastfed in the MAiN (43.6%; 48/110) and traditional care (48.9%; 174/356) groups (χ^2 [df = 2] = 1.14; $p = 0.57$). There was a significantly higher proportion of infants who had at least one case of child protective services involvement in the MAiN group (32.7%; 36/110) compared to the traditional care group (23.3%; 83/356) (χ^2 [df = 1] = 3.92; $p = 0.048$). While all MAiN infants were treated in level I care, 68.8% (245/356) of traditional care NAS infants received treatment in a level II–IV nursery.

The MAiN infants accumulated significantly less in total charges, with a median of $10,058 (IQR: $7,935–$11,518), compared to a median of $18,262 (IQR: $5,816–$40,922) in the traditional care group ($z = -4.75$; $p < 0.001$). The median LOS for the MAiN group was 8 days (IQR: 6–10), compared to a median LOS of 9 days (IQR: 4–18) for the traditional care group ($z = -1.49$; $p = 0.14$).

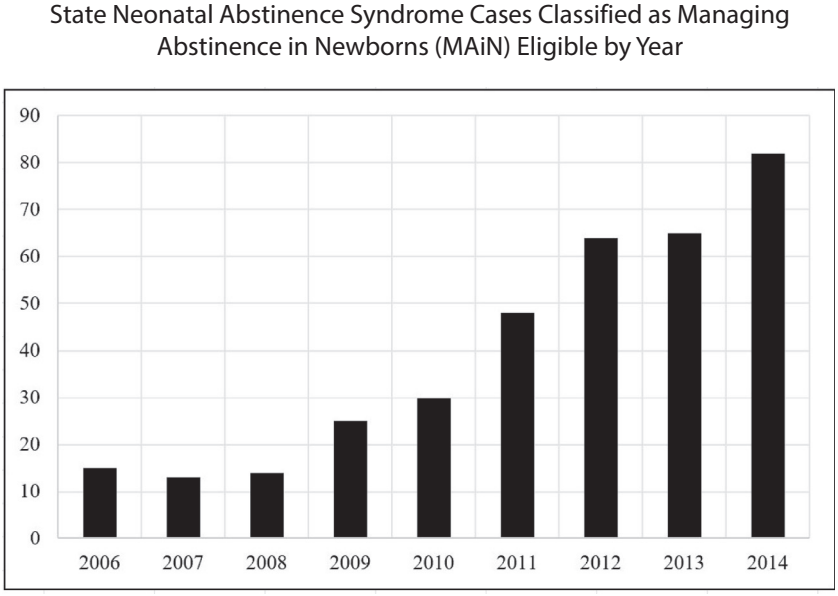

Figure 2: The number of state neonatal abstinence syndrome infants identified as MAiN eligible increased dramatically during the study period.

Table 1. Comparison of Neonatal Abstinence Syndrome Newborns and Mothers' Demographic and Clinical Characteristics, Managing Abstinence in Newborns (MAiN) vs. State Comparison Group

	MAiN (*N* = 110)	State (*N* = 356)	*P* Value
Infants			
Female, % (*n*)	49.1 (54)	45.2 (161)	0.48
Race and ethnicity, % (*n*)			
White	93.6 (103)	93.5 (333)	0.29
Black or African American	2.7 (3)	5.6 (20)	
Hispanic or Latino	0.9 (1)	0.6 (2)	
Other	2.7 (3)	0.3 (1)	
Gestational age, mean (SD)	38.6 (1.6)	38.2 (1.6)	0.01
Birth weight (grams), mean (SD)	2,953.7 (464.7)	2,946.6 (503.4)	0.90
Low birth weight (<2,500 g), % (*n*)	18.2 (20)	20.5 (73)	0.59
Insured by Medicaid, % (*n*)	91.8 (101)	92.1 (328)	0.91
Mothers			
Age, mean (SD)	27.6 (5.1)	27.9 (5.0)	0.61
Education attained, % (*n*)			
Less than high school graduate	26 (29)	25.8 (92)	0.08
High school graduate or GED	35 (38)	34.6 (123)	
Some college credit	36 (40)	29.5 (105)	
Associate's or bachelor's degree	3 (3)	9.8 (35)	
Infections during pregnancy, % (*n*)	16.4 (18)	6.2 (22)	<0.001
Kotelchuck Prenatal Care Index, % (*n*)			
Inadequate	50.0 (55)	45.2 (161)	0.05
Intermediate	11.8 (13)	5.9 (21)	
Adequate/Adequate Plus	38.2 (42)	47.2 (168)	
Unknown	0 (0)	1.7 (6)	
Tobacco use during pregnancy, % (*n*)	74.5 (82)	60.4 (215)	0.007
Tobacco use prior to pregnancy, % (*n*)	77.2 (85)	60.4 (215)	0.001
WIC recipient, % (*n*)	64.5 (71)	66.9 (238)	0.10

SD, standard deviation; WIC, Women, Infants, and Children (Special Supplemental Nutrition Program).

MAiN infants and the traditional care NAS infants also had similar medical outcomes: cerebral irritability (0 vs. 0), convulsions (1 vs. 0), feeding difficulty (11/110 [10.0%] vs. 43/356 [12.1%]; χ^2 [df = 1] = 0.35; $p = 0.55$), and failure to thrive (0 vs. 0). Compared to traditional care infants, MAiN infants were coded more often for abnormal loss of weight (4/110 [3.6%] vs. 3/356 [0.8%]; χ^2 [df = 1] = 4.43; $p = 0.04$) and diaper rash (20/110 [18.2%] vs. 33/356 [9.3%]; χ^2 [df = 1] = 6.62; $p = 0.01$).

Regarding safety outcomes, none of the following events were identified for either group: suffocation; unspecified adverse effect of other drug, medicinal and biological substance; or unspecified fall.

Emergency Services Utilization and Inpatient Readmissions

The emergency services utilization and inpatient readmissions results are presented in Figure 3. In the MAiN group, there were 31 ED visits and 13 inpatient readmissions. In the state traditional care NAS group, there were 67 ED visits and 44 inpatient readmissions. Of the MAiN infants, 2.7% (3/110) had an ED visit that was assessed as likely or possibly

Table 2. Comparisons of Newborn Outcomes, Managing Abstinence in Newborns (MAiN) vs. State Comparison Group

	MAiN (*N* = 110)	State (*N* = 356)	*P* Value
Health Services Outcomes			
Breastfed, % (*n*)	43.6 (48)	48.9 (174)	0.57
Length of stay in days, median (IQR)	8 (6–10)	9 (4–18)	0.14
Total charges in dollars, median (IQR)	10,058 (7,935–11,518)	18,262 (5,816–40,922)	<0.001
Child Protective Services Involvement			
At least one case opened, % (*n*)	32.7 (36)	23.3 (83)	0.048

IQR, interquartile range.

Comparisons of Emergency Services Utilization and Readmissions Between Managing Abstinence in Newborns (MAiN) and State Comparison Group Within up to 60 Days of Birth Hospitalization Discharge

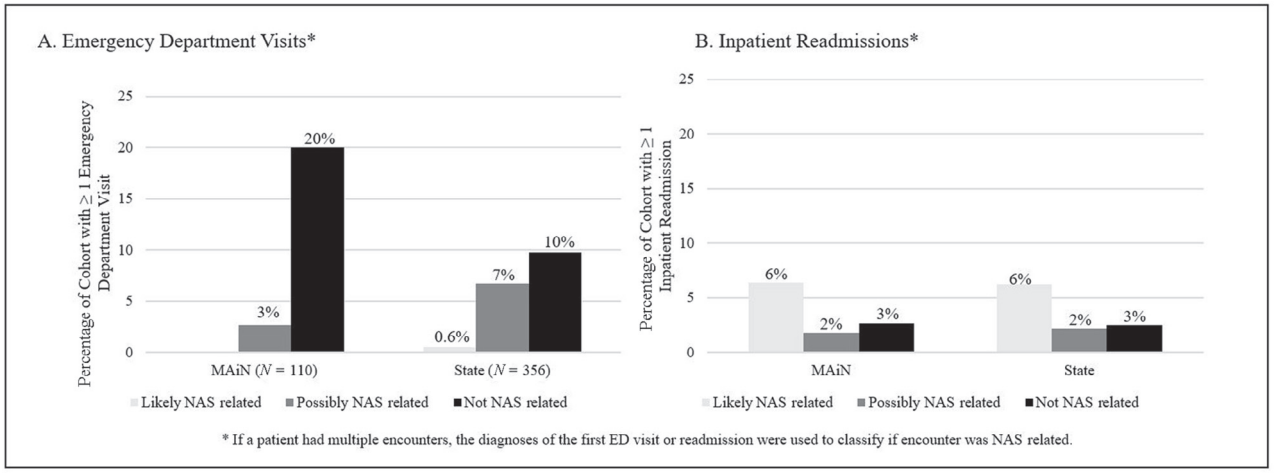

Figure 3: The emergency services utilization and inpatient readmissions results are presented. In the MAiN group, there were 31 emergency department (ED) visits and 13 inpatient readmissions. In the state traditional care neonatal abstinence syndrome (NAS) group, there were 67 ED visits and 44 inpatient readmissions.

NAS related, compared to 7.6% (27/356) of infants in the traditional care group. Approximately 6% of infants in both the MAiN and traditional care groups had a likely or possibly NAS related inpatient readmission.

For the MAiN group, the risk of an ED visit for a likely/possibly NAS–related diagnosis was 4.6%, compared to 7.9% for the traditional care group. For the MAiN group, the risk of readmission for a likely/possibly NAS–related diagnosis was 7.3%, compared to 9.8% for the traditional care group. In addition, in the traditional group, two cases of sudden infant death syndrome (SIDS) and one case of unattended death were documented by ICD-9-CM codes in the ED visits and readmissions, compared to no cases of SIDS or unattended death in the MAiN group.

The median total charges per ED visit were $833 (IQR: $528–$1,826) for the MAiN group and $581 (IQR: $280–$1,377) for the traditional care group ($z = -1.58$; $p = 0.11$). The median total charges per inpatient readmission were $6,154 (IQR: $3,694–$8,321) for the MAiN group, which was significantly lower than the $16,891 (IQR: $9,551–$47,503) median total charges for the traditional care group ($z = 3.58$; $p < 0.001$). The median LOS for an inpatient readmission for the MAiN group was 7 days (IQR: 6–8), compared to a median of 4 days (IQR: 2–12.5) for the traditional care group ($z = -1.44$; $p = 0.15$).

DISCUSSION

This is the first known study to compare infants receiving early initiated methadone (within 48 hours of birth) with a historical comparison group. This analysis showed that MAiN infants were similar with respect to outcomes, quality, and safety when compared to potentially MAiN–eligible infants receiving traditional care in South Carolina.

There was no difference in medical and safety outcomes between MAiN and traditional care NAS infants, with the exception of slightly more abnormal weight loss and diaper rash in the MAiN group. For these relatively minor health outcomes, differences may reflect documentation and coding variability rather than true differences in incidence. Overall, these findings are consistent with previous retrospective studies that showed outpatient methadone weaning strategies are not associated with increased risk of adverse outcomes.[12,21] We also found that neither MAiN infants nor traditional care NAS infants had documented ICD-9-CM codes for adverse safety events. The results that we report for MAiN infants are consistent with evidence that oral methadone therapy for inpatient neonates requiring pharmacologic treatment of NAS supports symptom stabilization with rare occurrence of somnolence, respiratory depression, or oversedation.[22,23] To date, no studies regarding the safety of outpatient methadone dosing have been conducted. Our findings add to a growing body of evidence that comprehensive, provider-managed outpatient weaning protocols can be safe and effective strategies for caring for infants with NAS.[12,21,24,25]

In our study cohort, ED visits and hospital readmissions up to two months from birth hospitalization discharge were different among MAiN and traditional care NAS infants. The traditional care group had a higher percentage of ED visits and inpatient readmissions assessed as likely or possibly NAS related than the MAiN group. While the current study examined ED visits and readmissions up to two months of discharge from hospital birth, Backes et al. report no difference in ED visits and hospital readmission rates within 12 months between patients receiving standard inpatient treatment and those in a combined inpatient/outpatient weaning group.[12] The MAiN model differs from other models used

in hospitals in the United States, which makes comparing ED visit and readmission rates difficult.

The most striking differences between the two groups were related to health services utilization outcomes. Most notably, there was a significant difference in hospital charges. The state group had median charges $8,204 higher than the MAiN population for the birth hospitalization and $10,737 higher median charges for any hospital readmissions ($p < 0.001$). Research on combined inpatient/outpatient methadone weaning protocols has documented similar charge and LOS reductions. Lee et al. found that infants completing combined outpatient weaning treatment had an average LOS of 11.4 days vs. 25.1 days for infants completing treatment in the hospital, resulting in a reduction of approximately $29,150 in charges per infant.[21] Lai et al. report an average LOS of 11.8 days for patients who underwent combined inpatient/outpatient wean and mean hospital charges of $58,400 per patient.[26] National data from 2012 showed that pharmacologically treated NAS infants had mean hospital charges totaling $93,400.[9]

Although the number of newborns in this study was small, NAS cases in the state and nation continue to rise at an alarming rate.[9,10] There is a clear, upward trend in length of hospital stay and resource utilization for infants requiring NAS treatment.[27] If statewide NAS births continue to increase, predicted hospital charges are expected to total more than $57,000 per infant.[28] Assuming current growth trends of state and national NAS cases, South Carolina and the rest of the United States should also expect exponential resource utilization growth.

There is a national impetus for nurseries to implement policies and standardized approaches to caring for substance-exposed newborns and mothers with substance use disorders.[14] Goals for improved protocols would include decreased transfers to tertiary care facilities, improved and sustained treatment in the community, and decreased readmission risk.[29] Recent research shows that standardizing treatment approaches has positive benefits for NAS neonates and decreases health care utilization.[30–32] MAiN provides a comprehensive approach to caring for opioid-dependent newborns and their mothers that may be replicated and customized in low-acuity nurseries around the country. Transitions from per diem to diagnosis-related group and bundled care reimbursement systems should further stimulate trends toward standardized care for NAS infants and their mothers. Meanwhile, additional problems exist, including high utilization of NICU beds, with up to 50% of NICU beds being used for NAS patients.[29]

Limitations

There are several limitations in this study that should be noted. The MAiN infants are a group with the highest likelihood of having withdrawal symptoms. Mothers of infants in the traditional care group were diagnosed with opioid dependence, but it is not known whether mothers were dependent on short- or long-acting opioids, or whether mothers were also using nicotine or SSRIs (selective serotonin reuptake inhibitors), which have been shown to increase NAS risk. Thus, this comparison group is diluted with lower risk compared to the MAiN infants, all of whom were exposed to at least 20 mg of methadone per day or at least 9 mg of buprenorphine per day for at least two weeks immediately prior to delivery.

Individual South Carolina physicians can choose to treat NAS infants, and infants identified by ICD-9-CM code may or may not have received treatment for NAS. Because this was a retrospective cohort study using data from state records, data limitations exist. For example, the state comparison group of NAS infants identified as MAiN eligible was based on available data from state records, which depended on the reliability of mothers being coded as opioid dependent and subject to errors of omission related to safety or medical outcomes. Available data were limited to ICD-9-CM diagnosis codes. In addition, the availability of data on ED visits and readmissions was such that the research team was not able to determine the number of days between birth discharge and the specific return ED visit or readmission. Only the month and year of these visits was available.

NAS infants treated with the MAiN model were similar in demographic and clinical characteristics to similar NAS infants treated with traditional care in South Carolina during the study period. Mothers of infants in both the MAiN and traditional care were similar, with the exception of tobacco use and infections during pregnancy, both of which were more common in MAiN mothers. However, it should be noted that this study has a non-randomized design, so there exists the possibility of unmeasured confounders. Thus, this should be considered as a hypothesis-generating study.

Planned future research include a prospective study with standardized data collection instruments, allowing the research team to capture real-time data instead of relying on administrative/billing data. Ideally, a randomized controlled trial would be performed to determine the efficacy of the MAiN model. In addition, study of long-term outcomes associated with the opioid withdrawal experience and of infants treated with methadone is warranted.

CONCLUSION

Alarming increases in NAS provide impetus for standardized approaches to caring for substance-exposed newborns and mothers with substance use disorders. With no difference in medical and safety outcomes and a significant reduction in charges, the MAiN model can be considered safe and cost-effective. This study demonstrates the potential value of implementing the MAiN model more widely across South Carolina and the rest of the United States, but further randomized controlled studies are warranted. Benefits of widespread implementation may include significant cost reduction over the long term and standardization of care without sacrificing safety.

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