Capstone title: Formula selection for term infants (≥37 weeks gestation) diagnosed with Neonatal Abstinence Syndrome (NAS).

Introduction:

Neonatal abstinence syndrome (NAS) can be defined as an drug withdrawal syndrome that occurs in infants that are exposed to addictive substances, opioids and other substances, while in utero.[1,2,3,4,5] Over the past decade, the prevalence of NAS has rapidly increased in New Mexico and across the United States.[2,3,4] From 2004 to 2014, the incidents of NAS in the US has increased by 433%, from 1.5 to 8.0 per 1000 hospital births.[3] In New Mexico, the incidents of NAS has increased 324% from 2008 to 2017 from 3.3 to 14.0 per 1000 births.[3] In New Mexico, Hispanic infants accounted for 48% of NAS cases followed by white at 30.9% and American Indian/Alaskan Native (AI/AN) at 5.0%, however, AN/IN showed the highest percent change in rates of NAS of 698.2% between 2008 to 2017.[4] The prevalence of NAS may be under or over reported. According to Jilani et al, NAS surveillance is often dependent on hospital discharge data that can underestimate the incidence of NAS.[3] Underreporting may be due unavailability of information in real time or that many pregnant women are not routinely screened for substance abuse.[3,6] However, Saavedra concluded that NAS ICD-9-CM diagnostic codes 779.5 and P69.1 had a combined predictive value of 70.2% indicating that New Mexico results may have been overestimated and that sensitivity and specificity of these codes should be assessed.[4] The rise in NAS incidence can be attributed to the increased use of opioids prescribed for pain or other management of disease, illicit use of opioids (oxycodone and heroine, methamphetamine), and an increase in opioid substitution treatments.[2,5]

NAS typically onsets within 24-48 hours after delivery, however, infants exposed to polysubstance abuse in utero can require earlier treatment with peak onset between 34-50 hours after birth.[7,6] Majority of NAS cases are identified within 5 days of birth.[6] Signs and symptoms of NAS vary between infants potentially due to variable or multiple drug exposures and/or the amount of the drug transported through the placenta.[2] Symptoms of NAS can include irritability, hypertonicity, uncoordinated suck swallow, nasal stiffness, jitteriness, poor sleep, poor growth, gastrointestinal (GI) distress, altered sleep-wake cycles, respiratory distress

and temperature instability.[2,3,5,7,8] Additionally, signs of withdrawal can also include excessive, high-pitched crying, sleeplessness, hyperactive reflexes, tremors, excoriation, mottling, nasal stiffness and flaring, tachypnea, and seizures.[6] GI symptoms can include nausea, vomiting, projectile vomiting, regurgitation, cramping, and loose stools.[2,5,6]

Children with NAS may require long term medical intervention as well as special education.[6] Infants with NAS face challenges in life that be linked to inconsistent care giving, family instability, placement out of the home, chronic stress, poverty, and exposure to parental drug use.[6] NAS has also been linked to vision problems such as strabismus, reduced visual acuity, nystagmus, refractive errors, and cerebral visual impairment.[5] NAS may also be associated with long-term motor development consequences.[6] Additionally, NAS can be associated with behavioral and cognitive problems that can continue to decline as the infant reaches 12 months of age.[6]

Breastfeeding in NAS mother infant dyads have been well researched. Breastfeeding has been shown to provide a protective factor for infants with NAS as it can delay the onset of NAS, decrease severity of NAS, decrease initial hospital length of stay (LOS), and decreased length of pharmacological treatment (LOT).[2,9] However, there are challenges associated with breastfeeding in this population. This can result in a decreased rate of initiating breastfeeding and a shorter duration of breastfeeding.[1,9] It is recommended that women who are stable in opioid substance treatment without contraindications should be encouraged to breastfeed regardless of methadone dose.[7] Contraindications include HIV positive status, use of illicit drugs including the use of marijuana.[7] There are many barriers to initiating breastfeeding in mothers of NAS infants that include inconsistent advice from healthcare providers, lack of clear or consistent guidelines, feeding problems due to drug exposure, LOS where mom and infant are separated, mother's low self-esteem, lack of knowledge, or feelings of guilt.[5,7] Inconsistent breastfeeding recommendations have stemmed from the change in recommendations from the American Academy of Pediatrics (AAP) whose stance from 1983 to 2001 was that breastfeeding was only recommended if the methadone treatment dose was 20 mg or less in a 24 hour period, which rendered breastfeeding incompatible for most mothers on a methadone

treatment program.[7] Recommendations were updated in 2001 that endorsed methadone use in breastfeeding mothers in a methadone maintenance program, regardless of dose.[7]

Due to decreased initiation and continued practice of breastfeeding for NAS infants, the aim of this literature review to determine if the use of low lactose formulas versus standard lactose formulas creates a difference in outcomes from NAS exposed infants.

Literature search:

A search was conducted for relevant literature October 2021 to March 2022 using PubMed, Cumulative Index to Nursing and Allied Health (CINAHL), and the Cochrane Library. A search was performed for articles published with in the past 11 years from initial search date, 2011-2022 utilizing the key words ("Neonatal abstinence syndrome") or (NAS) or (“drug withdrawal”) along with one of the following terms ("infant formula") or ("hydrolyzed formula") or (“feeding") or ("high-calorie formula") with each search conducted separately. Additional filters to include human trials and printed in English were selected. The initial search yielded 394 results, when the additional filters were applied these narrowed results to 218 articles, then after duplicate articles were removed there were 144 articles left to screen by title, after titles were screen, this resulted in 18 articles, then the article abstracts were reviewed resulting in 11 articles. After the 11 articles were read, five articles were excluded. Exclusion was due to focus on breast feeding versus formula feeding, exclusion of infant feeding in the review, and one article was an orchestrated test that did not include statistical analysis of data included. This resulted in a total of six articles included in this review.

Literature Review:

Pandey et al aimed to determine if lactose-free (LF) formula or lactose-containing (LC) were more beneficial in the management of NAS. Eligible participants were born between 36-42 weeks gestational age with intrauterine exposure (IUE) to opioids known to cause NAS. In this prospective double-blinded clinical trial, participants (N=69) were stratified based on gender and IUE then randomized into the LF group (n=34, 57% male) and provided Similac Sensitive, an improved tolerance formula, or the LC group (n=35, 51% male) and provided Similac Advance, a standard term milk-based formula, with study formula being provided in the first 24 hours of life. All formula was reconstituted to provide 20 calories per ounce from liquid

concentrate, caloric concentration could be adjusted based on physician request. Additionally, study formula was supplemented when breastfeeding was contraindicated, mother chose not to breastfeed, or mother's milk supply was inadequate. Study formula was mixed in a formula room, away from investigators, and provided to patients at bedside labeled "study formula A" and "study formula B". Study formula was used for the first 14 days of life or until the patient was discharged, whichever occurred first. Researchers found that when comparing the LF group the LC group they were similar for NAS scores during the first 72 hours of life (5.2 ± 1.8 vs. 5.1 ± 1.8), first 5 days of life (4.7 ± 1.7 vs. 4.8 ± 1.8), and at 7 days of life (4.6 ± 1.4vs 4.4 ± 1.4).[1] The cumulative morphine dose (20.7 ± 19.8 vs 23.0 ± 23.3 mg) and morphine per kilogram of body weight (7.2 ± 7.5 va 7.5 ± 7.6 mg/kg), highest dose (0.10 ± 0.09 vs. 0.10 ± 0.10 mg/kg), duration of NAS treatments (16.5 ± 13.6 vs 19.6 ± 19.5 days), and length of stay (LOS) in the hospital (22.4 ± 14.1 vs 27.0 ± 19.8 days).[1] The researchers did discover that NAS infants who predominantly consumed breast milk had associated improved outcomes. The limitations of this study include heroin use was higher in mothers of NAS infants that were assigned to the lactose-free group and the inability to follow patients who were discharged home before 14 days of life.[1]

McQueen et al aimed to determine if NAS scores of infants exposed to methadone during pregnancy differed by feeding method.[7] In this study researchers preformed a retrospective chart review of mother infant dyads (N=28) for infants born at a selected hospital who were scored for and met NAS criteria prior to discharge. The chart review included data on NAS scores, NAS treatment along with drug dosages, infant feeding method, and baseline maternal and infant demographics. The primary outcomes reviewed in this study were NAS scores assessed with the Modified Finnegan Scoring Tool and method of infant feeding. Infants were classified based on feeding method. Infants were placed in the predominantly breast-fed group (n=8, 62.5% male) if breastfed >75% of all feeds, combination-fed (n=11, 36.4% male) if breastfed between 25-75% of all feeds, and predominantly formula fed (n=9, 55.5% male) if breastfed <25% of all feeds. While inpatient, all infant feeds were assessed by documentation in the electronic medical record (EMR) and percentages were calculated by adding the total number of infant feeds and dividing by the number of times infant was breastfed.

Researchers found that the predominantly breast-fed infant group had a lower mean number of recorded NAS scores (mean=25.0, SD=23.5) when compared to the combination group (mean=56.2, SD=39.1) and the formula fed group (mean=95.6, SD=34.6).[7] Additionally, the predominantly breastfed group had lower severity of NAS scores when compared to the other groups (mean=4.9, SD=2.9 vs. mean=6.5, SD=3.7 and mean=6.9, SD=4.2, respectively).[7] The findings suggest that breastfeeding may be associated with decreased NAS symptoms, duration, and intensity.[7] Limitations of this study included self-allocation to feeding group, small study size, and self-reported data for methadone use.[7]

Alsaleem et al aimed to determine if partially hydrolyzed formulas (PHF) would decrease severity and short-term outcomes of NAS when compared to standard formula (SF).[2] In this retrospective chart review, infants were selected for inclusion if they had a gestational age of ≥36 weeks and their mothers self-reported or produced a urine drug screening positive for opioid mediation use. Infants that were born <36 weeks' gestation, had confounding variables that would have affected length of stay, and treatment with medication other than morphine as a first line treatment for NAS were excluded. Eligible infants (N=110) were sorted into groups based on the formula type they predominant received during hospitalization. Infants in the PHF group (n=34, 47% male) received the commonly used PHF formulas at the research site during the study period, Gentlease (Mead Johnson & Co) and Similac Sensitive (Abbott). The infants in the SF group (n=60, 65% male) received an unspecified standard infant formula. Infants in the Maternal breast milk (MBM) (n=16). Infants were provided the formula mixed to the standard 20 calories per ounce. Clinicians assessed infant growth each morning, if infant weight was not adequate, formula was concentrated to achieve a weight gain of 15-20 g/kg/day after the infant's initial expected weight loss. The researched found that after adjusting for confounding factors for the PHF and SF groups, there was no difference in length of stay (29 ± 19 vs 21 ± 12 days), maximum dose or duration of morphine (0.07 ± 0.05 vs 0.05 ± 0.05 mg/kg/dose).[2] Additionally, researchers did not find any benefit in reduction of overall dose of morphine (4 ± 2.2 vs 3.5 ± 1.2) or duration of morphine treatment (24 ± 19 vs 15 ± 14 days) for PHF and SF

groups respectively.[2] Study limitations included the study type of retrospective chart review and formula selection was based on clinicians' preference.[2]

Bogen et al conducted a randomized, double-blinded feasibility study to compare the efficacy of standard calorie formula (SCF), 20 calories per ounce, when compared to high-calorie formula (HCF), 24 calories per ounce, on preventing excessive weight loss and late return to birth weight of methadone-exposed newborns.[8] Eligibility criteria included a birth weight of at least 2200 grams, gestational age ≥35 weeks, and not admitted to the NICU for more than 24 hours for a medical condition other than NAS treatment before 3 days of life. Patients were excluded if they had a major congenital malformation that could interfere with feeding or weight gain, born to mothers who planned to feed infants with soy formula, and infants intended to be placed for adoption. Eligible infants (N= 49) were stratified by gestational age, sex, and feeding method and randomly assigned to the SCF group (n= 22, male=10) and the HCF group (n= 27, male=12) within 72 hours of birth. All infants were provided Enfamil ready to feed (RTF), a term cow's milk-based formula, with the original labels covered and infants were fed every 3-4 hours on demand. Infants stayed on the formula for the first 21 days of life, formula was provided to the patients who discharged prior to 21 days. Parents were provided education on how to fill out feeding longs and scale training and were checked up with daily via telephone or, if unable to be reached, in person at home or at the mother's methadone treatment center. The researchers determined there were no statistically significant differences when comparing the SCF and HCF groups for average daily weight after return to birth weight (mean=0.67, SD=0.69 vs mean=0.81, SD=0.65), days to nadir weight (mean=5.0 vs 4.4), and days to return to birth weight (mean=14.7 vs mean=13.6), however, the trends favored the HCF group.[8] Both groups gained increasing amount of weight over time, the HCF groups weight gain was larger when compared to the SCF group. The limits of this study are a small sample size, a limited duration of formula exposure, and limited generalizability due to only including methadone exposed NAS infants.[8]

Alsaleem, Dusin, and Akangire preformed a systematic review with the aim to determine if low lactose formula (LLF) decreases the severity and the duration of NAS symptoms of infants born at ≥35 weeks' gestation with NAS when compared to infants who

received regular standard formula (RSF). The researchers looked for studies where the authors compared outcomes for need of pharmacological therapy for NAS, duration and dose of pharmacological treatment, LOS, and effects of formula (LLF vs. SRF) on infant growth. Two researchers independently screened titles and abstracts and discrepancy for article inclusion were resolved and agreed upon by all investigators. Researchers assessed the certainty of the evidence using Grading of Recommendations Assessment, Development, and Evaluation (GRADE). Of the 41 articles identified through database searching, four articles were included in this systematic review as a meta-analysis could not be performed due to differences in the study type and statical heterogeneity of the outcomes. The authors finding showed no real difference between LLF and SLF on the length of pharmacological therapy. In the articles reviewed for differences in LOS, researchers found that low lactose + high calorie formula was less effective when compared to high lactose + high calorie formula but significance was not reported in the articles reviewed and the certainty in the body of evidence was very low due to bias, inconsistencies, and lack of precision. These researchers concluded that there is no added benefit to provide LLF when compared to SLF to infants with NAS when reviewing the limited research on LOS, and the need and duration of pharmacological treatment.[10]

Lembeck et al conducted a retrospective cohort study to determine if LLF versus SLF would have an effect on weight-change, length of pharmacological intervention (LOT) and LOS. A secondary analysis was conducted on infants who were exclusively breastfed or provided a single formula. Eligible patients were born at ≥35 weeks gestation, a NAS diagnosis (code 779.5, P961, or P962), and admitted to a general pediatric floor unit.[9] Infants with an admit to the NICU and infants who were provided a formula other than LLF, SLF, or breastmilk were excluded. Feeding method was determined by formula the infant consumed >50% of feedings. If mother elected not to breast feed, formula was selected based on the medical team's discretion. Infants (N=249) were divided into three sub-groups, term standard formula (n=147), term LLF (n=37), and breast milk (n=65). Infants that were breastfed lost 12.3 g/day more when compared to the SLF group and 9.9 g/day more when compared to LLF group. LOT was 6.9 days and 10.8 days shorter in the breastfeeding group compared to the SLF and LLF feeding groups, respectively. LOS was shorted in the breastfed group by 7.4 days and 10.3 days when compared

to the SLF and LLF groups, respectively.[9] When SLF and LLF were compared, there were no difference in weight-change, LOS, and LOT. Limitations of this study were the retrospective nature, no information if infants consumed expressed breastmilk (EBM) or at-breast feeding, limited information on other comorbidities, limited power to detect small differences in outcomes between groups, and potential bias in formula selection by the physician.[9]

Conclusion:

In conclusion, if a mother is adhering to an opioid maintenance program and breast feeding is not contraindicated, breastfeeding should be encouraged and supported. If a mother chooses not to breastfeeds, cannot breast feed due to contraindications, physical inability, adoption, or custody issues, infants with NAS should be provided with standard lactose formula unless signs of a cow's milk allergy (CMA) are present. CMA can appear during the first few months of life. CMA can also appear in infants who are exclusively breastfed if cow's milk protein from the maternal diet is transmitted through breastmilk in sufficient quantities. Immunoglobulin (Ig) E signs can occur within minutes and up to two hours after ingestion. General IgE reactions present on the skin, oropharyngeal, upper and lower respiratory traction, GI tract, and/or cardiovascular dysregulation with signs and symptoms ranging from mild to severe.[11] If signs and symptoms of IgE mediated CMA are present providers should consider a soy-based formula or hypoallergenic formula that is soy and lactose free if the infants symptoms persist. More research is needed to determine if hypercaloric formulas provide better outcomes for infants with NAS.

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