

Can growth be optimized in enterally fed very low birth weight infants who receive dexamethasone as compared to untreated peers: a retrospective study

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Abstract

Background: Growth is essential for very low birth weight infants, but is compromised in those receiving dexamethasone, especially when given as a consecutive 10-day treatment course to wean ventilatory support. The purpose of this review is to analyze growth outcomes of enteral nutrition practices for infants born < 1,500 grams who received at least one consecutive 10-day treatment course during hospitalization compared to untreated peers.

Methods: An IRB-approved retrospective chart review compared 17 dexamethasone-treated study infants vs. 34 untreated controls born < 1,500 grams. Wilcoxon rank sum test and Fisher's exact test compared continuous data and associations of categorical variables. Multiple regression analyzed predictors for growth outcomes when adjusting for birth gestational age. P-value < 0.05 was considered statistically significant.

Results: Treated infants were born younger (25⁺⁴ vs. 27⁺⁶ weeks gestational age [GA]) with smaller anthropometric measurements ($p < 0.05$). Growth from birth to 36 weeks GA approached significance (15.1 grams/kg/day study vs. 16.65 grams/kg/day control [$p = 0.07$]). Treated infants were discharged at similar weight percentiles as untreated infants ($p = 0.7$). Head growth percentiles were well-maintained for all infants (treated: median 12th% birth, 21st% discharge; untreated: 29th% birth, 43rd% discharge). Treated infants had lower length measurements at 36 weeks GA ($p = 0.011$) and discharge ($p = 0.095$). Treated infants received more nutrition, median 131 vs. 119 calories/kg/day ($p = 0.0005$), 4.4 vs. 4.1 grams protein/kg/day ($p = 0.0004$). Average

nutrition delivery during dexamethasone treatment was 138 calories/kg/day, 4.5 grams protein/kg/day. There were no differences in highest blood glucose ($p = 0.071$), BUN ($p = 0.053$), or alkaline phosphatase ($p = 0.17$) between groups.

Conclusions: Infants receiving at least one consecutive 10-day treatment course with dexamethasone during hospitalization experienced altered growth by 36 weeks GA, but comparable growth to non-treated infants for weight and head circumference can be achieved by discharge by optimizing enteral nutrition before, during, and after dexamethasone treatment. Future studies are needed to assess if this leads to improved developmental outcomes.

Keywords

Dexamethasone, enteral nutrition, growth, low birth weight, premature infant.

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Background

Providing adequate nutrition remains an essential therapy for very low birth weight infants. Born with high metabolic demands and limited nutrient reserves, premature infants require aggressive nutritional care to mimic the rapid growth and nutrient accretion achieved *in utero* [1, 2]. Growth must remain a priority during the neonatal period, as there is rapid ongoing brain development. Research has demonstrated that suboptimal growth may lead to poor neurodevelopmental and health outcomes, including a higher incidence of cerebral palsy, lower Bayley Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) scores, and a higher incidence of re-hospitalization after initial Newborn Intensive Care Unit (NICU) discharge [3]. Growth must

also be monitored closely in infants plotting less than the 10th percentile on their respective growth chart, whether they were born or fell below this point, as they may become more susceptible to worsened health outcomes [4]. Challenges to meeting growth goals exist because there are other essential medical therapies that can hinder critical growth in this high-risk infant population. One of these is dexamethasone administration. It is often given as a consecutive 10-day treatment course to improve respiratory management [5]. During this treatment, dexamethasone is given 20 times in four weight-based tapered doses [6].

Premature infants will often lose weight initially at the start of dexamethasone administration, primarily due to diuretic effects [7]. However as treatment continues, poor growth is often seen clinically in infants with an associated decrease in percentiles on their growth chart [8]. Rationale for poor growth is linked to an interruption in the growth hormone cycle, as plasma insulin-like growth factor and related binding proteins are markedly reduced in preterm infants after start of steroid administration [9-11]. Without catch-up growth after treatment, a treated infant may be highly susceptible to extra-uterine growth restriction, especially if they receive more than one course of 10-day treatment course during their NICU stay. There are research studies paralleling this theory of hindered growth with steroid administration [11-15, 17]. Infant size at birth has been analyzed for mothers who received steroids prior to delivery, with results showing that their infants are born smaller than infants of untreated mothers [12]. Secondary outcomes from dated research have demonstrated smaller weight around and after term age, decreased linear growth, smaller head circumferences [13-15], potentially reduced bone mineralization [16], and glucose intolerance [13]. Most available research regarding steroid treatment in premature infants focuses on neurodevelopmental outcomes, which are often impaired [15, 17]. Only a few small-scale studies analyze growth as a primary outcome [14, 16, 18], with one concluding that the amount of protein provided improves growth and growth factors in premature infants receiving steroids [14]. To date, there are limited studies analyzing both detailed growth and nutrition measures.

Nutrition management varies widely for infants who are on dexamethasone therapy. Growth remains a high priority in our patient management so we choose to aggressively

adjust enteral feedings to help offset significant weight loss and poor growth. These adjustments typically consist of increasing the caloric density of feedings, which also increases the amount of protein, vitamins, and minerals an infant receives. Once dexamethasone treatment is complete, infants may remain on these higher nutrient feedings to promote catch-up growth if needed. Growth success from our current feeding practices has been documented [19], but this does not specifically include data on infants who received steroids. The purpose of this study is to analyze growth outcomes for premature infants born < 1,500 grams who received at least one consecutive 10-day treatment course of dexamethasone compared to those who did not, and to assess if adjusting enteral feedings is well tolerated and contributes to improved growth.

Methods

Participants and data collection

The institutional review board at the University of Nebraska Medical Center (Omaha, NE, USA) approved this study with a waiver of consent and ethical standards of the institutional committee on human experimentation were followed. Data was retrospectively collected from inpatient electronic medical records of all infants admitted to the NICU between August 2012 and March 2015 if they met the following criteria; birth weight (BW) < 1,500 grams, received at least one consecutive

10-day treatment course of dexamethasone during NICU hospitalization, and had established full enteral feedings prior to start of dexamethasone administration. Only infants achieving full enteral feedings by start of dexamethasone administration were included as full volume enteral feedings are achieved primarily within the first 1-2 weeks of life in this population and dexamethasone is not used within the first weeks of life if clinical status allows. Infants meeting set criterion were frequency matched with untreated infants who were as comparable in weight and gestational age as available. After extensive review, 17 treated infants were eligible for the study and 34 frequency matched, untreated control infants.

In further clarification, this was not a randomized-controlled trial. It is also important to note that dexamethasone-treated infants in this study were not participants in the original DART (Dexamethasone-A Randomized Trial) study, as published [5]. Instead, treated infants received dexamethasone at similar dexamethasone dosing to the original DART study in an attempt to wean respiratory support [5]. The decision of if or when to treat with a 10-day consecutive dexamethasone course was at the discretion of the attending neonatologist, though it is used conservatively and infrequently within our unit. Six investigators familiar with the electronic medical record obtained all data and closely reviewed it for accuracy. Available data on each infant was included in the analysis and is displayed in **Tab. 1** and **Tab. 2**.

Table 1. Baseline characteristics and outcome data.

| Variable | Treated group (n = 17) Median (SD) | Untreated group (n = 34) Median (SD) | Overall p-value |
|--|--|---|--------------------|
| GA at birth (weeks) | 25 ⁺⁴ (1.95) Range 22 ⁺⁶ -30 ⁺² | 27 ⁺⁶ (1.07) Range 26 ⁺⁰ -29 ⁺⁵ | < 0.0001 |
| GA at discharge | 42 ⁺³ (5.68) Range 38 ⁺² -63 ⁺⁰ | 39 ⁺¹ (1.9) Range 35 ⁺⁵ -43 ⁺³ | < 0.0001 |
| Gender | 59% male, 41% female | 56% male, 44% female | NS |
| ROP (Stage 2 or >) | 12/17 (71%) | 0% | < 0.0001 |
| IVH (Grade 3-4) | 2/17 (12%) | 1/34 (3%) | 0.25 |
| GA off oxygen (weeks) ^a | 39 ⁺⁴ (n = 8) Range 35 ⁺¹ -41 ⁺⁵ | 34 ⁺⁶ (n = 33) Range 27 ⁺⁶ -42 ⁺⁴ | < 0.005 |
| Number of consecutive 10-day dexamethasone courses | 2 Range 1-4 | 0 | < 0.0001 |
| Highest blood glucose ^b (mg/dL) | 122 (82) | 108 (31) | 0.071 |
| Highest BUN ^b (mg/dL) | 29 (22.6) | 17 (15.3) | 0.053 |
| Highest alkaline phosphatase ^b (U/L) | 410 (226.8) | 327 (165.5) | 0.17 |

SD: standard deviation; GA: gestational age; BUN: blood urea nitrogen; NS: not significant.

^aFor infants not discharged home on oxygen; ^bwhile on full enteral feedings.

Table 2. Growth and nutrition data.

| Variable | Treated group (n = 17) Median (SD) | Untreated group (n = 34) Median (SD) | Overall p-value |
|--|--|--|--------------------|
| Birth weight | 710 (230) Range 420-1,025 | 1,050 (220) Range 540-1,400 | 0.0002 |
| Birth weight percentile ^a | 40 (27) | 37 (23) | 0.61 |
| 36 week GA weight | 2,190 (350) Range 1,570-2,780 | 2,490 (300) Range 1,640-2,990 | 0.022 |
| 36 week GA percentile ^a | 14 (15) | 24 (16) | 0.025 |
| Discharge weight | 3,530 Range 2,830-6,430 | 3,130 Range 2,150-3,116 | 0.0032 |
| Discharge weight percentile ^a | 24 (19) | 26 (15) | 0.7 |
| Growth in grams/kg/day from birth to 36 weeks GA ^a | 15.10 (2.0) | 16.65 (1.9) | 0.07 |
| Birth HC | 22 (1.4) | 25.25 (1.8) | < 0.0001 |
| Birth HC percentile ^a | 12 (24) | 29 (22) | 0.25 |
| 36 week GA HC | 31.4 (1.4) | 32 (1.2) | 0.03 |
| 36 week GA HC percentile ^a | 16 (22) | 36 (22) | 0.024 |
| Discharge HC | 35.2 (2.3) | 34.5 (1.6) | 0.032 |
| Discharge HC percentile ^a | 21 (24) | 43 (21) | 0.024 |
| Birth length | 31 (3.7) | 35 (2.5) | 0.0001 |
| Birth length percentile ^a | 20 (13) | 12 (17) | 0.88 |
| 36 week GA length | 44 (3.3) | 45 (2.1) | 0.008 |
| 36 week GA length percentile ^a | 5 (7) | 13 (19) | 0.011 |
| Discharge length | 49 (4.7) | 47.5 (2.5) | 0.056 |
| Discharge length percentile ^a | 6 (13) | 18 (18) | 0.095 |
| Weight < 10 th percentile ^a at birth | 5/17 (29%) | 3/34 (9%) | - |
| Weight < 10 th percentile ^a at 36 weeks GA | 8/17 (47%) | 5/34 (15%) | - |
| Weight < 10 th percentile ^a at discharge | 4/17 (24%) | 4/34 (12%) | - |
| Highest caloric density feedings (median) | 30 calories/ounce | 27 calories/ounce | < 0.0001 |
| Average calories/kg/day ^b | 131 (4.6) | 119 (8.6) | 0.0005 |
| Average protein/kg/day ^b | 4.4 (0.2) | 4.1 (0.2) | 0.0004 |
| Average calories/kg/day during dexamethasone administration | 138 | - | - |
| Average protein/kg/day during dexamethasone administration | 4.5 | - | - |

Weight reported in grams, head circumference and length reported in centimeters.

SD: standard deviation; GA: gestational age; HC: head circumference.

^aAssociated percentiles on the Fenton growth curve; ^buntil 36 weeks GA.

Demographics and clinical outcomes

Demographic information was collected for all infants including gender, gestational age at birth and discharge, and day of life at discharge. Additional clinical outcomes were collected including the incidence of retinopathy of prematurity (ROP) Stage 2 or greater, intraventricular hemorrhage (IVH) Grade 3-4, being discharged home on oxygen, length of days to wean off oxygen, number of days receiving steroids, and number of consecutive 10-day dexamethasone therapy courses.

Dexamethasone administration

Dexamethasone administration is initiated according to attending neonatologist discretion according to the infant's clinical status. Dexamethasone dosing for this population follows Neofax recommendations which consist of 0.075 mg/kg/dose every 12 hours for 3 days, 0.05 mg/kg/dose every 12 hours for 3 days, 0.025 mg/kg/dose every 12 hours for 2 days, and 0.01 mg/kg/dose every 12 hours for 2 days [6]. Dexamethasone was given enterally for the study infants as they were receiving full enteral feedings at time of treatment.

Anthropometrics, growth, and nutrition

Infants were weighed nightly on an electronic gram scale, and length and head circumference measurements (centimeters) were taken once weekly on Sunday evenings using a measuring tape by nursing staff. Percentile rankings from the Fenton growth chart were electronically plotted for each documented measurement. Weight, length, and head circumference measurements with associated Fenton percentile rankings were recorded for infants at birth and 36 weeks gestational age (GA) if available. Infant weight was reviewed at birth, 36 weeks GA, and discharge to assess if weight plotted below the 10th percentile. Growth was also analyzed in grams/kilogram (kg)/day from the start of full enteral feedings (140 milliliters [mL]/kg/day) until 36 weeks GA. Growth velocity was calculated as follows: $[1,000 \times \ln(W_n/W_1)] / (D_n - D_1)$ [20]. In this calculation, W_1 is the starting weight (in grams) for the growth assessment period with W_n being the weight in grams on day n . This is similar for D_n and D_1 , which refer to the day W_1 and W_n were taken. \ln refers to the natural logarithm function. One infant was discharged beyond 50 weeks GA, so growth information was collected at 50 weeks GA, the highest age plotted on the Fenton growth chart.

Enteral feeding data collected included the average calories/kg and grams protein/kg per day from start of full enteral feedings until 36 weeks GA. Full feedings was defined as the infant receiving at least 140 mL/kg/day of enteral feedings and no parenteral nutrition, of either premature infant formula or fortified human milk. Average calorie and protein provision was also analyzed during each 10-day consecutive dexamethasone treatment period to more closely capture nutrition during this period. Average nutrition from fortified maternal breast milk was estimated according to manufacturer information on milk additives and assuming a protein content of mature milk at 10.5 grams/Liter [21-23]. Maximum caloric density of feedings was recorded for each infant. Nutrient provision was captured by an electronic medical system (Intuicare), which contained protein references based on the caloric density of specified formulas or fortified human milk. Nursing staff recorded daily intake (in milliliters) of specified feedings, and daily calories and proteins per kilogram was electronically calculated using the daily recorded weight.

Full enteral feedings are generally achieved within the first 1-2 weeks of life in our population of infants as parenteral nutrition is simultaneously

discontinued. Standard practice in our unit is to fortify human milk to 24 calories/ounce using a non-acidified liquid human milk fortifier [21]. A liquid protein modular is also added to provide a standard dose of approximately 4.2 grams protein/kg/day when provided 120 calories/kg/day [22]. Infants weighing less than 1,250 grams standardly receive a protein dose of 4.4 grams/kg/day when provided 120 calories/kg/day. Occasionally infants will have an increased protein dose based on growth and clinical acuity. Standard practice is to fully fortify breast milk feedings to 24 calories/ounce with human milk fortifier and a liquid protein modular before discontinuation of parenteral nutrition. Infants unable to maintain their own growth percentiles for weight after initial diuresis while on full enteral feedings are increased to 27 or 30 calories/ounce feedings by adding preterm infant formula powder in addition to human milk fortifier and protein modular. Donor human milk is used as a supplement to mother's own milk during the first 14 days of life. If minimal mother's milk is available or growth is deemed inadequate by the medical team prior to 14 days of life, a transition from donor milk to preterm infant formula will be implemented over a 2-3 day period. Formula fed infants receive high protein preterm infant formulas at either 24, 27, or 30 calories/ounce [24, 25]. Feeding volumes are generally maintained around 140-160 mL/kg/day to provide appropriate total calories as needed for growth. Incidence of necrotizing enterocolitis remains low in our unit, previously documented at 3% [18]. All infants receive vitamin D3 (cholecalciferol) supplementation (400 international units daily) while on full enteral feedings, which is started before discontinuation of parenteral nutrition.

Laboratory measurements

Highest blood glucose, blood urea nitrogen (BUN), and alkaline phosphatase were recorded as available at any point while on full enteral feedings, despite timing of dexamethasone administration. Highest values were selected to be reported in order to identify if high calorie and protein provisions positively or negatively influenced metabolic outcomes at any point while on full enteral feedings.

Data analysis

The Wilcoxon rank sum test was used to compare continuous data between the treated

and untreated groups. Associations of categorical variables were assessed with the Fisher's exact test. Individual regression models were performed which included group and gestational age as predictors of weight and length, because of concern that treated infants were born smaller and more prematurely at baseline. A p-value < 0.05 was considered statistically significant.

Results

There were 17 infants in the study group who received at least one consecutive 10-day dexamethasone treatment course during hospitalization, matched with 34 untreated control infants. Baseline demographic and clinical outcome data are displayed in **Tab. 1**. Growth and nutrition outcomes are displayed in **Tab. 2**.

Baseline characteristics and outcomes

Treated study infants were born at significantly younger gestational ages, with smaller measurements for weight, length, and head circumference. There were no differences in infant gender between groups. Treated infants received an average of 20 days of combined dexamethasone therapy during hospitalization compared to no treatment days for the untreated group ($p < 0.0001$). This equates to two consecutive 10-day treatment courses with dexamethasone. Untreated infants came off oxygen support earlier than treated study infants, median of 34⁺⁶ weeks GA. Three percent (1/34 infants) of untreated infants discharged home on oxygen vs. 53% (9/17) in the treated group. Study infants developed higher rates of ROP compared to untreated peers (71% vs. 0%, $p < 0.0001$). Twelve percent of treated infants had IVH grade 3-4 vs. 3% of untreated infants, but this was not significant ($p = 0.25$).

Laboratory data was collected on a clinical basis only. There were no statistically significant differences in highest blood glucose, highest BUN, or highest alkaline phosphatase between groups while on full enteral feedings during NICU stay.

Growth and nutrition outcomes

Treated infants exhibited lower weights at 36 weeks GA compared to the untreated group, but there were no differences in discharge weight growth percentiles because treated infants were discharged at older gestational ages (42⁺³ vs. 39⁺¹

weeks; $p < 0.0001$). There were no statistically significant differences in growth from birth until 36 weeks GA as measured in grams/kg/day (15.1 vs. 16.65), although this approached significance ($p = 0.07$). More infants in the treated group had weights plotting < 10th% on the Fenton growth curve than in the untreated group at birth, 36 weeks GA, and at discharge. Both groups had a higher incidence of weights plotting < 10th% at 36 weeks GA compared to birth or discharge, but this was more notable in the treated group. Head circumference growth was adequately maintained for infants in each study group throughout NICU stay. Linear growth was well maintained for the untreated group. The treated group experienced a decline in linear growth percentiles from birth until 36 weeks GA, but was maintained from 36 weeks to discharge. After adjusting for gestational age at birth, treated infants were anticipated to weigh 365 (± 118) grams less at 36 weeks GA than untreated infants ($p = 0.003$). Similarly, treated infants were anticipated to have a recorded linear measurement 2.1 cm (± 1.0) smaller at 36 weeks GA compared to untreated infants ($p = 0.039$).

Treated infants received higher average calories (131 vs. 119 calories/kg/day, $p = 0.0005$) and protein (4.4 vs. 4.1 grams/kg/day, $p = 0.0004$) from birth until 36 weeks GA. Treated infants also received higher caloric density of enteral feedings compared to control infants (30 vs. 27 calories/ounce, $p < 0.0001$). On average, treated infants received 138 calories/kg and 4.5 grams protein/kg/day while on dexamethasone treatment. Breast milk use was equivalent between groups with 68% (23/34) of the untreated and 65% (11/17) of the treated infants receiving > 50% of feedings as human milk during their NICU stay.

Discussion

Weight

Treated infants were born at smaller weights and more preterm GAs compared to the untreated infants, the most likely reason for their development of chronic lung disease. Initial results from our research coincide with previous studies that suggest altered growth in dexamethasone-treated infants. For example, Bartholomew et al. compared growth outcomes for more than 1,000 infants born between 23-27 weeks GA, in which they reported an odds ratio of 2.8 (95% CI 1.2-6.5, $p < 0.05$) for being in the lowest growth velocity

if treated with dexamethasone [26]. In our study at 36 weeks GA, dexamethasone-treated infants were statistically smaller than the untreated group ($p = 0.022$), with a lower associated percentile on the Fenton growth curve ($p = 0.025$). These findings are similar to those of Stark et al. who reported smaller weight, length, and head circumference measurements at 36 weeks GA for infants born $\leq 1,000$ grams and started on early dexamethasone [13]. Dosing for this study by Stark et al. was different than dosing for our treated infants with 0.15 mg/kg of dexamethasone daily for three days, followed by 0.10 mg/kg for three days, 0.05 mg/kg for two days, and 0.02 mg/kg for two days [13]. Growth from birth until 36 weeks GA approached, but did not exceed significance in our study when comparing the treated to untreated infants, 15.1 vs. 16.65 grams/kg/day ($p = 0.07$). In clinical review of each treated infant's growth chart, many of the treated infants had recently completed a consecutive 10-day dexamethasone course by this time point at 36 week GA. These infant's had not yet experienced catch-up growth and were likely experiencing weight plotting in the lowest growth percentiles since birth. While both ranges fall below ideal growth of at least 18.0 grams/kg/day [3], it must be noted that these calculated velocities include initial days of diuresis. Per Horbar et al., calculating growth from birth until discharge results in a velocity that is ~ 3 grams/kg/day less than if calculating velocities based on day of life birth weight regained until discharge [27].

Treated infants did exhibit catch-up growth prior to discharge with persistently optimized nutrition, even discharging at similar weight percentiles as the untreated group ($p = 0.7$). They were also discharged at higher weights than the untreated group, but this is attributed to being discharged > 2 weeks later for GA. We did not assess growth measurements following discharge. Dated studies provide mixed reports of altered growth findings into early childhood and adolescence. Stark et al. reported no growth differences at 18-22 months of age in infants born 501-1,000 grams receiving either dexamethasone or placebo [28]. Dexamethasone dosing was also lower than our dexamethasone doing [28]. Contrarily, Wang et al. reported that the smallest, most preterm infants who received dexamethasone (for at least 7 days) demonstrated lower weights, shorter stature, and lower bone mass up to ages 5-10 years compared to untreated peers [29]. Given lack of follow-up post discharge, it remains questionable if these

aggressive nutrition practices will favorably influence growth outcomes at later points in life.

Head circumference

Head circumference growth was well-maintained for infants in both groups from birth until discharge, even showing an upward trend in percentiles over time. We attribute this to adequate nutrition, given a low incidence of high grade IVH and no shunt required in either group. At no point did head circumference percentiles drop below the 10th% on the associated growth curve, showing that head growth for dexamethasone-treated infants can be maintained given adequate nutrition.

Our findings contradict those of Stark et al. who associated dexamethasone use to smaller head circumferences at 36 weeks gestational age [13]. Again, there are varying reports about this same finding at later ages. Another study by Stark et al. found no difference at 18-22 months [28], yet Yeh et al. reported significantly smaller head circumferences in dexamethasone-treated infants at school age [15]. Yeh et al. began dexamethasone within 12 hours after birth, then provided twice daily dosing at 0.25 mg/kg from day 1-7, 0.12 mg/kg from day 8-14, 0.05 mg/kg from day 15-21, and 0.02 mg/kg from day 22-28 [15]. Reduced brain matter volume has been reported in term-corrected infants treated with dexamethasone compared those untreated [30], and has been further linked to a higher risk of cerebral palsy and lower intelligence quotient [17, 31]. Timing of dexamethasone administration within these studies remains variable (i.e. shortly after birth or after four weeks of life) as well as dosing (0.25 mg/kg every 12 hours for 6 doses, mean duration 6.8 days with mean cumulative dose 2.8 mg/kg; mean duration 22-28 days with median dose 0.25 mg/kg/day) [17, 30, 32]. Maintaining appropriate head growth must remain a priority, as improved head growth is directly correlated to positive neurological outcomes [33, 34].

Length

In our sample of treated infants, median percentiles for linear growth decreased from birth to 36 weeks GA but were maintained from this point until discharge. It is unclear if this primarily occurred due to dexamethasone administration, overestimation of birth length, or some other unknown reason. Our goal is to maintain linear

growth, as it reflects appropriate lean tissue accrual and has been correlated with improved neurodevelopmental outcomes [35]. Linear growth was well maintained for the untreated control group, which is mainly attributed to the adequacy of our standard nutrition practices. The dexamethasone-treated infants received higher median caloric density feedings compared to the untreated group, which simultaneously provides higher administration of protein, vitamins, and minerals. It therefore remains unlikely that suboptimal nutrition was the primary cause for the altered linear growth in our subset of patients. Weiler et al. similarly reported lower linear growth from birth until 6 months in nine dexamethasone-treated infants compared to nine untreated peers despite receiving equivalent protein, calcium, phosphorus, and supplemental vitamin D [16]. There remain theories that non-nutritional factors hinder linear growth, such as disease severity and inflammation [35]. Our treated study group certainly exhibited higher disease severity compared to untreated controls given their steroid requirement, prolonged need for oxygen support, and higher incidence of ROP. These theories do remain confounding though, as sicker infants require more clinical treatment with oxygen or steroids, which further alters baseline degree of inflammation and poor growth.

Median length percentiles remained lower than weight percentiles at all measurements during NICU hospitalization for both groups. Our nutrition goals are to promote appropriate growth in all measurements so as not to accrue high adiposity in our infants. However it remains notable that very low birth weight infants are intrinsically at higher risk for developmental delay due to extreme prematurity and high morbidity. Methods to minimize risk for poor neurological outcomes include providing adequate growth for weight [3] and head circumference [33, 34], which was achieved in both groups by discharge despite limited linear measurements. It is unclear how these growth outcomes influence long-term development and anthropometric measurements in later life.

Nutrition

Dexamethasone-treated infants required more calories (131 vs. 119 calories/kg/day) and protein (4.4 vs. 4.1 grams/kg/day) to parallel similar weight and head circumference growth as the untreated infants by point of discharge ($p \leq 0.0005$). On average, treated infants received median higher

caloric density of enteral feedings (27 vs. 30 calories/ounce, < 0.0001). Assessing average nutrient provision during dexamethasone therapy, treated infants received an average of 138 calories/kg/day and 4.5 grams protein/kg/day because of enhanced nutrition. Based on our results, treated infants tolerated the optimized enteral nutrition well from a metabolic standpoint. Previous literature findings report increased risk for hyperglycemia while receiving steroid treatment [8, 36], yet in our study there were no significant differences in highest glucose level despite receiving higher total daily calories (median highest level of 122 mg/deciliter [dL], $p = 0.071$). Highest BUN levels approached significance ($p = 0.053$) in the treated group (median highest level 29 vs. 17 mg/dL) but a contributing difference to this may also be the younger GA of the treated infants at birth, resulting in more immature metabolic processes.

Increasing protein provision may be key in blunting poor growth effects in dexamethasone-treated infants. A highly dated study by Brownlee et al. assessed protein catabolism in dexamethasone-treated preterm infants, reporting appreciable lower nitrogen balances after start of treatment [37]. Tsai et al. reported alterations in measured blood amino acids after start of steroid administration [38]. They additionally reported higher urinary 3-methylhistidine levels, all of which they correlated as markers of increased protein catabolism. Additional calories around point of treatment should also be considered. Bolt et al. analyzed the body composition of 18 dexamethasone-treated infants with chronic lung disease compared to 14 untreated infants without lung disease [18]. Dexamethasone was given after 2-3 weeks of life at 0.25-0.5 mg/kg/day, mean cumulative dose 4.4 ± 0.9 mg/kg, and mean duration 17 ± 2 days [18]. Treated infants received an additional 20 calories/kg/day during dexamethasone treatment until term. Results demonstrated a trend towards lower weight in the treated group at term, but percentage of fat mass was not different between groups despite higher calorie intake. This supports the optimization of enteral feedings to enhance overall growth in treated infants and not just gains in adiposity. The standard enteral goals for very low birth weight infants advocate a minimum of 120 calories/kg/day and 4.0 grams protein/kg/day, but suggested safe recommendations increase as high as 150 calories/kg/day [1] and 4.9 grams protein/kg/day [39].

There were no significant differences in available alkaline phosphatase levels between

groups. Alkaline phosphatase can indicate poor bone mineralization, so high levels suggest inadequate nutrient provision or absorption. The highest levels available to be analyzed for both groups remained within the suggested range for preterm infants, 100-500 U/L [40]. There are varying reports regarding bone mineralization for the dexamethasone-treated infant. Some research reports no difference in bone mass or density [18], while others report lower rates in both infancy and at school age [16, 29]. Dexamethasone treatment has been correlated with lower levels of serum osteocalcin [41] and plasma phosphorus [16], which may impede adequate mineralization. While measured alkaline phosphatase levels suggest appropriate mineralization in our infants, we did not assess bone mass via dual-energy x-ray absorptiometry (DEXA) scan at discharge. Of additional note, our routine practice during the period of these infants' hospitalization was to supplement all infants with minimum of 400 international units of vitamin D3 (cholecalciferol) daily, despite enteral feeding type or volume.

Clinical impact

Our study results indicate that dexamethasone-treated infants indeed experience altered growth. This is primarily evident in clinical practice when transient poor growth is seen during dexamethasone administration, resulting in a decline in percentiles on the growth chart. Yet despite transient poor growth, our results more importantly demonstrate that providing appropriate enteral nutrition can sustain adequate head growth and can support weight gain that approximates that of untreated infants by the time of discharge. Also important is that the median weight percentiles of our treated infants remained above the 10th% at all points during NICU hospitalization. These outcomes are primarily attained by increasing both enteral calories and protein. It remains imperative to promote early adequate growth before potential dexamethasone administration, such as with DART therapy. We also optimize calories and protein once DART therapy is started and will continue with this following treatment in order to promote catch-up growth.

While recognized that dexamethasone can have unfavorable secondary effects on treated infants, we do note that multiple studies referenced in this manuscript report outcomes for preterm infants born between the late 1980s to early

2000s. Nutrition regimens during this time varied significantly compared to current aggressive practices. The most notable difference is the lower provision of protein, one study even reporting enteral amounts as low as 2.8 grams/kg/day [16]. Extrauterine growth restriction was also a highly prominent occurrence at that time [27], which further contributes to worsened outcomes [3]. In terms of bone mineralization, infants during this early period may have received prolonged parenteral nutrition due to delay of enteral feedings and additional enteral vitamin D supplementation was not a routine practice. This raises the question if some of these deleterious long-term effects can be blunted by optimizing enteral nutrition and growth. More long-term studies are needed to assess detailed nutrition, growth, and developmental outcomes of steroid treated infants.

Strengths and limitations

The uniqueness of this study is that it solely analyzes both growth and detailed enteral nutrition data, unlike previous studies. It also provides a current perspective on these two areas, as it reflects outcomes following advancements in medical management and optimized nutrition for very low birth weight infants.

Limitations of this retrospective review include that there is a limited number of subjects in the study group receiving steroids, as they are used conservatively in this population. Additionally, study infants remained smaller at baseline. Also included is our reliance on electronic documentation for data collection, as we cannot quantify unrecorded or misrecorded data. However, the system does allow for review of daily entered data for each subject if needed. Evaluation of head circumference and length measurements may vary among nursing staff due to differences in measuring tape placement. While head circumference growth was maintained for treated infants, we cannot determine if this leads to improved neurodevelopmental outcomes. Growth was analyzed primarily by weight gain. Adipose and lean body tissue was not assessed, nor was body mass index. Bone mineral density was also not analyzed between treated and untreated groups. The calculated provision of calories and protein for infants receiving fortified human milk may only serve as a general estimate for our comparisons, as the composition of human milk varies continuously.

Conclusions

Infants receiving at least one consecutive 10-day treatment course of dexamethasone experienced altered growth, but comparable growth to untreated infants for weight and head circumference can be achieved by discharge by optimizing enteral nutrition. Additional calories and protein before, during, and after dexamethasone administration may contribute to growth without significant concern for metabolic intolerance. Treated infants required oxygen longer than untreated infants, but this is attributed to baseline needs for dexamethasone treatment. More research needs to be conducted to assess early neonatal nutrition and its effects on growth and neurodevelopment post NICU discharge in dexamethasone-treated infants.

Ethics approval and consent to participate

The institutional review board at the University of Nebraska Medical Center (Omaha, NE, USA) approved this study with a waiver of consent and ethical standards of the institutional committee on human experimentation were followed.

Declaration of interest

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