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Identifying Growth Correlates in Premature Infants

by

Valerie Anne Ruth

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

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Abstract

Growth Correlates in Preterm Infants

Valerie A. Ruth

This research aims to identify growth correlates in preterm infants in order to develop interventions to prevent growth failure. The majority of very low birth weight (VLBW<1500g) infants are affected by extrauterine growth restriction (EUGR), which is defined by a weight less than the 10th percentile at hospital discharge and associated with developmental delay and other long-term sequelae. Research to date has identified no definite causes but some correlations with gestational age, birth weight, and caloric intake. Identifying infants at risk of EUGR in the early stages of hospitalization is critical for interventions to prevent growth failure. This research involved a retrospective chart review of 186 preterm infants born at 27 to 32 weeks gestation admitted and discharged between January 2004 and December 2006 from Lucile Packard Children's Hospital at Stanford University. This dissertation takes the form of three publishable papers.

The first paper is a critical review of selected literature on EUGR. Longitudinal and cross sectional studies are reviewed to contrast the merits of each type of analysis for studying EUGR.

The second paper analyzes data from the retrospective chart review in order to replicate findings by previous researchers. In the previous study, researchers found that preterm infants born between 32 to 34 weeks gestation with higher baseline heart rates experienced greater weight gain than infants with lower heart rates. These findings were not replicated in the LPCH sample.

The third paper aims to determine if weight loss in the first week of life affects subsequent weight gain and length of stay. Using the same sample, results demonstrated that early weight loss did not affect subsequent weight gain or length of hospital stay in the total group. However, in a subgroup of VLBW infants, early weight loss was significantly different between EUGR and non-EUGR infants. Gender differences in growth occurred between EUGR and non-EUGR infants.

Future research should further investigate gender and weight loss in the first week of life as potential growth correlates. Identifying these growth correlates in VLBW preterm infants is imperative for developing interventions to reduce EUGR and related morbidities in this vulnerable population.

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Introduction

Infants who are born premature are at significant risk for poor growth in the neonatal period. Once behind in their growth, it can take months and even years for catch-up growth to occur, depending on the severity of their failed growth. However, achieving normal size is not enough; research has found correlations between failed growth in infancy and developmental delay as well as chronic diseases later in life. This failure to grow is called extrauterine growth restriction (EUGR).

Medicine's success at managing the crises of prematurity has led to the survival of an ever increasing population of premature infants, making the problem of EUGR even more urgent. Research into EUGR is constrained by the unique and urgent situation of caring for the premature infant. EUGR represents not an illness or disease process, but a failure to grow in the extraordinary way that happens in utero during gestation. EUGR is thus a challenge to the nursing environment of the neonatal intensive care unit (NICU) to not be just a safe repository for the patient between medical procedures directed at specific illnesses, but to be as good as the natural uterine environment in nurturing the infant during this period of rapid development. While a good initial impulse might be to consider the womb as the baseline environment to replicate, NICU care involves monitoring the infant and doing procedures that would be prevented by such a protected environment, but which are necessary to help the infant survive the crises of prematurity.

Studies to identify the causes of EUGR have been inconclusive, but it is generally surmised that failure to gain weight is a very late indicator that the infant's development has not proceeded at a normal rate. EUGR studies thus often seek to identify clinical

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correlates of development that can be measured during or even before development delay, in order to identify, study, and treat at-risk infants sooner.

Researchers encounter a number of problems resulting from the rapidity of infant development during this period. From earlier research, it appears that growth happens in stages, many of which are interrelated (Bertino, et al., 2006). For example, consider the situation when infants change from one biological system to another, e.g., from a more primitive vagal feedback loop to a more mature one. This transition has direct consequences for heart rate, cerebral blood flow, and gastric motility, as well as a host of other systems and measures. Further, the transition may impact development of similar neurological systems that require increased nutrition, such as brain development. Similarly, sleep patterns develop during this period if brain development is normal; sleep in turn may be required for certain kinds of cellular growth. These kinds of biological system relationships have been indicated but not delineated by research.

In the face of such change in the underlying biology, it can be difficult even to establish baseline biological measures or comparative populations. For example, infants who are only a week apart in gestational age might not be comparable on basic measures such as heart rate or blood pressure. What is normal at one gestational age may not be normal at another. A researcher faced with different average heart rates or weights in two studies might need to know the gestational age or nutritional uptake more precisely before understanding the different results. Furthermore, the results of a study might be interpreted differently and have different clinical meaning depending on the infant's underlying biological condition or level of maturation.

It can be difficult to collect data in this population because no one can speak for the patient, because consent can be hard to obtain, and because the physical body is so small. Because infants cannot speak for themselves, observers must identify basic conditions like needing food, being at rest, or being asleep. It is not clear that different researchers can always be trained to do this consistently and accurately. Further, many studies are retrospective, comparing measurements taken for medical purposes at different hospitals, possibly in different ways. The accuracy obtained might be sufficient for medical purposes for that patient in that hospital, but not sufficient for tightly controlled research comparing patients and hospitals. Finally, the infant is probably more dependent on the environment than any other type of hospitalized patient, and might be more affected by differences in that environment than other patient populations, making cross-study comparisons difficult without controlling for the environment.

These variables could be identified and corrected statistically if there were good measures for each, and if measurements were standardized across studies. Researchers have generally identified nutritional intake, birth weight and gestational age as the key variables for EUGR, with work proceeding on measures like sleep state, heart rate, and ideal nutritional composition. But because of the biological variability, progress in quantifying environmental factors and normalizing study methods is painstaking, and is prioritized after interventions necessary for survival.

Nursing has an essential and unique perspective on EUGR. Given the rapid growth pattern of neonates, the NICU environment takes on an affirmative obligation not just to avoid harm or to remedy a specific illness, but to support growth in all the biological systems of the infant. Of all the morbidities of preterm infants, EUGR raises

the question of NICU care most directly. By definition, patients suffering EUGR are normal for gestational age at birth and present no other illnesses for medical intervention. Nursing care in the NICU environment is the primary intervention; unless the cause of EUGR is revealed as a hidden illness or genetic predisposition, any advance in remedying EUGR is likely to be an advance in nursing care or the NICU environment.

Addressing EUGR at this stage involves a certain intellectual tolerance for approximations in research models, available data, and clinical practice. Clinicians use weight and head circumference as a readily-obtained but relatively gross and late signs of development. Researchers proposing metabolism as a factor in growth may have to consider heart rate as the best available indicator for metabolism. Although nutrition is a key factor in EUGR, nutritional guidelines specify only overall calories and only more recently protein. The guidelines are not adjusted for catch-up growth or metabolic needs specific to the neonate, and there is little published data on compliance rates for dietary guidelines.

To use known gross models and measures correctly, researchers must be mindful of the potential complexity of the rapidly-changing, inter-related biological systems. To find new better models and measures, researchers must consider alternative inhibitors of growth and look for timely and simplifying measurements. As a constraint on the solution, researchers and clinicians alike prefer models and measures that are within the grasp of NICU practice, in order to enable the nurse to do something now to avoid potential problems later in life.

As an example of the difficulty in pursuing an unknown factor contributing to EUGR, consider the relatively simple question of whether the NICU inhibits sleep

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necessary for growth. Although sleep is known to be required for daily restoration and for

adolescent growth surges, for premature infants researchers know less about the sleep

patterns under development and their relationship to neonatal growth surges. Instruments

for measuring sleep have yet to be validated in this population. Sleep instruments would

have to be integrated into the time- and space-congested environment of the NICU,

meeting any objections of clinicians or parents about equipment interfering with clinician

access to their baby. Then even if researchers could show that sleep was inhibited and

this caused EUGR, it would not necessarily be clear how to encourage proper sleep,

especially in the face of the need for clinical monitoring and access.

 To overcome these obstacles the researcher would need to resolve any issues with

theory, data collection, and clinical practice. These affect each other. Since the NICU is

an urgent care environment working with highly-valued infants, the clinical practice

constraints are high. That increases the need for un-intrusive data collection to minimize

interference and for a good conceptual model to motivate experiment and adoption.

 This dissertation addresses the question of EUGR from a nursing perspective in a

series of three papers. The first is a critical review of the literature on extrauterine

growth restriction in preterm infants. It aims to identify mechanisms of failed growth in

preterm infants and delineate what is currently known about EUGR.   From this paper,

the reader should get a more thorough understanding of the known causes of EUGR and

what intervention and prevention measures exist today. The second paper introduces the

study of heart rate in preterm infants undertaken with data from infants in the NICU at

Lucile Packard Children's Hospital. The study attempts to validate the findings of a

previous study by and to replicate these findings in infants born at earlier gestations. In

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the previous study (Ferber, et al., 2006), researchers found that infants 32 to 36 weeks gestation who had heart rates greater than 139 beats/min. had better weight gain compared to infants with mean heart rates less than 140 beats/min. This dissertation failed to replicate that finding. The third paper is a study of the same group of infants, comparing those who gained weight in the first week of life to those who lost weight in the first week of life to determine whether weight loss in the first week of life has an effect on subsequent weight trajectory or length of hospital stay. Both this introduction chapter and the conclusion chapter make reference to a study of sleep and growth also undertaken by this researcher. That study failed to enroll enough infants to validate the sleep instruments or to justify the relatively expensive cost of interpreting and analyzing the data. It is important to recognize specific difficulties in pursuing research in the area of EUGR in order to overcome them.

Chapter 2: Critical Review of Literature And Selected Research on EUGR

EUGR is a common condition in very low birth weight (VLBW) preterm infants (under 1500 grams) and the most common morbidity among VLBW survivors (Clark et al., 2003; Garite, Clark & Thorpe, 2004). In this condition, preterm infants who are born at an average weight for their gestational age are unable to maintain a normal pattern of growth in the extrauterine environment, despite a theoretically sufficient diet and the lack of other debilitating medical conditions. For reasons that are not fully understood, infants appear to develop a severe caloric deficit in the first few weeks of life that manifests in failed weight gain and can continue for several years (Embleton, Pang & Cooke, 2001;

Bosque & Hirata, 1997). At the time of their discharge from the hospital, between 60-89% of VLBW infants will suffer from EUGR (Clark et al., 2003, Radmacher, 2003).

Prevalence of EUGR

EUGR is defined by the premature infant's failure to achieve adequate weight gain in extrauterine life despite the provision of established nutritional requirements (American Academy of Pediatrics (AAP), 2003). The typical term newborn gains approximately 200 grams/week or an average of 30 grams per day (Bloom, 2006; Schanler, 2005). Expected growth velocity for the premature infant is 15 grams/kg/day, comparable to the rate of intrauterine growth (Gibson, Carney & Wales, 2006). The failure of preterm infants to grow in the neonatal intensive care unit (NICU) at the same rate as infants in the womb is significant because it has been associated with long term developmental effects (Lucas, Morley & Cole, 1998; Barker, 2004). Radmacher (2003) found that 86% of 221 preterm infants with a birth weight less than 1000g and gestational age less than 29 weeks had birth weights that were average for gestational age; yet, by their time of discharge from the NICU, 59% were EUGR. Clark (2004) found that more than 30% of the infants who were extremely low birth weight (ELBW, 400g-1000g) remained below the fifth percentile for growth at 18 months corrected gestational age (CGA).

Long Term Consequences of EUGR

Recent studies have found an association between EUGR, developmental outcome and long term morbidity. In two longitudinal studies comparing 242 VLBW infants to 233 normal birth weight infants at 20 years of age, VLBW subjects scored significantly lower on measures of academic achievement, and fewer graduated from

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high school (Bhutta et al., 2002; Breslau et al., 2004). Low birth weight and preterm infants were also twice as likely to develop Attention Deficit Hyperactivity Disorder (Hack et al., 2002). According to Barker (2004), the slow pace at which infants catch up their growth during childhood can also predispose them to chronic diseases such as coronary heart disease, hypertension, or type II diabetes mellitus. These findings emphasize the critical nature of better understanding low birth weight and long term morbidity.

Factors Associated with EUGR

Studies to identify specific causes of EUGR have been inconclusive or have not fully explained the phenomenon (Clark et al., 2003; Radmacher, 2003). A study by Radmacher found that 46% of the infants who developed EUGR had a birth weight of <750 grams. Priham and colleagues (2002) found that infants who developed EUGR have a greater accumulated caloric deficit. Accumulated caloric deficit is calculated by subtracting actual caloric intake from recommended caloric intake over an extended period of weeks to months (Embleton, Pang & Cooke, 2001).

Although some of the contributing factors to EUGR have been identified through clinical research, EUGR continues to be a significant problem in infants who are born premature. While birth weight is inversely proportional to the incidence of EUGR (Clark et al., 2003; Garite, Clark & Thorpe, 2004), Embelton, et al. (2001) found that 45% of the variance in weight gain was attributable to caloric/energy deficit, and birth weight accounted for only 7% of this variance. This suggests that much remains to be discovered about the causative factors for EUGR.

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Understanding EUGR

EUGR is the most common morbidity for VLBW premature infants. Studies suggest that EUGR is related to nutrition, birth weight, and prematurity. Recent studies suggest that vagal activity might also be a factor. In these studies, infants with increased vagal activity experienced greater weight gain than infants with lower vagal activity. This suggests that the increase in gastric motility may enhance nutritional absorption. Heart rate variability is one way to detect vagal tone if it increases with increased vagal activity.

Chapter 3: Does Higher Heart Rate Contribute To Growth Of Preterm Infants?

A study of heart rates was conducted from medical chart reviews of156 preterm infants ranging from 27 to 34 weeks gestation. This study aimed first to validate a study by Ferber, et al. (2006) that reported a correlation between heart rate and weight gain in preterm infants 32 to 36 weeks gestation and, second to test the findings in gestationally younger infants. If such a correlation existed, it could most benefit the smaller and less mature infants in whom the benefit of a growth correlate would be even greater. Identifying correlates of growth could provide a basis for intervention.

These studies are important because the Ferber, et al. (2006) finding is counter to a conventional understanding of metabolism. One would expect increased metabolic rate, in this case evidenced by increased HR, to increase caloric utilization. Furthermore, expending more calories would decrease weight gain. Because the findings from Ferber's study run counter to what is currently known about metabolism, it is possible

that the relationship between metabolism and growth is more complex in premature infants and therefore requires further investigation for a more complete understanding.

If some traditional metabolic principles do not apply to the preterm infant, it could help to explain the inconclusive findings from previous studies of EUGR; they may differ in the underlying metabolism in ways that are not corrected for in the study design. Thus, continuing to study growth in preterm infants using the familiar principles will continue to yield confusing and incomplete findings. Developing a better understanding of preterm infant metabolism will undoubtedly increase the reliability of future research.

One explanation for preterm metabolism differing from that of older infants and adults is that vagal activity and gastric motility initially branch in development from the same nerve. Therefore, in the preterm infant who enters the world prematurely and with underdeveloped organs and organ systems, an increase in vagal activity (reflected by increased HR) could actually enhance gastric absorption (secondary to increased gastric motility) in the premature infant.

Chapter 4: SGA, EUGR and early weight loss: How do these factors affect daily weight gain and length of stay in preterm and very low birth weight infants?

The third paper explores the effect of early weight loss on subsequent weight gain in the same sample of preterm infants. It also compares infants <1500grams who were EUGR at discharge to those who were not EUGR. For the first part of the study, the theoretical basis was to test two prevalent models of thinking among caregivers in the NICU. One is that early weight loss is almost exclusively related to loss of excess body water and not related to metabolism or nutritional effects and therefore, should have no

effect on subsequent weight trajectory. The second perspective is that early weight loss, particularly profound weight loss, could alter metabolism in preterm infants in such a way that subsequent weight gain is affected. Furthermore, because weight gain is one of the few objective indicators of health for parents of premature infants, weight loss can cause significant anxiety for parents. Knowledge that early weight loss is unrelated to subsequent weight gain or hospital stay, for that matter, would be important information for reassuring parents of premature infants.

For this analysis, infants who were at or below birth weight by the second week of life were compared to those who were above birth weight by the second week of life. Groups were analyzed for differences in subsequent daily weight gain and length of stay to determine if early weight loss had a significant effect on either of these factors.

Additionally, the proportion of weight lost relative to birth weight was compared to subsequent weight trend to determine whether there is a critical threshold at which subsequent weight gain is affected.

For the second part of the study, demographic and growth characteristics of the EUGR and non-EUGR infants were compared. The theoretical basis for this was that comparison of these groups might allow the emergence of a distinct pattern of growth or unique characteristics of growth that would be useful for early identification of infant's at greatest risk for EUGR. These patterns or characteristics of growth could be used to develop interventions that reduce, and possibly even prevent, growth failure in this population.

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Extrauterine Growth Restriction: A Review of the Literature

Abstract

Extrauterine Growth Restriction (EUGR) is a common condition in very low birth weight (VLBW) preterm infants ($\leq$1500 grams). The majority of infants affected have a birth weight that is average for gestational age, but by the time of hospital discharge, have a weight that is less than the 10th percentile for corrected gestational age. EUGR is the most frequent morbidity among VLBW survivors at their time of discharge from the hospital. Studies to elucidate the causes of EUGR have been inconclusive. Recent research has found an association between EUGR, developmental outcomes and long-term morbidity. Low birth weight has also been associated with chronic diseases later in life. These findings emphasize the critical nature of understanding the phenomenon of EUGR and ways in which it can be prevented.

Definition of EUGR

Failure to achieve adequate extrauterine growth is a common phenomenon in preterm infants and is known as extrauterine growth restriction (EUGR). EUGR is most frequently defined as a weight less than the 10th percentile for corrected gestational age at the time of hospital discharge. For reasons that are not fully understood, EUGR infants appear to develop a severe caloric deficit in the first few weeks of life that manifests in failed weight gain that can continue for several years (Embleton, Pang & Cooke, 2001; Bosque & Hirata, 1997). Although this phenomenon can be partially explained by periods of inadequate nutrition, feeding intolerance common to premature infants, and critical illness (Embleton, Pang & Cooke, 2001, Clark, Thomas & Peabody, 2003), research has shown that expected growth may not occur even during periods of adequate nutritional support and in the absence of extenuating illness (Embelton et al; Wood et al, 2003).

Population Affected

The majority of infants who experience EUGR have birth weights that are average for gestational age, indicating that intrauterine growth was adequate, but fall behind with regard to overall growth during their hospitalization (Clark et al., 2003; Garite, Clark & Thorpe, 2004). EUGR is a common condition in very low birth weight (VLBW) preterm infants under 1500 grams and the most common morbidity among VLBW survivors (Clark et al., 2003; Garite, Clark & Thorpe, 2004). Radmacher (2003) found that 86% of 221 preterm infants with a birth weight less than 1000g and gestational age less than 29

weeks had birth weights that were average for gestational age; yet, by their time of discharge from the NICU, 59% were EUGR. Lemons and colleagues (2001) found that 99% of 163 ELBW preterm infants were EUGR after 10 weeks in the NICU. Clark (2004) found that more than 30% of infants with birth weights 400g-1000g remained below the fifth percentile for growth at 18 months corrected gestational age.

Expected Growth & Caloric Support

The typical term newborn gains approximately 30 grams per day (Bloom, 2006). Expected growth velocity for the premature infant is 15 grams/kg/day and is comparable to the rate of intrauterine growth (Gibson, Carney & Wales, 2006). A recent review of the literature by Denne (2001) determined that for extremely low birth weight (ELBW<1000g) and very low birth weight (VLBW < 1500g) infants, an enteral intake of 125 to 130 kcal/kg/d of energy or 100 to 110 kcal/kg/d parenterally, and 3.5 to 4 g/kg/d of protein appears adequate for growth.

Long Term Consequences of EUGR

Recent studies have found an association between EUGR, developmental outcome and long term morbidity. In two longitudinal studies comparing 242 VLBW infants to 233 normal birth weight infants at 20 years of age, VLBW infants scored significantly lower on measures of academic achievement, and fewer graduated from high school (Bhutta et al., 2002; Breslau et al., 2004). Low birth weight and preterm infants were also twice as likely to develop Attention Deficit Hyperactivity Disorder (Hack et al., 2002). According to Barker (2004), the slow pace at which infants catch up

their growth during childhood can also predispose them to chronic diseases such as coronary heart disease, hypertension, or type II diabetes mellitus. These findings emphasize the critical nature of better understanding low birth weight and long term morbidity.

Factors Associated with EUGR

Studies to identify specific causes of EUGR have been inconclusive or have not fully explained the phenomenon (Clark et al., 2003; Radmacher, 2003). Radmacher found that 46% of the infants who developed EUGR had a birth weight of <750 grams. Priham and colleagues (2002) found that infants who developed EUGR have a greater accumulated caloric deficit. Accumulated caloric deficit is calculated by subtracting actual caloric intake from recommended caloric intake over an extended period of weeks to months (Embleton, Pang & Cooke, 2001). Although some of the contributing factors to EUGR have been identified through clinical research, EUGR continues to be a significant problem in infants who are born premature. While birth weight is inversely proportional to the incidence of EUGR (Clark et al., 2003; Garite, Clark & Thorpe, 2004), Embelton and colleagues. (2001) found that only 45% of the variance in weight gain was attributable to caloric/energy deficit, and birth weight accounted for only 7% of this variance. This suggests that much remains to be discovered about the causative factors for EUGR.

Review of Literature on Factors Associated with EUGR

This review of research on EUGR in premature infants is organized by cross-sectional and longitudinal study designs to highlight the merits and utility of each design. Studies were selected for review if they specifically related to EUGR with normal intrauterine growth. Studies that included a significant proportion of infants who were small for gestational age (SGA) at their time of birth or studies that did not distinguish between SGA and average for gestational age (AGA) at the time of birth were excluded because SGA is a distinctly different phenomenon from EUGR.

The PubMed data base was searched using the following search terms: extrauterine growth restriction, EUGR and postnatal growth restriction. Search terms also included preterm, premature infant, and neonate. Studies were limited to the last decade because increased survival and decreased morbidity in VLBW survivors in recent years has allowed for better delineation of the causative factors for isolated EUGR (See Table 1 for details of each study reviewed here).

Cross-sectional studies of EUGR

In a cross-sectional study of 283 infants born at $\leq$ 25 weeks gestation, Wood and colleagues (2003) assessed these infants at 30 months corrected gestational age (CGA) and documented that: 1) poor growth was associated with feeding problems, neuron-developmental disability, and respiratory problems after hospital discharge, and 2) later severe growth failure was associated with early clinical findings and demographic variables. The sample included 283 of 314 infants discharged from the hospital who met

the study criteria. Of those not included, 19 families declined enrollment, six infants had died and six families were out of the country. Children were examined in a hospital outpatient clinic (n = 235) or in the family home (n = 48) if a clinic visit could not be arranged.

At 30 months CGA, this sample of infants was smaller than population norms. Weight for 25% of the group was more than two standard deviations (SD) below the mean, and 8% of the infants were more than three SD below the mean. For head circumference 37% were more than two SD below the mean and 16% were below three SD. With regard to co-morbidities, the study found that 33% (n=94) of parents reported infant feeding problems and that the infants with feeding problems were smaller on most growth parameters. The infants who were discharged home on oxygen also tended to be smaller than those who went home on room air. No significant differences in growth parameters were found between oxygen-dependent infants at 36 weeks CGA. However, for oxygen-dependent infants after 36 weeks CGA, heights and head circumferences were significantly smaller, but there was no significant difference in weight.

These researchers also explored the influence of demographic variables and early clinical variables on later growth. Race was a significant factor, with more (16%) non-White infants who were smaller compared to White infants (6%). Necrotizing enterocolitis (NEC) had the highest association with poor growth, although only a small number of infants (n = 11) were affected. When infants with NEC were excluded from the analysis, breast milk was associated with growth at 30 months, and time to full enteral feeding was related to height as a measure of infant growth. A long course of postnatal steroid use was also a clinical variable associated with poor growth at 30 months CGA.

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Children who continued to experience feeding problems at 30 months CGA had poorer growth as assessed by both weight gain and head circumference. For head circumference, this poor growth was independent of the association with neurological disability. NEC was associated with poor growth when assessed by both height and head circumference, whereas severity of early respiratory disease and abnormal head ultrasound were only correlated with poor growth when assessed by height.

Wood and colleagues (2003) confirmed many previous studies that report poor growth with NEC (Clark, Thomas & Peabody, 2003; Simichen et al, 2000). Long term steroid use, oxygen dependency at >36 weeks CGA, and neurological disability are all related to poor growth in extremely premature infants (Clark et al, 2003; Hay et al, 1999; Radmacher, Looney, Salisa & Adamkin, 2003). Problems with somatic growth are very stressful for parents and these findings confirm that infants born at <25 weeks gestation are at significant risk for poor growth. The discovery that parental report of feeding problems may be a reliable indicator of poor growth could be beneficial for the child and parents as well as researchers and clinicians. Training parents of extremely premature infants to report problems related to growth could empower them as a valuable tool for alerting the health care provider to the risk of early or sustained growth problems.

With regard to growth estimates, a cross-sectional study lacks the ability to identify windows of opportunity for "catch-up" growth that a longitudinal study with repeated measures might identify. For example, if growth is not steady and is more intermittent, a cross-sectional study is not adequate for identifying patterns of growth and potential growth correlates. From other studies of infants with EUGR, the period from hospital discharge to 30 months is known to be a critical period for growth. Assuring

adequate growth during this time begins a growth trajectory for childhood and adolescence (Hirata & Bosque, 1997). Frequent assessments during this period could provide valuable information for new and better ways to support adequate growth. Some of the demographic associations in this study, such as poorer growth in the non-White population, require additional study to replicate these findings and explore potential inherent genetic factors or environmental contributors to poor growth.

Another limitation of this cross-sectional study involves the use of population norms as the normative data for comparison to expected growth at 30 months in this study sample of infants. A more appropriate comparative group would be disease-specific mortality rates for children with NEC or chronic bronchopulmonary dysplasia, for example, or a comparable group of preterm infants matched on weight or gestational age. Using appropriate comparison groups would better facilitate data interpretation. For example, if infants in this study grow better than other infants who are <25 weeks CGA, it would be important to look at differences in clinical practice standards so that interventions to promote growth could be developed and tested. Conversely, if growth in this sample is worse than other infants who are <25 weeks CGA, it would be important to identify potential practice differences that may interfere with growth.

Clark, Thomas and Peabody (2003) evaluated the incidence of EUGR in 23-34 week premature infants at their time of hospital discharge in a multi-center study using a cross sectional design and retrospective chart review. The sample included 24,371 neonates discharged from 124 neonatal intensive care units managed by Pediatrix Medical group, Inc. between January 1, 1997 and December 31, 2000. Inclusion criteria were estimated gestational age of 23 to 34 weeks, birth and discharge from the same

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intensive care nursery, and no congenital anomalies. Data on discharge weight, length and head circumference were included.

At hospital discharge, 28% of infants were EUGR according to weight, 34% had EUGR according to height, and 16% had EUGR according to head circumference. For each measure, the incidence of EUGR increased with decreasing estimated gestational age and birth weight. Factors independently associated with EUGR were male gender, need for assisted ventilation on the first day of life, history of NEC, need for respiratory support at 28 days of age, and exposure to steroids during hospitalization.

Consistent with findings from other studies, Clark, Thomas & Peabody (2003) found that it was rare to achieve recommended dietary intake in the NICU environment and that periods of adequate intake were not sustainable to allow for catch up growth to occur (Embleton, Pang & Cook, 2001).   For those clinical factors independently associated with EUGR (such as history of NEC, need for respiratory support for $\geq$ 28 days, and exposure to steroids), these findings support previous studies of EUGR (Wood, et al., 2003).

To strengthen their findings, the researchers used a predicted EUGR rate from a calculated estimate. According to their calculation, if infants received 120 kcals/day during hospitalization, an EUGR rate of approximately 10% in <28 week infants would be expected. However, the actual rate of EUGR was closer to 30%. This finding further confirms that there are more factors influencing weight gain than simple caloric intake. Other key individual factors, such as absorption or utilization and general metabolic efficiency, require more intensive investigation in future research with this population.

Although evidence is mounting that caloric needs are not being met or maintained in this vulnerable population, and some of the risk factors for EUGR have been identified, no specific strategies for increasing caloric replacement during these periods of additional stress have been developed or studied. Practical issues limit feeding volume and caloric density for caloric catch up (Clark et al, 2003; Embelton, Pang & Cooke, 2001). Safer parenteral nutrition formula that can be rapidly advanced without metabolic compromise is one avenue of research to develop with the goal of enhancing caloric intake (Clark et al, 2003). Testing the effectiveness of current methods of nutritional replacement for more aggressive utilization during periods of stress and illness, when the infant is not receiving enteral feedings, may offer new insights for maintaining caloric stability in this vulnerable population of infants.

Longitudinal studies of EUGR

Embleton, Pang & Cooke (2001) conducted a longitudinal prospective study of all infants admitted to an intensive care nursery over a six-month period with a gestational age less than 34 weeks and a birth weight less than 1750 grams who survived past the second day of life. The purpose of their observational study was to compare actual nutrient intake to recommended nutrient intake. Intakes were prospectively calculated by a single observer nurse practitioner on a daily basis, and all infants were fed according to a standard protocol to achieve a caloric intake of 120kcals/day.

There were 105 infants with birth weight 1285 grams ± 322 grams and gestational age 30 ± 2.3 weeks. Infants were followed until discharge to home (n = 37), until transfer to another facility (n = 57) or until death (n = 11). Infants were stratified according to

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gestational age ≤30 weeks and ≥31 weeks for data analysis using repeated measures ANOVA. Step-wise regression analysis was used to examine the relationship between birth weight, gestational age, postnatal age, energy deficit, protein deficit and dietary intake.

By the end of week one, cumulative energy deficit was 406 ± 92 kcals/kg and protein deficit was 14 ± 3 g/kg for infants ≤ 30 weeks gestation. For infants ≥ 31 weeks, energy deficit was 335 ± 86 kcals/kg and protein deficit was 12 ± 4 g/kg. By the end of week five, cumulative energy and protein deficits for those infants ≤30 weeks were 813 ± 542 and 23 ± 12 g/kg, respectively. For infants ≥31 weeks cumulative energy deficit was 382 ± 263 kcal/kg and cumulative protein deficit was 13 ± 15 g/kg. After two weeks, the change stabilized in infants ≥31 weeks. In infants ≤ 30 weeks gestation, the deficits continued until 5 weeks. Half (52%) of the variance in weight could be explained by cumulative energy deficit (45%) and gestational age (7%), whereas cumulative protein deficit had no significant effect on infant weight.

Although expected, this study's most clinically significant finding was that the current recommended standard of nutritional intake is inadequate for replacement of accumulated caloric deficit. Thus, revision of the current recommended dietary intake standards through interventional study would seem to be a critical step toward improving nutrition in preterm infants. One particular strength of the study was the presentation of nutritional findings according to gestational age ≤30 weeks and ≥31 weeks. Stratification by gestational age allows the opportunity to focus on a shorter and more homogeneous feeding period for both groups of infants. This may be useful in developing strategies for

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nutritional replacement, as replacement strategies would necessarily be tailored according to the infant's maturity.

The study was not designed to follow the infants after hospital discharge. Post discharge data would offer information on how quickly catch up growth occurs and if there are compensatory times for catch up that occur in a reasonable time period following discharge. For infants >31 weeks in this sample, energy deficit peaked at 14 days of life and they were unable to achieve catch up prior to discharge approximately four weeks later. How aggressive to approach catch up growth by prescribed intake of calories would depend on whether the opportunity for catch up is static or dynamic. For example, if the factors that influence weight gain are dynamic, and if there are critical periods of accelerated growth during which infants gain more weight in response to increased caloric intake, it would be important to provide those increased calories during that particular critical period

Radmacher and colleagues (2003) conducted a 4-year longitudinal retrospective chart review of 220 infants ≤1000 grams and ≤29 weeks gestation. The study goal was to identify predictors of EUGR and to evaluate nutritional intake and subsequent growth of VLBW infants. Infants were included in the sample if they were admitted to the nursery within 24 hours of birth, alive at seven days, and not diagnosed with any major congenital anomalies.

Infants who developed EUGR had significantly lower birth weight (46% were <750g at birth) and were more likely to be SGA at birth. Hypotension, sepsis, and bronchopulmonary dysplasia were more common in EUGR infants; however, surfactant usage was significantly less frequent (69%) than in non-EUGR infants (82.5%). Birth

weight percentile was the greatest predictor of EUGR; days of total parenteral nutrition and head circumference percentile at return to birth weight were the only independent predictors of EUGR. Mean energy intake failed to reach 120kcal/kg/day for either group during the study period, although EUGR infants consistently received less energy and protein than non-EUGR infants. Significant differences in energy intake occurred at weeks 5, 6, and 9-11 and significant differences in protein intake occurred at weeks 5, 9 and 11. Since protein and energy were both decreased during the same weeks, it is likely that overall volume was decreased during these periods. A more detailed comparison of the EUGR and non-EUGR groups for week six and week ten, when protein and energy intake were significantly decreased, might reveal clinically important differences to pursue in further research. Delineating these differences could be illuminating for understanding when one type of intake is restricted and not the other, or how protein and energy intake might independently influence weight.

In this study, 86% of the infants were AGA at the time of birth, yet 60% had evidence of EUGR by the time they returned to their birth weight (Radmacher et al, 2003). This study supports the findings of Embleton, et al. (2001) in which EUGR infants were chronically undernourished with regard to recommended energy intake of 120kcal/kg/day and recommended protein intake of 3g/kg/day. Although the sample included some infants who were SGA or IUGR, AGA infants were not differentiated in the analysis. Including these SGA and IUGR infants in the analysis may have overestimated the incidence of EUGR and confounded the results. Separate analysis of the EUGR and SGA infants could be useful in identifying key demographic and clinical

differences between these groups of infants that could be tested in future intervention research.

Comparable to other studies (Embelton, Pang & Cooke, 2001; Clark, Thomas & Peabody, 2003), findings from this study support the conclusion that infants in intensive care units do not consistently receive current recommended caloric intake. Furthermore, when recommended caloric intake is achieved, the caloric intake is not adequate for achieving catch up growth. Comparison groups of EUGR and non-EUGR infants offer a cross-sectional design and useful approach to evaluating the risk factors for EUGR while controlling for differences in nutrition and healthcare management. Another strength of this study was the researchers' analysis of data in weekly increments to allow for greater scrutiny at each time period and a more sensitive analysis of the risk factors unique to each time period.

Berry, Abrahamowicz, and Usher (1997) conducted a prospective longitudinal descriptive study of 109 VLBW infants < 1000 grams to quantify factors associated with growth during three different age periods of their hospitalization: 0-14 days, 15-56 days, and then the entire 56 days combined. Mean birth weight was 817 grams and growth was defined as a change in weight during each of the three time frames. There were two main purposes of the study: 1) correlate differences in growth at the three time periods with specific clinical characteristics, complications and therapeutic interventions, and 2) assess the relative contribution of these potential determinants of growth failure and estimate the nutritional intake that might be required to correct for them. Variables that significantly contributed to the model at all three time periods were caloric intake, protein intake, respiratory support duration, patent ductus arteriosus, dexamethasone use, gestational age

and maternal betamethasone prenatal exposure. At each time period, these variables significantly accounted for the variance in growth (43%, 80%, and 85%, respectively).

The average change in weight was -16 ± 82 grams for the 1-14 day period, 785 ±215g for days 15-56, and 770 ±245g for all 56 days. Of the variables assessed, significant determinants of growth included: 1) higher caloric intake during 15-56 days and higher protein intake during 0-14 days; 2) less respiratory support during 15-56 days; 3) for every day of respiratory support, weight gain decreased by 1.4 grams during the entire 56-day period; and 4) steroid treatment was negatively correlated with weight gain at 15-56 days. Weight decreased an average of 190 grams for the 15-56 day period and an average of 144 grams for the overall 56-day period

Findings from this study did not support conclusions that achieving intrauterine growth in the extrauterine VLBW infant will allow catch up growth to occur. In fact, for the period of 15-56 days, mean growth closely paralleled the intrauterine growth curve; yet, catch-up growth still did not occur. Thus, findings confirm that accumulated caloric deficit has an effect beyond the non-growth period that is not overcome with maintenance calories. For the infants in this study, although intrauterine growth velocity was achievable, they may have already been lagging too far behind in caloric intake by day 15 for catch up growth to occur. Another possibility is that metabolic derangements caused by very early growth failure or weight loss may trigger a metabolic state that is less responsive to growth, even in the face of adequate caloric support.

What is also difficult to reconcile from the findings in this study is that infants born at term are not physiological or clinically expected to regain birth weight until two weeks of life. In this group of infants, however, weight loss before two weeks of age

seemed to place them at risk for continued impaired growth rather than a normal transitional period.

It is also possible that neonatal disease and consequences of severe prematurity require greater caloric support. This hypothesis does not have any empirical or clinical support, since infants were able to achieve weight gain comparable to intrauterine rates, and simply could not catch up on their growth. There are likely to be other, yet unidentified, confounding factors that interfere with weight gain in this population. The most logical approach to further study would be to attempt to catch up for accumulated caloric deficit and measure when adequate growth can be achieved. The problem with this approach is the limited capacity for increasing calories and protein in the already vulnerable preterm infant.

While previous studies have identified infection as a predictor of poor growth in this population of infants (Clark, Thomas & Peabody, 2003; Radmacher, Looney, Rafail & Adamkin, 2003), findings from this longitudinal study did not support this association. Although 47% of infants in this sample experienced an infection, and infection should have the potential of increasing metabolism, it was not a significant predictor of poor growth in their sample.

Hirata and Bosque (1998) conducted a prospective longitudinal study of infants <1000 grams and followed their growth through adolescence. The cohort was comprised of 32 preterm infants with a mean birth weight of 818 ± 110 grams, and gestational age of 26.6 ± 1.4 weeks. There were 20 females and 12 males, with 22 White, 8 Black and 2 Asian infants. Exclusion criteria included major health or neurological problems. Height, weight, and head circumference were measured twice in the first year of life and

then again at ages two, three, five, eight and ten years, and again during adolescence at about 12 and 18 years.

Mean height, weight and head circumference of these adolescents were at the 50th percentile. Up until this age, many were less than the 50th percentile and most crossed multiple percentiles during adolescence. By adolescence, females had achieved heights greater than or equal to their mother's height, and male heights were the same or greater than those of their fathers.

Findings from this study are important because, rather than using population parameters to determine growth success, genetic potential based on a parent's height was used. This is a more accurate assessment of long term growth, since we know that growth potential, height in particular, has a strong genetic determinant. The study also has important implications for clinical practice as well and for understanding and studying extremely low birth weight (ELBW) infant growth. ELBW infants experienced catch up growth into adolescence and eventually attained predicted parental genetic height. A shorter duration study would have failed to detect this growth pattern. This is evidenced when the adolescent cohort (n=32) was compared to the entire cohort (n=103) that was only followed to ten years of age. Up until ten years of age, there was no statistically significant difference in the growth patterns of the adolescent group compared with the rest of the cohort. Until age ten, the majority of children in the entire study group were less than the 50th percentile for growth. It was only during adolescence that the children measured for more than 10 years crossed the 50th percentile for height and later achieved their genetic potential as assessed in relation to their own parents.

More measures of growth during the adolescent period may be useful for predicting or establishing growth patterns and identifying periods of high and low growth, since most adolescents in this sample passed through many percentiles for height between measurements. This information may be useful for determining and following growth in ELBW infants as well as for allaying parental and clinician concerns if growth is sporadic. Determining patterns of growth with greater precision can be useful in many ways. Other health and growth issues could provide insight about how birth weight influences growth velocity in this population.

Summary of Salient Points

These studies consistently provide evidence that the majority of preterm infants do not achieve adequate caloric intake during hospitalization (Clark et al, 2003; Embleton et al, 2001). Even during periods of adequate intake, expected growth is not always achieved suggesting that there are other important factors contributing to growth in this population that have yet to be identified (Embelton et al; Wood et al, 2003). Additionally, it is likely that the nutritional needs and the growth patterns of very low birth weight and extremely low birth weight infants differ from those of term and low birth weight infants. Future research on unique nutritional needs and growth patterns of VLBW and ELBW infants will allow testing of nutrition interventions to be tailored to match these specific variations and facilitate more normal growth patterns. Although common factors for EUGR are identified by various researchers, there are an equal number of factors that are not common between studies or supported across studies. This suggests that there are confounding variables unique to individual hospital practice or

patients that contribute to EUGR. Sorting out these issues is an important aspect of future research.

Difficulties with Research on EUGR

Research in this area is difficult not only because of confounders such as these, but because in the face of critical illness, nutrition is often not considered a clinical priority. The negative effects of inadequate nutrition are often insidious and cumulative and may not be fully realized for several weeks and sometimes years, thus, the urgency to prioritize nutrition in the face of critical illness is not seen in clinical practice.

It is not uncommon for infants in the NICU to go days without proper nutrition. Nutritional support may be stopped and started, altered and manipulated without the usual scrutiny of other clinical interventions because of its non-critical nature. Furthermore, nutrition seems to fall into either "no man's land" or "everyman's land" with regard to clinical domain. Pharmacy, dietary, medicine and nursing all contribute and advise on infant nutrition, but until primary ownership is claimed it may continue below the radar screen of clinical priority until the infant's clinical status is stable and nutritional status will naturally take a place of clinical priority. Waiting to optimize nutritional support until an infant is clinically stable is clearly no longer an acceptable method of practice.

EUGR is a difficult problem to study because many individuals are involved in the formulation and administration of feedings. From breast milk to formula, to gavage feedings, to breast feeding; the inability to standardize the input makes quantifying difficult and assumes that the end result (in this case, weight gain) is the more

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quantifiable variable. Yet, weight gain is a gross estimate of intake since so many confounding variables exist before this end point.

Implications for Future Research

Of utmost importance to future research is how best to nutritionally support critical organ growth during periods when potential precursors to long term morbidity may be latently developing. Research that seeks to determine how to optimize early nutritional support to avoid such potential morbidity is paramount to ensuring a better future for VLBW and ELBW survivors.

Studies are needed to determine or redefine the caloric needs of preterm infants in order to change practice to reflect actual metabolic need that will achieve adequate growth and prevent EUGR. Additionally, studies to determine the specific caloric composition best for promoting growth will be useful in developing nutritional regimens that better meet the preterm infant's specific metabolic needs. There may be critical time points during hospitalization when increased caloric intake is better tolerated and better utilized for growth. There is also strong evidence that the period of hospitalization is not long enough for catch up growth to occur (Bosque & Hirata, 1997; Wood et al, 2003). Although catch up growth appears to continue through adolescence (Bosque & Hirata, 1997), it is possible that the earliest period of growth, during hospitalization, may be the most critical for preterm infants to avoid subsequent neurologic impairment due to failed growth. Therefore, future studies to identify whether periods of critical growth exist, and when they occur, would be essential for preventing or minimizing neurologic morbidity.

Future research is needed to critically sort out the issue of safety with respect to increasing caloric intake through higher feeding volumes or greater caloric concentration. A systematic method for studying the various approaches to increasing calories in the preterm infant is needed to compare the efficacy of increasing weight gain against the risk of gut injury since safe practice is the most critical factor for limiting increased calories. It is not known if this approach will be effective in ameliorating extrauterine weight deficit, but until the safety of such approaches is established, clinical interventions in this area cannot progress. Research efforts should continue in order to better understand the mechanisms of EUGR, which may be substantially different from mechanisms for normal and expected intrauterine growth.

How Nurses Can Affect the Problem of EUGR

EUGR is an important problem because it affects a large proportion of the population of infants born prematurely. It is an interesting problem because it pertains not to illness or injury in a specific biological system but to the coordinated growth of all biological systems. It is a difficult problem because it takes place during one of the most accelerated periods in human development rendering baselines and comparisons transitory. It is a nursing problem because it is likely that some of the causative factors that remain to be identified may be related to nursing care and environmental factors that nurses are well positioned to affect in their daily practice.

Nursing is key to solving the problem of EUGR for two reasons. First, clinical observations form the starting-point for research, both in collecting data and in forming theories. Second, the end-point of the solution will likely take the form not of medication

or invasive surgery, but of nursing and medical practices in nutrition and handling and other modifications in the NICU environment to create a less hostile environment to support premature infant growth and development. Research in this area must be responsive on both points to be effective.

Table 1. Review of Study Findings

Citation	Findings
Wood, N., Costeloe, K., Hennessy, E., Marlow, N. & Wilkinson, A. for the EPICure Study Group (2003). *Archives in Childhood, Fetal, Neonatal Education, 88*, F492-F500.	283 (92%) of the 308 survivors who were ≤26 weeks gestation infants were evaluated at 30 months CGA. Cerebral palsy, severe motor disability, and Bayley scores were used as dependent variables in multiple regression analyses to factors associated with adverse outcomes. Factors independently associated with neurological and developmental disability were: Male infants had 2x the risk for poor neurological and developmental disability as female infants. Factors related to perinatal illness, ultrasound evidence of brain injury, and treatment (particularly postnatal steroids) were associated with adverse motor outcomes. Increasing duration of postnatal steroid treatment was associated with poor motor outcomes. Mental development was associated with: ethnic group, maternal education level, use of antenatal steroids, and prolonged rupture of membranes in addition to chronic lung disease. 19% had cerebral palsy 10% had severe motor disability
Clark, R., Thomas, P. & Peabody, J. (2003).Extrauterine growth restriction remains a serious problem in prematurely born neonates. *Pediatrics, 111*(5), 986-990.	28% of 23,970 premature infants born between 23-34 weeks gestation, were determined be extrauterine growth restricted (weight ≤10th percentile) at the time of discharge from the NICU. Need for assisted ventilation on the first day of life, male gender, history of necrotizing enterocolitis, and treatment with exposure to steroids were all factors associated with extrauterine growth restriction (EUGR). The incidence of EUGR increased with decreasing gestational age and birth weight.
Embleton, N.E., Pange, N. & Cooke, R.J. (2001). Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? *Pediatrics, 107*, 270-273.	Energy and protein deficits in the preterm infant are often unable to be caught up and frequently continue to accumulate throughout periods of feeding intolerance in the first several weeks of life such that these deficits can be directly related to subsequent postnatal growth restriction. By end of 1st week: ≤30wks gestational age energy 406 ± 92 kcal/kg protein 14 ± 3 g/kg ≥31wks gestational age

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	energy 335 ± 86 kcal/kg protein 12 ± 4 g/kg By end of 5th week: ≤30wks gestational age energy 813 ± 542 kcal/kg protein 23 ± 12 g/kg ≥31wks gestational age energy 382 ± 263 kcal/kg protein 13 ± 15 g/kg Only ~45% of variation in weight could be explained by nutrition thus, non-nutritional factors require exploration.

Radmacher, P., Looney, S., Rafail, S., & Adamkin D. (2003). Prediction of extrauterine growth retardation (EUGR) in VVLBW infants. *Journal of Perinatology*, 23(5), 392-395.	During hospitalization, mean E and protein intakes did not reach recommended values of 120kcals/kg/d and 3g/kg/d.
	
	Extrauterine growth rates were not consistent with in utero growth rates.
	
	Measures found to be highly predictive of EUGR:
	   - BW percentile (p<.001),
	   - days of TPN (p<.001),
	- HC percentile at return to BW made a significant contribution to the prediction of EUGR, once the effect of BW was taken into account.

Berry, M., Abrahamowicz, M. & Usher, R. (1997). Factors associated with growth of extremely premature infants during initial hospitalization. *Pediatrics*, 100(4), 630-646.	-achieving intrauterine growth rate did not allow catch-up growth -accumulated growth deficits have impact that goes beyond non- growth period

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Does Higher Heart Rate Contribute To Growth Of Preterm Infants?

Abstract

Background: Research indicates that preterm infants with higher baseline heart rate (HR) experience greater weight gain than preterm infants with lower baseline HR, suggesting that HR could be a prognostic indicator for weight gain.

Aim: 1) replicate previous research on preterm infants born between 32 to 36 weeks gestation in which those with higher resting HR in the first few days of life experienced significantly greater weight gain than infants with lower resting HR, and extend these findings to younger infants born between 27 and 31 weeks gestation.

Methods: A retrospective chart review was used to collect HR and growth data on 156 infants between 27.0 and 34.0 weeks gestation from birth to hospital discharge.

Results: There was a significant difference in weight gain from day 10 of life in infants with higher resting HR compared to infants with lower resting HR.   However, once birth weight and gestational age were controlled in the analyses, there was no significant relationship between HR and weight gain for any gestational age group of premature infants.

Conclusions: Contrary to previous findings, there was no significant relationship between HR and growth at any gestational age after controlling for birth weight and gestational age. Continuing to search for correlates of growth in preterm infants to improve developmental outcomes remains an important issue.

1. Introduction

Weight gain is one of the best predictors of survival for preterm infants (Brandt et al., 2003). Yet, more than 80% of very low birth weight (VLBW) preterm infants ($\leq$1500 grams) weigh less than the 10th percentile for their corrected gestational age by their time of discharge from the hospital (Clark et al., 2003; Radmacher, 2003,). This condition is known as extrauterine growth restriction (EUGR). EUGR is a common condition in VLBW preterm infants and is the most common morbidity among VLBW survivors (Clark et al., 2003; Garite, Clark & Thorpe, 2004). In this condition, preterm infants who are born at average weight for gestational age are unable to maintain a normal pattern of growth in the extrauterine environment despite the provision of established nutritional requirements (AAP, 2003). The typical newborn gains approximately 30 grams/day (Bloom, 2006). Expected growth velocity for the premature infant is 15 grams/kg/day, which is comparable to intrauterine growth (Gibson, Carney & Wales, 2006).

Failure of preterm infants to maintain adequate growth rates in the neonatal intensive care unit (NICU) is significant because it has been associated with long-term detrimental effects. Two longitudinal studies comparing 242 VLBW infants to 233 normal infants at 20 years of age found that VLBW infants scored significantly lower on IQ and academic achievement tests (Bhutta et al., 2002; Breslau et al., 2004). Low birth weight infants were twice as likely to develop Attention Deficit Hyperactivity Disorder in a retrospective review (Hack et al., 2002). Chronic diseases later in life, such as coronary heart disease, are also associated with low birth weight (Barker, 2004). These findings emphasize the critical nature of understanding low birth weight, growth patterns, and

long-term morbidity. Early identification of preterm infants at risk for poor growth could allow for timely intervention to reduce morbidity. Identifying correlates of growth in this population could provide a mechanism for recognition of those infants who are at greatest risk for failed growth.

Efficient use of calories is traditionally associated with reduced energy expenditure. However, there is increasing evidence in preterm infants that weight gain may actually be enhanced by increased sympathetic activity (DiPietro & Porges, 1991; Harrison, et al., 2000). One possible explanation is that increased vagal tone representing sympathetic activity, may increase metabolic efficiency by improving gastric absorption through increased peristalsis (Diego, Field & Hernandez, 2005). This hypothesis is supported by a study which found that infants who underwent 10 minutes of gentle massage for seven consecutive days had better weight gain than controls (Diego et al. 2005). Another study by DiPietro and Porges (1991) found that infants who experienced an increase in vagal tone during gavage feeding, as assessed by electrocardiogram recording of beat-to-beat variability based on respiratory sinus arrhythmia, had significantly shorter hospitalizations than infants who did not demonstrate this pattern.

deKlerk and colleagues (1997) evaluated 142 preterm infants at a mean gestational age of 31 weeks and 1364 grams. They identified infants as rapid growers or slow growers based on their weight trend and found a significant difference ($p < .005$) in HR between rapid growers (163± 8 beats/min) and slow growers (157±9 beats/min). Ferber and colleagues (2006) also provide more recent evidence for a relationship between increased HR and growth. They studied 90 Israeli infants born between 32 and

36 weeks gestation. To test whether sympathetic activity contributes to growth in preterm infants, resting HR was used as their measure of sympathetic activity to examine effects on subsequent weight gain in this population.

Given these findings, it would be important to replicate these results before adopting HR as a clinically valuable prognostic indicator of the preterm infant's rate of growth potential during hospitalization. Therefore, the purpose of this study was to replicate prior research on infants (Ferber et al., 2006) born between 32-36 weeks gestation, and also extend the sample to preterm infants born before 32 weeks gestation. The specific hypothesis was: there will be a positive correlation between resting HR in the first three days of life and weight gain/day regardless of gestational age. We also hypothesized that infants with higher HR would have greater weight gain/day than infants with lower HR after controlling for birth weight, gestational age, and length of stay.

2. Methods

2.1 Study design

This retrospective chart review identified all 27.0 to 34.0 week preterm infants born and discharged from the NICU between June 2002 and December 2006. Data were obtained from the patient's electronic medical record. In the medical record, nurses record HR manually every one to four hours, depending on acuity, from values obtained by continuous EKG monitoring while the infant is in a stable resting state. Weight is recorded daily; and length and head circumference are recorded weekly.

2.2 Inclusion and Exclusion Criteria

The sample included infants born at Lucile Packard Children's Hospital at Stanford University Medical Center. Infants greater than 34 weeks gestation are not admitted to the Neonatal Intensive Care Unit at this facility. Therefore, all infants between 27 and 34 weeks gestation admitted and discharged from the same hospital after a minimum length of stay of 13 days were included.

To ensure independent samples, only the first sibling from a multiple birth was included. Infants with genetic and congenital anomalies and infants with grade 3-4 intraventricular hemorrhage were excluded. Any infant who required surgical intervention or had undergone any type of surgery during hospitalization was also excluded.

Patients on medication were not excluded but medications were noted. Medications that could potentially affect HR include caffeine and indomethacin. Echo diagnosed patent ductus arteriosus (PDA) was also noted. There were no differences in HR between infants with diagnosed PDA and those being treated with caffeine or indomethacin compared to infants who were not on medications or did not have an active PDA.

2.3 Procedure

This study was approved by the Internal Review Board. In this NICU setting, HR measures are implicitly obtained and recorded during a restful state. Depending on the acuity of the infant's condition, HR is recorded on the medical flowsheet ranging from hourly in the first few weeks of life, to every 4-6 hours coinciding with demand feeding for infants who are closer to hospital discharge. Hourly HR measures were collected

from the medical chart recordings and entered into a database. Other data collected from each patient's medical record included gender, birth weight, gestational age, caffeine and other medications, and conditions that could effect HR, such as diagnosis of patent ductus arteriosus and treatment with indomethacin or dopamine.

2.4 Predictor measures

From the infant's electronic medical records, all available HR measures for each 24-hour period on days 3, 4, 5, 8, 9, and 10 of life, and on the 3 days prior to discharge were entered into a database. Theses days were chosen to exclude the effects of maternal medications for her labor or other medications that women in preterm labor often receive. For each infant, the mean HR for the time period between 0100 to 0500 hrs for each day was calculated because this time frame is the most quiet period in the NICU and best reflects resting HR.

2.5 Outcome measure

The primary outcome measure was weight gain/day, calculated as the difference between weight at day 0 (birth weight) and day of discharge divided by length of hospitalization. For further analysis, weight gain/day from day 10 of life to day of discharge was also calculated. In the first 10 days of life, weight loss is common and weight gain is more variable. By day 10 of life, nutritional support is more similar for all premature infants.

2.7 Statistical Analysis

The sample was categorized into three age groups: 1) 27.0 - 28.9 weeks' gestation, 2) 29.0-31.9 weeks' gestation, and 3) 32.0-34.0 weeks' gestation. A fourth group excluded infants <1460 grams from the 32-34 week group in order to make this group

similar to the Ferber et al. (2006) sample for comparison. Demographic and HR characteristics for each gestational age group are presented in Table 1. HR at all time points (day 3, days 3 to 5, days 8 to10, and day -3 to discharge) was compared with weight gain/day to control for length of stay. To replicate the previous studies (deKlerk, et al., 1997; Ferber et al., 2006), a hierarchical regression analysis was also conducted and independent sample t-tests were used to compare differences in weight gain/day between infants with high and low baseline HR.

3. Results

Birth weight (BW) ranged from as low as 550g to 2723g in this sample of 156 preterm infants. Length of stay ranged from a mean of 82 days for the youngest group, to 26 days for the oldest group of infants (see Table 1). Mean weight gain/day from birth to day of discharge ranged from 20g in the 23-24 week group to 24g in the 29-31 week group. The range was between 12 and 33 g/day. Mean resting HR for days 3 to 5 was 152±7 (SD) beats/min for the youngest group and 149±8 beats/min for the oldest group. Mean resting HR was higher for all three groups on days 8 to10 (see Table 1). In the 27-28 week group of 40 infants, 29 (73%) were on caffeine at day 8, and in the 29-31 week group 29 (50%) were on caffeine, whereas only 1 of the 58 infants in the 32-34 weeks gestation group was on caffeine. Unpaired t-tests revealed no significant differences in mean resting HR or weight gain/day between the 20 infants on caffeine and the 20 infants not on caffeine in the 27-28 week gestation group.

Weight gain/day from birth to hospital discharge, from birth to day 10 of life, and from day 10 of life to hospital discharge are presented in Table 1 by gestational age

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group. There was a statistically significant difference in weight gain/day from day 10 of life to discharge for the three gestation groups. For the entire sample of 156 infants, there was no relationship between HR and weight gain/day.

HR on day 3 was significantly correlated ($p < 0.001$) with mean HR for days 3 to 5 ($r = .725$), days 8 to 10 ($r = 0.389$), and day 8 to discharge ($r =. 413$). There was a weak positive relationship between HR days 8 to10 and weight gain during the entire length of hospitalization ($r = .226$, $p = .005$) for all infants, but this relationship does not control for length of stay and was not evident when each gestational age group was examined separately. In the youngest group of premature infants, weight gain/day from day 10 of life to hospital discharge was inversely correlated with mean HR on days 8 to 10 ($r = -.354$, $p= .025$) and mean HR from day 8 to discharge ($r = -.317$, $p= .046$), such that the higher the HR, the less weight gain/day in 27 and 28 week gestation infants. There was no relationship between HR and weight gain/day in the other two groups of infants.

In the first multiple regression analysis, 82% of the variance in overall weight gain from birth to hospital discharge was accounted for by length of stay ($sr = .73$, $p < .001$), gender ($sr = -.19$, $p = .02$). Mean resting HR at any time point was not a significant predictor of overall weight gain after controlling for birth weight, gestational age, and length of stay.

When weight gain/day from birth to hospital discharge was the dependent variable, 15% of the variance was explained by gender ($sr = -.21$, $p = .01$) and gestational age ($sr = -.17$, $p =.04$). When weight gain/day from day 10 of life to hospital discharge was used as the dependent variable, 25% of the variance was explained by birth weight

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(sr = .25, p =.002), mean HR on day 3 (sr = -.18, p = .02) and gender (sr = -.17, p = .035). Use of caffeine (yes/no) was not a significant variable in these models.

Post hoc tests for gender differences revealed that the 76 male infants in the sample gained 23 ± 5.9 g/day from birth to hospital discharge compared to the 80 female infants who gained 21 ± 5.7 g/day (t = 2.0, p = .04). This difference was also significant (t = 2.9, p = .004) when average daily weight gain from day 10 of life to hospital discharge was examined (males: 32 ± 6.9 g/day; females: 29.0 ± 7.1 g/day).

To replicate prior research suggesting an association between mean resting HR throughout the hospital stay and weight gain in a sample of infants between 32-36 weeks gestation (Ferber et al, 2006), mean resting HR from day 3 to discharge was correlated with weight gain/day from birth to discharge for just those preterm infants in the current sample who were 32 to 34 weeks gestation, and the correlation (r = .104) was not significant. Absolute weight gain from birth to day of discharge was weakly and inversely correlated with mean resting HR d3 (r = -.22, p = .09).

Ferber and colleagues (2006) dichotomized their sample of 90 infants into two groups based on mean resting HR at day 3 of life (≤ 139 and ≥140 beats/min). In our sample, no resting HR was below 140 beats/min on day 3. Therefore, HR was dichotomized at 150 beats/min; 84 of the 155 infants were 150 beats/min or less and gained 31.95 ± 7.36 g/day from day 10 of life to hospital discharge. This was significant compared to 71 infants who were above 150 beats/min on day 3 and gained only 28.9 ± 6.73 g/day from day 10 of life to hospital discharge (unpaired t = 2.7, p = .009). There was no significant difference in mean resting HR between males and females at any point in time.

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3. Discussion

After controlling for birth weight, gestational age, and length of stay by using the average daily weight gain, we did not find resting HR to be a significant predictor of weight gain in any gestational age group. Ferber and colleagues (2006), deKlerk and colleague (1997), and our sample had different mean values for resting HR, suggesting that the three study groups might not be comparable. To investigate this finding, this discussion compares the results and methods of the previous two studies with the current sample. Differences in mean HR, gestational age and birth weight between study samples may partially explain the outcomes.

Differences in Gestational Age

Mean daily HR differed by approximately 10-20 beats/min between the current study sample (154 beats/min) with our mean age of 33.1 weeks, and the 142 beats/min noted by Ferber and colleagues (2006) for 34 ± 1.0 week infants and the 160-166 beats/min noted by deKlerk and colleagues (1997) in a comparison of slow and fast growers with a mean gestational age of 31 weeks. Gestational age could explain the differences in HR between samples. Since HR is inversely correlated with gestational age, a sample with older gestational age may have a lower resting HR.

Similarly, birth weight differed somewhat between study samples, but is likely explained by gestational age differences. Ferber's group of 90 infants had a mean birth weight of 2019 ± 308 g. The comparable age group of 32-34 weeks gestation in the 48 infants from the current sample was 1961 ± 298 g. deKlerk's group of 142 infants had the highest HR and the youngest sample, averaging 1364 g at birth.

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Since the differences between samples are largely due to gestational age, we would expect the results to be similar, after controlling for gestational age. However, results were not similar and possible differences in data collection were then considered. Different techniques for obtaining HR may have contributed to the difference in mean HR found between the three studies. The technique used for collecting HR in the Ferber et al (2006) sample is not clearly described. They did not specify whether their two morning HR values on each infant were obtained from continuous EKG monitoring, intermittent or spot EKG monitoring, or from auscultation. In our nursery, nurses record HR onto a flow sheet from a continuous EKG monitor when the infant is in a quiet resting state. It is possible that the difference in technique could have influenced HR values.

The time that HR was collected, and the number of HR values collected could have also influenced the difference in mean HR between the samples. In the Ferber et al (2006) study, two daily readings were collected retrospectively from the nursing record. They report using two morning heart rates during "restful sleep" to calculate mean resting HR, whereas we used all HR data available between 0100 and 0600 hrs. Thus, these differences in collection time and number of HR values used to compute mean heart rate could have influenced study findings.

Another possible explanation for differences in mean HR between the groups is the infant's state (rest or sleep) when HR was collected. Ferber and colleagues (2006) noted that for their sample, HR was obtained by nurses "only during restful sleep." Our HR data were recorded while the infant was in a restful state, but not necessarily in a sleep state. Since HR has different characteristics in different sleep states, and is likely to

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be lower in quiet sleep stages, and higher and more variable in rapid-eye-movement sleep

(where newborns typically spend 50% of their sleep time), differences in the infant's

behavioral state during HR collection is another potential explanation for the difference

in mean heart rate between study samples. It is not clear from the deKlerk et al (1997)

article when HR was collected or the state that the infant was in when it was collected. If

HR was consistently collected during quiet sleep, this could explain the lower resting HR

found in the Ferber et al (2006) sample.

Differences in Length of Stay

The Ferber et al. (2006) sample appeared to gain less weight than our sample, but

the length of stay (LOS) was longer for our group of infants, possibly accounting for the

difference. Weight gain from birth to discharge in the Ferber group was 181.8 ± 152.6 g

(range -85 to 615 g) and LOS was 11.25 ± 5.17 days (range 4-27 days). For our

comparable sample of infants >32 weeks and >1460 g, weight gain from birth to

discharge had a more normal distribution and averaged 503 ± 301 g (range -31 to 1444)

and our LOS was 26 ± 10 days (range 13-55 days); LOS for the deKlerk sample was not

reported. For weight gain, a more direct comparison between the three samples would be

average weight gain/day, as reported in Table 1. Our weight gain/day was substantially

lower and more normally distributed than the 88.6 ± 88.26g reported by Ferber et al

(2006). It is likely that LOS difference between our sample and the Ferber sample is

related to the younger average gestational age of our sample, as we were unable to enroll

any infant greater than 34 weeks gestation. The significant differences in LOS may also

have contributed to the differences in findings between these studies, since most preterm

infants are not discharged from our facility until they reach either 40 weeks corrected gestational age or a weight of 2000 grams.

In our study, we found that male infants gained significantly more weight/day than their female counterparts. This difference was not reported by Ferber and colleagues (2006), or deKlerk and colleagues (1997). Although both studies report the number of males and females daily weight gain by gender was not reported. However, this finding is consistent with that of other researchers who report males consistently weigh more at each gestational age. These studies report than the differences in weight are less as gestational age increases and then level off after 30 weeks (Karma, Brooks, Muttineni & Karmaus,2005; Thomas, Peabody, Turnier & Clark, 2000; de Zegher, Devlieger, Eeckles, 1999). Thus, our finding that males had greater weight gain than females is consistent with male infants maintaining a higher expected weight.

One limitation of our study design was that calorie intake data were not available, so we were unable to account for this variable. Since weight gain is correlated with caloric intake, we attempted to minimize variation in caloric intake by calculating the weight gain/day beginning after infants reached day 10 of life, when caloric intake is a more standard prescription in the setting where the study took place.

Conclusion

This study did not support resting HR as a prognostic indicator for weight gain in preterm infants, either in infants similar to Ferber and colleague's (2006) sample, or in infants of younger gestational age. Differences in sample selection, data collection and study design may have affected the results, and the most relevant potential differences were discussed and suggestions offered to improve future research. If our study findings

are replicated, resting HR alone is not a useful indicator of weight gain once birth weight and gestational age are considered, and vagal tone or heart rate variability may be a better indicator of sympathetic activity than resting HR for further research.

The greatest factor for increasing the clinical utility of research in this area would be standardizing units of measure and measurement techniques in data collection. Standardization will permit the interpretation of results without requisite questioning and filtering of results based on differences in data collection technique. First, it is important to measure the same "restful" state when obtaining baseline HR to make comparisons across studies. Second, weight gain must be reported in comparable ways in order to make comparisons across studies. Reporting daily weight gain as a function of length of stay to obtain an average weight gain/day would enable researchers and clinicians to compare study groups, correcting for length of stay. Third, gestational age is a critical factor in virtually all assessments of the preterm infant, so it is important to accurately report age. Fourth, establishing a simple method for accurately tracking daily caloric intake is an important component in the calculation and understanding of metabolic concepts related to weight gain in terms of energy intake and expenditure.

Prospective studies that control for nutritional intake and caloric composition could lend clarity to identifying and quantifying the contribution of the more elusive factors associated with EUGR. If daily caloric intake cannot be tracked, studies should identify whether infants are in a relatively normalized period of intake, such as in the second week of life when changes in weight are more likely to be due to nutrition rather than interstitial fluid loss (Ehrenkranz, et al., 1999).

Finally, rather than resting HR, future research should examine heart rate variability or vagal tone maturation as a better indicator of sympathetic activity to provide a theoretical basis for weight gain. Future research should also continue to investigate early clinical correlates of growth in preterm infants in order to study problems with growth as they are occurring rather than waiting for EUGR to manifest at the time of hospital discharge.

Table 1. Sample Characteristics, Weight (wt), by gestational age group (means ± SD, and ranges).

	27.0-28.9 wks (n=40)	29.0-31.9 wks (n=58)	32.0-34.0 wks (n=58)
Birth Wt (g)	1037 ± 238 550 - 1498	1384 ± 323 618 - 2118	1844 ± 376 1121 – 2723
Wt change (g) birth to day10	-36 ± 78 -215 to 161	-11 ± 72 -167 to 135	12 ± 88 -162 to 176
Mean wt gain/day (birth to day10)	-3.6 ± 7.8 -21.5 to 16.1	-1.1 ± 7.2 -16.7 to 13.5	1.2 ± 8.7 -16.2 to 17.6
Mean wt gain/day (g)* (day 10 to discharge)	26.3 ± 6.11 13.7 – 38.8	30.8 ± 6.39 16.4 – 45.9	33.2 ± 7.4 16.8 – 52.0
Weight change (g) BW to discharge	1884 ± 668 697 to 3287	1250 ± 417 332 to 2375	54 -31 to 1444
Mean wt gain/day (birth to discharge)	22 ± 5 13 - 33	24 ± 5 12 - 33	20 ± 6 2.21 - 31.4
Length of stay (days)	82 ± 24 35 - 157	52 ± 15 27-101	26 ± 10 13 - 55
Dopamine day 3 (% treated)	2	0	0
Caffeine day 8 (% treated)	29 (73%)	29 (50%)	1 (2%)
Gender: Male Female	17 (43%) 23	26 (45%) 32	33 (57%) 25

* Group difference significant ($F_{[2,153]}$ = 12.4, p <.001)

Table 2. Mean Resting Heart Rate (HR)* by gestational age group.

Gestational Age Group

	27.0-28.9 wks (n=40)	29.0-31.9 wks (n=58)	32.0-34.0 wks (n=58)
Mean resting HR days 3-5	152 ±7 138 - 165	153 ± 9 124 – 167	149 ± 8 131 – 171
Mean resting HR days 8-10	163 ± 10 144 - 184	158 ± 9 141 – 177	153 ±8 139-181
Mean resting HR day 3 to discharge	152 ± 8 135 - 171	155 ± 8 129 – 172	154 ± 6 141-166

* HR (beats/min) calculated from all entries in the medical record between 01:00 and

06:00 a.m.

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SGA, EUGR and early weight loss: How do these factors affect daily weight gain and length of stay in preterm and very low birth weight infants?

Abstract

Objectives. To determine if early weight loss in the first week of life affects subsequent weight gain and length of stay in preterm infants 27 to 34 weeks gestation, and describe growth characteristics of VLBW(<1500g) infants to identify patterns of failed growth.

Study Design. Using a data base created by retrospective chart review, data were analyzed to determine weight change in the first week of life for 156 infants 27 to 34 weeks gestation who were born and discharged from the neonatal intensive care unit between June 2002 and December 2006. The incidence of EUGR was determined in the subgroup of VLBW infants and data were analyzed for differences in growth patterns and characteristics between EUGR and non-EUGR infants.

Results. Weight gain/day after the first week of life did not influence LOS for the entire sample (n=156) or for the subsample of 83 VLBW infants. The incidence of EUGR in VLBW infants was 60% for weight and 31% for head circumference. All infants who were SGA at birth were EUGR at discharge except one. EUGR infants differed from non-EUGR infants by change in weight from birth to day 8, BW, GA, discharge weight and daily weight gain. Further differences in BW, daily weight gain, and LOS were identified between EUGR male and females

Conclusions. Weight loss in the first week of life does not affect weight gain/day or length of hospital stay. However, the significant difference in weight change in the first 8 days of life between EUGR and non-EUGR infants requires further investigation.

The differences identified between EUGR and non-EUGR infants can provide important

information for guiding future research.

Introduction

Studies show preterm infants continue to contribute significantly to infant morbidity and mortality rates in this country despite representing only 1.5% of births and despite increased survival of VLBW preterm infants (Lemons, et al., 2001; Ehrenkranz, et al., 2006). Morbidities can range from mild to devastating, but the most prevalent morbidity in VLBW infants is the failure to achieve adequate growth, known as extrauterine growth restriction (EUGR) (Clark, et al., 2003; Garite, Clark & Thorpe, 2004). EUGR has been correlated with developmental delay and chronic diseases later in life (Barker, 2004, Ehrenkranz, et al., 2006).

Research on the causes of EUGR has been inconclusive. Although BW and nutrition have been identified as significant contributing factors, they account for less than 50% of known causative factors to EUGR (Embleton, Pange & Cooke, 2001). Research has demonstrated that VLBW infants experience different growth patterns and have different nutritional requirements than full term infants (Bertino, et al., 2006). For these reasons, developing a better understanding of VLBW growth patterns, particularly as they relate to EUGR, may provide important information for preventing failed growth in this population. Identifying factors that contribute to failed growth could provide valuable insight for developing intervention and prevention strategies for EUGR.

The failure of VLBW infants to gain weight in the first few months is associated with subsequent growth delay (Clark, et al. 2003; Ehrenkranz, et al., 2006). However, transient weight loss in the first week of life in VLBW infants has been found to be primarily related to fluid losses (Bauer, et al. 2006; Denne, 2002). The purpose of this study was to determine if length of hospital stay (LOS) was associated with early weight

loss in the first week after birth and compare growth data of EUGR and non-EUGR

VLBW infants.

Methods

Data were collected on 160 preterm infants born and discharged from the neonatal

intensive care unit (NICU) at Lucile Packard Children's Hospital from June 2002 through

December 2006. This study was approved by the hospital's Internal Review Board and

by the University of California, San Francisco. Infants included in this medical chart

review study had gestational ages between 27.0 and 34.0 weeks. To maintain independent

samples, only the first infant listed on the roster was included in cases of multiple birth.

Also excluded were infants with genetic and congenital anomalies and infants with grade

3-4 intraventricular hemorrhage. Any infant who required surgical intervention or had

undergone any type of surgery during hospitalization was also excluded. For the

statistical analysis, a minimum length of stay of 13 days was required, so infants with

LOS $\leq$ 13 days were excluded.

Patients on medication were not excluded but medications were noted. Echo

diagnosed patent ductus arteriosus (PDA) was also noted. There were no differences in

these infants when controlling for medications compared to those infants who were not

on medications or had an active PDA. Four infants were excluded from the analysis after

data collection. One infant was LGA and three infants had missing data, so the final

sample included 156 patients.

From the infant's electronic medical record, all available weights were recorded

in the study database for days of life (DOL) 0, 3, 4, 5, 8, 9 and 10, and for the 3 days

prior to discharge. Demographic data were also obtained from the electronic medical record. In this NICU setting, weight is routinely obtained daily in the early morning hours between midnight and 6 a.m. using a standardized electronic neonatal scale. Daily weight is recorded by the nurse on the nursing flowsheet. LOS was calculated from date of birth to discharge date. Average weight gain/day from DOL 8 to discharge was calculated as the difference between discharge weight and weight on day 8 divided by length of hospitalization minus the first 7 days.

Statistical Analysis

The infant's weight on DOL8 was transformed to percent gain or loss from birth weight to test for correlations with GA, BW, LOS, average weight gain/day from DOL 8 to discharge, and magnitude of weight loss in the first week. Infants who were greater than or equal to 100% of birth weight on DOL 8 were compared to infants less than 100% of their BW on DOL8. Independent t-tests and Chi-square statistics were used to compare EUGR and non-EUGR infants. Two-way analysis of variance (ANOVA) was used to compare group differences by gender.

Results

Sample characteristics for the entire study cohort (n=156) and for the subset of VLBW infants (n=83) are listed in Table 1. Comparisons of EUGR and non-EUGR infants are provided in Table 2. For the entire sample, mean BW was 1466 ± 456g and mean GA was 30.5 ± 2.1 weeks. LOS was 51 ± 26 days. On DOL 8, 86 infants were below their BW and 70 were above their BW. Mean weight gain/day from DOL 8 to

discharge was 30.7 ± 7.2g. No significant difference in LOS or average weight gain/day after the first week of life was found for the entire sample or for the subset of VLBW infants.

For the 83 VLBW infants, mean GA was 29.3 ± 1.8 weeks and mean BW was 1116g ± 241g. Mean LOS was 67 ± 25 days. On DOL 8, 43 of these VLBW infants were below their BW and 40 were at or above their BW. Average weight gain from DOL 8 to discharge was 27.4 ± 6.1g.

Given the variability in birth weight, the percent change from their birth weight to DOL 8 was calculated and correlated with GA, BW, LOS, weight gain/day from DOL 8 to discharge, and magnitude of weight loss in the first week of life. Infants who were 100% or more of their birth weight on DOL 8 were compared to infants less than 100% of their BW on DOL 8. There was a significant negative correlation ($r = -.215$, $p = .008$) between percent weight change on DOL 8 and BW, indicating that infants with lower birth weights experienced a greater weight gain from birth to DOL 8. Weight gain/day from DOL 8 to hospital discharge was also significantly correlated with LOS ($r = -.449$, $p < 001$) and GA ($r = .438$, $p<.001$). Weight change at DOL 8, as a percentage of their birth weight was not associated with LOS for the entire sample or for the subsample of VLBW infants.

Small for gestational age (SGA) and EUGR are defined as either a weight, occipital frontal circumference (OFC), or body length that is <10th percentile for gestational age at birth and discharge, respectively (Clark, Thomas & Peabody, 2003). For the VLBW infants, 70% (n=58) had a BW that was average for gestational age (AGA) with growth parameters between the 10th and 90th percentile; 30% (n=25) were

SGA by weight and 31% (n=26) were SGA by OFC. For EUGR, 60% (n=50) of the VLBW infants were EUGR by weight at discharge and half (n=25) also had an OFC that was <10th percentile at discharge. This may indicate head sparing despite failed weight gain.

Independent sample t-tests were used to determine significant differences between EUGR and non-EUGR infants (see Table 2). A significant difference in BW (p = .001) and percent weight change in the first 8 days of life was demonstrated between EUGR and non-EUGR infants (p = .015). On average, EUGR infants were smaller at birth and gained weight in the first week of life while non-EUGR infants were larger at birth and lost weight during the first week. A significant difference was also found in daily weight gain from DOL 8 to discharge between EUGR infants (n=50) and non-EUGR infants (n=33); EUGR infants gained less (25.07 ± 5.73g/day) compared to non-EUGR infants (31.7 ± 4.3g/day) (t = 6.02, p≤.001). Other significant differences between EUGR and non-EUGR infants included gestational age (t = -2.98, p=.004), BW (t = 3.3, p = .001), and weight at discharge (t = 8.75, p <.001). There was no significant group difference in LOS or corrected gestational age (CGA) at discharge (See Table 2).

Two-way ANOVA was used to analyze differences between EUGR and non-EUGR infants based on gender. These analyses demonstrated no significant interaction between EUGR and gender on LOS (p=.15). There was, however, a significant main effect of gender on LOS (F(1,82) = 4.61, p=.035). LOS was also found to be significantly different between EUGR males (54 days ± 21 days) and EUGR females (69 days ± 29 days). Furthermore, EUGR males had significantly greater weight gain/day

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from DOL 8 to discharge than EUGR females (F(1,82)=6.6, p=.012). Males gained an average of 27 ± 6g/day compared to 23 ± 5g/day by females.

To investigate the association between SGA at birth and EUGR at discharge, Chi-square was used and found to be significant for the 83 VLBW infant group (Chi-square =19.1, p < .001). Of the 25 infants who were SGA at birth, 24 were EUGR at discharge. The one infant who was SGA at birth and AGA at discharge was a male born at 31 weeks gestation with both BW and OFC in the 3-9th percentile. He was 6% below BW on DOL 8, and his weight gain was 31.8g/d from birth to discharge and 37.9g/d from DOL 8 to discharge. Length of stay for this infant was 71 days and CGA at discharge was 40.14 weeks. Of the 58 VLBW infants who were AGA at birth, 26 (45%) were EUGR at discharge.

Discussion

This paper examined the influence of early weight gain or weight loss in the first week of a preterm infant's life and this effect on LOS. Analyses were run on the entire sample of 27 to 34 week infants (n=156) and then on a subgroup of 83 VLBW infants. Early weight gain or loss in the first 8 days of life did not affect LOS or subsequent weight gain/day for either group after controlling for initial BW. Our findings support clinical assumptions that weight loss in the first week of life is primarily due to fluid loss. Furthermore, the recognized nutritional deficiencies that occur concurrently with interstitial fluid losses following birth do not appear to affect LOS for the preterm infant. Weight loss in the first week of life did not affect later growth or length of hospitalization.

It was not unexpected that non-EUGR infants would experience greater weight gain/day than EUGR infants. However, an unexpected finding was that LOS and CGA did not differ between the groups in the face of significantly different daily weight gain. It seems reasonable that LOS would be extended in order to achieve adequate weight for discharge and therefore CGA at discharge would be older. It is possible that the significant difference in discharge weight between EUGR and non-EUGR infants could account for this. Discharge weight of non-EUGR infants was significantly higher than the discharge weight of EUGR infants and even higher than the usual weight criteria for discharge of 2 kg (Ehrenkranz, 2006). This difference may be reflective of EUGR infants remaining hospitalized until weight criteria are achieved and that non-EUGR infants remain hospitalized for reasons other than weight. Further information on hospital course and severity of illness would be useful in interpreting this finding.

The finding that EUGR infants experienced significantly less weight gain in the first week of life than non-EUGR infants could be accounted for by the significant differences in gestational age and BW between these groups. Free body water is known to be greater in infants of lower gestational age and birth weight. However, one would expect that this difference would also exist in non-EUGR infants. To understand the meaning of this finding and to determine the potential utility of early weight change as a potential indicator of EUGR, further exploration is warranted.

The gender difference in daily weight gain between EUGR and non-EUGR infants may be explained by the knowledge that male infants have higher weights at each gestational age (Thomas, Peabody, Tunier & Clark, 2000; de Zegher, Devieger, Eeckles, 1999). However, if this were the case, one would also expect to find greater weight gain

in non-EUGR males. It is also possible that this finding can be explained by the difference in GA between the EUGR and non-EUGR groups, as gender differences in weight are known to narrow in the third trimester of fetal growth (Karna, Brooks, Muttineni & Karamus, 2005). Further investigation of this finding is warranted in future research. If this finding is replicated in other studies, gender-specific expectations for weight gain may be more accurate for assessing and preventing EUGR.

One important finding was that approximately half of SGA infants recovered head growth, while more than 95% remained <10th percentile for weight at discharge. This reflects the preferential provision of nutrients to the brain in times of inadequate nutrition. This finding is consistent with other researchers. Berry Conrad & Usher (1997) found that 109 preterm infants <1000 grams and AGA at birth who were exclusively receiving parenteral nutrition, had head circumferences in a higher percentile than weight and length at 56 days of life. Head sparing, as a model of growth recovery, may be useful in future research. Because head circumference is better correlated with development than body weight, further investigation of infants who demonstrate greater head growth relative to an increase in body weight would be important to include in future study.

This study confirms the significant risk for failed extrauterine growth in SGA infants and underscores the importance of developing early interventions to promote growth in this vulnerable group. A larger study that identifies characteristics of SGA infants who experienced growth recovery might be particularly useful in developing such interventions.

Recognizing the limitations of the current study provides useful information for future research. In this sample, intermittent weights at the beginning and end of

hospitalization were collected. The utility of overall weight trend in identifying

contributors to EUGR is limited even when based on length of stay. Daily weights

throughout hospitalization would allow greater scrutiny of growth patterns and permit

precise timing of when the infant's weight falls below the 10th percentile. This

information, combined with greater detail about the infant's hospital course and severity

of illness, could be useful for identifying factors that precede failed growth. Furthermore,

identifying infants who fall below the 10th percentile and then recover to a higher

percentile might be useful for identifying factors that could support recovery from failed

growth. For this study, infants with factors known to affect weight gain were specifically

excluded. Future research that includes some of these factors such as severity of illness,

nutritional intake, accumulated caloric deficit and return to birth weight could lend clarity

to current findings and be useful for developing interventions during critical time periods

that may improve growth and prevent EUGR. It is possible that lesser known factors or

combinations of factors could be identified if more information regarding the infant's

hospital course were available for analysis.

Table 1. VLBW Sample Characteristics (means ± SD)

	Entire Sample (n=157)	VLBW <1500 grams (n=83)
Gestational age (weeks)	30.5 ± 3.1	29.3 ± 1.8
Birth weight (grams)	1466 ± 456	1116 ± 241

Weight on DOL 8
    Below birth weight
    At or above birth weight
	86 (55%)
	70
		43 (52%)
		40

Weight gain/day from DOL8 to discharge (grams)	31 ± 7	27 ± 6
Length of stay (days) range	51 ± 27 (13-157)	67 ± 25 (23-157)

Table 2. Comparison of EUGR and non-EUGR VLBW Infants

	EUGR (n=50) Male (n=22) Female (n=28)	Non-EUGR (n=33) Male (n=14) Female (n=19)	Statistical Tests
Birth weight (g) Male Female	1049 ± 622 1139 ± 212 979 ± 275	1218 ± 470 1245 ± 153 1198 ± 178	t = 3.60, df = 81, p = .001 t = 2.26, df = 48, p = .028
Gestational age (wks) Male Female	29.73 ± 1.92 ** 30.1 ± 1.9 29.5 ± 1.9	28.6 ± 1.2 ** 28.6 ± 1.3 28.6 ± 1.2	t = -2.98, df = 81, p = .004
Corrected gestational age discharge (wks) Male Female	38.65 ± 2.8 37.8 ± 2.0 39.3 ± 3.2	39.08 ± 2.4 39.0 ± 2.3 39.2 ± 2.7	
Length of Stay (days) Male Female	62 ± 27 54 ± 21* 69 ± 29*	73 ± 21 74 ± 23 73 ± 21	t = -2.1, df = 48, p = .042
Weight at discharge (g) Male Female	2284 ± 350** 2271 ± 362 2294 ± 346	3168 ± 571** 3074 ± 527 3295 ± 623	t = 8.8, df = 81, p <.001
Weight gain from birth to discharge (g/day) Male Female	20.43 ± 3.93 21.75 ± 4.11* 19.39 ± 3.52 *	26.70 ± 3.94 28.0 ± 4.1 26.0 ± 3.7	t = 5.96, df = 81, p< .001 t = 2.18, df = 48, p = .034 t = 1.35, df = 31, p = .187
Weight gain from DOL 8 discharge (g/day) Male Female	25.07 ± 5.73 27.21 ± 6.00* 23.38 ± 4.98*	31.70 ± 4.30 33 ± 4.5 31 ± 4.1	t = 6.09, df = 81, p < .001 t = 2.47, df = 48, p = .017 t = .634, df = 31, p=0.531

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Conclusion

Conclusions and Recommendations for Nursing and Further Research

The aim of the studies was to identify early and easily obtained clinical indices of development failures that otherwise first present after several weeks of life in the gross form of failure to gain weight. Heart rate and early weight loss were not predictive of growth or length of stay in preterm infants 27 to 34 weeks' gestation. While there are plausible biological theories behind each study, the study aimed to find correlates that could be used clinically and could drive conceptual advances in this area of research.

The unique and adverse conditions in which premature infants must grow is such that known growth factors may not apply. The last trimester of fetal development and first three months of neonatal life are a period of rapid somatic and neurologic growth for the human neonate. For preterm infants, this potentially critical period of accelerated growth is interrupted when the infant is forced into extrauterine existence before its organs and life-sustaining systems are properly developed. Furthermore, the preterm infant's hospital course is characterized by episodic crises. The initial critical period of transition from intrauterine to extrauterine environment may last for only a few hours, but the adaptation to extrauterine life may take several weeks to many months depending on individual characteristics and degree of prematurity. Following this initial transition, the preterm infant is vulnerable to other conditions such as infection, anemia, vitamin deficiency, and decreased bone mineralization. These diseases are considered consequences of prematurity as well as iatrogenic conditions that are a complication of prolonged hospitalization. Complications can occur at any time during the infant's

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hospitalization and often regress the infant's condition back to a state of instability. Thus, the premature infant's progression to a recuperative stage does not ensure continued well being or controlled care patterns that can facilitate adequate growth.

The current state of knowledge about EUGR is inadequate to form easily tested hypotheses. Lack of understanding of the specific sequence and interactions required for the rapid development that occurs in the last trimester of pregnancy and the ways in which these conditions interact with growth in a hostile environment, does not support traditional theory-driven research in this area. Given the complexity of the biological model for the preterm infant, it seems likely that similar data driven strategies are indicated in EUGR research in the future.

Optimizing data driven strategies involves a thorough understanding of the issues surrounding NICU research, and careful scrutiny of candidate factors observed in clinical experience that have not yet undergone the rigor of research that can determine cause and effect. Using clinical experience as a starting point at this stage in EUGR research ensures that clinically possible data collection and interventions are considered, and it informs the conceptual model with practical judgments about the state and interactions of the infant's biological systems.

Review of Papers

Paper 1: Limits in understanding EUGR

EUGR occurs when the infant fails to achieve adequate weight gain in extrauterine life despite the provision of established nutritional requirements. It is

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distinct from intrauterine growth restriction (IUGR) which occurs in utero and is most commonly caused by specific illnesses, genetic conditions or placental insufficiency. In this condition, the infant's weight is small for their gestational age at the time of birth. Conversely, EUGR infants have birth weights that are average for gestational age, so their growth failures occur after birth and during hospitalization (Clark et al., 2003; Garite, Clark & Thorpe, 2004). Research has shown that the majority of VLBW infants are effected by EUGR (Bertino et al., 2006, Lemons et al., 2001) and that EUGR is the most common morbidity among VLBW survivors (Clark et al., 2003; Garite, et al., 2004).

From a clinical perspective, inadequate weight gain may have appeared at first to be a benign consequence of prematurity, particularly since initial longitudinal studies demonstrated catch up growth on measures of weight and height.   However, more recent follow-up studies of VLBW and extremely low birth weight (ELBW ≤1000grams) infants have found that catch up growth in these smaller and less mature infants can continue throughout adolescence or may not occur at all. Hirata & Bosque (1998), in a prospective longitudinal trial, followed the growth of infants with birth weights < 1000 grams through adolescence. They found that mean, height, weight, and head circumference of these patients did not cross the 50th percentile for growth until adolescence at 12 to 18 years of age. A study by Cooke (2004) compared the adult height and weight of 79 former preterm infants to 71 controls who had been born at term at 19 to 22 years of age. The study found that adult males who had been born early had an average adult weight weighed 8.1 kg less and height that was 4cm shorter than control males. Females on average were 2.9 kg lighter and 8cm shorter.

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The causes of EUGR have not been explicitly delineated. Studies have identified both birth weight and nutrition as strong but not sufficient factors (Radmacher, Looney, Rafail & Adamkin, 2003; Clark, Thomas & Peabody, 2003). In one study, only 46% of the variance in weight in VLBW infants was explained by nutritional intake (Radmacher, et al., 2003). Many studies have shown that infants rarely receive recommended dietary intake resulting in accumulated caloric deficit. For most, this deficit was never caught up during their hospitalization (Embleton, Pange and Cooke, 2001; Clark, et al., 2003; Radmacher, et al., 2003), but a study of VLBW infants that expressly provided the required intake still resulted in a high incidence of EUGR (Clark, Wagner, et al., 2003).

Researching EUGR requires some care in study design. Longitudinal studies are required to identify and separate the causative factors. Comparison groups must be comparable, so using norms from larger or older infants is not appropriate.

Catch-up growth is a period of growth accelerated over the norm (either faster or normally accelerated period extending their duration into slower periods). Catch-up growth suggests that growth delays may be relatively benign if they are "erased" by periods of "catch-up". This concept motivates longitudinal studies to evaluate growth over the developmental lifetime. However, more useful measures of catch-up growth must be studied and demonstrated for each kind of growth (height, weight, head circumference, cognitive and social skills, etc.) for the real effect to be known.

The idea of caloric deficit has the opposite consequences. It suggests that undernourishment has cumulative effects over time and questions whether the deficit can ever be repaid. Further, it does not imply that increased nutrition will result in accelerated catch-up growth. Because of the strong association between caloric deficit

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and EUGR, clinicians can anticipate that failure to provide adequate nutrition will likely result in EUGR, (Berry, Abrahamowicz, & Usher, 1997).

These studies do not target more nuanced theories of growth. Nutrition is broken down into macro components of calories and protein or fat and carbohydrate, but not into micro components that might offer a finer resolution that can explain the individual effects of different types of nutrients. Catch-up growth is denominated in units of gross physical measure, but not neurological or systemic development. The studies do not discuss a relationship between sleep and growth, they do not offer a usable measure of metabolism for potential standardization, and they do not address the question of how premature infant metabolism affects nutritional uptake or growth rates. In many cases, research is prevented from more telling investigations by the practical limitations of the infant and the NICU.

Paper 2: Correlations between heart rate and later weight gain

Studies by deKlerk, et al. (1997) and by Ferber, Makhoul & Weller (2006) of preterm infants born at 31 to 36 weeks suggest that HR could be a prognostic indicator for weight gain. Our study attempted but failed to replicate that finding or to extend it to infants born between 27 and 31 weeks gestation. Although initial analysis indicated a significant difference in weight gain between infants with low HR and infants with high HR, once birth weight and gestational age were controlled for in the analyses, this relationship was no longer supported in any gestational age group.

Although the study findings were not significant, the biological basis for the study is interesting and worthy of consideration for future studies. It is a relatively novel

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concept and deserves further exploration. Weight gain has been shown to be enhanced by increased sympathetic activity (DiPietro & Porges, 1991; Harrison, Williams, Leper, Stem & Wang, 2000), and LOS was lower in infants who experienced an increase in cardiac vagal tone during gavage feeding (DiPietro and Porges, 1991). Elevated sympathetic function may increase vagal tone and improve gastric absorption through increased peristalsis (Diego, Field & Hernandez, 2005). Thus, identifying prognostic indicators of vagal tone and vagal activity could lend some clarity to our current understanding of preterm infant metabolism, as well as provide a useful clinical tool.

Failure to replicate the findings raises concern for differences in study procedures or population. The three studies differed in mean HR for the groups, but we could not correct for GA between studies because the data on individual subjects was not reported. HR may have differed because it was obtained using different instruments or in different "rest" states. Another difference between our study and the Ferber study was weight gain. However, the length of stay was longer for our group, which would produce some differences that we could not correct for lack of individual subject data in the Ferber group. Finally, we did not correct for caloric intake, a known factor in weight gain, except by attempting to avoid early confounders by starting the analysis at DOL 10, when clinical experience would suggest that caloric intake is more standard.

In summary, establishing and defining standardizing measurements and data reporting would be extremely useful in facilitate cross-study comparisons of slightly different study populations. Since many studies are retrospective chart reviews that cannot control the primary collection of data, reporting relevant details about the data collection techniques is an acceptable minimum standard.

Paper 3: Correlations between early weight gain and later weight gain and length of stay

A second study on the same sample population as paper 2 attempted to correlate early weight loss with LOS and later weight gain. The goal was to quantify two generally accepted clinical assessments. First, length of stay (LOS) in the hospital is considered an indicator of general health, with healthier infants being discharged earlier. For patients without confounding conditions and relatively constant growth pattern, LOS is also indicative of weight gain and velocity since many NICU's use weight as a primary factor for making discharge decisions. Second, early weight loss in the term infant is considered physiologic and is the result of infants utilizing excess interstitial fluid until maternal milk supply comes in at 3 to 5 days after delivery. It is unclear if this affects VLBW infants or whether the magnitude of loss in this early period affected subsequent weight trend. Furthermore, merely transferring this expectation to the preterm infant and interpreting it as physiologic when there is evidence that weight gain in VLBW infants is differs from that of larger infants might lead clinicians to ignore early weight loss when it could have different meaning in the VLBW population.

Results showed that weight loss in the first week of life does not appear to affect LOS or weight gain during hospitalization. Observed differences were explained by known factors (GA, birth weight). Results were similar for the subgroup of VLBW infants. This result allows NICU staff to assure parents that weight loss and magnitude of weight loss in the first few days does not appear to be a risk factor for the majority of preterm infants or affect the length of time it will take the infant to achieve adequate weight gain for discharge.

More generally, this result shows how clinical judgments can and should be tested in research. Such judgment can reveal or hide a relevant factor. Further, given the cost of prospective studies, it can be useful to validate the significance of data readily available in retrospective chart reviews even when it replicates results from other factors, because it can then be used to validate known measures.

In the subgroup of VLBW infants, EUGR and non-EUGR infants were compared. In this group, early weight loss was found to be significantly different. Infants who were EUGR tended to gain weight in the first week of life, whereas those who were not EUGR tended to lose weight in the first week. Gender differences in growth were also noted between the EUGR and non-EUGR infants. Future research is warranted to understand the significance of these findings as prognostic indicators of EUGR. Additionally, all infants who were small for gestational age at birth except one male patient, were EUGR at discharge. Larger studies that seek to identify infants who cross percentiles for growth during their hospitalization, could provide important information about successful growth patterns. Continuing to search for correlates to growth in VLBW preterm infants is imperative to reducing EUGR and its associated co-morbidities in this vulnerable population.

Final Comments

EUGR is an important problem because it affects a large proportion of the growing population of infants born prematurely. It is an interesting problem because it pertains not to illness or injury in a specific biological system but to the coordinated growth of all biological systems. It is a difficult problem because it takes place during

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one of the most accelerated periods of growth in human development, rendering baselines and comparisons transitory. It is a nursing problem because it is likely that some of the causative factors that remain to be identified may be related to nursing and environmental factors that nurses are well positioned to affect in their daily practice.

Nursing is pivotal to solving the problem of EUGR for two reasons. First, clinical observations form the starting-point for research, both in collecting data and in forming theories. Second, the end-point of the solution will likely take the form not of medication or invasive surgery, but of nursing and medical practices in nutrition and handling and other modifications to the NICU environment to create a less hostile environment to support premature infant growth and development. Research in this area must be responsive on both points to be effective.

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