Serial Assessment of Body Fat Accrual in Very Preterm Infants

Study Protocol

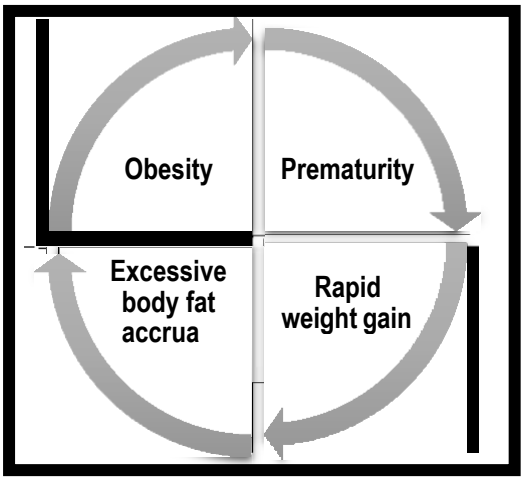
Lead Study Investigator(s):
Ariel A. Salas
University of Alabama at Birmingham

ClinicalTrials.gov number:
NCT03575897

Version date:
March 14, 2018

SPECIFIC AIMS

Figure 1. Prematurity & obesity: a perpetual cycle



With one of the highest rates of obesity[1] and one of the highest rates of prematurity (approximately 30% higher than the national average)[2], the state of Alabama suffers two problems of public health importance that disproportionately affect racial/ethnic minorities and increase health disparities in the United States. Obesity and prematurity are related **[Figure 1]**. Obesity is not only a risk factor for prematurity, but also an unanticipated consequence of prematurity in the increasing number of preterm infants that survive into adulthood. The use of high-calorie diets to improve neurodevelopment and prevent postnatal growth failure among preterm infants is associated with rapid weight gain and excessive body fat accrual**.** Metabolic reprogramming may play an important role in this long-lasting cycle. Although adults born at term and adults born preterm have a similar body mass index (BMI)[3], adults born preterm have higher blood pressure, more insulin resistance[4,5] and higher body fat accrual[4,5]. The higher body fat accrual found in adulthood has also been documented at term-equivalent age and during early infancy[6], a critical period for infant development during which high-calorie diets are frequently used to promote rapid weight gain.

Despite evidence that both rapid weight gain[7] and excessive body fat accrual[8] are associated with overweight and obesity, usual neonatal care for preterm infants does not include the assessment of body fat accrual. Similarly, screening programs to assess body composition in infants with a history of prematurity have not been established. By monitoring body fat accrual in preterm infants before and after hospital discharge, clinicians could modify dietary interventions in early infancy and prevent obesity and long-term related morbidities. In this pilot randomized trial, we will test the central hypothesis that very preterm infants (28 to 32 weeks of gestation as defined by the World Health Organization) managed using information from monthly serial assessments of infant body composition from birth to hospital discharge will have lower percent body fat (%BF) at 3 months of age than infants managed using standard care (weight and other routine growth parameters). %BF at 3 months of age has a strong correlation with %BF at 4 years of age[9]. Our long-term goal is to develop a comprehensive nutritional program that incorporates assessment of body composition in the routine care of preterm infants and reduces variability in feeding practices before and after hospital discharge to minimize the risk of obesity mediated by rapid weight gain.

Specific Aim 1: To test the hypothesis that provision of serial body fat accrual reports during hospitalization will enable personalized dietary interventions and reduce adiposity at 3 months of age in very preterm infants. We chose %BF at 3 months of age as the primary outcome of the trial because at this age: 1) body fat accrual can be measured with non-invasive methods[10]; 2) loss to follow-up rates are low[9]; 3) physical activity and other risk factors for obesity are less likely[7]; and 4) correlation with body fat accrual at preschool age is strong[9]. We selected very preterm infants as the ideal population to study the risk of obesity in preterm infants because they: 1) experience a high risk for adverse health outcomes[3,5]; 2) usually do not require supplemental oxygen after postnatal day 7; and 3) receive strictly controlled diets for more than 30 days from birth to hospital discharge. With our improved understanding of the interaction between infant weight, body fat accrual, and dietary interventions, we plan to examine whether the provision of body fat accrual reports to clinicians and parents will impact infant weight gain and body fat accrual[11].

Specific Aim 2: To test the hypothesis that serial assessment of infant body composition attenuates health disparities in body fat accrual at 3 months of age by slowing weight gain following hospital discharge. The rationale for this aim is: 1) rapid weight gain during early infancy is highly prevalent among racial/ethnic minorities[12,13]; and 2) adjustment for rapid weight gain attenuates disparities in childhood obesity between racial/ethnic minorities and white infants[7,12]. We hypothesize that our intervention focused on personalized dietary interventions based on changes in infant body composition will reduce rapid weight gain and attenuate health disparities in body fat accrual.

RESEARCH STRATEGY

SIGNIFICANCE

Rapid weight gain increases the risk of metabolic reprogramming in preterm infants. For many years, the high prevalence of postnatal growth failure (weight below the 10th percentile for expected intrauterine growth) in the preterm population made weight the most important outcome of growth among preterm infants. Similarly, the association between rapid weight gain and improved neurodevelopment led clinicians to assume that slow weight gain was "inadequate growth" and that high-calorie diets to promote rapid weight gain were needed.

Available clinical evidence no longer supports these assumptions. Current dietary interventions have not appreciably reduced postnatal growth failure. Postnatal growth failure remains prevalent and occurs in approximately 60%[14-16] of the nearly 80,000 infants born preterm at 32 weeks of gestation or less every year in the United States[2]. Similarly, the benefits of rapid weight gain on neurodevelopment of preterm infants have not been consistently demonstrated. While 19 observational studies of low to moderate quality have associated rapid weight gain with improved neurodevelopmental outcomes[17], 3 randomized trials of hospital-based nutritional interventions that reversed postnatal growth failure through rapid weight gain did not show benefits in neurodevelopment[18-20]. These inconsistencies between results from randomized trials and results from low to moderate quality observational studies suggest the presence of unmeasured confounding factors that affect both growth and cognition[17] and demand caution with the assumption that promoting brain development through rapid weight gain outweighs the risk of potential long-term metabolic dysfunction.

Rapid weight gain also known as catch-up growth could trigger changes in metabolic reprogramming. Results from interventional and observational studies indicate that high-calorie diets before and after hospital discharge to promote catch-up growth and prevent postnatal growth failure among preterm infants[21] may result in hypertension, insulin resistance[22], and disproportionate increase of body fat[17,23], particularly when carbohydrates and fat are the primary source of energy. This clinical evidence of metabolic dysfunction resulting from rapid weight gain has been demonstrated in humans and animal models. Clinical studies consistently show that growth-restricted preterm infants are more likely to experience catch-up growth[15,24] and corroborate conclusions from animal experiments that reveal an increased susceptibility to early metabolic reprogramming of adverse health outcomes in developing infants exposed to high-calorie diets[17,25,26]. In rats and mice with growth restriction as a result of poor maternal diet, rapid growth due to high-calorie diets increases susceptibility to obesity and reduces longevity[27,28]. The mechanisms of early metabolic reprogramming include permanent changes in organ structure due to suboptimal nutrition, epigenetic modifications that lead to changes in gene expression, and permanent effects on regulation of cellular aging[25].

Assessment of infant body composition offers important advantages over BMI as outcome of growth. BMI and infant body composition are outcomes of growth associated with long-term health. BMI is a widely accepted anthropometric index that is used to define obesity, but in early infancy, BMI has poor predictive accuracy for obesity and poor correlation with body fat accrual. In term infants, BMI only explains up to 43% of the variation in fat mass (FM)[29,30]. Furthermore, reduction of infant BMI to prevent obesity in adulthood is not currently recommended because high infant BMI values are associated with greater lean mass[31]. Body fat accrual during early infancy is a marker of fetal adaption and metabolic reprogramming that has a significant association with obesity and other adverse health outcomes[32]. Rapid weight gain is associated with higher risk of %BF, abnormal fat distribution, and overweight at school age[8,33].

Air-displacement plethysmography (PeaPod®, Life Measurement Instruments, Concord, CA) is one the less invasive and more accurate methods to assess infant body composition in early infancy[32,34] Using air-displacement plethysmography, several studies have determined reference values of neonatal body fat accrual at different gestational ages[6,10]. At birth, body fat accrual expressed as %BF ranges from 6% at 30 weeks of gestation to 9.5% at 37 weeks of gestation.[10] At term-equivalent age, all preterm infants have significantly higher %BF than infants born at term (up to 6% higher when measured by air-displacement plethysmography)[29], irrespective of history of intrauterine growth restriction[35].

While studies that assessed infant body composition with either dual energy X-ray absorptiometry or bioelectrical impedance analysis suggest that fat free mass (FFM) can be predicted using weight data[36], studies that assessed infant body composition with air-displacement plethysmography, a method with high accuracy and validity when compared to the gold standard carcass analysis[32], suggest an unreliable correlation between anthropometric data and neonatal adiposity[37] and body composition[30] in preterm infants.

Body fat accrual at 3 months of age predicts infant body composition at 4 years of age. Unlike body composition at term-equivalent age, body composition at 3 months of age has a strong correlation with body composition at 4 years of age in infants born preterm[9]. Large observational studies suggest that differences in body composition between term and preterm infants persist into adulthood[4,5], but the implications of early alterations of growth and body composition are largely unknown despite evidence that early rapid weight gain and body fat accrual are determinants of later obesity risk in full-term and preterm infants[5,38-40]. Taken together, these data suggest that early changes in body composition following hospital discharge could be an important outcome of growth to analyze long-term health risks of rapid weight gain and body fat accrual during early development. Serial monitoring of body composition during infancy may allow nutritional support optimization that balances neurodevelopmental benefit and metabolic risk[9].

Slow weight gain after hospital discharge attenuates the risk of obesity among racial/ethnic minorities. Observational studies show that obesity and rapid weight gain in early infancy are more prevalent among blacks and Hispanics than among whites and that differences in feeding practices (breastfeeding rates, early introduction of complimentary foods and others) contribute to these disparities in infant weight gain and obesity[12,13]. Adjustment for these early risk factors related to infant feeding attenuates disparities in childhood obesity between minority and white infants[7,12]; therefore, it is plausible that, by providing more specific information about early changes in body composition instead of using an anthropometric index, clinicians and parents may alter their feeding regimens before and after hospital discharge in a manner that will reduce the risk for unhealthy gains in adiposity. Modifications of these early risk factors could have a substantial impact on preventing disparities in childhood obesity[12].

INNOVATION

Despite clinicians' ability to effectively control all external sources of nutrition in the immediate neonatal period, current dietary interventions and methods to assess postnatal growth have not led to significant improvement in growth and neurodevelopment. Comprehensive evaluation of postnatal growth with infant body composition is essential to guide appropriate and effective nutritional interventions for infants at high risk of obesity.

The incorporation of a longitudinal assessment of infant body composition into current practices of neonatal care is innovative because it will provide a more sensitive index of the infant's body habitus and thereby guide clinician decisions about dietary interventions. This change in practice could reduce the risk of overweight and obesity in very preterm infants.

Serial assessment of infant body composition using air-displacement plethysmography, a validated method with reliable accuracy, to report body fat accrual in a randomized clinical trial is also one of the novel aspects of our proposal, as other research studies have used low-accuracy methods to estimate infant body composition[6].

APPROACH

Our central hypothesis is that very preterm infants managed using information from serial assessments of infant body composition during their initial hospitalization will have lower percent body fat ($^{\%}$BF) at 3 months of age, irrespective of sex and race/ethnicity.

Specific Aim 1 will test the hypothesis that, after establishing a program to monitor infant body composition before and after hospital discharge, identification of changes in body fat accrual will prompt individualized recommendations for dietary interventions that reduce $^{\%}$BF at 3 months of age in very preterm infants.

Overview: Aim 1 will be a pilot randomized trial in which 50 very preterm infants will be randomly assigned in a 1:1 allocation ratio to either routine neonatal care (control group) or neonatal care with serial assessments of infant body composition (intervention group). The primary outcome will be %BF at 3 months of age **[Table 1]**.

Table 1. Project timeline

Critical steps	Month											
	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May
Anticipated IRB approval (protocol & consent form)												
Patient screening and enrollment												
Body fat assessment at 3 months of age												
Primary & secondary data analyses												
Results available for manuscript preparation												

Rationale: While weight, the key element of the operational definition of postnatal growth failure, remains useful to assess nutritional status, its limitations as the only method to assess nutritional status and health risks[41] should not be ignored. The assumed benefit of catch-up growth on neurodevelopment should be weighed against the possibility that catch-up growth might cause harm and increase the risk of adult-onset metabolic disease[24,26,42]. Because infant weight gain predicts later obesity risk[43], central adiposity[44] and insulin resistance[45], more research is needed to define the best strategies to provide adequate nutrition with a goal of preventing growth failure without increasing health risks of public health importance. The problem of increased adiposity soon after birth and into adulthood among preterm infants suggests that assessment of body fat accrual along with weight gain could be an effective strategy to achieve the goal of ideal growth while preventing unnecessary health risk. As defining the risk for abnormal cardiovascular and metabolic outcomes in this population has become critically important[46], it is possible that early detection of atypical changes in infant body composition characterized by excessive body fat accrual could prompt changes in dietary interventions to reduce the risk of obesity, cardiovascular disease, and metabolic syndrome later in life.

Study design

Setting: The neonatal unit at UAB is one of the largest neonatal academic centers in the United States. We have admitted more than 200 very preterm infants over the past 2 years. This large numbers of very preterm infants admitted makes our unit the ideal environment to conduct comparative effectiveness trials.

Participants: Very preterm infants with gestational ages between 28 and 32 weeks of gestation at the time of admission to our neonatal unit will be eligible for this trial. Gastrointestinal or neurologic malformations, and terminal illness requiring limited or withheld support will be exclusion criteria.

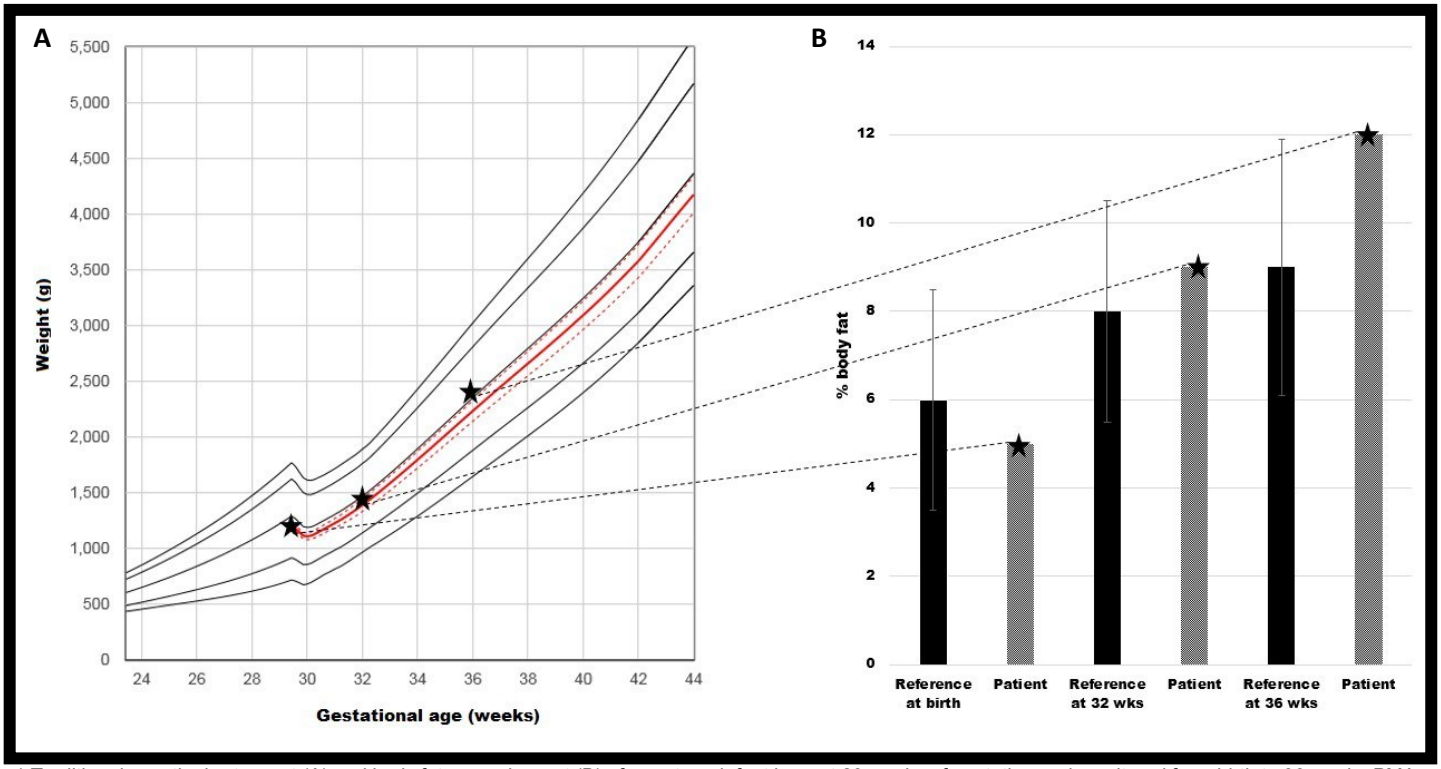
Randomization, allocation concealment, and masking: After receiving approval by the Institutional Review Board (IRB) at UAB to conduct this trial, research nurses and investigators will obtain written parental consent before randomization. We will randomize study participants using computer generated random-block sequences and numbered, opaque, sealed envelopes that will be opened in sequential order. Twin infants will be randomized individually. The intervention will not be masked.

Intervention: Infants randomly assigned to the intervention group will have the information about infant body composition known to the clinicians caring for them (including reference data). The use of this patient-specific information about nutritional status will assist clinicians to optimize nutrition using feeding guidelines that will be provided. Infants randomly assigned to the control group will also undergo serial measurements of body composition, but this information will not be available to the clinicians.

Primary and secondary outcomes: The primary outcome will be %BF estimated by air displacement plethysmography at 3 months of age. Secondary outcomes will include %BF and fat-free mass (FFM) at 36 weeks of postmenstrual age (PMA) or hospital discharge (whichever occurs first), postnatal growth restriction (below 10th percentile) at 36 weeks PMA or discharge, weight gain (g/kg/d) from birth to the end of the intervention, anthropometric measures at time of hospital discharge (weight, head circumference, and length), weight gain (g/kg/d) from hospital discharge to 3 months of age, anthropometric measures at 3 months of age (weight, head circumference, and length), and blood pressure values at 3 months of age.

Assessment of infant body composition: Serial assessments of infant body composition with air displacement plethysmography in very preterm infants using the PeaPod® (Life Measurement Instruments, Concord, CA)[32] will occur in the first 14 days after birth (baseline measure), at 32 weeks PMA, at 36 weeks PMA or hospital discharge (whichever occurs first), and at 3 months of age **[Figure 2]**. The PeaPod® and the neonatal unit are located in the same building. During hospitalization, nursery staff and parents, if present, will transport the infant to the exam room where the PeaPod® is located. In the exam room, nursery staff will undress the infant, place the snug cap, and transfer the infant to the PeaPod® when ready for weighing and scanning. The infant will wear only a cap on his/her head and will lie inside the scanner for approximately 2-3 minutes to estimate total fat and fat-free mass according to body weight and volume[47]. The infant will breathe the normal air in the room and will be able to see and hear his/her parents. Equipment for respiratory support or monitoring will not be used during the assessment to avoid unnecessary recalibration of the PeaPod®. For assessment of body composition at 3 months of age, a follow-up visit will be scheduled prior to discharge from the hospital. The 3-month visit will also include a brief questionnaire about feeding practices at home and blood pressure measurements. The study coordinator will mail a reminder letter approximately 2 weeks prior to the date of the visit and will call the caregiver to remind them on the day prior to their scheduled appointment. Infants and a caregiver will return to the hospital to repeat the body composition assessment. A trained technician from the Nutrition Obesity Research Center (which owns and manages the PeaPod®) will operate it.

Figure 2. Serial assessment of body fat accrual in very preterm infants*



* Traditional growth chart report (A) and body fat accrual report (B) of a preterm infant born at 29 weeks of gestation and monitored from birth to 36 weeks PMA

Control or monitoring of co-interventions: Clinical care and decisions about enteral nutrition will be conducted at the discretion of the attending physician.

Study specimens. Because several experiments suggest that changes in gut microbiota can influence obesity[48], we will obtain written informed consent from the parent(s) to collect 2 stool samples, 1 stool sample before hospital discharge and 1 stool sample at the 3-month follow-up visit for possible use in future studies. Similarly, consent from the parent(s) will be obtained to collect a serum sample and measure biomarkers of anabolism and growth prior to hospital discharge.

Statistical Analysis Plan. This trial will record core data on nutrition as recommended by consensus groups[49]. For analysis of the primary outcome, an unadjusted T-test comparison of the mean %BF between control and intervention groups will be performed assuming a normal distribution of this variable[50]. In consideration of relevant biological variables, a pre-specified adjusted analysis for demographic and nutritional characteristics will be conducted to improve precision in treatment comparisons and remove variability associated with these covariates[51,52]. A similar approach will be used for secondary outcomes. Descriptive data will be expressed as the mean (SD) or number (percentage) of observations. The primary statistical analyses will be performed on an intention-to-treat basis[49] with SAS software.

Sample Size and Power Estimates. At our institution, the mean and SD of %BF in preterm infants at time of discharge is 15 and 3.6, respectively (unpublished data). Therefore, to detect a 3-point difference in %BF between groups with SD of 3.6, 0.05 level of significance, and 80% power for a T-test that compares means from two independent samples, a sample size of 46 patients will be necessary in this superiority trial. Anticipating that approximately 10% of study participants will be lost to follow-up for assessment of the primary outcome at 3 months of age, 2 patients will be added to each group and the sample size will be increased to 50. We will include a total of 25 patients in each group (n=50).

Potential Problems

Enrollment rates: An average of 7 study participants per month were enrolled in a recently completed trial that assessed body composition of very preterm infants at our institution (unpublished data). To define a timeline for patient enrollment in this trial, we assumed that 50% of parents will refuse participation.

Sample size: A negative outcome (i.e. %BF) was selected as the primary efficacy end point of this trial. We used our own institutional data to calculate the sample size for this trial and estimated that a 3% absolute difference was clinically meaningful because the average difference between term and preterm infants is 3%.[6]

Follow-up: We estimated that follow-up rates at 3 months of age will be higher than our follow-up rates at 2 years of age for extremely preterm infants (approximately 80% at our institution). Follow-up at 3 months of age to assess infant body composition will allow comparison of our results with reference data in term infants.

Generalizability: Given the pilot nature of this trial, we will focus on minimizing systematic errors in the trial to improve accuracy of our results and increase internal validity. It is expected that the precision of our estimates and the external validity of our results will be affected by our small sample size.

Specific Aim 2 will test the hypothesis that serial assessment of infant body composition slows weight gain following hospital discharge and attenuates health disparities in body fat accrual at 3 months of age.

Overview and preliminary data: Aim 2 will be a secondary analysis of our pilot randomized trial. In a prospective study of body composition, we corroborated that racial/ethnic minorities have higher in-hospital growth rates than white infants (unpublished data).

Inclusion criteria, exclusion criteria, and outcome: Demographic and nutritional data from infants who participated in the pilot trial will be used for this analysis. Infants with missing follow-up data will be excluded. %BF at 3 months of age will be the dependent variable in the primary analysis.

Statistical analysis: In this analysis, race/ethnicity will be entered as a dichotomous variable: white (reference group) and black or Hispanic. To examine the association between weight gain at 2 different time points (before and after hospital discharge) and body fat accrual at 3 months of age within each racial/ethnic group, we will use multivariable regression models. Subsequently, to quantify the degree to which weight gain explains racial/ethnic disparities in body fat accrual, we will employ a decomposition analysis which will help us determine if changes in weight gain after serial monitoring of body fat accrual reduces differences (i.e. observed and predicted) in body fat accrual between minority and white infants[7].

HUMAN SUBJECTS

RISKS TO HUMAN SUBJECTS

Human Subjects' Involvement, Characteristics, and Design. This is non-exempt human subjects research.

Characteristics of participants: Our study population will reflect the epidemiology of prematurity in the state of Alabama, with approximately 56% being Black (African-American), 41% White (Non-Hispanic Caucasian), and the remaining 4% Hispanic/Other. This study population has been selected based on the frequency of nutritional problems observed at these gestational ages and the increased risk of adverse health outcomes in this vulnerable population.

Sampling plan, recruitment, and retention. Patients admitted to the neonatal unit of UAB from June 2018 to January 2019 will be screened to determine eligibility for the study. Because the protocol is designed to establish a new hospital-based practice early in life, mothers will be approached by the research staff before eligible very preterm infants reach full enteral feeding.

Sources of Materials

For study participants, data will be collected from electronic medical records. Data containing identifying information will be available only to the PI (Dr. Ariel A. Salas) and research personnel directly involved with this study. Information about the study will be shared without individual identifiers. Data will be collected from medical records in accordance with the study protocol. This will include demographic data and other nutrition/feeding data.

Potential Risks

Potential risks: The probability of risk for higher $^{\%}$BF in a patient that participates in this trial is not different than the probability of higher $^{\%}$BF in a patient that does not participate in the trial[53]. Other theoretical risks of this study are related to clinical decompensation during assessment of infant body composition. They include increased risk of bradycardia or desaturations. Previous studies, including ours (unpublished data), have not reported an association between assessment of infant body composition and any of the above-mentioned risks. Infants may experience some transient discomfort during the PeaPod® assessment which requires them to wear a tight-fitting cap but no other clothing or blanket. Therefore, there are no known risks associated with this trial except loss of confidentiality, as it involves data collection.

Breach of confidentiality: The main potential risk of this study is breach of confidentiality. This is one of the most common risks of participation in clinical research. Accordingly, our team has designed a strategy to protect participant confidentiality. All participants will be informed of study procedures and gauged for understanding of study tasks. In addition, study personnel will follow regulatory guidelines for obtaining informed consent.

Alternative treatments and procedures: Participants in the intervention and control groups will have full access to all available standard of care clinical services at our neonatal unit, and parents are permitted to withdraw or refuse participation at any time.

Adequacy of Protection against Risks

Recruitment and Informed Consent

Recruitment: When a potential participant is identified, a member of the study will see the parents and/or mother in her room or the baby's room and explain the study. The risks and benefits will be discussed with the parents and time will be given to them to ask questions. It will be made known to them that no treatment will be withheld from their child if they participate in the study.

Informed consent: The research team will attempt to obtain written consent after giving the parents a minimum of 24 hours to think about the study information and ask questions. Randomization will define study group assignment

Study Monitoring Plan. This protocol will be reviewed by the IRB at UAB. Serious adverse events including severe clinical deterioration after assessment of infant body composition will be reported to the principal investigator. Moderate to major complications, defined for the purpose of this trial as events requiring immediate medical attention and/or interventions due to worsening clinical status, will also trigger a notification to the principal investigator. In previous studies that assessed infant body composition in stable preterm

infants, including ours (unpublished data), serious adverse events including bradycardia, desaturations, hypothermia, sepsis, or death were not reported. No interim analyses are planned.

Protections against Risk. Our team will make every effort to protect all participants' confidential and private information in order to minimize possible study-associated risks. All findings related to any research will be available and provided to study participants in accordance with standard practices. We will also inform all participants that their participation is voluntary, and we will utilize study identification codes in place of personal identifiers on study materials. We will also employ storage and encryption techniques in compliance with UAB Data Security standards to safeguard all electronic data, as well as protections outlined in Subpart C of title 45, part 4 Code of Federal Regulations. All study personnel are required to renew Human Subjects training biannually. No data will be accepted from or distributed to the principal investigator or study staff if regulatory training is not current.

Any provider or caregiver involved in the trial will be able to write to the study coordinator to draw attention to any concern they may have about the possibility of harm arising from the intervention under investigation.

Potential Benefits of the Proposed Research to Human Subjects and Others

Potential benefits of this study are to provide stronger evidence for the safety and efficacy of monitoring body fat accrual as a way of optimizing caloric intake, growth, and fat-free mass in preterm infants. Better quantitative and qualitative outcomes of growth may also be associated with improved long-term neurodevelopmental outcomes.

The potential benefits of this research may include reduction of postnatal growth restriction, reduction in infant morbidity mediated through improved neonatal nutrition, and better growth at time of discharge. Reductions of postnatal growth restriction and improved nutritional parameters could improve long-term neurodevelopmental outcomes of infants. There will be benefit to the medical community in providing additional information on infant body composition in preterm infants.

Importance of the Knowledge to be Gained

As the risk to individual participants is small and potential benefits are significant, the risk/benefit ratio is favorable.

ClinicalTrials.gov Requirements

A description of this randomized trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify participants. The submission for review and approval of the proposed research by an IRB will be initiated after peer review of the research protocol. Certification of IRB approval will be sent to the Office of Sponsored Programs. Education in the protection of human research participants will be required for all research team members involved in this trial. Our data sharing plan will protect the rights and confidentiality of participants.

Inclusion of Children and Minorities

Inclusion of Minorities. Selection of participants for inclusion in the study will be completely independent of ethnicity or race.

Inclusion of Children. Children have been selected as the study population based on the frequency of nutritional problems observed at these gestational ages and the increased risk of postnatal growth restriction in this vulnerable population.

REFERENCES

1. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity Among Adults and Youth: United States, 2015-2016. NCHS Data Brief 2017:1-8.
2. Hamilton BE, Martin JA, Osterman MJ. Births: Preliminary Data for 2015. Natl Vital Stat Rep 2016;65:1-15.
3. Parkinson JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the metabolic syndrome in adult life: a systematic review and meta-analysis. Pediatrics 2013;131:e1240-63.
4. Raju TNK, Buist AS, Blaisdell CJ, Moxey-Mims M, Saigal S. Adults born preterm: a review of general health and system-specific outcomes. Acta Paediatr 2017;106:1409-37.
5. Morrison KM, Ramsingh L, Gunn E, et al. Cardiometabolic Health in Adults Born Premature With Extremely Low Birth Weight. Pediatrics 2016;138.
6. Johnson MJ, Wootton SA, Leaf AA, Jackson AA. Preterm birth and body composition at term equivalent age: a systematic review and meta-analysis. Pediatrics 2012;130:e640-9.
7. Isong IA, Rao SR, Bind MA, Avendano M, Kawachi I, Richmond TK. Racial and Ethnic Disparities in Early Childhood Obesity. Pediatrics 2018;141.
8. Karaolis-Danckert N, Buyken AE, Bolzenius K, Perim de Faria C, Lentze MJ, Kroke A. Rapid growth among term children whose birth weight was appropriate for gestational age has a longer lasting effect on body fat percentage than on body mass index. Am J Clin Nutr 2006;84:1449-55.
9. Scheurer JM, Zhang L, Gray HL, Weir K, Demerath EW, Ramel SE. Body Composition Trajectories From Infancy to Preschool in Children Born Premature Versus Full-term. J Pediatr Gastroenterol Nutr 2017;64:e147-e53.
10. Demerath EW, Johnson W, Davern BA, et al. New body composition reference charts for preterm infants. Am J Clin Nutr 2017;105:70-7.
11. Harrison M, Brodribb W, Davies PSW, Hepworth J. Impact of Maternal Infant Weight Perception on Infant Feeding and Dietary Intake. Matern Child Health J 2018.
12. Taveras EM, Gillman MW, Kleinman KP, Rich-Edwards JW, Rifas-Shiman SL. Reducing racial/ethnic disparities in childhood obesity: the role of early life risk factors. JAMA Pediatr 2013;167:731-8.
13. Tester JM, Phan TT, Tucker JM, et al. Characteristics of Children 2 to 5 Years of Age With Severe Obesity. Pediatrics 2018.
14. Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a serious problem in prematurely born neonates. Pediatrics 2003;111:986-90.
15. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006;117:1253-61.
16. Navarrete CT, Wrage LA, Carlo WA, et al. Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth. J Pediatr 2016;176:62-8 e4.
17. Ong KK, Kennedy K, Castaneda-Gutierrez E, et al. Postnatal growth in preterm infants and later health outcomes: a systematic review. Acta Paediatr 2015;104:974-86.
18. Biasini A, Marvulli L, Neri E, China M, Stella M, Monti F. Growth and neurological outcome in ELBW preterms fed with human milk and extra-protein supplementation as routine practice: do we need further evidence? J Matern Fetal Neonatal Med 2012;25 Suppl 4:72-4.
19. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. BMJ 1998;317:1481-7.
20. Lucas A, Morley R, Cole TJ, Gore SM. A randomised multicentre study of human milk versus formula and later development in preterm infants. Arch Dis Child Fetal Neonatal Ed 1994;70:F141-6.
21. Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics 2001;107:270-3.
22. Bayman E, Drake AJ, Piyasena C. Prematurity and programming of cardiovascular disease risk: a future challenge for public health? Arch Dis Child Fetal Neonatal Ed 2014;99:F510-4.
23. Kashyap S, Ohira-Kist K, Abildskov K, et al. Effects of quality of energy intake on growth and metabolic response of enterally fed low-birth-weight infants. Pediatr Res 2001;50:390-7.
24. Martin CR, Brown YF, Ehrenkranz RA, et al. Nutritional practices and growth velocity in the first month of life in extremely premature infants. Pediatrics 2009;124:649-57.
25. Tarry-Adkins JL, Ozanne SE. Mechanisms of early life programming: current knowledge and future directions. Am J Clin Nutr 2011;94:1765S-71S.

26. Wiedmeier JE, Joss-Moore LA, Lane RH, Neu J. Early postnatal nutrition and programming of the preterm neonate. Nutr Rev 2011;69:76-82.
27. Jennings BJ, Ozanne SE, Dorling MW, Hales CN. Early growth determines longevity in male rats and may be related to telomere shortening in the kidney. FEBS Lett 1999;448:4-8.
28. Ozanne SE, Hales CN. Lifespan: catch-up growth and obesity in male mice. Nature 2004;427:411-2.
29. De Cunto A, Paviotti G, Ronfani L, et al. Can body mass index accurately predict adiposity in newborns? Arch Dis Child Fetal Neonatal Ed 2014;99:F238-9.
30. Ramel SE, Zhang L, Misra S, Anderson CG, Demerath EW. Do anthropometric measures accurately reflect body composition in preterm infants? Pediatr Obes 2017;12 Suppl 1:72-7.
31. Johnson W, Choh AC, Lee M, Towne B, Czerwinski SA, Demerath EW. Is infant body mass index associated with adulthood body composition trajectories? An exploratory analysis. Pediatr Obes 2017;12:10-8.
32. Demerath EW, Fields DA. Body composition assessment in the infant. Am J Hum Biol 2014;26:291-304.
33. Kruithof CJ, Gishti O, Hofman A, Gaillard R, Jaddoe VW. Infant weight growth velocity patterns and general and abdominal adiposity in school-age children. The Generation R Study. Eur J Clin Nutr 2016;70:1144-50.
34. Ellis KJ, Yao M, Shypailo RJ, Urlando A, Wong WW, Heird WC. Body-composition assessment in infancy: air-displacement plethysmography compared with a reference 4-compartment model. Am J Clin Nutr 2007;85:90-5.
35. Lee W, Riggs T, Koo W, Deter RL, Yeo L, Romero R. The relationship of newborn adiposity to fetal growth outcome based on birth weight or the modified neonatal growth assessment score. J Matern Fetal Neonatal Med 2012;25:1933-40.
36. Dung NQ, Fusch G, Armbrust S, Jochum F, Fusch C. Body composition of preterm infants measured during the first months of life: bioelectrical impedance provides insignificant additional information compared to anthropometry alone. Eur J Pediatr 2007;166:215-22.
37. Kiger JR, Taylor SN, Wagner CL, Finch C, Katikaneni L. Preterm infant body composition cannot be accurately determined by weight and length. J Neonatal Perinatal Med 2016.
38. Young BE, Johnson SL, Krebs NF. Biological determinants linking infant weight gain and child obesity: current knowledge and future directions. Adv Nutr 2012;3:675-86.
39. Euser AM, Finken MJ, Keijzer-Veen MG, et al. Associations between prenatal and infancy weight gain and BMI, fat mass, and fat distribution in young adulthood: a prospective cohort study in males and females born very preterm. Am J Clin Nutr 2005;81:480-7.
40. Kerkhof GF, Willemsen RH, Leunissen RW, Breukhoven PE, Hokken-Koelega AC. Health profile of young adults born preterm: negative effects of rapid weight gain in early life. J Clin Endocrinol Metab 2012;97:4498-506.
41. Heymsfield SB, Stevens J. Anthropometry: continued refinements and new developments of an ancient method. Am J Clin Nutr 2017;105:1-2.
42. Rochow N, Raja P, Liu K, et al. Physiological adjustment to postnatal growth trajectories in healthy preterm infants. Pediatr Res 2016;79:870-9.
43. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. BMJ 2000;320:967-71.
44. Demerath EW, Choh AC, Czerwinski SA, et al. Genetic and environmental influences on infant weight and weight change: the Fels Longitudinal Study. Am J Hum Biol 2007;19:692-702.
45. Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. Lancet 2003;361:1089-97.
46. Lapillonne A, Griffin IJ. Feeding preterm infants today for later metabolic and cardiovascular outcomes. J Pediatr 2013;162:S7-16.
47. Fields DA, Gunatilake R, Kalaitzoglou E. Air displacement plethysmography: cradle to grave. Nutr Clin Pract 2015;30:219-26.
48. Komaroff AL. The Microbiome and Risk for Obesity and Diabetes. JAMA 2017;317:355-6.
49. Koletzko B, Fewtrell M, Gibson R, et al. Core data necessary for reporting clinical trials on nutrition in infancy. Ann Nutr Metab 2015;66:31-5.
50. Gianni ML, Roggero P, Liotto N, et al. Body composition in late preterm infants according to percentile at birth. Pediatr Res 2016;79:710-5.

51. Huang P, Zhou J, Yin Y, Jing W, Luo B, Wang J. Effects of breast-feeding compared with formula-feeding on preterm infant body composition: a systematic review and meta-analysis. Br J Nutr 2016;116:132-41.
52. Atkinson SA, Randall-Simpson J. Factors influencing body composition of premature infants at term-adjusted age. Ann N Y Acad Sci 2000;904:393-9.
53. Lantos JD, Spertus JA. The concept of risk in comparative-effectiveness research. N Engl J Med 2014;371:2129-30.