IRB #: IRB19-00200
Date Approved: 6/18/2019
Expiration Date: 6/16/2020 11:59 PM

TITLE**: Targeted fortification of human breast milk and adjustment of Total Parenteral Nutrition (TPN) for Very Low Birth Weight infants to optimize growth and nutrition using the Miris Human Milk Analyzer**

Introduction

You and your baby are being asked to participate in this research study of human breast milk content and the growth of premature infants. Before you can decide whether or not to volunteer for this study, you must be informed of the purpose of the research study, how this study may help you and your baby, if there are any risks to you and your baby, and what is expected of you and your baby. This process is called informed consent.

You and your baby do not have to participate in this study. You and your baby may stop your participation in this study at any time without changing your current or future relations with MetroHealth Medical Center or its doctors.

If you decide to participate in this study you will be told about any new information learned during the course of the study that might cause you to change your mind about staying in the study. If you and your baby withdraw, we will still provide you with information regarding possible impacts to your health status or future health care decisions.

Mothers of premature infants are being asked to participate in this study so that the nutritional composition of human breast milk can be studied to improve premature infant growth and nutrition. You and your baby are being asked to participate because you are providing expressed breast milk (the breast milk that is collected by using a breast pump and stored for feeding your baby), or you consented to donor breast milk for your baby who has been admitted to the Neonatal Intensive Care Unit (NICU) and weighs less than 3.3 pounds.

Why is this study being done?

The purpose of this study is to compare the growth and body composition of preterm infants on TPN (total parenteral nutrition, an IV form of nutrition) and breast milk, comparing TPN and breast milk adjusted and fortified (in which extra calories and nutrients are added) in the standard way, compared to preterm infants whose IV nutrition is adjusted and breast milk fortification based on the results of breast milk analysis to meet the baby's specific nutritional needs.

You are encouraged to express breast milk for your baby in the NICU because it is the best form of nutrition that we can feed your preterm infant. Previous studies have shown that the composition of breast milk varies from person to person and within each mother over a period of time. Preterm infants

HUMAN INVESTIGATION CONSENT FORM

HUMAN INVESTIGATION CONSENT FORM

IRB #: IRB19-00200
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have higher nutritional needs than larger babies born full term. When we adjust the IV nutrition (TPN and lipids) and fortify breast milk we assume the breast milk has a certain nutritional value without testing it. The standard way of fortifying breast milk in the NICU is to add a standard amount of commercial human milk fortifier base to the assumed nutritional value of the breast milk in order to give more nutrients to the baby. This study aims to show that it is better for the baby to measure the nutritional value of the breast milk first and then decide how to adjust the content of the IV nutrition and how much to fortify the breast milk, instead of always adjusting IV nutrition in the standard way and adding the standard amount of fortifier to breast milk.

A total of 60 mother and baby couples at MetroHealth will be enrolled in the study.

What is involved in the study?

If you and your infant meet all the necessary criteria, and you choose to participate, your infant will receive breast milk and it will be fortified when your baby's doctor decides it is time. Initially, until preterm babies are ready to coordinate their feeding, breast milk is given through a tube inserted into the stomach through the mouth or nose, which is the routine practice in the NICU regardless of whether you and your baby enroll in the study. One group of babies will receive IV nutrition and breast milk fortified the standard way (standard fortification group), assuming uniform composition of breast milk. The other group (targeted fortification group) will receive IV nutrition and breast milk that is adjusted and fortified based on the measured nutritional value of the breast milk that was analyzed by the Miris Human Milk Analyzer. Your infant will be randomly assigned by chance (like the flip of coin) to either the standard fortification group or the targeted fortification group. Your infant will have an equal chance of being assigned to either group. This is called randomization.

The duration of the study will be from the time of consent and enrollment in the study, until 4 weeks after achieving full feeds by mouth. This time frame depends on the size of your baby at birth, and will range from 6-12 weeks.

Study procedures

Human milk is the preferred feeding for all infants, including premature and low birth weight infants. In this study you will be asked to come to the NICU as often as you can. You will have access to a breast pump in the NICU, and also will be assisted in obtaining a breast pump to have at home. You will be given containers to store your breast milk in, in the refrigerator at home, and be asked to bring it to the NICU when you visit your baby, where it will be stored for feeding your baby in the future.

IRB #: IRB19-00200
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Once a week, you will be asked to give the study staff a 24 hour collection of your breast milk for testing. Only one tablespoon of milk will be removed for testing, and the remainder will be stored for later use to feed your baby.

In both groups the milk will be analyzed once a week in the lab at MetroHealth, using the Miris Human Milk Analyzer, which will tell us the nutrients in your breast milk.

If your baby is assigned by randomization to the targeted fortification group, the IV nutrition will be optimized and adjusted based on milk analysis to provide a goal of 4 g/kg/day of protein and 100-130 calories/kg/day. Once your baby's doctor decides it is time to fortify your milk, it will be fortified to meet your baby's nutritional requirements using commercially available nutritional products intended for preterm infants in the NICU, with additional liquid protein fortifier to increase protein intake and microlipids (fat) to increase caloric density if needed. If you do not have enough breast milk and you consent, we will use donor breast milk to feed your baby. If we use donor milk, we will analyze the donor milk and fortify it in the same way. The use of donor milk is a routine practice for feeding premature and low birth weight infants.

If your baby is assigned by randomization to the standard fortification group, the IV nutrition will be adjusted in the standard way per NICU guidelines and your milk will be fortified in the standard way. These are the nutritional guidelines that we follow for all babies in the NICU at MetroHealth.

Information about your baby's nutritional intake and growth will be collected from the medical chart. Your baby's involvement in the study will be during his/her routine medical care in the NICU. He/she will have growth measurements assessed weekly. Your baby will have routine blood work as part of his/her NICU stay and will not receive any additional needle sticks or blood draws due to participation in the study.

Toward the end of the hospital stay, your baby's body composition will be measured to look at the amount of fat and muscle mass in his/her body. This is done in the research unit, which is on the same floor and down the hall from the NICU. Your baby will be taken to the research unit in an open crib one hour before a feed is scheduled. They will be placed on a warmer, and vital signs (including heart rate, breathing, and oxygen levels) will be monitored, just like they are in the NICU. They will be placed in the PeaPod, which looks like an incubator, but is connected to a special computer which measures fat and muscle. Your baby will be accompanied by medical staff and will be visible at all times to the doctors and nurses performing this test. The PeaPod test takes about 2-3 minutes to complete, and the entire procedure including transport takes about twenty minutes to complete. Your baby will then be taken back to the NICU in time for the next feed.

Your baby will not stay in the hospital any longer for the purpose of this study.

IRB #: IRB19-00200
Date Approved: 6/18/2019
Expiration Date: 6/16/2020 11:59 PM

What happens if I discontinue or withdraw from the study?

If you decided to withdraw yourself and your baby from the study we will still provide you with information regarding possible impacts to your baby's health status or future health care decisions.

Your baby might be withdrawn from the study if he/she does not tolerate the fortification, which may be represented by excessive vomiting, otherwise unexplained abdominal distention, or blood in the stool. Also, if at any time during the study your baby's clinical status significantly worsens he/she may be withdrawn from the study. This may be in case where your baby has worsening respiratory status requiring higher ventilator support, develops a severe infection, or has concerning abdominal symptoms (distention, blood in stool, significant vomiting). If at any time during the study your baby is unable to receive breast milk feedings he/she may also be withdrawn from the study.

What are the risks of this study?

Babies in the targeted fortification group may be given extra protein and fat. There is a slight risk of feeding intolerance. Your baby's doctor will assess feeding tolerance no matter which group your baby is in and will change the fortification plan as necessary. Sometimes a higher protein intake can lead to elevated BUN (Blood Urea Nitrogen) levels in the blood, which is routinely monitored during the NICU stay. Your baby will not require additional blood draws than necessary just because he/she is enrolled in the study. Babies will be taken out of the NICU for the Clinical Research Unit for a body composition measurement, but this is only done when they are ready to go home and able to maintain their temperature in an open crib. This is the standard of care in the NICU and will be done regardless of participation in the study. There may also be additional unforeseen risks of participating in the study and receiving the intervention.

Another risk of participating in this study is breach of confidentiality. We will make every effort to keep your research records private, but confidentiality cannot be assured. The data collected in this study will be deidentified (removal of personal information that is specific to you) and stored in a secure place and only the study investigators will have access to it.

Are there benefits to taking part in the study?

Your baby may or may not benefit from participation in this study. Your baby may experience better growth, health, neuro-developmental outcome, and decreased susceptibility to infections.

We hope the information learned from this study will benefit other premature infants' growth and nutrition in the future.

What other options are there?

HUMAN INVESTIGATION CONSENT FORM

HUMAN INVESTIGATION CONSENT FORM

IRB #: IRB19-00200
Date Approved: 6/18/2019
Expiration Date: 6/16/2020 11:59 PM

This is a research study. You and your baby may decide not to participate and instead your baby will be given breast milk with standard fortification as is the current practice and standard of care in the NICU.

What are the costs?

There is no cost to you or your insurance company for participation in this study.

What happens if I am injured while participating in this study?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If such problems occur during the course of the study, you must contact your study doctor, Dr. Sharon Groh-Wargo at (216) 778-5600. Necessary medical care will be provided to you by The MetroHealth System. The MetroHealth System has not set aside funds to pay you for any such reactions or injuries or for the related medical care. This medical care is not free. You and/or your insurance company will be responsible for the costs. However, you can still try to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research, including the hospital.

Will I be paid for participating in this study?

You and your baby will not be paid or compensated for your participation in this study.

HIPAA:

If you give permission, Stacey Ramey, MD, Sharon Groh Wargo, PhD, RDN, LD, Stephanie Merlino, MS, RDN, LD, and research staff members under their guidance will collect the following Protected Health Information (PHI) from you and your baby for this study: name, medical record number, telephone number, your baby's date of birth, date of admission, and discharge date. We will also collect your baby's measurements including weight, length, head circumference, and mid upper arm circumference or flank skin fold at birth, periodically throughout the hospital stay, and at discharge. We will also collect the total calorie, protein, and lipid intake of your baby and collect results of blood tests. At discharge we will collect the body composition data. We will also collect your breast milk analysis data.

PHI will be deidentified using a code and a key to this will be stored in REDCap (Research Electronic Data Capture) which is a secure, web application designed to support data capture for research studies. It was developed by a multi-institutional consortium which includes The MetroHealth Medical Center and was initiated at Vanderbilt University. The deidentified data will be collected in a secure

HUMAN INVESTIGATION CONSENT FORM

HUMAN INVESTIGATION CONSENT FORM

IRB #: IRB19-00200
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Expiration Date: 6/16/2020 11:59 PM

computer drive of MetroHealth Medical Center which will only be accessible to the study investigators by password access.

MetroHealth is required by law to protect you and your baby's health information. By signing this document, you authorize MetroHealth to use and/or disclose (release) your and your baby's health information for this research.

The study investigators will have access to your PHI until data analysis is complete, after which the PHI will be destroyed. The study file will be kept for 22 years after study completion, at which time it too will be destroyed. You have the right to withdraw your permission/authorization for us to access your PHI at any time except to the extent the PHI already collected by the investigators before your withdrawal has already been acted upon based on your signed Authorization. No new PHI about you or your baby will be collected for study purposes unless required by law.

Existing information or information created during you and your baby's participation in this study will be made available by The MetroHealth System.

What about Confidentiality?

We will make every effort to keep your research records private, but confidentiality cannot be assured. The milk sample collected for this study will be identified by a unique identification number. The milk will be analyzed in the lab at MetroHealth. Only the study investigators will have the key for the identification numbers.

Records that identify you and your baby and this consent form may be looked at by a regulatory agency such as:

The Food and Drug Administration (FDA)
Department of Health and Human Services agencies
MetroHealth Institutional Review Board
National Committee for Quality Assurance

If the results of the study are published or presented in public, neither your name nor your baby's name will be used.

What are my rights as a study participant?

By signing this consent form, you are not waiving any of your or your baby's legal rights. Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you and your baby do not

HUMAN INVESTIGATION CONSENT FORM

HUMAN INVESTIGATION CONSENT FORM

IRB #: IRB19-00200
Date Approved: 6/18/2019
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take part in the study, your doctor will still take care of you and your baby. You and your baby will not lose any benefits or medical care to which you are entitled. If you and your baby withdraw from the study, with your written permission, clinical data will continue to be collected from your medical records.

If you chose to take part, you have the right to stop at any time. You will be told of any new findings from this or other studies that may affect your health, welfare, or willingness to stay in this study.

If you are an employee or student, whether or not you take part in this study will not affect your job, current or future medical care, or studies.

Does MetroHealth or any member of the research team have a financial conflict of interest in this study?

No, MetroHealth and study team members do not have a financial conflict of interest in this study.

Whom do I call if I have questions or problems?

If you have questions about any part of the study now or in the future, or if you wish to communicate concerns or a complaint you should contact Dr. Stacey Ramey, who may be reached at (216) 778-5600. If you have any questions about your rights as a research participant, or if you wish to express any concerns or complaints please contact the MetroHealth Medical Center's Institutional Review Board (which is a group of people who review the research to protect your rights) at (216) 778-2021.

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Patient/Subject Acknowledgement:

The procedures, purposes, known discomforts and risks, possible benefits to me, my baby, and to others, and the availability of alternative procedures regarding this research study have been explained to me. I have read this consent form or it has been read to me, and I have been given the opportunity to ask questions or request clarifications for anything I do not understand. I voluntarily agree to participate and allow my baby to participate in this study. I have been given a copy of this consent form.

_____	_____	_____
Print baby's name	Date	Time
_____	_____	_____
Patient/Subject Signature	Date	Time
_____	_____	_____
Signature of authorized person if Parent is a minor	Date	Time
_____	_____	_____
Signature of Person Obtaining Informed Consent	Date	Time