Effect of donor human milk on severe infections and mortality in VLBW infants, a double blind randomized controlled trial

Published: 04-01-2012
Last updated: 19-03-2025

To determine whether (supplemental) human donor milk has beneficial effects (in terms of reduction of infectious episodes and mortality) when compared to (supplemental) preterm formula during the first 10 days of life in VLBW infants. Amendement ESS...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal infections
Study type	Interventional

Summary

ID

NL-OMON39540

Source
ToetsingOnline

Brief title
Early nutrition study

Condition

- Gastrointestinal infections
- Bacterial infectious disorders
- Food intolerance syndromes

Synonym
infections

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Academisch Medisch Centrum;Amsterdam

Intervention

Keyword: human donor milk, Human milk bank, nutrition, Very low birth weight infants

Outcome measures

Primary outcome

- Combined incidence of serious infections/NEC and death.

Amendement ESS:

- Bone density as determined by DXA at term corrected age for infants from VUmc

and the UMCN.

Amendement Adrenocortical funtion:

- Production and metabolism of cortisol at ages 10 and 30 days, in infants in

VUmc.

- Physiological responses (hart rate, saturation and respiratory rate)

following a 35 dB stimulus (ALGO test), in infants from VUmc.

Amendement Body Composition:

- Body composition at corrected age of 1, 2 and 5 years measured with air

displacement plethysmography (ADP) en deuterium dilusion in infants from VUmc

and AMC.

- Relation between the timing of introduction and the composition of

complementary feeding and body composition.

Secondary outcome

- Composition of fecal microbiota

- Time to full enteral feeding

- Days on TPN

- Growth rate during admission (comparable to infants fed preterm formula) and at corrected age of 2 years

- Bone density comparable to infants fed preterm formula, by ultra sound (in sub group)

- Cognitive, motor and language development at 2 years of corrected age (Bayley Scales of Infant Development III test, BSID III)

Amendement ESS:

- An improved bone mineral content (BMC) measured by SOS (ultrasound) measurement during admission and at term corrected age

- An incidence of feeding intolerance comparable to infants who receive late supplementation

- Earlier attainment of full enteral feeding (defined as an intake of >=150 ml/kg/day)

- Improved mineral homeostasis

- Reduced number of days on TPN (lipids and amino acids)

- Improved growth rate until term corrected age compared late supplementation

To determine whether higher amounts of parenterally administered minerals (standard regimen at the RUNMC) results in a increased BMC compared to a lower

amount (standard TPN regimen at the VUmc).

Amendement Adrenocortical Function:

- Cortisol (in urine) at 2 years of age in infants from VUmc.

Amendement Body Composition:

- Relation between the timing of introduction and the composition of

complementary feeding and the development of allergic diseases.

Study description

Background summary

Lack of enteral nutrition results in intestinal atrophy potentially causing increased bacterial translocation, thereby making VLBW infants more prone to sepsis. According to current feeding protocols in NICU*s, minimal enteral feeding is initiated within 6 hours after birth. After premature delivery the onset of lactation is often delayed and therefore VLBW infants are often being fed with preterm formula during the first few days of life. Feeding VLBW infants with own mother*s milk is to be preferred because it reduces the incidence of sepsis and NEC. When own mother*s milk is not available during this period, donor milk might be of benefit to these infants when compared to formula. We hypothesize that feeding VLBW infants with a diet that is completely based on human milk during the first 10 days of life will result in a decrease in the incidence of serious infections, necrotizing enterocolitis (NEC), and neonatal mortality.

Amendement ESS:
Both donor milk and milk of the own mother do not contain enough minerals for a proper bone mineralization. Extra minerals are added to the milk by using "breast milk fortifier" (BMF). BMF is not added to the milk directly after birth: it is assumed that milk with BMF is tolerated less well by premature infants. On the other hand: if administration of BMF is delayed too long, bone mineralization will be impaired. It iscurrently unknown what is the optimal timing to add BMF to breast milk: there are no large randomized controlled trials on this subject. Therefore the moment at which BMF is administered for the first time differs substantially between the Dutch NICU's. Since a few

years infants in the RUNMC (Nijmegen) receive BMF as soon as they're able to tolerate 50 ml of enteral nutrition per day, on average on day 4 - 5 of life ("early supplementation"). Infants that participate in the Early Nutrition Study receive BMF from the 10th of life onwards ("late supplementation"). In this amendement the effects of both these regimens are evaluated.

Amendement Adrenocortical Function:
Preterm birth has been associated with increased risks of neonatal mortality and adverse neurodevelopment, particularly in boys. Giving breast milk to preterm infants seems to be associated with improvements in neurodevelopment and cardiovascular parameters, again particularly in males. Among the candidate mechanisms that may underlie these sex-specific associations are variations in the adrenocortical function. Adrenocortical insufficiency is common in the early neonatal course of preterm infants and is followed by a rapid adaptation of the hypothalamus-pituitary-adrenal (HPA) axis by the end of the second week, with the largest improvement in adrenocortical function being observed in ill preterm infants.
Infants that participate in the Early Nutrition Study receive either donor milk or formula as a complement to own mother's milk. This makes it possible to assess a difference in production and metabolism of cortisol between infants that are fed with human milk only and infants that are partly fed with formula.

Amendement Body Composition:
Premature infants have less lean tissue with a similar fat mass at term equivalent age. The mechanisms responsible for this difference in body composition are likely to be multifactorial. The pattern of body composition is in part a consequence of the nutrition that preterm infants receive the first period of life. We hypothesis that a diet completely consisting of human milk during the first period of life have a beneficial effect on body composition in preterm infants. Infants that participate in the Early Nutrition Study receive either donor milk or formula as a complement to own mother's milk. This makes it possible to assess a difference in body composition between infants that are fed with human milk only and infants that are partly fed with formula.
Introduction of complementary foods is an important dietary change and associated with major modifications in both macronutrient and micronutrient intake. It is relevant to consider whether complementary feeding influences the risk of obesity. Not only the composition but also timing of introduction of complementary foods seems to have effect on long-term health. Infants who received complementary foods before 15 weeks of life are heavier and their percentage of body fat is greater at 7 years of age compared to those given complementary feeding at 15 weeks or later. The long-term consequences of early introduction of complementary feeding and their effect on body composition and development of allergic diseases in preterm infants are unknown. In this study these consequences and effects will be determined.

Study objective

To determine whether (supplemental) human donor milk has beneficial effects (in terms of reduction of infectious episodes and mortality) when compared to (supplemental) preterm formula during the first 10 days of life in VLBW infants.

Amendement ESS:
Evaluating the effect of "early" (day 4-5) administration of BMF or "late" administration of BMF (day 10 of life) on bone mineralization and feeding tolerance.

Amendement Adrenocortical Function:
To determine whether the production and metabolism of cortisol differs between infants fed with a completely human milk based diet compared to infants (partly) fed with formula and to assess whether this difference is sex-related.

Amendement Body Composition:
To determine whether body composition of infants with a completely human milk based diet differs from that of infants (partly) fed with formula.
Additionally, to determine whether the timing of introduction and the composition of complementary feeding is related to body composition and the development of allergic diseases.

Study design

Double blind randomized controlled trial. The Early Supplementation Study (the add-on study intended to be performed in the UMCN) is a unblinded study.

Intervention

If own mother*s milk is not available in sufficient amounts, the intervention group (group A) will receive additional donor milk and the placebo group (group B) will receive additional standard preterm formula. Donor milk and formula therefore serve as *add-on* therapy to own mother*s milk.

Amendement ESS:
No intervention. Infants from the RUNMC can be randomized to participate in group C. This group will receive nutrition according to standard feeding protocol in use at the RUNMC. The differance with the other participents from the ENS is that group C will receive BMF as soon as they tolerate 50 ml of enteral nutrition per day.

Amendement Adrenocortical function:
No additional intervention.

Amendement Body Composition:
No additional intervention.

Study burden and risks

The parameters used as endpoints (incidence of infection, morbidity, feeding tolerance) are routinely assessed as part of standard care. For the determination of fecal microbiota, stool samples will be collected from the diaper. This is of no burden to the infant.
Administration of banked pasteurized human donor milk to VLWB infants has been proven to be safe in respect to transmission of infectious disease. Quantity of macronutrients will be guaranteed by near-infrared analysis of each milk sample. The benefits of feeding children with their own mothers* milk are clearly documented in literature. There are various reasons to hypothesize that pasteurized donor milk exhibits similar effects. Therefore it is possible that infants fed with donor milk will benefit from this intervention.

Amendement ESS:
To determine the bone density participants of the RUNMC and VUmc will be subjected to a DXA scan at term corrected age. For this scan infants will be placed on the scanning table (comparable to a Xray investigation) after they have received nutrition. Usually the infants will fall asleep and will not notice the research. The duration of the DXA scan is less then 15 minutes.
In the RUNMC Speed of Sound (ultrasound) measurements will be performed 7 times to monitor bone mineralization. This procedure is not painful and will be performed after routine nursing procedure so infants will not be disturbed/ woken up. In the VUmc SOS measurements are part of routine care.
Infants admitted to the NICU of the RUNMC will be subjected to a kidney ultrasound to check for nephrocalcinosis. This procedure is not painful.

Amendement Adrenocortical Function:
At the age of 10 days, 30 days and 2 years urine cortisol will be measured. Urine will be collected by absorbating gazes in the diaper. This is non-invasive and not painful. The ALGO screening, as well as the non-invasive monitoring of heart rate, respiratory rate, and transcutaneous saturation, are part of standard care.

Amendement Body Composition:
At the age of 1,2 and 5 years body composition will be measured by using air displacement plethysmography (ADP) systems: Pea Pod and Bod Pod and by using Deuterium Dilution.
Measurements with Pea Pod and Bod Pod are non-invasive, not painfull and take less than 10 minutes. Infants will be placed on the scanning table (< 2 years of age) or on a chair (>2 years of age) and can move freely.
The use of Deuterium Dilution is save and non-invasive. Stable isotopes are non-radioactive, not detrimental and are already naturally present in the human body in small amounts. An amount of 3 ml / kilogram body weight of 2H2O will be administered orally. Saliva samples can be easily collected by swabbing a dry cotton rod in the child*s mouth for 2-5 minutes.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

birth weight < 1500 gram

Exclusion criteria

- Child of mother that abused drugs and/or alcohol during pregnancy
- Major congenital anomalies or birth defects
- Suspected congenital infection
- Perinatal asphyxia with (umbilical or first neonatal) pH < 7.0
- Intake of any cow*s milk based products prior to randomization

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-03-2012
Enrollment:	396
Type:	Actual

Ethics review

Approved WMO Date:	04-01-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2014
Application type:	Amendment

Review commission: METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 24223
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL37296.029.11
OMON	NL-OMON24223