Parental information: supplementation with probiotics and the effect of growth and health outcomes in extremely preterm infants

Do you want to participate in a study that investigates how supplementation with probiotics affects extremely preterm infants?

Infants born extremely preterm (below 28 weeks' gestational age) are vulnerable and at risk for complications. One of the most serious complications is inflammation of the intestine called necrotizing enterocolitis (NEC). How can we reduce the risk of this complication? We want to investigate this question in a randomized intervention study where half of the children receive probiotics (good intestinal bacteria) and half receive no probiotics/placebo to best measure the effect of probiotics.

Research Principal: Region Stockholm

Why probiotics?

Large scale studies have investigated probiotic supplementation and its effect on preterm infants. In some of these studies, reduced incidence of necrotizing enterocolitis has been seen. However, these studies did not include enough infants born before 28 weeks' gestational age to be able to say with certainty that probiotic supplements have a beneficial effect on extremely preterm infants as well. Due to this, probiotic supplementation recommendations in Sweden only extend to infants born after 28 weeks' gestational age. This differs from other European countries, where extremely preterm infants are also given probiotics. The product used in this study is called ProPrems and is a combination of three different bacterial cultures. European guidelines for preterm nutrition consider this product safe, and the study product is currently being given to children born over 28 weeks' gestational age.

Who can participate?

All infants born between gestational 22+0 to 27+6, who do not have any congenital disease or malformation may participate.

How does the study work?

Infants must be included in the study within 72 hours after birth. After parents have given written consent, the infant is randomized to either the intervention or control group. In the intervention group, the infant will receive the probiotic product, ProPrems, once a day from when the infant tolerates 3 mL breastmilk per meal until the child has passed 34 weeks' gestational age. The probiotics are mixed with the mother's breastmilk or donated breastmilk. In the control group, the infant will receive 3 mills of breastmilk without probiotics.

The study is double-blinded, which means neither the parents nor the research, medical, and nursing personnel know which group the infant has been randomized to. Only the assistant nurses working in the nutritional kitchen who prepare breastmilk for infants will be aware of what the infant receives. This blinded, randomized study with a control group is considered the highest quality of study to provide the best, unbiased statistic data. Thus, this study provides the greatest opportunity to determine whether probiotics reduce the risk of NEC.

The analysis of results will not be carried out until the last participant has been included and the intervention has ended. The study is registered based, which means that data collection will be made from the Swedish Neonatal Quality Register (SNQ). Some basic, necessary information that SNQ does not collect will be obtained from medical records.

As we are interested in whether good intestinal bacteria affect the intestinal function and immune system, a small subgroup analysis of stool will be conducted. If your child is included in this analysis, stool samples will be collected after inclusion, at 2 weeks of age, 34 weeks gestational age, and 12 months correlated age. The samples will be taken directly from the children's diaper. Collected samples will be frozen and transferred to Karolinska Institutets biobank for storage and future analysis. Otherwise, no extra sampling in addition to the clinic's routines will be carried out. The infants included in the study will, in addition to receiving breastmilk with or without the study product and stool samples, not be treated differently than children who are not included in the study.

Insurance and compensation

No compensation for participation will be issued. Patients' social health insurance applies to infants in this study, as with all other care during hospital admission.

Voluntary participation

The participation is voluntary, and you can choose to withdraw your child's participation without giving a reason at any time. If you choose not to participate or interrupt your child's study participation, it will not affect your child's continued care and treatment.

Are there any risks with probiotics?

European guidelines developed by the European Society for Paediatric Gastroenterology Hepatology and Nutrition have assessed the product as safe, even for extremely premature infants. The product is already being used in infants born after 28 weeks' gestational age in Sweden.

Handling of personal data and study results

No unauthorized people will have access to personal data and those with access are bound by professional secrecy. The Department of Neonatology at Karolinska University Hospital is responsible for your child's personal data. You can contact the data protection agency at Karolinska University Hospital if you have any questions (karolinska.dataskyddsombud@regionstockholm.se). According to the EU's General Data Protection Regulation (GDPR), you have the right to access your child's information handled in the study, and if necessary, correct any errors. You can request that data be deleted and that the processing of personal data be restricted. However, the right to delete and restrict the processing of personal data does not apply when the data is necessary for the research in question. If you want information about the processed data, you must contact the principal researcher. If you are not content with how personal data is processed, you have the right to submit a complaint to Swedish Authority for Privacy Protection, which works as supervisory authority.

At inclusion, the participants will receive a study ID. This code will be used instead of the infant's social security number. This also applies to any stool samples that will be frozen in a biobank at each hospital and then moved to Karolinska Institutet for future analysis. The analysis and publishing of the results will be at a group level so that no individuals can be traced.

What happens to my samples?

If your child is selected to undergo stool sampling, the samples taken will be coded in a so-called biobank. The biobank's name is IVOnr-914 and it is available at Karolinska University Hospital. The research principal for the biobank is Region Stockholm.

All aforementioned tests will be coded (pseudonymized), which means that they cannot be linked directly to your child. The code key is stored in ME Neonatology, Karolinska University Hospital, Eugeniavägen 27, Norrbacka, S3:03, 171 76 Stockholm,. No unauthorized people can access it.

You have the right to say no to the samples being saved without explanation. If you consent to the samples being saved, you have the right to withdraw consent later and without explanation. Your samples will then be discarded or de-identified. If you wish to withdraw consent, please contact Alexander Rakow, 08-517735 03, ME Neonatology, Karolinska University Hospital, Eugeniavägen 27, Norrbacka, S3:03, 171 76 Stockholm,

The samples may only be used in the manner for which you have given consent. If you agree that we may retain and use your samples for future purposes, you must specifically consent to this. If additional research analysis is added that is not yet planned for, the Ethical Review Authority will decide whether you should be asked for consent again.

Information about the study result

The results will be published in scientific journals. Parents of the participants can receive information about the by contacting the principal researcher.

Responsible for the study

Principal Investigator	Study coordinator
Alexander Rakow	Sofia Söderquist Kruth / Emma Persad
Phone: 08-517 735 03	Phone: 08-517 797 45
S3:03 Norrbacka Eugeniavägen 27 SOLNA	Q2:05 Karolinska vägen 37 SOLNA

Head of Department
Lars Navér
ME Neonatologi S3:03 Norrbacka Eugeniavägen 27 SOLNA