Antenatal breastmilk expression from 34 weeks of gestation.

Safety in pregnancy and benefits for the newborn infant: protocol for a pilot randomized study

The EXPRESSMOM Study

Background

The World Health organization (WHO) recommend exclusive breastfeeding to 6 month of age, and for up to 2 years of age along with introduction to solid foods (1). According to their data, only 38% of all children aged 0-6 months are exclusively breastfed. The 2025 goal for WHO is to increase the rate of exclusively breastfed infants aged 0-6 month to at least 50%. In Denmark, only 16.9% of infants are exclusively breastfed at 6 months, although between 97 – 99.5% initiate breastfeeding right after birth (2, 3).

Mother's own milk (MOM) is the best feeding option for all newborn infants, including those born preterm. Besides being a source of macronutrient nutrition, MOM is also a source of vitamins, minerals and bioactive components, such as growth factors, immunoglobulins, lactoferrin, antioxidants and cytokines. These bioactive components contribute, among others, to activate the immune system, maturate the infant intestine and promote neurodevelopment (4). In addition, breastfeeding has benefits for both mother and infant. Breastfed children have a reduced risk for various diseases later in life e.g. cardiovascular and metabolic diseases and obesity (5-7). Furthermore, women who breastfeed seem to have a reduced risk for breast- and ovarian cancer, osteoporosis as well as diabetes later in life (7).

MOM is complex and changes throughout the lactation period and by that adapt to the current need of the infant (8). The first milk, colostrum, is very valuable and contains a high amount of fat, protein and bioactive components, important for the infant, compared to mature milk, which primarily content is carbohydrates. If MOM is not available right after preterm birth, the infant receives donor human milk (DHM) or infant formula (IF) depending on gestational age. Mothers who deliver preterm often have a delayed onset of lactation (9), and they do not produce enough MOM until several days after delivery. Therefore, the primary source for enteral feeding for the preterm infants the first days of life will be DHM. DHM is mature milk, and contains lower amounts of protein, fat and bioactive components.

We know that receiving MOM as primary enteral feeding is critical for preterm infants with regard to gut health (4), lowering risk of infections and improve neurological development, both during infancy and later in life (10), but the mothers are often struggling with breastfeeding establishment in the Neonatal Intensive Care Unit (NICU) due to environmental factors, stress and maternal disease or blood loss related birth.

A study from 2015 showed that if mothers of preterm born infants less than 32 weeks of gestation starts to express milk within an hour after delivery, they produce nearly twice the amount of milk during the first week after delivery compared to mothers who initiate breastmilk expression 1-6 hours after birth (11). The difference in milk volumes were also statistically significant in week 3 and 6 after delivery, although the

number of lactating women declines. Despite the low number of participants in the study, this indicates that early expression can enhance milk production and maybe accelerate the onset of lactogenesis.

Within the last couple of years, a rising interest is seen in expression and storage of breastmilk before birth (antenatal breastmilk expression = aBME), to ensure an exclusive mother's milk diet and enhance the process of lactogenesis. It has been a general concern that aBME, could induce preterm labor due to rising oxytocin levels. This does not seem to be the case: In a recent published randomized controlled trial by Forster et al (12), 635 pregnant women with diabetes were randomized to either start aBME from week 36 of pregnancy or standard care (no aBME). During the first aBME they were monitored with cardiotocography surveillance, and some women had increased uterine activity, but no episodes of tachysystole, hyperstimulation or preterm birth. These findings were evaluated by a safety committee and was not found to be a risk factor for the fetus or for preterm birth. The authors found no difference between the groups in the proportion of infants admitted to the NICU or gestational age at birth. Furthermore, they found no difference between the groups in birth characteristics (eg. Onset of labor, type of birth or blood loss). They conclude that their study indicates that it is safe to advise low risk pregnant diabetic women to express breastmilk from gestational age 36. In addition, a systematic review of breastfeeding (of siblings) during pregnancy, found comparable rates of preterm birth between breastfeeding pregnant women and non-breastfeeding pregnant women (13). Furthermore a randomized study from 2015 comprising 200 pregnant women found that starting aBME at term, shortened the time from initiation to full establishment of breastfeeding (14). Recently, Foudil-Bey et al. did a scoping review to evaluate aBME outcomes (15). They identified twenty articles eligible for the review. The initiation time of aBME differs among the included studies, with twelve of the studies expressing BM after week 36. Four studies recommend to start expressing BM between 32 and 36 weeks of gestation, two before week 32 and the remaining two studies did not specify the timing of aBME. The studies who recommend to start aBME before week 36 were old and week in methodology. They conclude, that existing studies on aBME varies widely in objectives, target population, interventions and outcomes, and that higher quality studies with clear hypothesis and populations are needed to determine safety and efficacy of aBME.

A couple of studies also included in the review by Foudil-Bey et al, evaluated feedback from the women with regard to perception and experience with aBME. The negatives aspects were among others discomfort or pain during aBME, time or energy burden, anxiety about having insufficient colostrum supply and feeling of internal pressure to succeed. On the other hand, they reported a sense of ownership and confidence with breastfeeding after performing aBME. They had positive feelings about having done something for the

baby and had a feeling of preparedness by having collected colostrum ready for the first feed to the infant (12, 16-18).

On this background we hypothesize that antenatal breastmilk expression

1) is a safe procedure before week 36 of pregnancy
2) can ensure sufficient supply of MOM for the preterm infants immediately after birth
3) promotes feeding with exclusively MOM for preterm infants
4) has a positive effect on the mothers feeling of confidence and preparedness for breastfeeding

Objective

In this pilot study, we want to investigate if aBME from week 34 of pregnancy is a safe and feasible procedure for the mother and fetus. Furthermore as secondary outcomes, we want to evaluate breastfeeding rates and mother's experiences with aBME. The evaluation of the mothers experience with aBME will be a separate study conducting qualitative methods.

Methods:

Intervention

In a pilot randomized study, we will include 60 healthy pregnant women. We will allocate 30 women to start aBME from week 34+0 of pregnancy until delivery and compare them to 30 women who does not perform aBME. All women included in this study will receive standard care, and have an individual consultation with a breastfeeding trained midwife in week 33 of their pregnancy. The women allocated to the intervention group will besides breastfeeding consultancy, also be taught how to perform aBME and store breastmilk correctly during the midwife consultation. To detect any signs of uterine contractions or fetal influence a cardiotocography (CTG) will be performed in the intervention group before, during and after the first aBME. In total 40 minutes of CTG surveillance. If the CTG is unclear, it will be assessed by the obstetric doctor in charge of this study, Christina Anne Vinter or a substitute. In case of pathological CTG, the women will be send to the obstetric emergency department for further assessment. If the CTG is normal the women in the intervention group can perform aBME 5 minutes from each breast two times per day from week 34 until birth, and collect and store any expressed milk. They will be provided with a schedule to register their aBME sessions (Please see attachment).

Participants will receive both written and oral information about the trial and the intervention group will in addition receive safe storage of MOM (please see attachment 1, 2) and be provided with the needed syringes and labels for expressed milk. Participants will be instructed to be aware of precautions

related to aBME such as: continuous excessive painful contractions, vaginal bleeding or decreased fetal movements. In case of such symptoms they have to contact obstetric emergency department. During the intervention and 8 weeks after birth the participating women will receive weekly push-messages through an application on their smartphone. The messages include short questions about the aBME as well as regarding feeding of the infant after birth. At the end of the study we want to evaluate the mothers experience with the study through an online questionnaire. The questionnaire will be submitted as a supplement to this protocol when finished. All data is managed through OPEN/REDcap and stored in a secure server (OPEN - Open Patient data Explorative Network - forside (rsyd.dk))

Trial design

Randomized pilot study with 1:1 into one of two arms: Group A aBME from week 34+0 or Group B no aBME. Randomization in this pilot trial will not be blinded to participants or investigators performing the data analysis due to the intervention.

Participants/Population

Participants are nulliparous pregnant women from the island of Funen who plan to give birth at Odense University Hospital. We intend to include 60 pregnant women, 30 in each group. If recruitment rate is low, we will widen the inclusion criteria and also include multiparous women who do not breastfeed siblings.

Inclusion criteria:

1. Healthy nulliparous women with no major chronic or pregnancy related diseases
2. BMI <27
3. Danish speaking
4. Singleton pregnancies
5. Planning to exclusively breastfeed their infants and deliver at Odense University Hospital (Odense and Svendborg)

Exclusion:

1. Suspected fetal intrauterine growth restriction or known major fetal anomaly
2. Women at risk of preterm birth with one of the following diagnoses: Placenta previa, premature preterm rupture of membranes (PPROM) or previous cervical conization
3. Women taking medications where breastfeeding is contraindicated
4. Women with prior breast surgery: Breast reductive surgery or breast implants

Ethical approval

Application for the Ethical Committee of Southern Denmark (project number: 86409) is done and the committee decided that no regional ethical approval is necessary in order to perform this study. The Research Ethics Committee of University of Southern Denmark has approved the study (Project ID: RECID281). All data collected will be entered and stored on a secure server in the Region of Southern Denmark, OPEN (www.open.rsyd.dk) and the project is approved by the Data Protection Agency at the Region of Southern Denmark. The study will be registered at clinicaltrials.gov.

Recruitment and information

Participants will be recruited using video and text announcing on social media and in outpatient/midwife clinics in the department of obstetrics. If the women are interested in participation, they click on a link and fill in an online document with contact information (telephone and email) and confirm that they comply with the inclusion criteria. After conforming their interest in participating, they receive written information about the trial (Appendix 1) through email. Following, primary investigator or others in the study group will contact them by telephone within 2-4 days to give oral information. Signed written consent will be obtained using E-Boks. Then randomization can be done and consultation in week 33 can be planned by the project-midwife by telephone.

Randomization

When the women have given informed written consent, they will be randomized to either group A (intervention) or B (control). Randomization will be done using a web-based randomization program (REDCap in OPEN). Baseline maternal characteristics, obstetric and neonatal will be obtained through medical records:

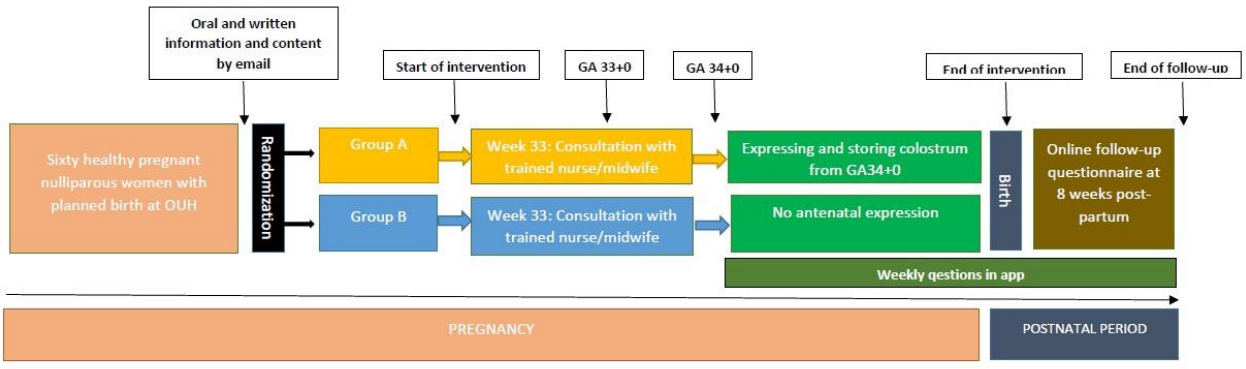
Maternal:

- Age
- Smoking
- Medications
- Prepregnancy BMI
- Delivery mode

Neonatal:

- Gestational age at birth
- Gender
- Anthropometry at birth
- APGAR scores at 1 and 5 min
- Umibilcal cord pH
- Feeding mode if hospitalized

Figure 1: Overall study design

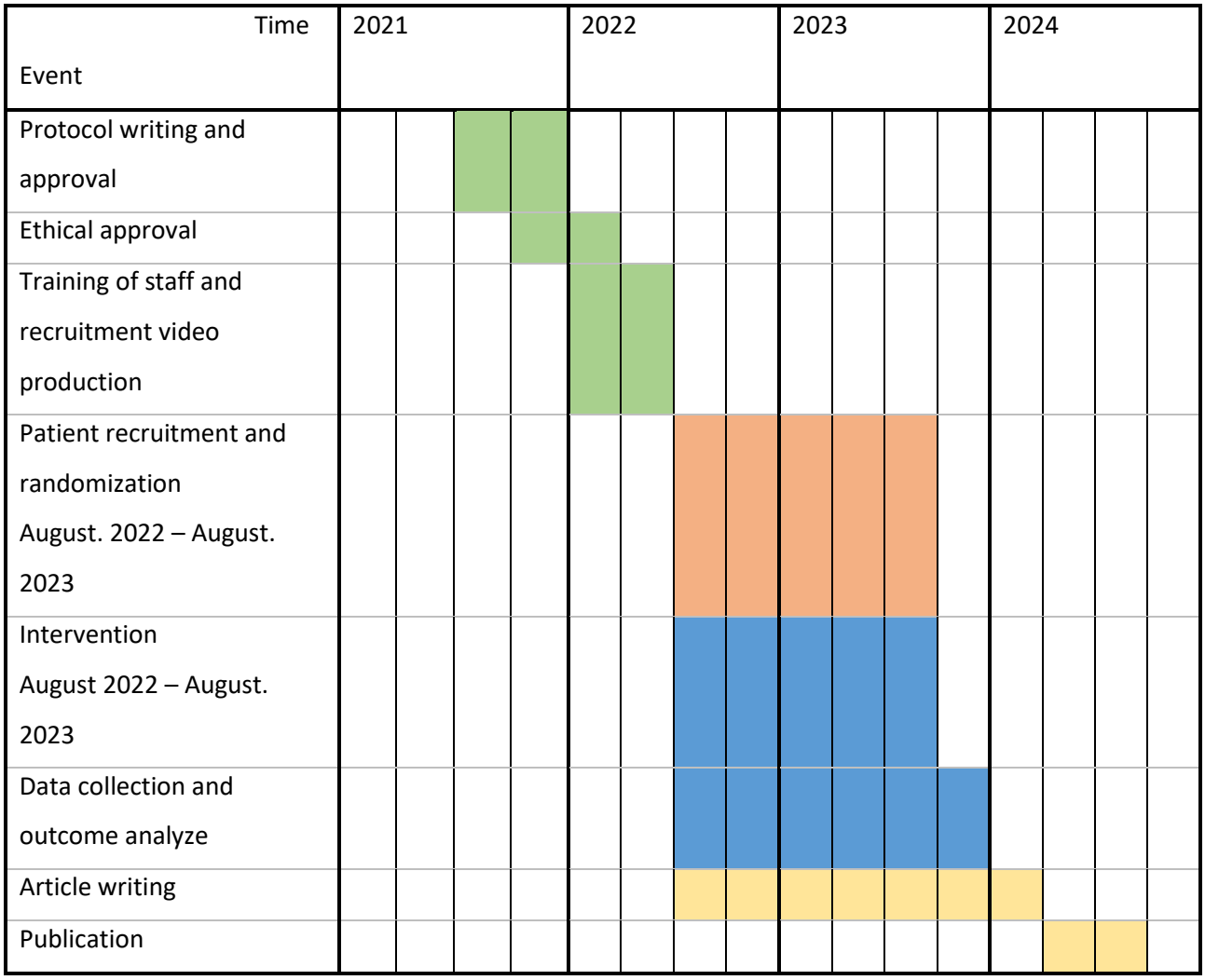


Time	**28-32 weeks of pregnancy**	**33 weeks**	**34 weeks**	**36 weeks**	**37 weeks**	Admission for birth	8 weeks post partum
ENROLLMENT *Eligibility for study screen*	✖						
Informed content and information on email	✖						
Randomization to either active aBME or no aBME	✖						
INTERVENTION *Group A: Midwife consultation*		✖					
Group A: aBME 10 min a day intervention group A			→	→	→	→	
Group B: Midwife consultation		✖					
Group B: no aBME			→	→	→	→	
DATACOLLECTION *Demographic maternal data*	✖						
							✖
							✖
			✖	✖	✖	✖	✖

Obstetric data from medical records							
Neonatal data from medical records	Enrollment	Post randomization (intervention?)				Post-partum	
aBME data, and infant feeding data (App-tracking) *Mother's experience with the intervention (questionnaire)*							

Figure 2: Detailed schedule of participant enrolment, intervention and data assessmen

Figure 3: Gantt diagram of project main time schedule



Outcomes:

Primary outcome:

1. Gestational age at birth comparing the two groups

Secondary outcomes

1. number of weekly antenatal stimulations/expressions (aBME) before birth
2. number of women in intervention group capable of expressing any milk
3. breastfeeding rates 1, 2, 4, 6 and 8 weeks after birth comparing the two groups
4. number of exclusively breastfeeding versus partial breastfeeding in each group at 1, 2, 4, 6 and 8 weeks after birth

5. Contractions and/or fetal stimulation during aBME, assessed with CTG
6. Women's experience with the intervention (separate qualitative study)

Sample Size

In general the evidence in aBME is limited. A few prospective studies has been conducted, and only one larger RCT. This RCT included 635 participants, where aBME was performed from week 36 of pregnancy. They were not able to detect any difference in gestational age at birth or report any adverse events in relation to the aBME. Before the larger RCT they conducted a pilot study, which consisted of 43 participants. Our aim with this study is to primarily test safety and feasibility with the procedure aBME from week 34, and since no study has been done from this week of pregnancy, a reliable power calculation is not possible to make. Therefore we estimated that 30 participants in each group is a realistic and feasible number to include in the pilot study. To detect a difference in gestational age at birth based on 80% power, we estimated that we would need a total of 176 participants, 88 in each group (mean, SD, derived from Soltani et al(19)). If the pilot study shows no trend towards a higher proportion of preterm birth in the intervention group, we will proceed to the larger trial.

Data collection:

Demographic data on the mothers (maternal age, education level, ethnic background, parity and smoking status) will be obtained through medical files. Infant data on gestational age, complications such as preterm contractions or birth and feedings from birth, will be obtained from medical records after birth. To obtain data on aBME and breastfeeding rates after birth, we will use SMS tracking via an app based in the RedCap system. From intervention start until 8 weeks after birth participants in the intervention group will receive a weekly sms, with questions on how many times they stimulated and if they were capable of expressing any milk. The control group will receive a weekly message which regards if they have been giving birth, to be able to initiate the questions on breastfeeding. After birth questions will regard breastfeeding initiation. After eight weeks the mothers experience and evaluation on the study will be evaluated in an online questionnaire.

Data analysis and statistics:

Data will be collected in order to meet the CONSORT guidelines for Randomized Controlled Trials. Comparability of the two groups by intention to treat analysis. Where data are normally distributed, comparison of means will be done using unpaired t-tests. If data are not normally distributed a non-parametric test for unpaired data will be used, eg. Mann-Whitney test or permutation test. Multivariate

analysis will be carried out, if data shows differences in maternal or infant characteristics possibly affecting outcome.

Interruption of the trial

The involved investigators can stop the trial if the protocol is not followed or unexpected adverse effects in relation to the aBME such as contractions, vaginal bleeding or overrepresentation of preterm birth in the intervention group. The investigators in charge can pull out participants if they find it irresponsible to continue due to side effects or new pregnancy related conditions, where aBME could be contraindicated. Participants can at any time retract their content and stop the intervention.

Patient insurance

This trial is covered by the Patient Compensation Scheme and Labour Market Insurance.

Publication

All results, positive, negative as well as inconclusive results will be published.

Possible clinical implication:

We expect this initiative to have positive impact on both mother and infant with improved breastfeeding rates and mothers confidence with breastfeeding. If aBME from 34 weeks does not induce preterm birth, we aim to investigate if this procedure is safe earlier in pregnancy and especially among pregnant women at increased risk of preterm delivery. In the long term, this could increase the number of preterm infants fed exclusively MOM and possibly contribute to improved gut health and neurodevelopmental outcome for preterm infants.

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