Study Protocol

Maximising **I**nitial **L**actation **Q**uantities for Preterm Infants (The **MILQ** prem Study)

Daily breast milk volume in mothers of preterm born ≤33 weeks and/or VLBW ≤1500g Randomized controlled trial comparing early electrical breast pump expression versus hand expression

Dr Sarah Kasha[1,2], Roberta Mc Carthy[1], Ramita Dangol[1], Harriet Kinsman[1], Aoife Kenny[1]
Dr Mary O 'Dea[1], Dr Madeleine Murphy [1,2], Prof Mary Higgins[1,2], Anna Curley[1,2]

1. Department of Neonatology, National Maternity Hospital, Dublin, Ireland
2. School of Medicine, University College Dublin, Dublin, Ireland

Hypothesis:

(P) Among mothers of infants born at or ≤ 33 weeks of gestation and/or with a birth weight ≤1500g
(I) Does the use of a hospital-grade double electrical breast pump as soon as possible after delivery followed by hand expression for 10 minutes for the first 48 hours post-delivery followed by hospital grade double electrical breast pump
(C) Compared to routine hand milk expression for the first 48 hours post-delivery followed by hospital-grade double electrical breast pump
(O) Increase the volume of breast milk produced by mothers
(T) By 14 days postpartum

Background:

Maternal milk is the gold standard in infant nutrition, providing significant advantages, in preterm and term infants. Maternal milk plays a major role in reducing the risk of necrotizing enterocolitis (NEC) in preterm and low birth weight infants (1) as well as improving neurodevelopmental outcomes in this cohort. A prospective study of 775 extremely low birth premature infants concluded that those who received maternal breast milk exhibited higher scores in mental and psychomotor development indices at 18 months corrected age (2).

Evidence suggests that the first two weeks after preterm delivery are the critical period for initiation and development of lactation. The process if made more complicated following preterm delivery due to immaturity of mammary glands, delayed onset of phase two lactogenesis and absence of suckling by preterm infants (3). Preterm delivery also leads to

increased levels of stress and anxiety about breast milk expression, especially during the first days after delivery (4). All these factors can contribute to low milk volumes and reduced nutritional substrate for babies. Inadequate breast milk production during the first few days after delivery leads to longer duration of parenteral nutrition and increased use of donor milk Donor milk is less effective nutritionally and an expensive resource (200 euro per liter). In babies where donor milk provides sup optimal nutrition, formula milk is required, and this significantly increases the risk of NEC in preterm infants. Suboptimal breast milk supply is also associated with prolonged use of central lines, greater rates of sepsis and chronic lung disease and leads to prolongation of hospital stay.

International guidelines for production of expressed breast milk (EBM) for premature infants under 34 weeks' gestation from tertiary-level hospitals in Canada, Australia, and the United Kingdom suggest starting with hand expression of milk ideally within the first 1- 3 hours as a gold standard and if that is not possible within the first six hours after delivery, they recommend switching to a double electrical breast pump after the first 24-48 hours post-delivery. Use of hand expression in the first instance is based on the small volumes of colostrum which are likely to be collected. There is no evidence to say whether hand or electrical pump expression from birth is more effective. Hand expression for seven days from birth has been shown to be less effective than pump expression over the same time period but there have been no published studies to compare hand expression as per international guidelines for 2 days followed by use of the electric pump, to use of electric pump from birth (5).

Different guidelines internationally also target differing aspirational milk volumes. The UK and Canadian guidelines target similar volumes of expressed breast milk by day 14 post birth (UK: 500- 600 ml/day, Canada: 500 ml/day) (6,7). Australian guidelines aim for greater volumes of 600- 800 ml /day by two weeks postnatal (8). Current data from our institution shows that 404 ml/day of EBM is achieved on average by day 14 post-delivery by mothers of preterm infants. Cumulative breast milk production at 14 days post-delivery therefore remains suboptimal despite multiple preexisting initiatives at our institution such as targeted antenatal counselling prior to impending preterm delivery, antenatal breast-feeding classes, intensive lactation support by lactation consultants and provision of free pumps to mothers of premature babies.

In a prospective observational study published by Xifang Ru et al, 30 mothers of preterm infants less than 32 weeks' gestation were allocated to exclusive electrical pumping from the first 6 hours post-delivery. Their aim was to achieve milk volumes of 750 ml/day by day 14. They demonstrated that mothers using a hospital-grade pump with a pumping frequency of ≥ 6 times/d could reach full lactation volumes successfully (9). This was not a randomized controlled trial, and we did not know therefore whether other variables led to improved milk production. We still do not know whether the internationally recommended practice for initial hand expression followed by use of an electric pump is the most effective method to achieve ideal volumes by two weeks post-delivery in mothers of preterm infants.

A randomized controlled study by Lussier et al. on 26 mothers of preterm infants (born at <32 weeks, weighing <1500g) found that using an electric pump immediately after birth led to significantly higher milk production compared to hand expression. The mothers were

randomly assigned to either hand expression or electric pumping. The group using the electric pump produced considerably more milk in the first 7 days (1270 ml vs. 456 ml) and maintained higher volumes at both 14 and 28 days postpartum. (10) .

Several factors, beyond initial pumping method, are linked to achieving coming to volume (i.e. over 500 ml) by day 14. These include the frequency of expression and the timing of the first expression. Based on a study by Parker et al., the timing of a mother's first milk expression is a significant factor in achieving a milk volume of over 500 ml by day 14. This prospective study involved 40 mothers of preterm infants (less than 32 weeks and 1500 grams). The researchers compared milk production between two groups: one that began expressing milk with an electric breast pump within six hours of delivery, and another that started after six hours. The findings showed that mothers who started expressing early had a much higher milk volume on days 6 and 7 (803 ml vs. 394 ml). On day 21, the early expression group still had a greater volume (296 ml/day vs. 240 ml/day) (11).

A retrospective study by Mago-Shah et al. on 427 mothers with newborns in the NICU found similar results. The study's main goal was to see how many mothers reached a full milk volume by 14 days postpartum. Out of the 427 mothers who produced milk, 201 (50.1%) reached this goal. The study found that mothers who achieved coming to volume were more likely to have pumped an average of five times a day by day five and were also more likely to have pumped between 1:00 AM and 5:00 AM (12).

Bin-Nun et al. conducted an observational study on mothers of preterm infants (born after 24 weeks and weighing 1500g) to assess the impact of delivery method on milk expression. The study compared mothers who had a vaginal delivery to those who had a Caesarean section, both groups used electrical pumping after delivery. Key findings were mothers who delivered vaginally initiated milk expression earlier, at an average of 3.8 hours postpartum versus 11 hours for c/s group. They also had a higher frequency of expression, averaging 6 sessions per day. Their milk volume was significantly higher, producing 584 ml on day 7 and 810 ml on day 14. In contrast, mothers who had a C-section had lower milk volumes, with 361 ml on day 7 and 420 ml on day 14. The study concluded that vaginal delivery was associated with earlier and more frequent milk expression, resulting in a substantially higher milk volume in the first two weeks (13).

The initial days after birth can present challenges to hand expression, with issues like breast oedema in mothers with preeclampsia and IV lines making it difficult to collect milk. This can cause significant anxiety. However, a study by Ohyama et al. offers insight into the effectiveness of different methods. In their research, 11 mothers in the NICU were asked to alternate between manual and electric expression for 14 sessions. The findings revealed while manual expression yielded a greater median milk volume (2 mL vs. 0.6 mL), electric pumping was perceived as significantly less painful, with 90% of mothers reporting no pain compared to only 36% for manual expression (14).

PATIENTS AND METHODS:

Population

Inclusion criteria:
Mothers of infants will be eligible for enrolment if

- the infant/s are born at the National Maternity Hospital with a gestational age at birth ≤33 weeks by best obstetric estimate and/or with a birth weight of ≤1500g; or
- the infant/s are born in another centre with a gestational age at birth ≤33 weeks by best obstetric estimate and/or with a birth weight of≤ 1500g and the mother is admitted to the National Maternity Hospital within 24 hours of delivery

Exclusion Criteria:

- Maternal medications contraindicate the use of breast milk
- Breast hypoplasia on examination or recent breast surgery affecting ability to produce adequate breast milk

Sample size estimation:
Baseline local data show that mothers achieve breast milk volumes of 404ml by day 14 postpartum with current practice, i.e. using hand expression for 48 hours followed by use of an electrical pump. 43% of mothers reach minimal target volumes of 500mls by day 14. We want to show a clinically meaningful increase from 43% to 65%. Using 80% power and significance value of $\alpha = 0.05$, we will need to recruit 160 mothers. Anticipate 15% drop out,the plan to enrol 180 mothers over 2 years (7 – 8 per month)

RANDOMISATION AND GROUP ASSIGNMENT:
Mothers of infants will be randomised to early pump or late pump groups in a 1:1 ratio. We will use block randomisation with a block size of 4. We will stratify the randomisation by gestational age (<28 weeks and 28-33 weeks).

INTERVENTION:
Pump first group:
Mothers assigned to the early pump group will be advised to start pumping using a hospital-grade double electrical breast pump as soon after birth (target within first 6 hours after delivery) follow by hand expression for 10 minutes for the first 48 hours then continue using a hospital –grade double electrical breast pump without additional hand expression

CONTROL:
Hand express first group:
Mothers assigned to hand express group will be advised to start hand expression for the first 48 hours postpartum, and then start using a hospital-grade double electrical breast pump, as per routine practice.

Mothers enrolled in the study will be given a breastfeeding booklet to record their daily milk production for the first two weeks after birth, they will be advised to pump at least eight times

every 24 hours, with pumping sessions spaced 2-3 hours apart during the day and no more than a 5-hour break overnight. All mothers will use the 'Initiate' pump program, which features irregular, rapid sucking and pausing to stimulate milk secretion. Once a mother's milk output is established, which is defined as producing over 20 ml in one pumping session, she can transition to the 'Maintenance' program to further build and sustain her milk supply.

Consent:
A member of the research team or a senior doctor will approach the parents or guardians of eligible infants to discuss the study prior to or immediately following delivery. The discussion will cover the study's purpose and methodology, and a written information sheet will be provided for their records. To facilitate comprehension and ensure support, parents or guardians will be offered the opportunity to have a family member, support person, or a professional interpreter (if applicable) present during the conversation.

Following the explanation of the study, we will ask for written consent for enrollment. Parents will be informed that participation is voluntary and they are free to withdraw their infant at any time without affecting the standard of care their baby receives. The signed consent forms will be kept in a secure location, and a copy will be made available to the parents alongside with patient information leaflet.

Semi structured interviews:

Dr Sarah kasha will conduct interviews with parents looking at aspects of feasibility, comfort, accessibility, lactation support, education trying to identify any factors that could enhance service provision in this area. We plan a pragmatic sample size of 18 representative parents looking at different nationalities, English language fluency and socioeconomic or cultural background.

MASKING:
It is not possible to mask caregivers to group assignments.

Maternal and neonatal characteristics:
Maternal characteristics:
Age, mode of delivery, mode of conception, educational qualification, parity, breast feeding of previous babies, maternal health status during pregnancy (GDM, HTN, thyroid disease, PPROM, antenatal steroid, MGSO4), multiple birth, ethnicity, mode of delivery, initial time of milk expression, frequency of expression, milk volume on day 1,3,7&14 .

Neonatal demographic:
Gestation age, birth weight, gender, apgar score, resuscitation at birth, ventilation, type of respiratory support, duration of respiratory support, etc

Primary outcome:
Percentage of women achieving > 500mls by 14 days' post-partum

Secondary outcomes:

- Parenteral nutrition days
- Time to full feeds
- Donor milk use
- Central line insertion
- Central line associated blood stream infections
- Necrotising enterocolitis
- Chronic lung disease
- Late onset sepsis
- Breastfeeding at hospital discharge
- Formula use
- Death before hospital discharge
- Duration of hospitalisation
- Parental attitudes and experiences (interviews with parents to access and enhance family centre care model)
- Antenatal education

Registration:

This trial protocol will be registered with a recognised clinical trials register (e.g. clinicaltrials.gov) before the first patient is enrolled.

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