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Review

Use of donor milk in the neonatal intensive care unit

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SUMMARY

Own mother's milk is the first choice in feeding preterm infants and provides multiple short- and long-term benefits. When it is unavailable, donor human milk is recommended as the first alternative. Donor milk undergoes processing (i.e. pasteurization) to reduce bacteriological and viral contaminants but influences its bioactive properties with potentially fewer benefits than raw milk. However, there is no clinical evidence of health benefit of raw compared to pasteurized human milk, and donor milk maintains documented advantages compared to formula. Nutrient content of donor and own mother's milk fails to meet the requirements of preterm infants. Adequate fortification is necessary to provide optimal growth. There are significant challenges in providing donor milk for premature infants; therefore, specific clinical guidelines for human milk banks and donor milk use in the neonatal intensive care unit should be applied and research should focus on innovative solutions to process human milk while preserving its immunological and nutritional components. In addition, milk banks are not the only instrument to collect, process and store donor milk but represent an excellent tool for breastfeeding promotion.

1. Introduction

Human milk (HM) is the gold standard to provide nutritional support for all healthy and sick newborn infants including the very low birth weight (VLBW) infant (<1500 g) [1]. It contains nutrients necessary for infant's growth but also numerous bioactive factors contributing to beneficial effects on gastrointestinal maturation [2], host defence, infection [3–6], cardiovascular risks [7], metabolic disease [7] neurodevelopmental outcome [8,9] as well as in infant's and mother's psychological well-being. Several studies in preterm infants have reported short- and long-term benefits of HM compared with preterm formula [4,8–10]. Due to the specific mother and infant dyad, own mother's milk (OMM) should always be the first choice in preterm infants [1,11]. Unfortunately, mothers of preterm infants are less likely to initiate milk expression, sustain lactation and to provide full OMM soon after birth, suggesting that donor milk (DM) and HM banks are necessary to provide an exclusive HM diet in VLBW infants during their first weeks of life [1,12]. Therefore, the use of DM is increasing in the NICU and the number of HM banks is growing worldwide [13–15]. DM is collected and distributed following standards similar to blood donation and is generally pasteurized [15–17]. As with OMM, DM needs to be fortified to provide the high nutritional requirements, to reduce cumulative nutritional deficits and promote optimal growth in VLBW infants. Although storage, processing and pasteurization could reduce the nutritional value of DM and alter some of the immune components found in HM [18], beneficial health outcomes are also reported in preterm infants fed with DM compared with those fed formula [19]. However, it is unclear whether the use of pasteurized OMM or of DM confers the same clinical health benefits as does raw OMM.

2. Clinical benefits of donor milk

2.1. Necrotizing enterocolitis

Donor milk is widely used to prevent necrotizing enterocolitis (NEC) for vulnerable premature infants when OMM is unavailable [1]. Both older and more recent studies suggest that DM is as efficacious in preventing NEC in preterm infants [14,20,21]. Many observational studies suggest that the incidence of NEC is HM dose-dependent in premature infants [10,22]. A recent meta-analysis of data from six trials found a statistically significantly higher incidence of NEC (twice the risk) and feeding intolerance (Risk Ratio: 4.92) in the formula-fed group compared to HM groups. It has been

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estimated that one extra case of NEC will occur in every 25 preterm infants who receive formula. This beneficial effect exists even when DM is given as supplement to OMM rather than as a sole diet and also when DM is fortified [19]. However, the specific effect of HM fortification on the incidence of NEC is still controversial. In a randomized control trial (RCT), Lucas et al. showed a small but not significant increase in NEC in preterm infants fed fortified HM (5.8%) compared to unfortified HM (2.2%) [23]. From that study, it has been speculated that a bovine protein diet may be associated with higher intestinal inflammation and permeability and that the use of bovine-derived HMF may be inadequate to protect infants against NEC. Thus, in two recent RCTs, an exclusive HM diet exempt from bovine-based formula (DM or OMM fortified with DM fortifier) has been reported to significantly reduce the incidence of NEC compared with an exclusive bovine based formula (3% versus 21%, p=0.04) [21] or a bovine-derived fortifier (6% versus 15.9%, p=0.02) [24]. However, in these prospective randomized trials the bovine-based cohorts had higher NEC rates (16% and 21%) than in many units using bovine fortifier and formula (3% and 6%) [25]. In our country between 2010 and 2015, the national rate of NEC in 8402 preterm infants at <32 weeks or <1500 g, fed HM supplemented by bovine-derived fortifier or fed preterm formula, is 4.4% (NICAUDIT, Belgian network), suggesting that the results of these trials should be interpreted with caution.

Similarly, it has also been suggested in one RCT that pasteurization by itself does not increase significantly the incidence of NEC $\geq$ Bell's stage 2 in preterm infants $\leq$32 weeks and $\leq$1500 g fed OMM (13/151, 8% raw OMM versus 9/152, 5% in pasteurized OMM; $P = 0.39$) [26]. Similarly, in California NICUs it has been suggested that the increased availability of DM over time has been associated with a significant reduction in NEC incidence [14]. More recently, it has been suggested that the introduction of preterm formula or DM as OMM supplementation during the first 10 days of life does not increase significantly the incidence of NEC in VLBW infants (8.9% versus 9.3%; $P = 0.95$) but that the provision of OMM >50% of the intake tends to improve the event-free survival rate in both groups [27].

These studies suggest that DM could be as effective as OMM in reducing the incidence of NEC but that the use of bovine-based fortifier or formula could be a major risk factor for NEC in VLBW infants, and that further studies are still required to determine whether raw OMM, pasteurized OMM or DM offers any advantage against NEC.

2.2. Infection

Human milk is not sterile and represents a complex ecosystem with a large diversity of bacteria reflecting mother's biotope [28]. HM is known to be colonized by non-pathogenic bacterial flora with a majority of bifidobacteria, promoting development of infant's healthy gut microbiota. These bacteria could protect the infants against infections and contribute, among other functions, to the maturation of the immune system. However, HM may also contain potentially pathogenic bacteria species [29,30]. The expression, collection, storage and transport of HM may introduce pathogenic contamination, increasing the risk of sepsis to these vulnerable premature infants, as suggested by several case-reports in the literature [31–33]. The need for bacterial screening of OMM before raw administration is controversial but when performed there is a general consensus to discard or pasteurize contaminated OMM [26,30]. Several studies demonstrate that HM reduces the sepsis risk in premature infants with a dose–response relationship [4,6,8]. They also suggest that OMM provision from the first few days of life plays a major role in this phenomenon [5].

Many studies do not record the type and proportion of HM used: pasteurized DM, pasteurized OMM or raw OMM. By contrast, DM is widely pasteurized to ensure safety [15–17]. Pasteurization alters cellular and some immunological properties of HM but many bioactive components and anti-infectious properties are preserved [34,35], maintaining health advantages over formula. Therefore, there are theoretical arguments suggesting that fresh OMM is superior in protective effects against late-onset sepsis (LOS) versus pasteurized OMM but no clinical evidence has been demonstrated. Recently, Cossey et al.'s RCT reported no significant difference in the rate of LOS between infants fed raw (22/151; 15%) versus pasteurized OMM (31/152; 20%; $P = 0.23$) [26]. In this study, bi-weekly bacteriological evaluations were performed in order to discard or pasteurize contaminated OMM. Similarly, Stock et al. did not find significant differences in the rate of LOS between unpasteurized and raw milk [36].

Therefore, these recent studies failed to demonstrate a significant superiority of raw OMM over pasteurized OMM on LOS, suggesting persistent protective effects [26,36]. By contrast, the clinical superiority of fresh OMM over DM to prevent LOS in preterm infants is still debated, with a recent study suggesting that the provision of fresh OMM for >50% of the diet reduces the incidence of LOS in VLBW infants [27].

Recently, there have been concerns about short- and long-term morbidities associated with postnatally acquired cytomegalovirus (CMV) infection in very preterm infants. Postnatal CMV infection related to fresh HM in preterm infants remains generally mild or asymptomatic, but a serious illness “sepsis-like syndrome” may be observed in 4% of preterm infants of seropositive mothers [37]. By contrast, the incidence can reach up to 40% in extremely low birth weight (ELBW) infants <26 weeks of gestational age [38]. The effect of postnatal CMV infection on long-term neurodevelopmental outcomes is unclear. Limited studies suggest that cognitive and motor function could be affected in contaminated infants compared with uninfected controls [39,40]. By contrast to the freezing process, the use of pasteurized OMM or of DM prevents completely the risk of postnatal transmission of CMV via breast milk [36].

2.3. Feeding tolerance and donor milk's influence on feeding practices

The trophic effects of HM are attributed to multiple HM components stimulating the maturation of the premature gut [2]. Clinically, it improves feeding tolerance and reduces delay to full enteral feeding. Available data from older studies support the hypothesis that DM improves feeding tolerance [12,19]. In a recent study, preterm infants fed exclusive DM-fortified diet required fewer median days of parenteral nutrition [27 (14–39) days] compared with those fed preterm formula [36 (28–77) days] ($P = 0.04$). However, the time to establish full enteral feeding was not significantly different [21].

An international survey evaluating differences in feeding practices found that most NICUs with access to DM started enteral feeding earlier and advanced more rapidly. Units without access to DM frequently delayed the introduction of enteral feeds until OMM was available [41].

2.4. Other long-term benefits

2.4.1. Neurodevelopment

The survival rate for early preterm infants is improving but with high risk of neurological impairments. More attention is being focused on the quality of survival through optimal nutrition management. Several studies suggested that the use of HM compared with preterm formula during the early weeks of life of VLBW infants was associated with better neurodevelopment outcome with a dose-dependent relationship despite a slower early growth rate (breastfeeding paradox) [8,42,43]. These studies suggest that HM

may have an independent, positive dose-effect on the psychomotor development of preterm infants. HM via multiple bioactive components provides optimal substrates [long-chain polyunsaturated fatty acids (LC-PUFA), oligosaccharides] for brain development and protects infants from morbidities associated with early preterm birth (NEC, infections), considered as risk factors for adverse neurocognitive outcome. However, these studies should be interpreted with caution due to the presence of many confounding factors and lack of detailed information about the HM diet (OMM or DM, OMM completed with DM, pasteurized or unpasteurized OMM). Moreover, no beneficial effect on neurocognitive outcome has been demonstrated in the only available RCT comparing non-fortified DM and formula despite higher growth in infants fed preterm formula [12].

There are several ongoing, blinded randomized trials to investigate the neurodevelopmental outcomes and other morbidities of very preterm infants fed DM compared with those fed formula (as supplement to insufficient OMM or as the sole diet) in the era of routine fortification [18,44].

2.4.2. Bronchopulmonary dysplasia

A reduction in the incidence of bronchopulmonary dysplasia has been observed in one RCT [45]. Further studies are needed to confirm this observation.

2.4.3. Long-term cardiovascular and metabolic diseases

Donor milk in early life may have beneficial effects on cardiovascular risk factors measured during adolescence; the significance of these findings for the development of cardiovascular diseases is uncertain [12]. A limitation of these findings is that the comparison was made between preterm formula and unfortified DM. It is important to consider whether positive effects would persist with use of fortified DM and early faster growth.

2.4.4. Allergy

The neonatal period is a critical window for immunological tolerance. HM contains many immune-modulating factors and could probably play a protective role against the development of allergy in preterm infants. The only available RCT does not show protective effects of DM against allergy later in life even when a protective effect against eczema in preterm infants at high risk of allergy is reported [12].

2.4.5. Breastfeeding rate of VLBW infants

Having a DM bank feeding practice in the NICU does not reduce OMM proportion in the infant's diet but significantly decreases the formula exposure [13,46]. The available evidence does not support the hypothesis that the introduction of DM has an adverse effect on breastfeeding rates in VLBW [12,47]. An Italian survey showed that exclusive breastfeeding at discharge was significantly higher in NICUs with an HM bank when compared to NICUs without (29.6% vs 16%, $P = 0.007$) [48]. In a recent study examining the impact of DM use in California NICUs, Kantorowska found that the availability of a donor HM bank in a hospital was associated with a mean increase of 10% in the breastfeeding rate at NICU discharge [14].

3. Concerns and problems of donor milk

3.1. Growth and nutritional composition of donor milk

Preterm infants and especially ELBW (<1000 g) infants are at risk of cumulative nutritional deficits and postnatal growth restriction during the first weeks of life up to the time of discharge or theoretical term [49,50]. It has been suggested that the neonatal period corresponds to a critical window when under-nutrition affects brain development [51]. Preterm infants have higher protein, energy, minerals and electrolytes requirements than term infants. Exclusive HM, even from OMM, cannot meet nutritional recommendations for ELBW infants [11,52]. Protein content of preterm mother's milk is generally higher in the early postnatal period and decreases during lactation. This problem may be amplified with banked DM which is most often provided by mothers of term infants who are in their later stages in lactation. Therefore, various HM fortifiers were developed to increase protein, energy, minerals, electrolytes, traces elements, and vitamin supplies [53,54]. Nevertheless, the use of fortified HM failed to obtain postnatal growth in the range of fetal growth or similar to that observed in infants fed adapted preterm formulas [24,55]. These differences could be related to the large variation in the macronutrient contents of expressed HM, especially in terms of energy, fat and protein [56,57]. A recent study performed in our NICU milk bank showed that protein, fat and energy contents of DHM were significantly lower than those of OMM (Table 1). Variability of DHM contents was also high, ranging from 0.9 to 3.2 g/dL for protein, from 1.8 to 5.5 g/dL for fat, and from 48 to 85 kcal/dL for energy [56]. Furthermore, out of all DM samples, 63% were <1.5 g/dL of protein whereas 90% were <4 g/dL of lipids and 81% were <67 kcal/dL energy, all values frequently considered as reference values for HM used in the NICU (Fig. 1).

In addition, growth differences between fortified HM and preterm formula-fed VLBW infants receiving an apparent similar energy and protein intake could also be related to a lower metabolizable protein and energy available for new tissue synthesis [55,57]. Metabolic balance studies [57,58] showed that nitrogen absorption as well as nitrogen utilization were lower in preterm infants fed fortified HM than in those fed preterm formulas. In all, the mean difference in nitrogen utilization (retention/intake) accounted for 11.8% and could be related to absorption of the non-nutritional proteins (lactoferrin, IgA) as well as to non-protein nitrogen utilization (urea) in HM. Net absorption of energy as measured by bomb calorimetry was reported lower (78.3%) in infants fed HM than in those fed formula (88.4%) resulting in a higher fecal energy loss [57,58]. This difference could be partially due to the use of pasteurized HM [59]. Pasteurization leads to inactivation of the bile salt-stimulated lipase of HM as well as possible changes in the milk fat globule structure [59].

Moreover, incomplete milk expression, manipulations of HM during expression, storage, transport, and processing are all additional factors influencing the high variability of expressed HM composition, especially reducing the fat content. In a recent prospective trial evaluating HM cream supplement on growth, 85% of the preterm infants fed DHM required the extra cream supplement because of energy density <20 kcal/oz (70 kcal/dL) [60]. In addition, VLBW premature infants are frequently continuously fed by gastric tube, inducing fat adherence to tubing and a substantial loss of phosphorus, calcium, and other nutrients bound to fat [61]. Fat lost may account for up to 25–34% and has been reported both in OMM and DM with or without fortification.

Table 1
Protein, fat, and energy concentrations of own mother's milk (OMM) and donor milk (DM).

	OMM[a] ($n = 428$)	DM[b] ($n = 362$)	P
Protein (g/dL)[c]	1.52 ± 0.28	1.42 ± 0.30	<0.0001
Fat (g/dL)	3.79 ± 0.73	3.41 ± 0.53	<0.0001
Energy (g/dL)	67.26 ± 6.49	63.80 ± 5.06	<0.0001

Values are expressed as mean ± SD.
[a] Own mother milks 28 ± 10 days of lactation.
[b] A proportion of DM is provided by preterm delivery mothers.
[c] Protein is measured as total nitrogen.

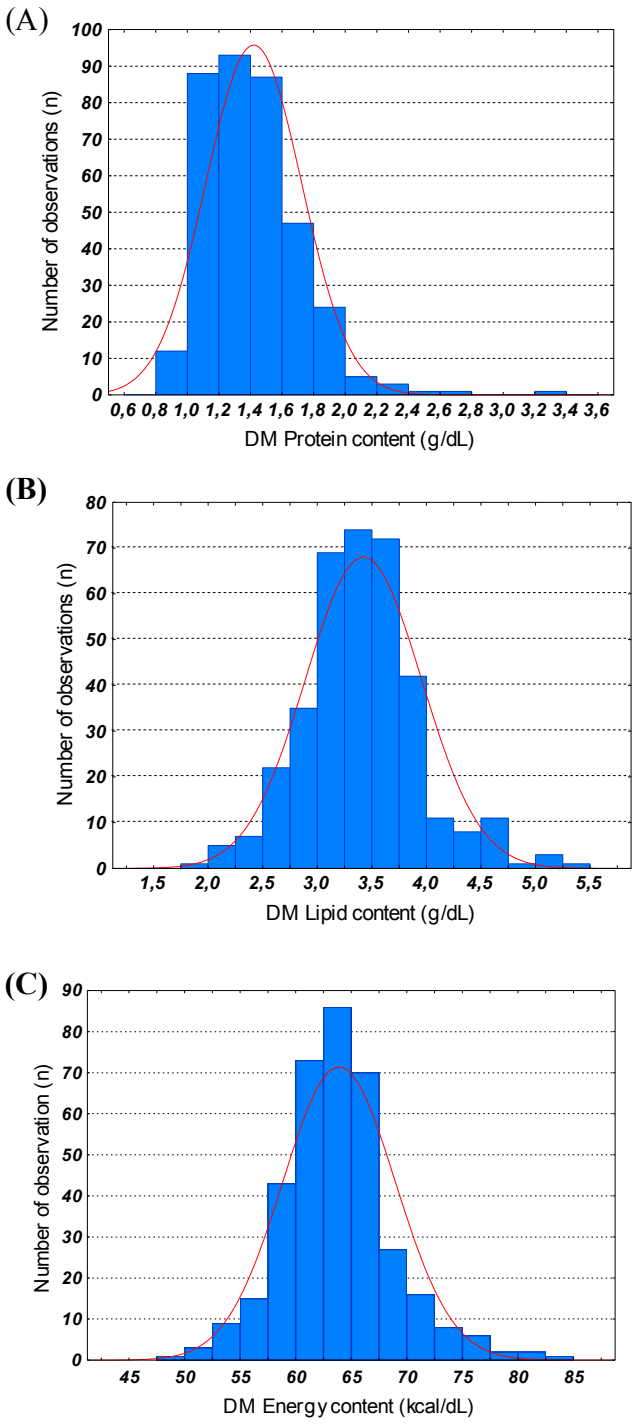

Figure 1. Variability of protein (A), fat (B), and energy (C) contents of donor milk (DM) ($n = 362$).

Standard fortification, adding a fixed amount of fortifier as recommended by the manufacturer, is the most widely used method to fortify HM. This method was not associated with a reduction in the variability of the HM macronutrient contents and often failed to meet the adequate nutritional supply for preterm infants [56]. Considering that true energy and protein contents are unpredictable and differ significantly from that calculated using a fixed composition for OMM or banked DM, new modes of fortification have been suggested.

In case of insufficient growth, some authors propose to increase fortifier strength or arbitrarily add extra protein, glucose or fat. We recently performed an RCT using a new, isocaloric HMF with a higher protein:energy ratio during a 21 d study interval in clinically stable preterm infants ($n = 153$). Infants in the intervention group had a significantly higher weight gain compared with the control HMF group. The adjusted beneficial effect amounted to 2.28 g/d (CI: 0.38–4.18; $P = 0.010$) compared with 1.18 g/kg*d (CI: 0.14–2.21) ($P = 0.013$) [62]. However, such an increase in protein fortification does not compensate for the variability of native HM composition and the risk of energy deficiency as well as protein overload with its potential long-term adverse effects [56]. Hair et al. provided an exclusive HM diet (OMM ± DM) with the use of a donor milk-derived fortifier (Prolacta®, Prolacta Bioscience, Inc., Los Angeles, CA, USA). Protein and energy intakes ranged from 130 kcal/kg/day with 3.6 g/kg/day of protein up to 150 kcal/kg/day and 5.25 g protein/kg/day when growth was <15 g/kg/day. The authors reported a high mean weight gain of 24.8 g/kg/day, exceeding targeted growth standards. In this study, HM composition was based on a fixed value. According to the variability of OMM and DM composition, overfeeding and protein/energy imbalance could be present and inappropriate to achieve a normal body composition [63].

Two new fortification strategies (adjustable and individualized fortification) were suggested to improve nutritional intakes and growth in preterm infants. Arslanoglu et al. adjusted the fortifier supply according to the values of blood urea nitrogen (BUN), considered as a marker of metabolic response for protein adequacy in preterm infants [64]. This BUN method, which was developed to avoid inadequate and excessive protein intake, is easy to apply and does not require daily milk analysis. However, it has been shown that BUN is not correlated to protein intakes during the first weeks of life but reflects the renal immaturity of preterm infants [65]. Therefore, the use of BUN as a threshold did not allow the provision of adequate nutrition and growth during the early weeks of life. Thus in the study of Arslanoglu, protein intake increased progressively from 2.9 to 3.4 g/kg*d during the three weeks of study (in mean from 2.5 to 5.5 weeks of life) leading to a cumulative protein deficit of around 7 g/kg during the study period.

Individualized fortification analyzes HM composition and provides fortification to achieve target recommended intakes related to postconceptional age. Polberger et al. have proposed analyzing, once or twice a week, the macronutrient content of 24 h OMM collections so as to adapt the fortification in the range of nutritional needs [66]. In 2007, we suggested that daily individualized HM fortification could provide nutritional supplies in the range of the nutritional recommendations and improve growth in VLBW infants. Infrared protein and fat determinations are performed daily for OMM and DM in our NICU milk bank. Fat content is first adjusted to 4 g/dL using a medium chain triglyceride solution, whereas protein intake is adjusted to provide 4.2 g/kg*d according to the daily volume order. This procedure of fortification was routinely introduced for feeding micropremies in our NICU, improving the mean weight gain up to 19–20 g/kg*d [67].

It has also been shown that targeted fortification of HM based on a daily measurement of macronutrient contents reduces the HM nutritional variability, provides nutritional intakes in the range of recent nutritional recommendations, and leads to adequate individual growth [56,68]. Although individualized fortification is time consuming, expensive and requires additional equipment and well-trained staff, the use of infrared technology to determine macronutrient composition of HM is likely to expand its availability in the NICUs and milk bank. Infrared analyzers could have practical applications in HM banks for DM composition to select specific HM pools with higher protein and/or energy content and allowing optimized fortification. Commercial infrared milk analyzers, originally developed for use in the dairy industry, are available but need to be validated before utilization for clinical HM analysis. Indeed there are

some differences in matrix composition between human and cow milk (oligosaccharides, fatty acid profiles, etc.) and these could interfere with the accuracy and precision of the results. Ideally, an independent calibration algorithm resulting from chemical analysis comparison should be generated for each infrared analyzer [69].

The currently available multicomponent fortifiers are not adequately designed for their use in VLBW infants. They are generally designed to obtain an energy content of 80 kcal/dL and a protein content around 3.1–3.5 g/100 kcal to mimic the nutritional recommendations mainly designed for preterm formula [11]. Due to the relative protein and fat deficit of expressed HM provided by HM banks to the NICU, as well as the difference in protein and energy bioavailability of fortified HM compared to preterm formula, VLBW infants fed fortified HM failed to reach an optimal growth and required extra protein and a lipid supplement. In Europe, fat supplementation is generally provided as a medium chain triglyceride emulsion. However, the fatty acid profile of the fortified HM remains inadequate for preterm infants, especially in terms of LC-PUFA content. An HM-derived cream supplement is now available in the USA, providing 2.57 kcal/mL, mainly as HM fat [60]. The use of an exclusive HM fortifier is attractive as suggested by recent studies [21,24,60] but these pasteurized DM-based liquid fortifiers replace a large proportion of OMM, potentially more beneficial for VLBW infants. In addition, exclusive HM fortifier use is very expensive and only available in USA.

Therefore, newer fortifiers providing high protein and energy intakes with balanced fatty acid and LC-PUFA content, need to be developed to improve the nutritional supply with minimal side effects for the preterm infants. From our recent data, we suggested that an intake of 140 kcal/g*d of energy and 4.2 g/kg*d of protein are necessary to ensure adequate growth [56,60]. These values are slightly higher than those recently recommended by the ESPGHAN [11] or expert committee (WRND) [70]. These recommendations are more related to preterm infants fed formula than to those fed fortified HM, and recent studies suggest that specific recommendations for the use of HM are necessary. These new recommendations need to consider the lower metabolizable energy and protein content of the fortified HM, the effect of pasteurization and the additional nutritional losses suggested during continuous feeding [61].

3.2. Safety

A first challenge of DM is to provide a safe feeding regimen to VLBW infants. For this reason, DM milk should be obtained from established HM banks that follow specific guidelines [15–17]. Donors should be screened by lifestyle questionnaire (alcohol, nicotine, drugs, etc.) and tested serologically for human immunodeficiency virus, hepatitis B and C, syphilis and human T-lymphotropic virus in some countries, in a similar way as for blood donation. DM samples should be checked microbiologically before and after processing. As a safeguard against the transmission of virus and pathogens, the DM must be pasteurized. Currently, Holder pasteurization (process at 62.5°C for 30 min) inactivates most of the viral and bacterial contaminants, is highly effective at minimizing the risk of disease transmission via HM and is recommended by the guidelines of most HM banks [36]. However, HM banks in Norway and Japan have a long tradition of using raw milk, preserving all its bioactive properties but requiring a strict control and screening of donors, especially for CMV infection and bacteria [31,71].

3.3. Effects of the pasteurization process

Indeed pasteurization and, to a lesser extent, storage and processing, result in the loss of some biological and nutritional properties of HM. Holder pasteurization destroys the beneficial microbiota, living white blood cells, IgM and lipase activity, decreases the concentration and activity of immunoglobulins IgA, IgG, lactoferrin, lysozyme, some cytokines [interleukin (IL)-10, IL-1β, tumor necrosis factor-α], some growth factors [insulin-like growth factor 1 (IGF1), IGF2, insulin and adiponectin] and vitamins (C and folate) [12,34]. Other nutritional and biological components, such as oligosaccharides, long-chain polyunsaturated fatty acids, lactose, vitamin A, D, E, B2, some cytokines (IL-2, IL-4, IL-5, IL-12, IL-13) and growth factors (epidermal growth factor and transforming growth factor-β1) are preserved. Therefore pasteurized HM, despite partial destruction of immune components, maintains some bactericidal activity, albeit significantly reduced compared with raw milk [35]. This in-vitro finding might suggest that preterm infants fed pasteurized HM may be more susceptible to clinical bacterial infections and other morbidities than those fed raw milk. However, recent studies did not confirm this hypothesis [26,36].

3.4. Costs

Expense is the most widely reported reason for not providing DM [72]. In 2013 in USA, the average cost of providing DM to preterm infants ranged from $27 to $590 for infants who received no OMM [73]. However, provision of DM to preterm vulnerable infants translates to substantial cost-saving in the NICU due to reduction in NEC and other potential long-term morbidities [6,72,74]. It is less clear whether an exclusive HM diet, including HM-derived fortifier rather than bovine-derived, is similarly cost-effective. The balance of short- and long-term costs and savings needs to be estimated through economic evaluation [18]

4. Criteria for donor milk use

Trends of increasing use of donor HM banks in NICU are increasing: 59% of respondents from level 3 and 4 NICUs in the USA are providing DM in the survey by Hagadorn et al. [72]. The criteria used to initiate DM varied but included: insufficient OMM supply or as a temporary substitute for formula feeding in high-risk preterm infants <1500 g (ranging from 1000 to 1800 g) and/or 32 weeks (ranging from 28 to 34 weeks) or severe intrauterine growth restriction, feeding after proven NEC and post gastrointestinal surgery and, sometimes, in cases of congenital heart disease with potential low gut perfusion. DM is generally discontinued after 33–34 weeks when mothers do not intend to continue breastfeeding. Most units using DM had specified guidelines (79%) for use and required signed parental consent (86%) [44,72].

5. Future research and development

Longer clinical impacts of pasteurized DM feeding of preterm infants need to be established. Several ongoing randomized trials in VLBW infants may answer important questions [18,44]. These studies are investigating the cognitive outcomes of very preterm infants fed DM compared to those fed formula (as supplement to OMM or as the sole diet) in the era of current clinical NICU practice, especially fortification. More than 1100 newborns will be included in the three studies combined, allowing secondary investigation of outcomes of other neonatal morbidities (mortality, NEC, LOS, chronic lung disease, retinopathy) and growth associated with DM. Further large controlled, masked and randomized studies are required to determine the NEC rates when HM is supplemented with HM fortifier compared to HM supplemented with bovine-derived fortifier but lacking formula.

Future research should also focus on development of alternative methods to process HM, preserving its nutritional and bioactive properties while inactivating potential pathogens with a high level

of safety. New pasteurization methods, including ultraviolet irradiation, ultrasonication and high-short-time pasteurization are under investigation [34].

6. Conclusion

Preterm infants are a vulnerable population and nutrition is a major element of care which may contribute to improved growth, and short- and long-term outcomes including neurodevelopment. Fortified OMM is the optimal way to feed VLBW infants. However, when OMM is unavailable or in short supply, fortified human DM bank is recommended as an alternative [1,11,12]. DM offers significant health benefits over formula, especially a reduction in NEC and an improvement in feeding tolerance. Growth may be lower with the use of DM because of its lower nutrient content but an adequate, individualized fortification plan can resolve this problem and achieve appropriate growth. Pasteurization of DM is usually recommended to ensure safety from infectious agents. Pasteurization and additional processing result in a loss of some nutrients and immune functions; however, many bioactive components, absent in formula, remain. Future research should focus on innovative solutions to process HM while preserving its nutritional and bioactive properties with a high level of safety.

In addition to DM availability, considered as one of many strategies to achieve better nutritional outcomes, increased efforts are needed to improve the provision of OMM to preterm infants in the NICU and at discharge, and to evaluate the impact of these combined efforts to reduce the rate of health morbidities in fragile preterm infants. HM banks may also play an important role in promotion of lactation.

Practice points

- Despite pasteurization, DM maintains documented advantages compared to formula.
- Nutrient content of DM is generally less than that of preterm OMM. That difference needs to be compensated with fortification.
- Early HM fortification ($\leq$50 mL/kg*d) for both DM and OMM is necessary to reduce protein and energy cumulative deficits and postnatal growth restriction during the early weeks of life in VLBW infants.
- Individualized fortification reduces the HM nutritional variability, provides nutritional intakes in the range of recommendations, and leads to adequate growth.
- Guidelines for the use of DM have been well established by HM bank organizations. By contrast, guidelines for the use of OMM in the NICU are lacking.
- Due to the variability of HM composition, and the differences in nutrient bioavailability between HM and preterm formulas, specific nutritional recommendations for VLBW infants fed OMM and/or DM need to be designed by scientific expert committees.
- Further research is needed to evaluate the clinical impacts of OMM pasteurization as well as the potential advantages of the use of OMM versus DM in VLBW infants. In addition, further studies are needed to determine, in VLBW infants, the effects on morbidities of HM supplementation with donor HM fortifiers versus specific bovine-derived fortifiers with the exclusion of preterm formula use.

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References

[1] Johnston M, Landers S, Noble L, Szucs K, Viehmann L. Breastfeeding and the use of human milk. Pediatrics 2012;129:e827–41.
[2] Donovan SM. Role of human milk components in gastrointestinal development: current knowledge and future NEEDS. J Pediatr Nutr Gastrointest Tract Dev Funct 2006;149:S49–61.
[3] Ronnestad A, Abrahamsen TG, Medbo S, Reigstad H, Lossius K, Kaaresen PI, et al. Late-onset septicemia in a Norwegian national cohort of extremely premature infants receiving very early full human milk feeding. Pediatrics 2005;115:e269–76.
[4] Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. Pediatrics 1999;103:1150–7.
[5] Corpeleijn WE, Kouwenhoven SMP, Paap MC, van Vliet I, Scheerder I, Muizer Y, et al. Intake of own mother's milk during the first days of life is associated with decreased morbidity and mortality in very low birth weight infants during the first 60 days of life. Neonatology 2012;102:276–81.
[6] Patel AL, Johnson TJ, Engstrom JL, Fogg LF, Jegier BJ, Bigger HR, et al. Impact of early human milk on sepsis and health care costs in very low birth weight infants. J Perinatol 2013;33:514–9.
[7] Lucas A. Long-term programming effects of early nutrition implications for the preterm infant. J Perinatol 2005;25(Suppl. 2):S2–6.
[8] Vohr BR, Poindexter BB, Dusick AM, McKinley LT, Higgins RD, Langer JC, et al. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. Pediatrics 2007;120:e953–9.
[9] Lucas A, Morley R, Cole TJ, Gore SM. A randomised multicentre study of human milk versus formula and later development in preterm infants. Archs Dis Childh Fetal Neonatal Ed 1994;70:F141–6.
[10] Sisk PM, Lovelady CA, Dillard RG, Gruber KJ, O'Shea TM. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. J Perinatol 2007;27:428–33.
[11] Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr 2010;50:85–91.
[12] Arslanoglu S, Corpeleijn W, Moro G, Braegger C, Campoy C, Colomb V, et al. Donor human milk for preterm infants: current evidence and research directions. J Pediatr Gastroenterol Nutr 2013;57:535–42.
[13] Delfosse NM, Ward L, Lagomarcino AJ, Auer C, Smith C, Meinzen-Derr J, et al. Donor human milk largely replaces formula-feeding of preterm infants in two urban hospitals. J Perinatol 2013;33:446–51.
[14] Kantorowska A, Wei JC, Cohen RS, Lawrence RA, Gould JB, Lee HC. Impact of donor milk availability on breast milk use and necrotizing enterocolitis rates. Pediatrics 2016;137:1–8.
[15] Updegrove KH. Donor human milk banking: growth, challenges, and the role of HMBANA. Breastfeed Med 2013;8:435–7.
[16] Donor breast milk banks: the operation of donor milk bank services. London: National Institute for Health and Clinical Excellence.; 2010.
[17] Arslanoglu S, Bertino E, Tonetto P, De Nisi G, Ambruzzi AM, Biasini A, et al. Guidelines for the establishment and operation of a donor human milk bank. J Matern Fetal Neonatal Med 2010;23(Suppl. 2):1–20.
[18] Unger S, Gibbins S, Zupancic J, O'Connor DL. DoMINO: donor milk for improved neurodevelopmental outcomes. BMC Pediatr 2014;14:123.
[19] Quigley M, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev 2014;(4):CD002971.
[20] Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. Lancet 1990;336:1519–23.
[21] Cristofalo EA, Schanler RJ, Blanco CL, Sullivan S, Trawoeger R, Kiechl-Kohlendorfer U, et al. Randomized trial of exclusive human milk versus preterm formula diets in extremely premature infants. J Pediatr 2013;163. 1592 5.e1.
[22] Chowning R, Radmacher P, Lewis S, Serke L, Pettit N, Adamkin DH. A retrospective analysis of the effect of human milk on prevention of necrotizing enterocolitis and postnatal growth. J Perinatol 2016;36:221–4.
[23] Lucas A, Fewtrell MS, Morley R, Lucas PJ, Baker BA, Lister G, et al. Randomized outcome trial of human milk fortification and developmental outcome in preterm infants. Am J Clin Nutr 1996;64:142–51.
[24] Sullivan S, Schanler RJ, Kim JH, Patel AL, Trawöger R, Kiechl-Kohlendorfer U, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. J Pediatr 2010;156. 562 7.e1.

[25] Hein-Nielsen AL, Petersen SM, Greisen G. Unchanged incidence of necrotising enterocolitis in a tertiary neonatal department. Dan Med J 2015;62(7). pii: A5091.
[26] Cossey V, Vanhole C, Eerdekens A, Rayyan M, Fieuws S, Schuermans A. Pasteurization of mother's own milk for preterm infants does not reduce the incidence of late-onset sepsis. Neonatology 2013;103:170–6.
[27] Corpeleijn WE, de Waard M, Christmann V, van Goudoever JB, Jansen-van der Weide MC, Kooi EM, et al. Effect of donor milk on severe infections and mortality in very low-birth-weight infants: the early nutrition study randomized clinical trial. JAMA Pediatr 2016;170:654–61.
[28] Jeurink PV, van Bergenhenegouwen J, Jiménez E, Knippels LMJ, Fernández L, Garssen J, et al. Human milk: a source of more life than we imagine. Benef Microbes 2013;4:17–30.
[29] Vervoort A, Delsat L, Pieltain C, de Halleux V, Rigo J. Evaluation de la qualité bactériologique du lait maternel dans un service de néonatologie (NIC). Revue médicale de Liège 2007;62:159–65.
[30] Schanler RJ, Fraley JK, Lau C, Hurst NM, Horvath L, Rossmann SN. Breastmilk cultures and infection in extremely premature infants. J Perinatol 2011;31:335–8.
[31] Nakamura K, Kaneko M, Abe Y, Yamamoto N, Mori H, Yoshida A, et al. Outbreak of extended-spectrum beta-lactamase-producing Escherichia coli transmitted through breast milk sharing in a neonatal intensive care unit. J Hosp Infect 2016;92:42–6.
[32] Behari P, Englund J, Alcasid G, Garcia-Houchins S, Weber SG. Transmission of methicillin-resistant Staphylococcus aureus to preterm infants through breast milk. Infect Control Hosp Epidemiol 2004;25:778–80.
[33] Gras-Le Guen C, Lepelletier D, Debillon T, Gournay V, Espaze E, Roze JC. Contamination of a milk bank pasteuriser causing a Pseudomonas aeruginosa outbreak in a neonatal intensive care unit. Arch Dis Childh Fetal Neonatal Ed 2003;88:F434–5.
[34] O'Connor DL, Ewaschuk JB, Unger S. Human milk pasteurization: benefits and risks. Curr Opin Clin Nutr Metab Care 2015;18:269–75.
[35] Van Gysel M, Cossey V, Fieuws S, Schuermans A. Impact of pasteurization on the antibacterial properties of human milk. Eur J Pediatr 2012;171:1231–7.
[36] Stock K, Griesmaier E, Brunner B, Neubauer V, Kiechl-Kohlendorfer U, Trawoger R. Pasteurization of breastmilk decreases the rate of postnatally acquired cytomegalovirus infections, but shows a nonsignificant trend to an increased rate of necrotizing enterocolitis in very preterm infants a preliminary study. Breastfeed Med 2015;10:113–7.
[37] Lanzieri TM, Dollard SC, Josephson CD, Schmid DS, Bialek SR. Breast milk-acquired cytomegalovirus infection and disease in VLBW and premature infants. Pediatrics 2013;131:e1937–45.
[38] Mehler K, Oberthuer A, Lang-Roth R, Kribs A. High rate of symptomatic cytomegalovirus infection in extremely low gestational age preterm infants of 22 24 weeks' gestation after transmission via breast milk. Neonatology 2014;105:27–32.
[39] Goelz R, Meisner C, Bevot A, Hamprecht K, Kraegeloh-Mann I, Poets CF. Long-term cognitive and neurological outcome of preterm infants with postnatally acquired CMV infection through breast milk. Arch Dis Child Fetal Neonatal Ed 2013;98:F430–3.
[40] Brecht KF, Goelz R, Bevot A, Krageloh-Mann I, Wilke M, Lidzba K. Postnatal human cytomegalovirus infection in preterm infants has long-term neuropsychological sequelae. J Pediatr 2015;166. 834 9 e1.
[41] Klingenberg C, Embleton ND, Jacobs SE, O'Connell LA, Kuschel CA. Enteral feeding practices in very preterm infants: an international survey. Arch Dis Child Fetal Neonatal Ed 2012;97:F56–61.
[42] Roze JC, Darmaun D, Boquien CY, Flamant C, Picaud JC, Savagner C, et al. The apparent breastfeeding paradox in very preterm infants: relationship between breast feeding, early weight gain and neurodevelopment based on results from two cohorts, EPIPAGE and LIFT. BMJ Open 2012;2. 2012–000834.
[43] O'Connor DL, Jacobs J, Hall R, Adamkin D, Auestad N, Castillo M, et al. Growth and development of premature infants fed predominantly human milk, predominantly premature infant formula, or a combination of human milk and premature formula. J Pediatr Gastroenterol Nutr 2003;37:437–46.
[44] Colaizy TT. Donor human milk for very low birth weights: patterns of usage, outcomes, and unanswered questions. Curr Opin Pediatr 2015;27:172–6.
[45] Schanler RJ, Lau C, Hurst NM, Smith EO. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. Pediatrics 2005;116:400–6.
[46] Marinelli KA, Lussier MM, Brownell E, Herson VC, Hagadorn JI. The effect of a donor milk policy on the diet of very low birth weight infants. J Hum Lact 2014;30:310–6.
[47] Williams T, Nair H, Simpson J, Embleton N. Use of donor human milk and maternal breastfeeding rates: a systematic review. J Hum Lact 2016;32:212–20.
[48] Arslanoglu S, Moro GE, Bellu R, Turoli D, De Nisi G, Tonetto P, et al. Presence of human milk bank is associated with elevated rate of exclusive breastfeeding in VLBW infants. J Perinat Med 2013;41:129–31.
[49] Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics 2001;107:270–3.
[50] Senterre T, Rigo J. Reduction in postnatal cumulative nutritional deficit and improvement of growth in extremely preterm infants. Acta Paediatr 2012;101:e64–70.
[51] Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006;117:1253–61.
[52] Tsang RC, Uauy R, Koletzko B, Zlotkin SH. Summary of reasonable nutrient intakes (mass units) for preterm infants. In: Tsang RC, Uauy R, Koletzko B, Zlotkin SH, editors. Nutrition of the preterm infants scientific basis and practical guidelines. 2nd ed. Cincinnati, Ohio: Digital Educational Publishing, Inc; 2005. p. 415.
[53] Kashyap S, Schulze KF, Forsyth M, Dell RB, Ramakrishnan R, Heird WC. Growth, nutrient retention, and metabolic response of low-birth-weight infants fed supplemented and unsupplemented preterm human milk. Am J Clin Nutr 1990;52:254–62.
[54] Kuschel CA, Harding JE. Multicomponent fortified human milk for promoting growth in preterm infants. Cochrane Database Syst Rev 2004;(1):CD000343.
[55] Pieltain C, De Curtis M, Gerard P, Rigo J. Weight gain composition in preterm infants with dual energy X-ray absorptiometry. Pediatr Res 2001;49:120–4.
[56] de Halleux V, Rigo J. Variability in human milk composition: benefit of individualized fortification in very-low-birth-weight infants. Am J Clin Nutr 2013;98:529S–35S.
[57] De Curtis M, Senterre J, Rigo J, Putet G. Carbohydrate derived energy and gross energy absorption in preterm infants fed human milk or formula. Arch Dis Child 1986;61:867–70.
[58] Rigo J. Protein, amino acid and other nitrogen compounds. In: Tsang RCUR, Koletzko B, Zlotkin SH, editors. Nutrition of the preterm infants. Scientific basis and practical guidelines. 2nd ed. Cincinnati, Ohio: Digital Educational Publishing, Inc; 2005. p. 45–80.
[59] Andersson Y, Savman K, Blackberg L, Hernell O. Pasteurization of mother's own milk reduces fat absorption and growth in preterm infants. Acta Paediatr 2007;96:1445–9.
[60] Hair AB, Blanco CL, Moreira AG, Hawthorne KM, Lee ML, Rechtman DJ, et al. Randomized trial of human milk cream as a supplement to standard fortification of an exclusive human milk-based diet in infants 750 1250 g birth weight. J Pediatr 2014;165:915–20.
[61] Tabata M, Abdelrahman K, Hair AB, Hawthorne KM, Chen Z, Abrams SA. Fortifier and cream improve fat delivery in continuous enteral infant feeding of breast milk. Nutrients 2015;7:1174–83.
[62] Spalinger J, Hascoet J-M, Billeaud C, Picaud J-C, Mosca F, Rubio A, et al. Growth and nutritional biomarkers of preterm infants fed a new powdered human milk fortifier: a multicenter, randomized, controlled, double bind clinical trial. Selected Abstracts of the 1st Congress of joint European Neonatal Societies (jENS 2015); Budapest (Hungary); September 16-20, 2015; Session "Nutrition and gastroenterology". J Pediatr Neonatal Individual Med 2015;4(2):e040210. doi: 107363/040210 2015:Abs 45 pp 37–8
[63] Hair AB, Hawthorne KM, Chetta KE, Abrams SA. Human milk feeding supports adequate growth in infants ≤1250 grams birth weight. BMC Res Notes 2013;6:459.
[64] Arslanoglu S, Moro GE, Ziegler EE. Adjustable fortification of human milk fed to preterm infants: does it make a difference? J Perinatol 2006;26:614–21.
[65] Roggero P, Giannì ML, Morlacchi L, Piemontese P, Liotto N, Taroni F, et al. Blood urea nitrogen concentrations in low-birth-weight preterm infants during parenteral and enteral nutrition. J Pediatr Gastroenterol Nutr 2010;51:213–5.
[66] Polberger S. New approaches to optimizing early diets. Nestle Nutr Workshop Ser Pediatr Program 2009;63:195–204. discussion 204 8, 259 68.
[67] de Halleux V, Close A, Stalport S, Studzinski F, Habibi F, Rigo J. Intérêt de la supplémentation du lait maternel «à la carte». Archives de Pédiatrie 2007;14(Suppl. 1):S5–10.
[68] Rochow N, Fusch G, Choi A, Chessell L, Elliott L, McDonald K, et al. Target fortification of breast milk with fat, protein, and carbohydrates for preterm infants. J Pediatr 2013;163:1001–7.
[69] Fusch G, Kwan C, Huang RC, Rochow N, Fusch C. Need of quality control programme when using near-infrared human milk analyzers. Acta Paediatr 2016;105:324–5.
[70] Koletzko B, Poindexter B, Uauy R. Recommended nutrient intake levels for stable, fully enterally fed very low birth weight infants. World Rev Nutr Diet 2014;110:297–9.
[71] Grovslien AH, Gronn M. Donor milk banking and breastfeeding in Norway. J Hum Lact 2009;25:206–10.
[72] Hagadorn JI, Brownell EA, Lussier MM, Parker MG, Herson VC. Variability of criteria for pasteurized donor human milk use: a survey of U.S. neonatal intensive care unit medical directors. J Parenter Enteral Nutr 2016;40:326–33.
[73] Carroll K, Herrmann KR. The cost of using donor human milk in the NICU to achieve exclusively human milk feeding through 32 weeks postmenstrual age. Breastfeeding Med 2013;8:286–90.
[74] Colaizy TT, Bartick MC, Jegier BJ, Green BD, Reinhold AG, Schaefer AJ, et al. Impact of optimized breastfeeding on the costs of necrotizing enterocolitis in extremely low birthweight infants. J Pediatr 2016;175. 100–5.e2.