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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 ≥ Bell's stage 2 in preterm infants ≤32 weeks and ≤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

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