

REVIEW ARTICLE

Review concludes that specific recommendations are needed to harmonise the provision of fresh mother's milk to their preterm infants

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ABSTRACT

Aim: There are no specific recommendations for using a mother's fresh milk for her preterm infant. We reviewed the available evidence on its collection, storage and administration.

Methods: The working group of the French Neonatal Society on fresh human milk use in preterm infants searched the MEDLINE database and Cochrane Library up to June 2017 for papers published in English or French. They specifically analysed 282 papers providing information on prospective, retrospective and clinical studies and examined guidelines from various countries.

Results: The review concluded that fresh mother's own milk should be favoured in accordance with the latest recommendations. However, it must be carried out under stringent conditions so that the expected benefits are not offset by risks related to different practices. The working group has summarised the best conditions for feeding preterm infants with human milk, balancing high nutritional and immunological quality with adequate virological and bacteriological safety. Professionals must provide parents with the necessary conditions to establish breastfeeding, together with specific and strong support.

Conclusion: Based on their review, the working group has made specific recommendations for using fresh mother's own milk under careful conditions, so that the expected benefits are not offset by risks related to practices.

INTRODUCTION

Providing preterm infants with human milk has been associated with significant health benefits. Mother's own milk is preferable, but when it not possible, the first alternative should be donor human milk that has been pasteurised and delivered by a human milk bank (1–4). While donor human milk has often been considered as a health product, fresh mother's own milk has been considered as a food in regulatory frameworks. As a result, donor human milk is subject to specific regulations, but there are no recommendations for the use of fresh mother's own milk. However, it is not desirable to apply the same criteria to both types of milk. Fresh mother's own milk is increasingly used, but the practices are very variable. To harmonise these practices, a working group met in France, under the auspices of the French Neonatal Society to propose specific recommendations.

It is important to check three points before a child is fed with its mother's own fresh milk or with donated milk from a human milk bank. Firstly, we need to consider whether any medical treatment the mother is receiving is compatible with breastfeeding. The number of drugs that are contraindicated during breastfeeding is low and clinicians should refer to reliable and updated databases for

Abbreviations

BW, Birth weight; GA, Gestational age.

Key notes

- The working group of the French Neonatal Society on fresh human milk use in preterm infants reviewed papers and guidelines up to June 2017 to fill this gap in the knowledge.
- They concluded that fresh mother's own milk should be favoured in accordance with the latest recommendations.
- However, its provision must be carried out under careful conditions so that the benefits are not offset by risks related to different practices.

information. Secondly, clinicians should consider the results of serological tests for viral infections, such as the human immunodeficiency virus, hepatitis B, hepatitis C and human T-lymphotrophic virus. Finally, the traceability from collection to the administration of human milk is important. This includes clear and precise labelling to identify the date and time of collection, which is required to prevent any risk of bottle exchanges between different children (4).

Providing fresh mother's own milk should be part of a global strategy that includes strong and specific breastfeeding support for mothers who deliver preterm (5) and healthcare organisations should optimise how they collect, store and handle the administration of fresh mother's own milk. This process should be associated with a donor human milk programme, which has been shown to increase consumption of mother's own milk during hospitalisation and at discharge (6). A study performed in 19 European regions showed extreme variations in the percentage of preterm infants receiving any breast milk at discharge, from 36 to 80% (7).

METHODS

The MEDLINE database and Cochrane Library were used to carry out a bibliographic search up to June 2017. We used the terms presented in Table 1, together with colostrum, breastfeeding, human milk composition, neonatal infection, cytomegalovirus and *Bacillus cereus*.

The search was restricted to papers published in English and French. Prospective, retrospective and clinical studies were reviewed. Recommendations published by French authorities, such as the National Agency for Food, Environmental and Occupational Safety, and the American Centers for Disease Control, were collected. Guidelines from societies in different countries were also compiled. For example, we considered the guidelines produced by the

American Academy of Pediatrics, the United Kingdom National Institute for Health and Care Excellence, the Swedish Milknet, French guidelines and the latest recommendations from Europe (1,3,8–13).

The working group selected 1077 papers and specifically analysed 282 papers to summarise the knowledge they contained and address the following questions. Firstly, they looked at how to support the breastfeeding of premature infants and examined the capacity of preterm infants to suckle directly. Secondly, they examined how to ensure that the nutritional needs of very preterm infants were met by fresh mother's own milk. Thirdly, they explored the question about how to ensure the microbiological safety of the administration of fresh mother's own milk to premature infants. The fourth question was how to ensure the safety of the administration of fresh mother's own milk to premature infants with regard to the risk of the cytomegalovirus infection. The fifth question concerned the demonstrated benefits of fresh mother's own milk compared to processed human milk.

RESULTS

Supporting the breastfeeding of premature infants

One of the keys to the success of breastfeeding a premature child is the precocity of breastfeeding (Table 2). No minimum gestational age has been reported, and the child does not need to demonstrate their ability to drink from a bottle in order to breastfeed (14). Given the opportunity, some premature babies have been shown to be capable of effective suckling as early as 31–32 weeks or being exclusively breastfed well before 37 weeks (15). The effectiveness of breastfeeding should be assessed by a validated observation scale. An evaluation of the child's ability to feed in sufficient quantities to gain weight regularly is an essential part of their individualised care.

Caregivers and parents must learn to recognise when a child can endure being stimulated and encouraged to suckle and when they need time to recover. Knowledge about breastfeeding in preterm infants should be updated and team practices should be harmonised so that parents receive clear and scientific information that is delivered without ambiguity.

The rate of premature infants that are breastfed at the end of the neonatal care period is a good indicator of the quality of care, and these data should be collected and monitored by each neonatal unit.

Table 1 Definitions

- **Mother's own milk.** Mother's milk for her own infant
- **Raw milk.** Milk which has not undergone any treatment
- **Refrigerated milk.** Milk stored at a temperature of 4°C
- **Fresh milk.** Milk which has not been frozen or pasteurised. Corresponds to 'raw' or 'refrigerated' milk. Often called 'expressed breast milk' in the literature
- **Frozen milk.** Milk preserved at a temperature of at least -18°C ($\pm 2^{\circ}\text{C}$)
- **Thawed milk.** Milk frozen and then returned to the liquid state
- **Pasteurised milk.** Milk heated at a temperature of 62.5°C for 30 minutes (holder method)
- **Donor milk.** Mother's milk intended for a child other than his own, after passing through a human milk bank (« banked milk »)
- **Milk-sharing.** Exchange of raw milk between mothers. In no case this milk can be called 'donor milk'
- **Human milk banks.** Structures authorised to collect, process and distribute donated human milk
- **Fortifier.** Product containing energy, protein, electrolytes, minerals, trace elements and vitamins ('multicomponent fortifier'), used to fortify human milk for premature infants

Table 2 Supporting breastfeeding of premature infants – Key points

- Premature infants have the ability to breastfeed early enough
- Caregivers and parents must be able to support these skills
- The time from which the child can suck is variable in each child
- The effectiveness of breastfeeding should be assessed on the child's ability to feed in sufficient quantities to achieve growth at least equivalent to fetal growth

Ensuring fresh mother's own milk meets the nutritional needs of very preterm infants

Enteral feeding should start as soon as possible, to shorten the exposure to the intravenous catheters required for parenteral nutrition, and this is the same for fresh mother's own milk and pasteurised human milk. The nutrients supplied by human milk depend on its composition and on treatments such as refrigeration, freezing, pasteurisation and fortification. It also depends on whether it is administered directly from the breast or through a tube, using continuous or bolus administration (Table 3). Mother's own milk should be used as quickly as possible, due to its particular composition. Compared to mature human milk, such as donor human milk, it has higher protein content and there are also differences in its energy and mineral content (16). This is particularly clear in the mothers of extremely preterm infants during the first eight weeks of lactation (17).

A recent review showed that fortified human milk improved growth when it was compared with unfortified human milk, without increasing the risk of feeding intolerance or necrotising enterocolitis (18). It is usually based on the use of a multi-component fortifier, allowing standardised fortification. As the nutrient content of human milk is naturally highly variable, fortification may prove to be insufficient or excessive. Therefore, individualised – targeted or adjustable – fortification has been proposed. Targeted fortification was based on adjusting the nutritional content of human milk to reach a target composition. Adjustable fortification consisted of adding protein based on serum urea concentration (19). There is no current consensus on the optimal method to fortify human milk. It appears to be desirable to begin fortification as soon as a significant volume of enteral feeding has been well tolerated, and this has been quantified as about 50–100 mL/kg per day. There has been no evidence so far of the growth benefits of starting fortification earlier (20). Considering that the nutritional requirements of premature infants remain high until 36 weeks, some studies have suggested fortifying human milk up to this corrected gestational age

(21,22). A review reported that there was no strong evidence to recommend human milk fortification after discharge (23). However, it could be relevant when nutritional requirements remain high at discharge, for example when the infant is experiencing a growth deficit or bronchopulmonary dysplasia.

Raw mother's own milk should be promoted, as it avoids human milk treatments such as refrigeration, freezing or pasteurisation. The impact that treating human milk has on its nutritional qualities has been investigated. Storing human milk at 4–6°C for up to 96 hours had no major effects on the nutritional content, enzymes and osmolality of human milk (24). However, it did reduce the concentration of vitamin C, alter the antioxidant capacities of human milk and induce lipolysis with increased free fatty acid concentrations and decreased pH (24,25). Fatty acids have cytolytic effect on pathogens (26). Freezing human milk at –20°C and thawing it has been shown to have a limited impact on nitrogen, lipids and lactose contents and on the activities of lipoprotein lipase and bile salt stimulated lipase. However, one study found that the vitamin C concentration in human milk was reduced by two-thirds after two months at –20°C (25). Pasteurisation has no major influence on the nutritional quality of human milk and one study reported that it induced a slight reduction in fat content (–5%) and bigger reductions in vitamins C, D and B6. Bile salt stimulated lipase has also been reported to be destroyed by pasteurisation (27). As this lipase has been said to contribute to only 20–25% of fat absorption in premature infants, it could explain the absence of its significant impact on short-term growth (28,29). However, direct breastfeeding should be favoured as it helps to avoid nutritional losses.

The way that human milk is administered has been shown to have a significant influence on its nutritional value. For example, when human milk is administered using tubes or syringes, it loses between a third and a half of the lipids as the fats adhere to the plastic walls (30) and fat losses have been shown to increase with the duration of administration, regardless of whether it is continuous or bolus. Therefore, the impact of feeding modes was much greater than the impact of pasteurisation.

Postnatal growth is influenced by the type of human milk ingested. There were no randomised studies that compared fresh and pasteurised human milk that considered postnatal growth in weight, length and head circumference as the primary endpoint. An observational study analysed postnatal growth in preterm infants fed fortified human milk. It compared fresh mother's own milk from mothers who delivered prematurely and pasteurised and freeze-dried donor human milk from mothers who delivered at term. The study found that weight gain was directly proportional to the amount of fresh mother's own milk received, with no effect on the other anthropometric parameters (31). A case-control study found no significant difference in weight gain between premature infants receiving their mother's own milk and others receiving pasteurised donor human milk (32). A randomised study of more than 300 premature infants receiving fortified mother's own milk, which was

Table 3 Ensuring fresh human milk meets nutritional needs of very preterm infants – Key points

- Start enteral feeding with human milk as soon as possible
- Promote the use of mother's own milk as quickly as possible, due to its particular composition
- Fortify human milk to cover nutritional needs. Individualise fortification
- Start human milk fortification early, when enteral intake reaches 50–100 mL/kg day
- Continue fortification at least until 35–36 weeks, or even longer in infants with sub-optimal growth
- Promote the use of raw mother's own milk to avoid treatment such as refrigeration, freezing or pasteurisation
- Favour breast feeding as early as possible, to avoid nutrient's losses
- Favour discontinuous feeding to reduce fat losses
- When human milk is fortified appropriately, pasteurisation of the milk has no deleterious effect on the postnatal growth of premature infants

either raw or pasteurised, showed no significant difference in growth between the two groups (33). Therefore, when human milk was fortified appropriately, pasteurisation has no adverse effect on the postnatal growth of premature infants.

In summary, premature infants should ingest their mother's own milk directly from her breast or as soon as possible after its collection when the infant does not yet have the ability to suckle. Continuous administration of human milk should be limited to situations where it is actually justified, such as instability or digestive intolerance. Organisations must favour the administration of fresh mother's own milk and the time between the extraction of milk and its administration must be as short as possible. Every effort should be made to ensure that the administration and treatment procedures have the least possible impact on the nutritional and immunological properties of the milk.

Ensuring the bacteriological safety of fresh mother's own milk

Human milk is a non-sterile complex ecosystem, which reflects the mother's biotope and may contain a combination of non-pathogenic germs and potentially pathogenic germs. Human milk microbiota has been shown to differ according to gestational age at birth (34). When mothers delivered preterm, the diversity was lower and the counts of staphylococci were higher, with more prevalent virulence-related genes (34).

As human milk is a biological product, there is always concern about its contamination, whether from a donor mother or from infant's own mother (3). Ensuring the microbiological safety of human milk requires avoiding any microbial contamination or proliferation, while preserving the immune components (Table 4). Bacterial contamination carried the risk of sepsis, with particularly significant consequences in the most immature infants (35,36).

Contamination of human milk has been reported during the collection, transport, handling, storage and pasteurisation stages, as well as during the cleaning of equipment. The micro-organisms most often involved were *Coagulase-negative Staphylococci*, *Staphylococcus Aureus* and *Enterobacteriaceae*. Studies have shown that approximately 10–40% of human milk samples collected from mothers in neonatal units were contaminated with pathogenic germs (37,38). The clean collection of expressed breast milk is crucial to obtain milk with very little bacteria, as it has an impact on acceptable storage duration (39). Collecting human milk in neonatal units was shown to significantly reduce the risk of microbial contamination when it was compared to home collection (40–42). The guidelines for the collection and handling of breast milk must be followed, both at the hospital and at home (42–44).

In 2005, the French National Agency for Food Safety recommended that mother's own milk should be pasteurised if it had not been used in the 48 hours since collection (43). Then it should be handled in the same way as human milk from an anonymous donor (11). In other

Table 4 Bacteriological safety of fresh human milk – Key points

- Human milk contains non-pathogenic germs and potentially pathogenic germs
- The risk of contamination or bacterial proliferation is related to the modalities of expression and failure to observe good hygienic practices. Breast feeding reduces this risk
- Collection of milk in neonatal unit significantly reduces the risk of contamination compared to home collection. The good hygiene of collecting and storing milk is essential
- Both raw and pasteurised human milk have bactericidal properties, which are higher in raw milk
- Fortified HM must not be stored for more than 30 hours refrigerated
- Considering the usual conditions of fresh milk storage at 4–6°C in daily practice, it should not exceed 48 hours. Longer duration – up to eight days – has been suggested, but requires very clean and strict conditions
- Fresh milk storage at –18°C should not exceed three months. An extension to nine months could be acceptable in strict conditions of storage, until further studies confirm that it is safe in different settings
- The administration of fresh maternal milk to premature infants should be coupled with monitoring of maternal health status during their maternity stay, but also after the mother's returned home
- The organisms usually considered as pathogens are gram negative bacilli, group B streptococci, *Staphylococcus aureus*, enterococci and *Bacillus cereus*
- The risks associated with pathogenic germs are particularly high in the most immature children (gestational age below 28 weeks or body weight below 1000 g)
- A strategy is proposed to reduce the risk of contamination of milk and transmission of bacteria to the child, based on the conditions of collection of the milk and on the characteristics of the infant (gestational age and body weight)

countries, mother's own milk is not pasteurised. It is either given to the preterm infant immediately, or kept frozen and then thawed before being given to them. It is managed by dedicated staff in dedicated places (45,46). Our working group considers that, if these conditions are met, the use of unpasteurised frozen mother's own milk may be considered by neonatal units.

Fortification, prolonged storage and pasteurisation can modify the anti-infectious properties of human milk. The bactericidal activity of human milk from mothers who delivered at term was greater than the milk from those who gave birth prematurely (47). It was efficient for at least 48 hours if the milk was refrigerated in good conditions, namely at a maximum temperature of 4°C (24). Both raw and pasteurised, human milk has been shown to inhibit bacterial growth and this inhibition was greater in raw (95%) than pasteurised human milk (80%) (47). This effect was reported both in human milk from mother who delivered at term or prematurely and whatever the germs (47). Human milk is routinely fortified in advance and refrigerated before its administration to hospitalised infants. Time is required to put human milk in bottles or syringes for all hospitalised infants and then to transfer and store the human milk in the unit. It usually takes 24–30 hours between the preparation of fortified human milk and the administration of the last bottle or syringe to the infants. On

in vitro study showed that fortification slightly reduced the bactericidal capacity of human milk (48). However, when this was evaluated in conditions that reproduced routine practice, fortification did not affect the bacterial growth in refrigerated human milk after 72 hours (49). As fortification has been shown to have other effects, such as increased human milk osmolality, it is not recommended that it is refrigerated for 72 hours. However, 30 hours is acceptable.

The effect of storage on the properties of human milk depends on the temperature and duration of storage. Storage at 4–6°C (39–43°F) for 48 hours did not result in a reduction in bactericidal capacity (50). When it was extended to 72 hours, bactericidal capacity and total antioxidant capacity were halved (50,51). An upper limit of 72 hours has been proposed by the Academy of Breast-feeding medicine for home use for full-term infants (39). The Academy considered that an upper limit of eight days was acceptable when the milk was collected in a clean, careful way and stored in the back of the refrigerator (39). One study reported that fresh human milk can be stored at 4°C for 96 hours without compromising its overall integrity (24). Another study that continuously monitored refrigerator temperature in the neonatal unit reported that despite the thermostat being set to 5°C, the temperature range was between 4 and 9.6°C (52). As ideal conditions for collection and storage are not the norm, an upper limit of 48 hours offers optimal safety. More studies performed in routine conditions are needed to validate any extended duration.

When the milk was stored at –18°C (0°F), an upper limit of six months and 12 months was considered respectively optimal and acceptable for home use for full-term infants (39). Human milk had to be stored in sealed containers placed in the back of the freezer to prevent intermittent rewarming due to the freezer door opening (39). There was scant data to justify these limits and there are still discrepancies. Few studies showed that lysozyme, secretory immunoglobulin A and macrophages were reduced in human milk frozen for one month and that freezing for three months or more lowered lactoferrin concentrations (53,54). Furthermore, it was reported that the bactericidal activity of human milk that had been frozen for seven days was similar to fresh human milk, but longer times were not tested (50). On the other hand, one study reported that immunoactive components were preserved and the bacterial count decreased in human milk stored for nine months at –20°C (55). Definitions of the upper limit should consider these data, together with the decrease in vitamin C and lactoferrin reported after two to three months. Then, an upper limit of three months for human milk storage at –18°C could be proposed. Nine months could be acceptable in well-controlled storage conditions, until further studies confirm that it is safe in different settings with different routine practices.

Proposed limits should aim to maintain fresh mother's own milk properties in routine daily practice, when storage conditions are not as well controlled as in research studies. Preferably, the storage should not exceed 48 hours at 4°C and three months at –18°C. However, longer storage

durations could be acceptable, but could have a greater impact on the anti-infectious and nutritional properties of human milk.

Pasteurisation has been shown to significantly decrease the concentration of lactoferrin, immunoglobulins, lysozyme and human milk cells (27). It has also been reported to decrease its bactericidal activity by 25% (27). The recommended shelf life of frozen pasteurised human milk is six to eight months (4,8,56).

Is the bactericidal effect of fresh mother's own milk sufficient to offset any microbial contamination of breast milk with pathogenic organisms? It has been shown that infants who received fresh mother's own milk were exposed to pathogenic bacteria without systematically developing an infection (38). On the other hand, there is a documented risk of severe infections in preterm infants fed with contaminated human milk. The most common microorganisms were *Streptococcus B*, *Staphylococcus aureus* and enterobacteria, namely *Escherichia coli*, *Klebsiella pneumoniae* and *Salmonella*. While fresh mother's own milk has been used in many countries, the incidence of bacterial infections transmitted by human milk has been difficult to quantify precisely, but seems very low (32). However, premature infants fed with fresh mother's own milk or pasteurised donor human milk had fewer infections than those fed with preterm formulas.

Infections related to the ingestion of fresh mother's own milk have sometimes been associated with symptoms in the mother such as mastitis, fever and endometritis. Therefore, the administration of fresh human milk must be associated with monitoring of maternal health in the maternity ward and after they return home. These clinical follow-ups must be organised, and the mothers need to be informed of the importance of reporting any evocative symptoms to health professionals. Any unexplained fever in a nursing mother should prompt the mother to look for mastitis. If severe mastitis is diagnosed, mothers should be advised not to give their infant fresh human milk pending the results of bacteriological tests on the milk (57).

Some authors have suggested bacteriological monitoring of fresh breast milk and removing human milk contaminated with pathogenic germs (58). Several bacteria are considered unacceptable because they are usually pathogenic, such as Gram negative bacilli, including *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella*, *Enterobacter*, *Serratia*, *Salmonella* and *Proteus*, Group B streptococcus, and *Staphylococcus aureus* (36,53,59). *Bacillus cereus* is an environmental pathogen that is found in neonatal units and has been associated with severe sepsis in preterm infants (60,61). However, these studies did not find any reported cases of *B. cereus* infection related to human milk. Despite that, this germ is highly dangerous for immunodepressed preterm infants and may be present when mothers pump their milk (62). Therefore, our working group has included *B. cereus* in the list of pathogens that are unacceptable.

Benefits of a diet with human milk have been reported in preterm infants (63,64). However, it is difficult to decide between the advantages of a diet with raw human milk and

the possible risks of contamination by pathogenic germs, especially for the most immature children whose immune competencies are lower than in infants born at term (65). Our working group considered that this risk particularly concerned preterm infants born before 28 weeks or with a birthweight below 1000 g.

The working group feels that it is necessary to check the bacteriology of fresh mother's own milk under certain conditions. However, in the absence of strong evidence, it can be acceptable to give the infant human milk pending the result of the culture. Considering the available evidence, the working group proposes a strategy that is based on the conditions of the human milk collection and on the characteristics of the infant (Fig. 1). The review found scant data to determine the limits of gestational age and birthweight below which bacteriological testing could be recommended more precisely. As a result, the limits that have been established by the working group are consistent with those proposed for the prevention of the cytomegalovirus infection (Fig. 1).

When a mother collects more human milk than her own preterm infant needs, this excess milk can go be donated to

a human milk bank. However, if it does not meet the bacteriological criteria for donor human milk, it should be destroyed according to the guidelines (8,9,11). The bacteriological criteria used for donor human milk in human milk banks should not apply to the fresh human milk given by a mother to her own infant in a neonatal unit.

Ensuring the virological safety of fresh human milk

In developed countries, it is considered that mothers with the human immunodeficiency virus should not breastfeed their child. Hepatitis B does not contraindicate breastfeeding, subject to effective passive-active immunoprophylaxis at birth, and Hepatitis C does not contraindicate breastfeeding. When human t-lymphotrophic virus serology is performed in at-risk populations originating from endemic areas, its positivity contra-indicates breastfeeding. However, feeding with unpasteurised mother's own milk can be started, even when the results of human T-cell lymphotropic virus serology are pending. Indeed, the risk of its transmission has been linked to prolonged breastfeeding (66). When maternal serology for all these viruses is positive, human milk cannot be used by human milk banks

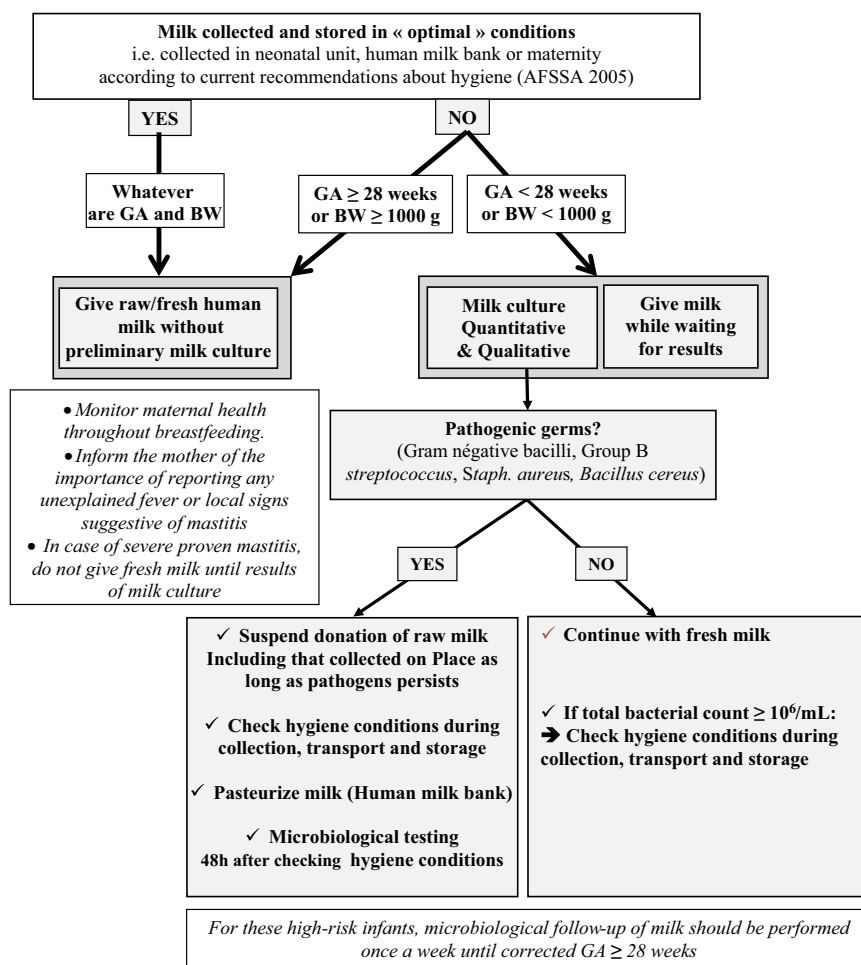


Figure 1 Proposed strategy to reduce the risk of transmission of pathogenic bacteria to preterm infants through fresh breast milk.

Table 5 Virological safety of fresh human milk – Key points

- Viral serology (human immunodeficiency virus, hepatitis B and C, \pm human T-lymphotrophic virus) should be checked before allowing fresh milk to be administered to preterm infants. Hepatitis B (subject to sero-vaccination) and C are not contraindications to breastfeeding
- Cytomegalovirus is virtually systematically excreted by all seropositive mothers from the colostral phase (but in small amounts) with a peak of excretion between four and eight weeks
- Pasteurisation destroys cytomegalovirus (not freezing)
- The postnatal transmission rate of raw or frozen mother's milk varies from 8 to 37% and the percentage of infected children from 7 to 10%
- The severity and consequences of postnatal cytomegalovirus infection are dependent on gestational age, early transmission, viral load in human milk, ratio of IgG anti-cytomegalovirus in newborn and in mother at birth and severity of the associated neonatal morbidities
- Available data about the longer-term neurosensory consequences are contradictory, due to low numbers and methodological weaknesses
- A strategy is proposed to reduce the risk of cytomegalovirus transmission, based on the maternal cytomegalovirus serological status at the end of pregnancy or delivery, and on the characteristics of the infant

(Table 5) (8,9,11,13). To date, there are no reported cases of pasteurised donor human milk causing an infection with hepatitis or human immunodeficiency viruses (3).

There is also a risk of the cytomegalovirus being transmitted via breast milk and one study showed that the prevalence of this virus was approximately 60% in pregnant women. The presence of immunoglobulin G anti-cytomegalovirus in maternal serum was nearly systematically associated with cytomegalovirus excretion in mother's milk (66). It is excreted very early, at the colostral stage, but in fairly low quantities. The cytomegalovirus content of human milk is at its highest level four to eight weeks postpartum (67). Some studies and meta-analyses have suggested that freezing human milk would reduce the risk of it being infectious, but that this would only be partially effective (68,69). On the contrary, pasteurisation eliminated the cytomegalovirus from breast milk (Table 5) (70).

The postnatal transmission of cytomegalovirus via human milk in term neonates and moderately premature infants is usually asymptomatic and has no long-term consequences. They are protected by maternal antibody transmission from the third trimester, which does not occur in infants born very preterm at <32 weeks. Indeed, their immunity has been shown to be immature (71).

The rate of postnatal cytomegalovirus transmission by raw or frozen human milk has been reported to be 8–37% (72) and another studied stated that the percentage of infected infants was 7–10% and that 3–5% presented with severe infections (70). Observational studies in small populations did not reveal additional morbidity during hospitalisation, while others reported significant postnatal morbidity and longer-term neurosensory consequences (70–74).

The reported risk factors for symptomatic cytomegalovirus infections have included low birthweight and extreme prematurity (71,72), as well as additional morbidity, the

viral load in human milk, premature rupture of the membranes and sepsis during the first weeks of life (75). In a review, severe infections occurred in infants born before 26 weeks, especially if they had significant co-morbidities and the cytomegalovirus transmission occurred before eight weeks of life (76). The authors advocated pasteurisation of human milk during the first six to eight weeks of life for those children (76).

The impact of postnatal cytomegalovirus infections on the neurodevelopment of preterm infants has been difficult to assess. In 2012, the American Academy of Paediatrics considered that the value of routinely feeding human milk from seropositive mothers outweighed the risks of long-term neurodevelopmental abnormalities (1,77). It was based on five studies published between 1980 and 2005. Since then some studies on infants born before 34 weeks have suggested a negative impact on cognitive development, while others did not find any effect (71,73,74).

In summary, the most immature infants face the highest risk of complicated cytomegalovirus infections. Therefore, infants born before 28 weeks, or with a birthweight below 1000 g, should benefit from specific prevention strategies when their mother is cytomegalovirus positive.

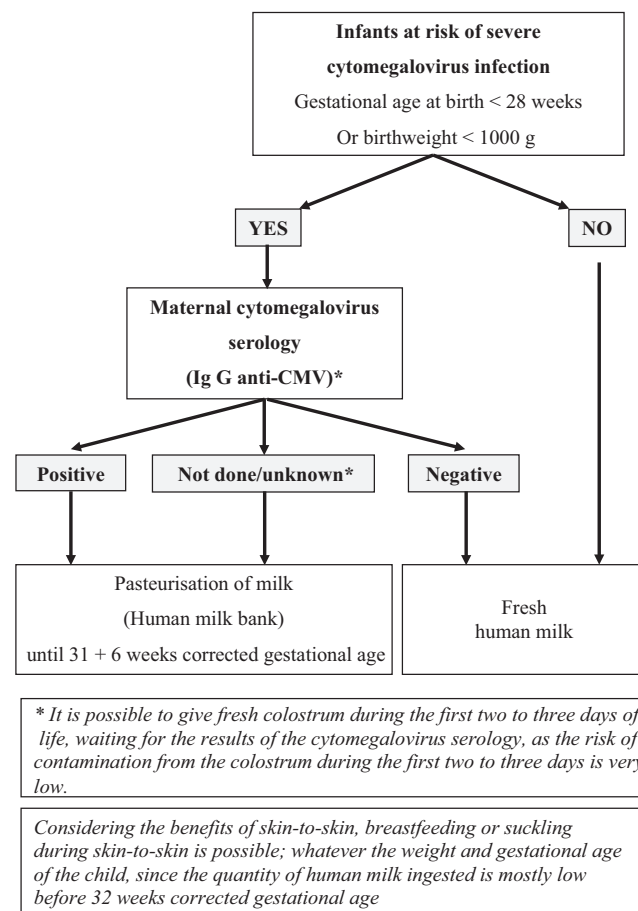


Figure 2 Proposed strategy to reduce the risk of transmission of cytomegalovirus to preterm infants through fresh breast milk.

Table 6 Benefits related to fresh human milk in preterm infants – Key points

- Human milk is beneficial for the health of preterm infants compared to preterm formulas
- Gastric emptying is faster with fresh human milk than with preterm formula
- Few studies have actually compared the fresh HM and the pasteurised HM
- Available studies reported an equivalent effect of fresh milk and pasteurised milk on digestive tolerance, prevention of necrotising enterocolitis, late-onset sepsis and weight gain during hospitalisation
- Studies are needed on the cognitive development of preterm infants fed with fresh or pasteurised human milk
- Fresh colostrum could be beneficial to the health of preterm infants, but further studies are needed. It is possible to administer fresh colostrum if this is performed under strict conditions of hygiene
- The administration of fresh milk is part of the individual care offered in neonatology and is useful for supporting the parent-child relationship

At present, there is no consensus on the risk-benefit balance of fresh breast milk and cytomegalovirus infections in very low birthweight infants. Therefore, our working group proposes a strategy based on the mother's serological status and on the characteristics of the infant (Fig. 2). It should be noted that there is no need to search for the cytomegalovirus in the mother's milk due to technical difficulties. The decision to administer fresh mother's own milk in the case of positive maternal serology should only be done after the parents are informed about the risks and benefits.

Evidence for the benefits of raw human milk versus treated human milk

The use of fresh mother's own milk is theoretically beneficial, as it retains the greatest nutritional and immune components. However, very few studies have actually compared neonatal morbidity and mortality and the long-term development of preterm infants fed fresh human milk or pasteurised human milk. Despite this, numerous studies have shown that raw or pasteurised mother's milk was superior to preterm formula (Table 6).

One study showed that gastric emptying was slightly faster in preterm infants fed with fresh human milk than with pasteurised human milk and, in turn, this was faster than infants fed with a preterm formula (78). In a randomised study, Cossey et al. did not report any significant difference in digestive tolerance and the incidence of necrotising enterocolitis, confirming previous observational studies (33,79). It was probably due to the fact that holder pasteurisation does not destroy the components that have a maturational effect on the digestive tract (27).

Theoretically, fresh or frozen human milk should be more effective than pasteurised human milk in preventing late-onset sepsis. However, two randomised studies reported a similar incidence of sepsis (33,80) and other non-randomised studies reported similar findings (32,67).

Data from the literature suggest that feeding premature infants with breast milk promoted their psychomotor development when compared to those fed with preterm formulas

(81). However, there have not been any studies that have compared the psychomotor development of premature infants fed with fresh or pasteurised mother's own milk.

Fresh colostrum has been proposed because of its composition, particularly when mothers who have given birth prematurely (82), but very few randomised studies have evaluated the health benefits of giving colostrum to preterm infants. One study suggested that it could help to reduce the number of cases of clinical late-onset sepsis, but without reducing the number of bacteriologically proven infections (83). Studies in preterm infants have not reported beneficial effects on mortality, digestive tolerance, necrotising enterocolitis or other morbidities (84). The potential benefits should be weighed against the risks associated with bacterial contamination of colostrum when handling colostrum during collection, storage and administration (84,85). In summary, there is insufficient evidence to recommend whether or not to administer colostrum. Each neonatal unit has to decide whether or not it will provide colostrum for hospitalised preterm infants and if they decide to do this it must be provided under appropriate hygienic conditions.

CONCLUSION

Providing infants with fresh milk from their own mothers should be the favoured method of feeding, in accordance with the most recent recommendations. It must be carried out under careful conditions so that the expected benefits are not offset by risks related to practices. Professionals must provide parents with the necessary conditions so that they can establish breastfeeding, together with specific and strong support for breastfeeding.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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