Original Article

# Evidence summary of human milk fortifier in preterm infants

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**Background:** To search for and collect evidence on human milk fortifier in preterm infants, and to summarize the latest and best evidence, so as to provide reference for clinical work.

**Methods:** We searched the databases of UpToDate, American Guide Network, Cochrane Library, Joanna Briggs Institute (JBI), PubMed, ResearchGate, China National Knowledge Infrastructure (CNKI), Wan Fang, Chinese Biology Medicine disc (CBM), and Yi Maitong, and collected relevant guidelines, systematic reviews, evidence summaries, expert consensuses, and randomized controlled trials (RCTs). The retrieval time limit was from the database establishment to July 2021. The quality of the literature was independently evaluated by 2 researchers, who then extracted and summarized the evidence from qualifying articles.

**Results:** A total of 16 articles were selected, including 3 guidelines, 3 systematic reviews, 5 expert consensuses, 3 RCTs, and 1 best practice guideline, including indications, time for usage, methods, monitoring and management, time of cessation, health education, and post-discharge feeding.

**Conclusions:** This study summarized the best evidence for human milk fortifier in preterm infants. Medical staff should assess the specific clinical conditions and parental wishes when applying the best evidence to ensure the effectiveness and safety of human milk fortifier, thus improving the quality of clinical nursing.

**Keywords:** Preterm infants; very low birth weight infants; human milk fortifier; evidence-based nursing; evidence summary

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## Introduction

Preterm infant refers to all live births with gestational age <37 weeks (1). About 15 million preterm infants are born every year, among which 6.7% die (2,3). As highlighted by the World Health Organization (WHO), preterm birth has become an important cause of death of children under 5 years old (4). Early nutritional support plays a vital role in the survival, growth, metabolism, and immunity of premature infants (5). Late pregnancy is a key period for accelerated absorption and accumulation of nutrients in the fetus. Premature delivery will lead to neonates missing this stage of nutrient accumulation, which will lead to nutritional deficiency, physical growth deficit, delayed neurological development, and affect long-term growth and development of the newborn (6). Breast milk is the best source of nutrition for premature infants (7), which plays an important role in establishing healthy intestinal nutrition and improving their neurological development and immunity. However, breast milk is affected by maternal nutrition, health, mental state, and other factors. As a single source of nutrition, breast milk cannot meet the nutritional needs of premature infants who are born in a state of nutritional deficit and need to catch-up to ensure their optimal growth and development. At the same time, due to their typically underdeveloped condition, premature infants

are prone to having a limited capacity for consumption of fluids and various nutrients, which hinders the ability for a range of nutrients to reach the recommended intake (8-10). A number of studies have reported that adding breast milk fortifier to breast milk can effectively supplement the needs of preterm infants for protein, calcium, iron, phosphate, and other nutrients (11,12). Breast milk fortifier (6), also known as breast milk nutritional supplement, is a multi-nutrient additive rich in protein, energy, vitamins, iron, and minerals which usually comes in a liquid or powder form. In the United States, United Kingdom, and other developed countries, breast milk fortifier has been used as an intervention to meet the nutritional needs of premature infants in neonatal intensive care units, neonatal care units, and after discharge (13,14). Milk is usually given at 6–48 hours after birth. Breast milk fortifier was added later when the volume of breast milk reached 100 mL/kg/d in experience. The use of breast milk fortifier supplements the deficiency of breast milk nutrition. Breast milk fortifier can ensure the nutritional needs and growth of premature infants. In use, it is necessary to exclude severe suffocation, allergy to milk protein, congenital malformation and premature infants who have received surgical operations after birth. Compared with breast-feeding infants with added bovine milk-derived fortifier, infants breast-fed with human milk-derived fortifier had a lower rate of necrotizing enterocolitis and better feeding tolerance (15). However, research on breast milk fortifier in China started relatively late, and medical staff have been lacking a unified understanding of indications, management, and precautions for its use. By searching for Chinese and international studies on the use and management of breast milk fortifiers, this study applied evidence-based methods to compile the best evidence of the use of breast milk fortifiers for premature infants, so as to provide a reference for the clinical formulation of the use and management measures of breast milk fortifiers.

## Methods

### *Retrieval strategy*

We used the English language keywords "preterm infant/premature/extremely low birth weight infant/extremely premature infant" and "human milk fortifier" and the Chinese keywords "Premature/very low birth weight babies" "Human Milk Fortifier". Literature retrieval was performed in the databases of UpToDate, American Guide Network, Cochrane Library, Joanna Briggs Institute (JBI), PubMed, ResearchGate, China National Knowledge Infrastructure (CNKI), Wanfang, China Biology Medicine disc (CBM), and Yi Maitong. These databases enabled access to all articles on the use and management of breast milk fortifiers for premature infants. The retrieval time ranged from database establishment to July 2021.

### *Literature inclusion and exclusion criteria*

The inclusion criteria were as follows: (I) participants were hospitalized and discharged preterm infants; (II) research on the use and management of breast milk fortifier; (III) literature types included guideline, systematic review, expert consensus, best practice, and randomized controlled trials (RCTs); (IV) language was either Chinese or English. The exclusion criteria were as follows: (I) literature type was guideline interpretation, research plan or proposal; (II) full text was not available.

### *Literature quality evaluation criteria*

#### Literature quality assessment tools

The guidelines were evaluated with Appraisal of Guideline for Research and Evaluation Instrument (AGREE II) (16). Systematic reviews, RCTs, and expert consensuses were evaluated with the corresponding evaluation criteria of JBI Evidence-based health Care Centers in Australia (17). The risk prediction model adopted the bias risk assessment tool Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) list (18) of the clinical prediction model to evaluate the quality of the included literatures. The quality evaluation of best practice required that we went back to the original literature on which the evidence was based and selected the corresponding evaluation criteria according to the literature type.

#### Literature quality evaluation process

Quality evaluation was completed independently by 2 researchers who had systematically studied evidence-based nursing, and in case of disagreement, the final decision was made by a third person who had evidence-based research training experience. The principles of triage for inclusion in this study were evidence-based evidence first, high quality, and newly published literature.

### *Criteria for determining evidence level and recommendation level*

The included evidence was graded and recommended according to the JBI grading of evidence and recommendation system (2014 edition) (19). The level of evidence was divided into levels 1–5 according to the design category of the included study, and was classified into grade A (strong recommendation) and grade B (weak recommendation) according to the JBI feasibility, appropriateness, mean-fullness, effectiveness (FAME) structure.

## Results

### *General characteristics of the included articles*

A total of 16 articles were included in this paper, including 3 guidelines (20-22), 5 expert consensuses (4,5,23-25), 3 systematic reviews (6,7,26), 3 RCTs (27-29), and 1 best practice report (30). The general information of the included articles is shown in *Table 1*.

### *Quality evaluation results of the included literature*

#### Quality evaluation results of the guidelines

There were 3 guidelines included in this study (20-22). The percentage of standardization in each field and the average score of the 2 comprehensive evaluations are shown in *Table 2*.

#### Quality evaluation results of systematic reviews

Among the 3 systematic reviews included in this study (6,7,26), all the items of the study by Premkumar *et al.* (6) and Brown *et al.* (26) were evaluated as "yes", with complete research design and high overall quality, and were approved for inclusion. In the study of Liu *et al.* (7), all the entries were "yes" except "Whether a comprehensive literature search was conducted", "Whether the publication status was considered in the inclusion criteria, such as grey literature", "Whether the list of included and excluded studies was provided", and "Whether the possibility of publication bias was assessed". The literature was included after an overall evaluation.

#### Quality evaluation results of expert consensuses

There were 5 expert consensuses included in this study (4,5,23-25). All 6 items in the JBI Evidence-based Health Care Center's evaluation criteria for Opinions and Consensus (2015) were "yes". All of these articles were included after an overall evaluation.

#### Quality evaluation results of RCTs

This study included 3 RCTs (27-29), 2 from Wanfang database (27,28) and 1 from ResearchGate database (29). Gao *et al.* (27) and Ji *et al.* (28) showed that all the other items were "yes" except for the items of "Blind study of participants and interveners" and "Outcome evaluators blindness", which showed high risk, and "sources of bias in other aspects" were unclear. The study design was relatively complete and the overall quality was high, thus it was approved for inclusion. In the study of O'Connor *et al.* (29), except for the high risk of "random sequence generation" and the unclear "sources of bias in other aspects", all other items were "yes". The study design was relatively complete and the overall quality was high, thus it was approved for inclusion.

#### Quality evaluation results of risk prediction model

This study included 1 best practice report (30), from which we traced the original literature corresponding to the evidence and obtained a risk prediction model (31). The evaluation result of this study was that the risk of bias was low except for the items "data source" and "sample size", which had high risk of bias. The study design was relatively complete and the overall quality was high, therefore it was approved for inclusion.

### *Summary and description of evidence*

By summarizing the evidence of breast milk fortifier for premature infants, 17 best evidence categories were formed from 7 aspects including indication, time for use, method of use, monitoring and management, time of cessation, health education, and feeding after discharge, as shown in *Table 3*.

#### Indications for the use of breast milk fortifier

Article 1 of the evidence summarized the indications for the use of breast milk fortifiers and was a grade A recommendation (5). Premature infants tend to have extrauterine growth restriction (EUGR) due to immaturity, disease, feeding difficulties, and restriction of fluid intake, which affects nutrient intake (9,13). Breast milk is the best source of nutrition for premature infants, but for such infants, especially those with very low birth weight, breast milk cannot meet their needs for rapid growth and metabolism after birth (25). Studies have shown

**Table 1** General information of included articles

| Included articles | Year | Source | Type of evidence | Topic of the article |
|---|---|---|---|---|
| Evidence-based Professional Committee of Neonatology Branch of Chinese Medical Doctor Association (20) | 2020 | Yi Maitong | Clinical guideline | Clinical guidelines for the diagnosis and treatment of feeding intolerance in premature infants |
| Dutta *et al.* (21) | 2015 | PubMed | Clinical guideline | Feeding guidelines for very low birth weight infants |
| Evidence-based Professional Committee of Neonatology Branch of Chinese Medical Doctor Association (22) | 2020 | Yi Maitong | Clinical guideline | Clinical guidelines for the management of necrotizing enterocolitis in neonates |
| Kumar *et al.* (4) | 2017 | PubMed | Expert consensus | Nutritional optimization of low-birth-weight preterm infants |
| Expert Consensus Working Group on the Use of Breast milk fortifiers for premature Infants (5) | 2019 | Yi Maitong | Expert consensus | Expert consensus on the use of breast milk fortifier in premature infants |
| Nutrition Committee of Neonatology Branch of Chinese Medical Doctor Association (23) | 2016 | Wanfang | Expert consensus | Recommendations to promote breastfeeding for premature infants in neonatal intensive care units |
| Editorial Board of the *Chinese Journal of Pediatrics et al.* (24) | 2016 | Yi Maitong | Expert consensus | Feeding recommendations for preterm and low birth weight infants after discharge |
| Arslanoglu *et al.* (25) | 2019 | PubMed | Expert consensus | European Milk Bank Association Working Group: Use of breast milk fortifiers for premature infants |
| Premkumar *et al.* (6) | 2019 | Cochrane Library | Systematic review | Effects of breast milk fortifiers derived from human and cow milk on the prevention of morbidity and mortality in premature infants |
| Liu *et al.* (7) | 2015 | PubMed | Systematic review | Effects of high protein and standard protein human milk fortifier on the growth of premature infants |
| Brown *et al.* (26) | 2016 | Cochrane Library | Systematic review | Systematic review of preterm infants taking breast milk fortifier |
| Gao *et al.* (27) | 2017 | Wanfang | RCT | Effect of time of breastfeeding fortifier on early growth and complication rate of very low birth weight preterm infants |
| Ji *et al.* (28) | 2020 | Wanfang | RCT | Effect of early use of breast milk fortifier on the short- and long-term growth and development of extremely low body weight infants |
| O'Connor *et al.* (29) | 2018 | ResearchGate | RCT | Study on nutrition intervention of human milk fortification and cow milk fortification in preterm infants (weight <1,250 g) |
| Steele *et al.* (30) | 2018 | PubMed | Best practice | Summary of the best evidence for the use of neonatal breast milk and donated breast milk during hospitalization |

RCT, randomized controlled trial.

**Table 2** Quality of included guidelines

| Included articles | Percentage of field standardization % | | | | | | ≥60% field number (n) | ≥30% field number (n) | Recommendation level |
|---|---|---|---|---|---|---|---|---|---|
| | Scopes and objects | Participant | Rigor of the guidelines | Clarity of guidelines | Application of guidelines | Independence of the guide | | | |
| Evidence-based Professional Committee of Neonatology Branch of Chinese Medical Doctor Association (20) | 93.05 | 81.94 | 67.7 | 97.22 | 66.67 | 87.5 | 6 | 6 | A |
| Dutta *et al.* (21) | 70.83 | 50 | 35.93 | 91.67 | 35.41 | 89.58 | 4 | 6 | B |
| Evidence-based Professional Committee of Neonatology Branch of Chinese Medical Doctor Association (22) | 97.2 | 76.3 | 61.5 | 91.7 | 56.3 | 97.9 | 5 | 6 | A |

that insufficient nutritional intake in early birth is one of the important causes of EUGR in preterm infants (32), which can affect their nervous system, kidney, and bone development to varying degrees. Breast milk fortifier is the preferred method to optimize the nutritional composition of breast milk. Studies (27,28) have shown that appropriate use of breast milk fortifier can improve the early body weight growth rate of premature infants, prevent EUGR and nutritional defects, and does not increase the risk of feeding intolerance (FI) and necrotizing enterocolitis (NEC) in newborns (20,26).

### The opportunity and method of breast milk fortifier application

Articles 2–8 of the evidence summarized when and how breast milk fortifiers should be used, which from 2 expert consensus (5,24), 2 clinical guidelines (20,22), 1 systematic review (7), 3 RCTs (27-29), and 1 best practice report (29). Except for article 2, which was grade B recommendation, the rest were grade A recommendations. The timing of the addition of breast milk fortifier is of great significance to the nutritional support of preterm infants, but there is no unified international standard for the specific timing of the addition. A study (27) showed that the addition of breast milk fortifier when the intake volume of premature infants reaches 50 mL/(kg·d) will increase the rate of early body weight growth, but will not increase the incidence of complications. The Chinese clinical diagnosis and treatment guidelines (20) and expert consensus (5) highlighted that for premature infants meeting the indications, it is recommended to start using breast milk fortifier when the breast-feeding volume reaches 50–80 mL/(kg·d). A number of studies (6,29) have shown that breast milk fortifiers derived from human milk and cow milk had no difference in weight gain, morbidity, and mortality of premature infants. Therefore, it is recommended that either human or cow milk are the sources of breast milk fortifier, and are added to the full dissolution of the use of breast milk. A systematic review of 5 RCTs involving a total of 352 preterm infants showed that for those with birth weight ≤1,750 g and gestational age ≤34 weeks, breast milk fortifier containing high protein preparations can promote the short-term physical development, but its influence on their long-term physical development needs further research (7). Inaccurate dosage of breast milk fortifier can lead to excessive or insufficient fortification and affect the incidence of FI in premature infants (33). Nursing staff should treat it as medicine, strictly follow the doctor's instructions,

**Table 3** Best evidence of human milk fortifier in preterm infants

| Category | Evidence content | Evidence level | Recommendation level |
|---|---|---|---|
| Indications | 1. Preterm infants with birth weight <1,800 g, preterm infants with extrauterine growth restriction, small preterm infants who have not completed catch-up growth, preterm infants with limited fluid intake due to disease conditions, and preterm infants with early growth lag after discharge (5) | 5b | A |
| Application time | 2. It is recommended to start the use of breast milk fortifier when the amount of breast-feeding reaches 50–80 mL/(kg·d) for premature infants with the indications (5,20,27) | 1c | B |
| Application method | 3. It is recommended to choose human milk source or breast milk source breast milk fortifier, breast milk fortifier can only be added to breast milk. For preterm infants with birth weight ≤1,750 g and gestational age ≤37 w, high protein preparations can be selected as breast milk fortifier (7,29) | 1a | A |
| | 4. The dosage of breast milk fortifier should strictly follow the doctor's advice, and the dosage should be accurate. It should be double checked before adding breast milk fortifier, and fully dissolve and mix it before use. It is recommended to be used immediately after preparation (5) | 5b | A |
| | 5. The addition of breast milk fortifier in hospital should be carried out in the milk mixing room according to the principles of sterility, and the addition of breast milk fortifier at home should follow hygienic principles (24) | 5b | A |
| | 6. For fortified breast milk, store at room temperature for no more than 4 h and in the refrigerator at 4 ℃ for no more than 6 h (30,31) | 1c | A |
| | 7. Breast milk fortifier should start with half a dose (dosage halved, breast milk energy density 72–74 kcal/100 mL), and within 3–5 days should reach the standard of adequate reinforcement (according to the product labeling standards). If preterm infants have poor tolerance to breast milk fortifier, the time for reaching sufficient reinforcement can be extended appropriately (5) | 5b | B |
| | 8. For premature infants with unsatisfactory growth of standard breast milk reinforcement, children with NEC, and children with FI, individualized breast milk enhancement should be implemented (22) | 5b | A |
| Monitoring and management | 9. Medical staff should regularly monitor the physical growth of preterm infants with growth curve and blood biochemical indexes during breast milk fortification. Body length and head circumference should be measured weekly during hospitalization and monthly after discharge. Blood biochemical indexes should be monitored once every 1–2 weeks during hospitalization (4,5) | 1c | A |
| | 10. Protein reinforcement was adjusted according to BUN: blood BUN <10 mg/DL (3.2 mmol/L), protein reinforcement should be increased; blood BUN >16 mg/DL (>5.0 mmol/L), protein reinforcement should be reduced. The rate of weight gain reached 15–20 g/(kg·d) during hospitalization and averaged 25–30 g/d in the early period after discharge (7) | 1c | A |
| | 11. Medical staff should evaluate FI before and during the use of breast milk fortifier for ultra-premature infants, very low birth weight infants, and preterm infants after NEC (20,21) | 5b | A |
| | 12. If the physical growth of premature infants continues to lag behind the growth target after active nutritional management, they should receive further medical evaluation and guidance (5) | 5b | A |
| Stop time | 13. When the body weight, length, and head circumference of preterm infants are suitable for $P_{25}$-$P_{50}$ of the same gender and gestational age infants, and small gestational age premature infants reach $P_{10}$, the addition of breast milk fortifier should be gradually withdrawn (5,23) | 5b | B |

**Table 3** (*continued*)

**Table 3** (*continued*)

| Category | Evidence content | Evidence level | Recommendation level |
|---|---|---|---|
| | 14. Growth status and blood biochemical indexes of preterm infants should be monitored during reduction and discontinuation periods (5) | 5b | A |
| Health education | 15. As for EUGR preterm infants, small preterm infants for gestational age who have not completed catch-up growth, premature infants with limited fluid intake due to a medical condition, and premature infants whose early growth lags after discharge from hospital, breast milk fortifiers should be used under the guidance and monitoring of medical personnel (5) | 5b | A |
| Post-discharge feeding | 16. Preterm infants with EUGR at discharge should continue to receive breast milk fortifier at least until 40 weeks of gestational age (25) | 5b | B |
| | 17. Preterm infants who take iron supplements after discharge and use breast milk fortifier at the same time should reduce the dosage of iron supplements as appropriate (24) | 5b | A |

NEC, necrotizing enterocolitis; FI, feeding intolerance; BUN, blood urea nitrogen; EUGR, extrauterine growth restriction.

and double check to prevent medication errors. The addition of breast milk fortifier should strictly comply with the principles of sterility. It should be stored at room temperature for no more than 4 h and in the refrigerator ≤4 ℃ for no more than 6 h (30,31). Breast milk fortifier is generally configured in accordance with the standard enhancement dose, but for premature infants, NEC (22), and infants with FI (21), individualized breast milk fortifier is recommended to achieve the target nutrient intake of corresponding gestational age premature infants (20).

### Monitoring, management, and withdrawal timing of breast milk fortifier

Articles 9–14 of the evidence summarized the important points for the use of breast milk fortifiers, which included 3 expert consensus (4,5), 2 clinical guidelines (20,22), and 1 systematic review (7). Except for article 12, which was grade B recommendation, the rest were grade A recommendation. During the use of breast milk fortifiers, the condition of the infant should be monitored, including growth curve, serum biochemical index, Blood Urea Nitrogen et.al. The application of breast milk fortifier should also be attention, like time, methods, storage, and infant condition. There is no difference in treatment effect of early fortification of human milk versus late fortification in preterm infants (34). Not all premature babies are good candidates for breast milk enhancers, severe suffocation, allergy to milk protein, congenital malformation and premature infants who have received surgical operations after birth should be pay attention to (15). Breast milk fortifiers containing hydrolyzed protein do not increase intestinal inflammation (35). One study (29) showed that too fast or too slow weight gain is detrimental to the short-term and long-term growth and development of premature infants, so it is very important to regularly monitor their physical development with growth curve and blood biochemical indexes during the use of breast milk fortifier (4,9). A study showed (7) that the use of adjusted breast milk fortifier, that is, under the condition of normal renal function and intake and output volume, can promote protein intake and physical growth by adjusting the amount of breast milk fortifier according to blood urea nitrogen (BUN >5.0 mmol/L indicates excessive protein intake, BUN <3.2 mmol/L indicates insufficient protein intake). For critically ill children (20), FI can affect the outcome of nutritional intervention and increase the risk of reflux, aspiration, and ventilator-associated pneumonia. Therefore, FI needs to be assessed throughout the duration of breast milk fortifiers use. The timing of cessation of breast milk fortifiers should depend on the growth of the premature infant. It is generally recommended (5,23) to gradually stop adding breast milk fortifier when the weight, length, and head circumference of gestational age infants are located in $P_{25}$-$P_{50}$ of the same gender and age infants, and when the small gestational age premature infants reach $P_{10}$. Physical growth and blood biochemical indexes should be monitored to ensure the proper growth of premature infants. If the physical growth of premature infants still falls behind the growth target after active nutrition management, further medical evaluation and guidance should be given to the existence of other influencing factors (5) to prevent blind nutrition

 

intervention.

### Health education

Article 15 summarized health education for children's families comes from 1 expert consensus (5), which was recommended for grade A. The use of breast milk fortifier will affect the osmotic pressure of breast milk, and high osmotic pressure in breast milk will delay the gastric emptying of premature infants and increase the intestinal osmotic pressure, thereby increasing the risk of FI and NEC in premature infants (5). Therefore, medical staff should provide appropriate health education to children's families.

### Feeding after discharge

Articles 16–17 summarized the use of breast milk fortifiers after discharge, which came from 2 expert consensuses (24,25). Article 16 was grade B recommendation and article 17 was grade A recommendation. It is recommended that preterm infants with growth restriction at discharge receive breast milk fortifiers at least until 40 weeks of gestational age (25). Trace elements contained in breast milk fortifiers include iron, so premature infants who take iron supplements after discharge should reduce the amount of iron supplements as appropriate (24).

### The challenges in breast milk fortification for preterm infants

There are still some challenges in the application of breast milk fortification. The role of fortification in infant growth and neurodevelopment still needs to be clarified. Whether early breast milk fortification could induce NEC needs to be studied. Preterm infants do not have mature buffer system, the application of acid loaded fortifiers might induce metabolic acidosis.

## Conclusions

This study summarized the best evidence of the use of breast milk fortifiers for premature infants and provided evidence-based evidence for the administration of nutritional intervention by clinical medical staff, with a view to optimizing the nutrition of premature infants during hospitalization and after discharge, improving clinical outcomes, and improving the quality of life in the short and long term. As a portion of the evidence came from international studies, it is recommended to localize the evidence when developing nutrition intervention programs, and selectively use the best evidence after assessing the actual circumstances of the medical facilities and the wishes of the child's parents.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tp-21-476). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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