

## Mother's Milk Ingredients and Newborns Breast Milk the Emergence of the Disease

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### Abstract

Breast milk is tailored for optimal growth of all infants. However, in some infants, it is associated with a unique phenomenon called breast milk jaundice (BMJ). BMJ is a form of persistent unconjugated hyperbilirubinemia that often presents late in seemingly healthy newborns, and its onset may be associated with breast milk itself. The aim of this review is to systematically assess the evidence for breast milk composition and BMJ development in healthy newborns. These include studies investigating both the nutritional composition (such as fats and proteins) and bioactive factors (such as enzymes and growth factors) of breast milk and various endogenous components of breast milk collected from formally assessed mothers. Includes studies examining differences in the concentration (or presence) of by BMJ infants and healthy infants were inconsistent and inconclusive for most substances of interest, and only one study was available (total energy and minerals, bile salts and cytokines, etc.). Inconsistent or even contradictory results were obtained when there were two or more studies on a subject (eg lipid and free fatty acid content, epidermal growth factor). The etiology of BMJ is probably multifactorial and no single component of breast milk can explain all her observed BMJ cases. Before advancing this field to uncover the pathogenesis of BMJ, more rigorously designed studies are needed to investigate the complex interplay between maternal physiology, breastfeeding system and infant physiology.

**Keywords:** Breast milk jaundice; Breast feeding; Neonatal

### Introduction

Hyperbilirubinemia, or jaundice, characterized by elevated levels of bilirubin in the blood, is a common physiological condition that occurs in many newborns early after birth. This is due to the rapid turnover of red blood cells, and the small liver volume and immature enzymatic system in neonates that cannot effectively remove catabolites and unconjugated bilirubin from the bloodstream. In most cases, gradually within the first week of life without specific intervention, unless there is concern that the blood bilirubin level is too high or there is a prior underlying pathological reason. It is a symptom with natural healing power to eliminate [1].

In 1963, pediatricians Newman and Gross first reported a series of long-lasting cases of jaundice associated with breastfeeding. These neonates had unconjugated hyperbilirubinemia and appeared healthy, but were excluded due to pathological concerns. In these infants, serum bilirubin levels drop markedly when breastfeeding is discontinued and rise again when breastfeeding is resumed [2]. This condition later became known as breast milk jaundice (BMJ). It often has a late onset and affects about one-third of infants. The prevalence of neonatal jaundice in infants of East Asian descent has been reported to be significantly higher regionally or racially than infants of Caucasian descent. Infants with BMJ often have high peak bilirubin levels and slow recovery [3]. Long-term and/or high-dose exposure to neonatal hyperbilirubinemia is associated with adverse neurodevelopmental outcomes in both childhood and adulthood. Acute kernicterus is rare in infants with BMJ, but it still causes great concern and concern for parents. Previous studies have shown that a significant proportion of parents believe that breastfeeding cessation is effective in preventing neonatal jaundice, leading this population to exclusively breastfeed [4]. This can become a maintenance bottleneck.

This unique phenomenon that rising and falling neonatal serum bilirubin concentrations are closely related to the cessation and resumption of breast milk production has led to the hypothesis that

the development of BMJ is triggered by breast milk itself. However, breast milk contains not only essential nutrients [5], but also live microorganisms, bioactive factors and microRNAs that are tailored for optimal infant growth and development. So far, there is no consensus on which components of breast milk can trigger the development of BMJ. Identifying the major components of breast milk associated with temporomandibular disorders is important in developing strategies to manage temporomandibular disorders while maintaining breastfeeding [6]. This systematic review therefore aims to critically review our findings on breast milk composition and temporomandibular joint development in healthy infants.

### Material and Methods

This systematic review was conducted according to the protocol published in Prospero, an international prospective registry of systematic reviews (CRD42023400486). The results of this review were reported according to PRISMA (Priority Reporting Items) guidelines for systematic reviews and meta-analyses [7].

### Search strategy

**We searched PubMed, Embase (via Ovid), and Scopus for records up to 13 February 2023 using the following keyword combinations:**

Covers all breastfeeding/lactation, jaundice/hyperbilirubinemia,

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neonatal/infant literature. A complete list of search strategies can be found here. We limit all search results to humanities studies and English language publications only and do not impose any other restrictions [8].

### Inclusion and exclusion criteria

There were no restrictions on the type of study. Both interventional and observational studies were considered, but were limited to term infants. Only primary studies were included (including short communications with sufficient methodological description). Other types of articles were excluded, such as case reports, reviews, comments and correspondence. Studies that reported differences (or the presence or absence) in breast milk composition between mothers of BMJ infants and mothers of healthy, non-jaundiced infants were eligible for inclusion. Studies focusing on physiological jaundice in the early neonatal period, pathological jaundice, or comparing breastfeeding with infant formula were excluded. Two authors completed the screening process against pre-specified inclusion and exclusion criteria using the systematic review software Covidence (Veritas Health Innovation, Melbourne, Australia). Any discrepancies that arose during the process were resolved through consultation with the first author [9].

### Data extraction and quality appraisal

Using a customized data collection table, two authors performed this process independently, providing study author and site information, population recruitment and screening procedures, diagnostic criteria for BMJ, and timing used for breast milk collection. and tools, and subsequent storage conditions, etc. Breast milk components associated with BMJ, associated detection methods, and statistical analyzes performed [10].

Quality assessment of individual studies was performed by two independent authors using the Quality Criteria Checklist (QCC) for Primary Studies developed by the American Dietetic Association. The QCC included 10 validity questions to assess study design, conduct, analysis and reporting, and 4 additional questions on the clinical relevance and importance of the study. The quality of the included studies was assessed based on the number of 'yes' responses to the above validity questions and the final scoring system.

His is the only study that used automated breast milk analyzers to examine the energy, lactose and mineral content of breast milk, and found a statistically significant difference between breast milk from BMJ infants and healthy infants. Using the climatocrit method, found that the fat content of breast milk from mothers of BMJ infants was significantly higher than that of mothers of healthy infants. In contrast, his two other studies using breast milk analyzers and colorimetric methods found no differences between breast milk samples from these two sources of hers. Three studies focused on the concentrations of free fatty acids in breast milk and measured them using selective transmethylation coupled with colorimetric or gaschromatographic identification. One study found that breast milk of mothers of BMJ infants had significantly higher levels of free fatty acids than mothers of non-jaundiced infants, whereas another study found no significant differences between these samples. With regard to protein and amino acid concentrations, Poland and co-authors found no difference, and another study found significant taurine concentrations in milk samples taken from mothers of BMJ infants compared with mothers of infants without jaundice. However, the glycine concentration did not increase significantly.

### Exogenous surfactant therapy in preterm infants

Surfactants are naturally occurring surfactant lipoproteins mixed with proteins that lower the surface tension of the alveolar fluid surface, keeping the alveoli open during exhalation and greatly reducing the work of breathing. Surfactants also improve mucociliary transport, prevent pulmonary edema formation, improve pulmonary compliance, and contribute to pulmonary defense against pathogens. For these reasons, exogenous surfactant therapy is one of the most important treatments for preterm infants. Administration of exogenous surfactant is life-saving in the management of IBS in preterm infants, especially ELGAN, and other neonatal respiratory diseases that exhibit altered surfactant homeostasis (e.g., meconium aspiration syndrome, pneumonia, pulmonary hemorrhage, acute neonatal respiratory disease). Over the past decade, new minimally invasive techniques for surfactant administration have been investigated to avoid or minimize trauma associated with endotracheal intubation and MV. These techniques are called minimally invasive surfactant administration (LISA) or minimally invasive surfactant therapy (MIST). A thin catheter or plastic tube is inserted into the trachea, either directly or under videolaryngoscope, and the patient breathes spontaneously, most commonly assisted by noninvasive respiratory support with either nasal CPAP or NIPPV, with surfactant placed in the airway.

### Discussion

#### Summary of main findings

In this review, we systematically reviewed the currently available evidence on the endogenous components of breast milk that differ between mothers of infants with BMJ and healthy infants without jaundice. This review focused on both the nutrient composition (total energy content, macro- and micronutrients) and bioactive factors (enzymes, cytokines, steroids, antioxidant capacity) of human milk. For most of these substances of interest (total energy, mineral content, bile salts, cytokines, etc.) only one study was available. Inconsistent or even contradictory results occurred when there were two or more studies on a subject (e.g. fat and free fatty acid content and his EGF), probably due to sample size and methodological approach. It is considered.

#### Interpretation of the results

These observational studies are drawn from human populations and are based on some evidence obtained through in vitro experiments. Unconjugated bilirubin released during erythrocyte degradation is converted to conjugated bilirubin by UDP-glucuronosyltransferase 1A1 (UGT1A1), a key rate-limiting enzyme in hepatocytes. Many believe this suggests that endogenous components of breast milk directly affect bilirubin metabolism, causing jaundice. He conducted the first such study and identified pregnane-3 $\alpha$ ,2- $\beta$ -diol as a potential pathogen of the temporomandibular joint. Subsequent experiments by the same authors observed changes in serum bilirubin levels in several infants and one adult who received orally administered weight-adjusted pregnane-3 $\alpha$ ,2- $\beta$ -diol. A slight increase in serum bilirubin was only observed in the youngest infants (1 month of age) and adults. This response is associated with infant immaturity and does not appear to be solely due to the action of pregnane-3 $\alpha$ ,2- $\beta$ -diol. We then attempted to measure pregnane-3 $\alpha$ ,2- $\beta$ -diol in another group of lactating mothers and found detectable levels of pregnane-3 $\alpha$ ,2- $\beta$ -diol in most of the BMJ milk samples. It has been found. However, the authors found that healthy infants without elevated serum bilirubin from 5 to 15 days of age and without persistent jaundice were fed milk containing the highest concentrations of pregnane-3 $\alpha$ ,2- $\beta$ -diol. This means that the

presence, or even high levels, of pregnane-3 $\alpha$ ,2- $\beta$ -diol in breast milk is unlikely to be the primary cause of BMJ.

## Conclusions

The etiology of BMJ is probably multifactorial, with genetic susceptibility and neonatal immaturity being the main causes. Based on the results of this review, no single component of human milk alone can explain all observed BMJ cases. Before further understanding the pathogenesis of BMJ in this area, it is important to first understand the dynamics of breast milk components and their interactions with maternal-infant physiology.

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