Breastfeeding during breast milk jaundice - a pathophysiological perspective

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ABSTRACT

Introduction: Exclusive breastfeeding for the initial six months of life is crucial and it is recommended . Breast milk jaundice is an innocuous condition that occurs in some healthy, breastfed infants. However, the potential dangers of jaundice in the neonate such as bilirubin induced neuronal pathology, mandates a better understanding of the pathophysiology of breast milk jaundice and the impact of breastfeeding during jaundice. In this context , advice on continued breastfeeding must consider both the benefits of breastfeeding and the possible disadvantages of the jaundice.

Methods. Reviewing literature and integrating relevant information facilitated the appraisal of this important topic. This article reviewed neonatal jaundice, the entry of bilirubin into the immature brain and how breastfeeding may impact jaundice in the neonate.

Results. While some substances in breast milk may be responsible for jaundice on the one hand, there is an irrefutable spectrum of advantages conferred by continued breastfeeding, on the other. As the breastfed infant benefits from fewer infections, enhanced organ and physiological barrier maturity, as well as the prospect of genetic modification of certain diseases, these useful actions could also reduce risks of early jaundice and its complications.

Discussion. An exciting field for further research, holistic integration of knowledge clarifies both the overall advantages of breastfeeding and wisdom of its continued counsel. In fact, breast milk jaundice may reflect a holistic expression of tissue protection and enhanced neonatal survival.

KEY WORDS:
breast milk jaundice, breastfeeding , bilirubin, integration

INTRODUCTION

Jaundice or clinically apparent hyperbilirubinemia occurs in 8% to 11% of neonates,[1] 54% develop jaundice within 1-3 days of birth.[2] The total serum bilirubin (TSB), a standard assessment in neonatal jaundice, when above the 95th percentile, in the first week of life, confirms hyperbilirubinemia.[3,4] It is critical to detect and to monitor serum bilirubin in the neonate because hyperbilirubinemia at this time of life is potentially dangerous.

Physiological hyperbilirubinemia, is common in newborns due to normal, biological extrauterine adaptation and newborn liver immaturity.[5] Increased bilirubin synthesis with reduced liver uptake, conjugation and excretion, high blood volumes and haemoglobin concentrations together with a shorter red blood cell life span are contributory.[5]

Risk factors for hyperbilirubinemia include maternal and foetal factors of which breastfeeding, prematurity, infections, illnesses, foetal-maternal blood group incompatability and specific drugs are recognised.[6] Unconjugated hyperbilirubinemia can cross the blood brain barrier (BBB) and enter the immature brain causing toxicities.[7] Bilirubin encephalopathy (BE), kernicterus and bilirubin induced neurological dysfunction (BIND) describe clinical syndromes of acute and chronic encephalopathies and subtle alterations of bilirubin associated neuronal pathology.[7,8] Sequalae such as spasticity, choreoathetotic cerebral palsy and nerve deafness are important preventable problems making this discussion of scientific and clinical importance.

In this article, I have reviewed causes of jaundice related to breast milk and possible mechanisms of entry of bilirubin into the immature brain. I have revisited mechanisms by which breastfeeding may directly or indirectly influence pathophysiological processes related to jaundice. Such processes include infection control, maturation enhancement, genetic potentials and tissue protection. Integration, extrapolation, deduction and hypothesis of information in these areas attempt to clarify the role and outcome of continued breastfeeding in breast milk jaundice.

METHOD

How beneficial is the continuation of exclusive breastfeeding when the breastfed infant has jaundice, attributed to breast milk, after excluding all other causes? This is answered by a literature search and by integration of information. The literature search was conducted in three areas; firstly, the review of mechanisms of newborn jaundice related to breast milk, the second appraises mechanisms of bilirubin entry into the immature brain and its complications and the third reviews breast milk or breastfeeding impacting any relevant area of cause, effect or complication of jaundice. The information gained from these areas of search were integrated for a holistic understanding of the topic.

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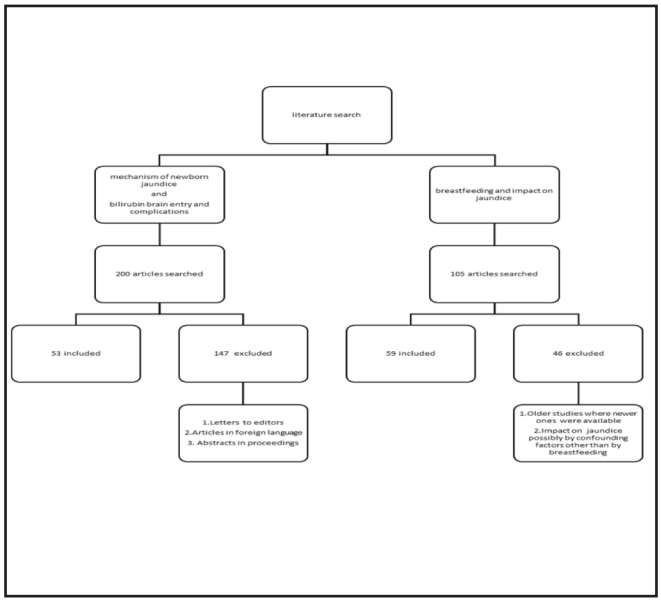

Fig. 1: Literature search.

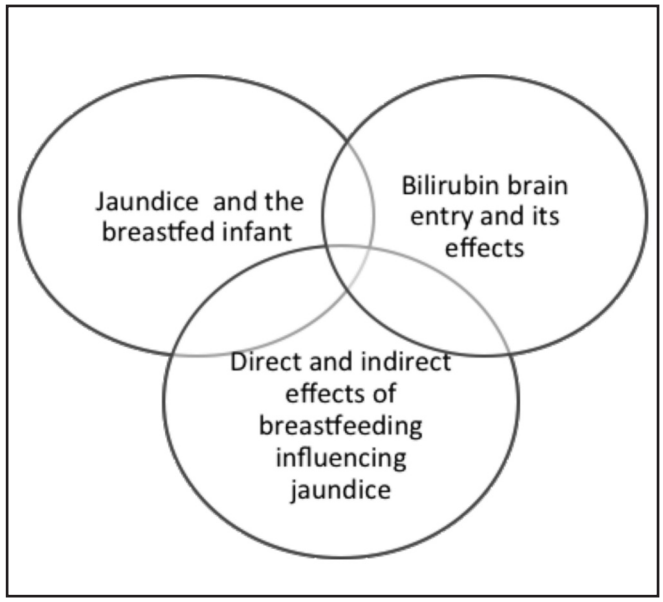

Fig. 2 Integration of information by reviewing three areas.

In the first area, literature searches used keywords such as "breast milk jaundice, breastfeeding jaundice, unconjugated hyperbilirubinemia, neonatal jaundice," and in the second, used key words such as "unconjugated bilirubin, brain, receptor". Perusal in accordance with the MeSH search strategy, in the PubMed, Scopus, Embase and other databases. Two hundred publications including original articles, systematic reviews, meta-analyses and experimental, prospective and retrospective studies were included. Fifty-three articles were included in the analysis for this section. Excluded were letters to editor, proceeding abstracts, and publications in foreign language. In the third area, literature search was on actions of breastfeeding with known or possible influences on jaundice or its complications and on breastfeeding influences on the immature brain or barriers. Analogies were made of actions of breastfeeding on the immature gut to postulated actions on the brain and its barriers. Systematic reviews, meta-analyses, experimental studies and one proceedings abstract were included. Animal experiments were considered important, due to ethical difficulties of such studies on human subjects. Among articles perused in this section, fifty nine were included. Letters to editors and older studies, where newer ones were available on the subject, and studies where the effects on jaundice were felt to be influenced by confounders, were excluded.

The next step involved the integration of the causes and complications of jaundice in the neonate with the impact of breastfeeding. Breast milk was found to have a role in neonatal jaundice and breastfed infants were at higher risk of jaundice. Pathophysiological mechanisms leading to jaundice or its complications in the breastfed infant were horizontally integrated with breastfeeding. Infections were found to worsen jaundice and its complications in the immature infant. Through breastfeeding, routes of infection protection were integrated to clarify mechanisms that reduce jaundice and its complications. The pathophysiology of enhanced bilirubin entry into the immature brain was integrated with breastfeeding actions. Better known breastfeeding functions on the immature gut were analogous to actions on the brain and facilitated comparison and postulation. Information on neonatal jaundice including breast milk jaundice, where linked to genetics, was vertically integrated to the passage of genes through breastfeeding with proposed potentials for genetic modification of diseases by breastfeeding. Horizontal and vertical integration of the role of breastfeeding on the mother and her breastfed infant allowed hypothesis of useful lactational pathways between them.

RESULTS

PATHOPHYSIOLOGY OF JAUNDICE AND EFFECTS ON THE IMMATURE BRAIN

Jaundice in the breastfed infant

Breastfed infants experience more jaundice than those not breastfed.[9] Two patterns of jaundice can occur with breastfeeding.[10] Breastfeeding jaundice, due to decreased breastfeeding or poor latch causes early unconjugated hyperbilirubinemia due to dehydration, starvation and an increased enterohepatic circulation of bilirubin.[10] Unconjugated bilirubin enters the liver by passive diffusion and membrane transport.[11] Hepatic canalicular export pumps potentially prevent accumulation of toxins.[12] Clinically, these infants show excessive initial weight loss and delayed weight gain.[13] It was found that feeding difficulties in exclusively breastfed infants significantly increased the likelihood for jaundice whereas a protective effect of breastfeeding against jaundice was observed when infants had no problems with feeding.[14]

The second pattern is a usually mild jaundice in a well suckling infant with satisfactory weight gain, observed as early as from 4-7 days of life,[15] and possibly prolonged for upto four months.[16] In such cases, hyperbilirubinemia decreases when breast milk is replaced with infant formula;[16] yet, jaundice still decreases when breastfeeding resumes.[17] In this scenario, breastfeeding interruption is not recommended

because the hyperbilirubinemia normalises even if breastfeeding continues.[16] Kernicterus in apparently healthy, full-term, breastfed newborns without other discernible causes of jaundice is recognised;[18,19] hence bilirubin levels require close monitoring even in the thriving , breastfed infant. Twenty to thirty percent of breastfed infants are jaundiced at age three to four weeks, and 30-40% of these infants have bilirubin levels of 85.5µmol/L (5mg/dL).[20] The cause of breast milk jaundice is still unclear but is probably multifactorial.[17]

Although inconclusive, socio-cultural and maternal dietary factors may impact jaundice. A questionnaire survey on the link between maternal diet, Chinese herbal medicines and prolonged jaundice of breastfed infants found that jaundice was more common in breastfed infants whose mothers did not consume traditional Chinese herbal medicines than in breastfed infants whose mothers consumed such medicines ($p<0.001$).[21] Another study found that a traditional Chinese herb may enhance bilirubin clearance by an activating nuclear receptor, inducing expression of bilirubin glucuronyl transferase and components of the bilirubin metabolism.[22] Randomised controlled trials will shed more light in this important field.[23]

Glucuronyl transferase or UDP-glucuronosyltransferase (UGT) 1A1 is the only enzyme that conjugates bilirubin.[5] Inadequate expression of UGT1A1 in the immature liver with activity at about 0.1-1% of adult levels, impairs bilirubin conjugation.[24] In breast milk jaundice, besides liver immaturity, a more prolonged jaundice attributed to inhibitors of the conjugating enzyme itself occurs.[25,26] UGT1A1 gene, influences synthesis of glucuronyl transferase.[27] Gene polymorphism and enzyme deficiencies cause inherited hyperbilirubinemia.[27] There is suggestion that defects of UGT1A1 are an underlying cause of prolonged unconjugated hyperbilirubinemia associated with breast milk.[28] When infants have mutations of UGT1A1, constituents in breast milk may trigger jaundice.[28]

Breast milk 5b-pregnane-3a,20b-diol inhibits conjugation by UGT1A1;[25] predisposing to jaundice. Thus, prolonged unconjugated hyperbilirubinemia may develop in infants with UGT1A1*6 fed milk containing 5b-pregnane-3a,20b-diol. Furthermore, extrahepatic tissues in the small intestine and skin possess UGT1A1 activity and breast milk 5a-pregnane-3a, 20b-diol may decrease activity of the enzyme by also acting on intestinal UGT1A1.[29]

Lipoprotein lipase, a breast milk enzyme, produces nonesterified free fatty acids, which decrease conjugation and excretion of bilirubin.[26] Breast milk substances may repress genes involved in bilirubin metabolism with increased colostral interleukin-1β (IL-1β) concentrations present in breastfeeding mothers whose infants had neonatal jaundice.[30] Population specific genetic mutations such as SLCO1B1 can predispose to jaundice.[31] Genetic polymorphisms linked to hyperbilirubinemia may be advantageous in specific circumstances;[32] validated by antioxidant actions of bilirubin.[33]

The rate of bilirubin elimination influences jaundice in the breastfed. Conjugated bilirubin in the liver is transported into bile by the multidrug resistance protein 2 (MRP2/ABCC2).[34] This enters the gastrointestinal tract (GIT), deconjugated by β- glucuronidase, and enters into the enterohepatic cycle.[5] In addition to GIT microbial β-glucuronidase, the enzyme in breast milk increases enterohepatic circulation of bilirubin causing breast milk jaundice,[35] an effect countered by probiotics.[36] Neonatal gut colonisation by diet impacts genes of innate immunity and specific breast milk bacterial species reduce breast milk jaundice.[37,38] However, breast milk jaundice may be caused by epidermal growth factors which may impact the gut leading to activation of bilirubin transport.[39] Breast milk may also contain factors that affect hepatocyte growth or function.[40]

Entry of bilirubin into the immature brain and its effects

The most feared complication of jaundice in the newborn is the entry of bilirubin into the immature brain and its toxic effects.

Brain development occurs throughout the fetal period, influenced by many factors including maternal infections and inflammation.[41] In the fetus, lipophilic, unconjugated bilirubin is excreted transplacentally into the maternal circulation;[42] but after delivery, unconjugated bilirubin has to be conjugated in the infant's liver for excretion.[42] The blood brain barrier(BBB) is a selective physiological barrier of endothelial cells (ECs) and tight junctions (TJs), that form blood vessel walls.[43] At birth, the BBB, has functional TJs; but barrier function and protection is not yet comparable to the adult.[44] Transmembrane proteins of the TJs in the BBB consist of claudins, occludin and junctional adhesion molecules (JAM)-A, B and C.[45]

As the neonatal BBB is not completely competent in its function, at least partly due to its immaturity and vascular fragility, it tends to permit entry of substances not otherwise found in the mature brain.[44] Lipid soluble unconjugated bilirubin, an isomer, bilirubin IX-alpha (Z,Z) , passes through the immature BBB, entering the neonatal brain;[8,42] facilitated by a process of transmembrane diffusion.[46] However, when bound to plasma albumin, it does not cross the BBB,[8] and developmental control and genetic polymorphisms of albumin,[47] influence albumin binding to bilirubin and the amount of free bilirubin that enters the brain.[44] Other variables influencing bilirubin brain entry include brain blood flow, blood concentrations of unconjugated bilirubin, drug displacement of bilirubin- albumin binding and inflammation.[8]

The brain barriers express proteins that use carriers for solute transport, or adenosine triphosphate (ATP)-mediated efflux of lipophilic molecules.[46] In the BBB, there are efflux transporters for lipophilic molecules;[44,48] nutrient transporters into the CNS and from the CNS into blood;[43,44] while multidrug transporters prevent accumulation of substances such as bilirubin in the brain.[43] The CNS endothelial cells express efflux transporters, P-glycoprotein (P-gp),[44] which importantly limit lipophilic substances entering the brain. When the efflux capacity of P-gp is exceeded, it predisposes to bilirubin neurotoxicity.[7,8] Efflux transport as well as cellular metabolism clear bilirubin from the immature brain.[7,8,44] Enzymes, such as bilirubin oxidase, cytochrome P-450 (CYP), and cytochrome C dependent mitochondrial membrane

enzyme with lower activity in the newborn, metabolise bilirubin.[7,8,44] The newborn suffers toxicities of unconjugated bilirubin due to neuronal immaturity;[8,44] mitochondrial activation of neuronal nitric oxide (NOS), glutamate, oxidative stress, neuroinflammation and reactive gliosis contribute.[49,50-52] Insults to the BBB cause reactive oxygen species (ROS) induced permeability changes which result in both acute and chronic brain diseases.[53]

Breastfeeding and its possible impact on jaundice

The immature brain and its barriers, via various mechanisms, is vulnerable to toxicities of unconjugated bilirubin.[54] Brain and barrier immaturity is reasoned in this context to be due to a smaller size of the brain, neurocognitive immaturity and immature barrier functions influenced by various factors. Bilirubin affects young hippocampal neurons especially in the preterm infant.[54] Immaturity via `inflammatory processes disrupts the BBB predisposing to diseases.[54] Consequently, the importance of early detection of jaundice in all newborns.[55]

Exclusive breastfeeding is associated with increased brain growth and cognition, both clinically and biochemically;[56-63] such increases in cognition may indicate neurocognitive maturity. Furthermore, psychosocial mother-infant bonding by exclusive breastfeeding,[64-67] may stimulate tangible emotional circuits, not yet fully elucidated, and these may enhance cognitive development. If enhanced cognitive development parallels neurocognitive maturity, breastfeeding indirectly reduces vulnerability to toxicities of unconjugated bilirubin. When holistic knowledge of breastfeeding is integrated with breast milk jaundice, breastfeeding confers protective potentials against possible impact of the jaundice to the immature brain.

Head circumference is greater and neurocognition better in breastfed infants.[56,57] It was found that head circumferences in breastfed infants at six months were larger than those who were not breastfed.[56] There were higher scores of cognitive development, with increases in cognitive function of 3.16 points (95% Confidence Interval: 2.35, 3.98) after adjustment for covariates in breastfed compared to formula fed infants,corresponding to the duration of breastfeeding.[57] Supporting brain growth, breastfed infants born at less than 30 weeks gestation, or with a birth weight of less than 1,250g, showed increases in total and regional brain volumes at term equivalent age tallying positively with the quantity of early breastfeeding.[58] Early breastfeeding induces brain development in specific areas;[59] an important observation when discussing toxin induced effects on the brain with predilection to specific areas, as occurs in BIND.

Breastfeeding effectively provides long-chain polyunsaturated fatty acids (LCPUFAs) necessary for brain growth and development;[60] omega-3 fatty acids encourage synapses and myelination, probably impacting cortical circuit connectivity.[61] Breast milk exosomes, extracellular vesicles (ECVs) whose functions continue to unfold, modulate immune responses and inflammation.[62] Inflammation tends to favour disruption of barrier function especially in the preterm;[54] however, breast milk has anti-inflammatory potential, cytokines and soluble receptors enhancing oral tolerance.[63] In the infant of extremely low gestational age, mother-child interactions enhance neurocognitive outcome.[64] Mother-infant bonding and the security by breastfeeding, are perceptible and intangible. The hypothalamic pituitary axis (HPA), oxytoxin and melatonin are stimulated by breastfeeding;[65-67] these may indirectly support neurocognition.

Embryological and functional similarities are impressive between the GIT and brain,[68] their postnatal growth, differentiation and microbial linkages;[69,70] allowing breastfeeding impact on the gut,[71,72] to be extrapolated to that of the brain. As in brain barriers, gut epithelia have tight junctions (TJ),[73] involved in intestinal epithelial integrity. The dynamics of the TJ proteins contribute towards intestinal health and function.[74,75] TJ inflammation disrupts intestinal barriers, causing necrotising enterocolitis (NEC), a multifactorial disease also linked to immaturity.[76] Efflux transporters such as P-gp are expressed in intestinal epithelia,[77] with toxin efflux important for intestinal health. Murine experiments indicate that intestinal expression of P-gp increases while breastfeeding, attenuating gut inflammation in NEC,[71] while milk growth factors and hormones stimulate GIT development.[72]

Apt comparison is made between the gut and brain. The BBB formed by endothelial cells, and choroid plexus epithelia have transporters, receptors and enzymes,[46] features analogous to the gut. In the brain, P-gp limits bilirubin entry into the CNS.[8] However, low brain capillary endothelial P-gp expression, in premature neonates, may enhance brain bilirubin levels during hyperbilirubinemia.[78] With embryological and physiological parallels made between the two organs, breast milk impact on P-gps in the premature BBB could induce greater efflux of toxic unconjugated bilirubin, protecting from BIND.

The glycocalyx of the vascular endothelium is pivotal for its integrity.[79] This barrier when disrupted favours infection and may worsen the complications of jaundice. The mucous layer in the GIT, a chemical barrier, is strengthened by breastfeeding because milk mucins, glycoproteins ,gangliosides and maternal cells enhance innate and adaptive immunity, as protection from infections.[80,81] The BBB has endothelial glycocalyx;[82] and breast milk glycoproteins protect brain and meninges, beta-casein against *Haemophilus influenza* and streptococci, alpha lactalbumin against reovirus, lysozyme against *Escherichia coli*, *lactoperoxidase* against *Helicobacter pylori* and human immunodeficiency virus (HIV) and others.[83] Antiinfective action of milk glycoproteins prevent a vicious cycle of barrier disruption predisposing to complications of jaundice.

The gut epithelium and BBB protect their internal milieu;[68] analogy between them and actions by breastfeeding allow comparison and integration of information. Breast milk trophic factors, endothelial growth factor (EGF), hepatic and epidermal growth factor, support intestinal growth,[84,85] while enterocytes are protected by bioactive, immunomodulatory and tissue maturational factors with some antioxidation.[72] Breast milk cells induce microchimerism mediated immune system maturation in the infant,[81] possibly important in

immune protection. Pluripotent maternal stem cells in breast milk can differentiate into functional cells,[86,87] and milk neurotrophic factors such as brain derived neurotrophic factor (BDNF), fibroblast growth factor 21 (FGF21), or autotaxin (ATX) could support neurodevelopment.[88] Analogous to the gut, brain development maybe enhanced by maternal cells, microchimerism, stem cells and neurotrophic factors. These offer protective channels against the effects of bilirubin induced neuropathology on vulnerable immature neurons by enhancing maturity of the immature neonatal immune system and by providing direction for organ growth and development.

Angiogenetic factors and antagonists, vascular endothelial growth factor (VEGF) and soluble VEGF receptor 1 (sFlt-1) regulate angiogenesis and are found in early breast milk of preterm and term infants.[89] Skin-to-skin contact and early, successful breastfeeding may protect against bilirubin brain toxicity if milk factors, postulated here, induce angiogenesis of the vascular endothelium of the BBB , and by so doing, enhance its development, lessening entry of toxins. Mesenchymal stem cells in breast milk differentiate into neuroepithelium[90] forming neurons, astrocytes and oligodendrocytes.[91] The stem cells of breast milk could cross the BBB, transfer and integrate into the neonatal brain,[92] suggesting potentials for brain growth and differentiation with a plausible role against BIND.

Individualised protection from specific diseases may offer another route against the problems associated with jaundice. Breast milk, by virtue of the enteromammary axis receives signals from the maternal gut and other mucosae associated lymph nodes (MALT), found at portals of pathogen entry,[93] and such signals may be influenced by maternal features and encounters. Maternal immunity, genes and environmental exposures transmitted by breastfeeding can thus be individually protective.[94] Maternal intestinal bacteria translocate into milk, providing immunity through microbial environments.[94-96] Breast milk oligosaccharides (HMOs), influence infant gut flora while ECVs transport micro ribonucleic acids (miRNAs) and messenger ribonucleic acids (mRNAs) which may modulate such interactions.[94] Epigenetic changes by breastfeeding can influence health,[97] with breastfeeding capable of transferring maternal to neonatal genomic information.[98] Genetics influencing jaundice is observed in specific populations alluded to earlier and hypothetically, genetic and epigenetic potentials by breastfeeding ,directly or by intervention, could favourably modify this.

Gut induced signals from the enteric nervous system (ENS),[99,100] can be transmitted to the brain, mediated by microbes, nerves, endocrine intermediates , and immune factors.[101,102] There is support for microbial gut-to-brain influences because in the germ free state, maturation of the fetal BBB is delayed with persistent permeability defects,[69,70] whereas gut recolonisation rectifies this.[69] Brain emotions may impact the gut through bidirectional signals;[103] empowering breast milk via pathways and intermediates such as serotonin and melatonin.[67] Hence, maternal emotions transmitted to the nursling's gut through breastfeeding could influence the nursling's brain through his or her own gut-brain connections.[103] Positive maternal emotions, 'imbibed' by exclusive and sustained breastfeeding empowers breast milk nutrition with capacity and defences against long- term emotional dysfunction.

Breast milk jaundice and enhanced tissue survival

In addition to breastfeeding protection from predispositions to bilirubin brain toxicity, can continued breastfeeding in breast milk jaundice enhance the survival of vulnerable tissues? Toxic oxygen free radicals (OFRs) are constantly produced in the neonate[104] causing neonatal morbidities.[105,106] The premature neonate has reduced concentrations of antioxidants for tissue protection.[104] Breast milk per se confers antioxidation , and is superior to formula milk in this regard.[107,108] In addition, low concentrations of bilirubin function as potent antioxidants;[109] under normal conditions, very small amounts of bilirubin are present in brain tissue, probably protective and therapeutic.[109-111] Furthermore, physiological jaundice is suggested to have an "evolutionary role" in protecting from early newborn infections , such as against Group B Streptococcus neonatal sepsis;[112] arguably, breast milk jaundice also provides such "physiological" levels of bilirubin for protection.

If, during breast milk jaundice, small quantities of unconjugated bilirubin escape into the brain, close monitoring of bilirubin levels is advantageous. Additive, synergistic or complementary actions of breastfeeding per se by antioxidation and antiinfective protection, together with bilirubin brain antioxidation and antibacterial action , through bilirubin in breast milk jaundice, could confer potent cytoprotection

DISCUSSION

This review will be useful to support clinicians on the advice of exclusive breastfeeding during breast milk jaundice. Breastfeeding confers infection protection, superior neurocognition, maternal cells with capacities for optimal immune direction and pluripotency as well as genetic capabilities. These empower breast milk nutrition with well-timed and broad- based potentials for protection against rare complications that may occur during breast milk jaundice.

Quantitative analyses of this topic would offer an objective, evidence- based conclusion, but they have a number of constraints including ethical issues, challenges with multiple confounders and maternal recall of exact feeding method. Additionally, unpredictable in vivo breastfeeding dynamics may vary amongst mothers and at different gestational ages. Clearly, information integration , as outlined, is essential to highlight areas for investigation. Research, integrated with clinical outcome may underscore the obligatory role of breastfeeding in breast milk jaundice.

CONFLICT OF INTEREST

None

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