SUPPLEMENT

Overview of Nutrients in Human Milk

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ABSTRACT

The WHO recommends exclusive breastfeeding for the first 6 mo of life to promote optimal infant health and development. Understanding the micro- and macronutrient concentrations of human milk and how each nutrient fluctuates with lactational stage, maternal factors, and supplementation is imperative for supporting good breastfeeding practices. Where maternal undernutrition compromises human milk quality, a thorough awareness of the effectiveness of interventions can direct efforts to achieve both maternal and infant nutrient sufficiency. This review of current knowledge covers trends in nutrient concentrations over the course of lactation and describes the influence of maternal intake, status, supplementation, and other factors on human milk concentrations of each nutrient. *Adv Nutr* 2018;9:278S–294S.

Keywords: breastfeeding, breast milk, human milk lactation, micronutrient, nutrient

Introduction

As the sole source of nutrition for infants in the first 6 mo of life, breast milk plays a critical role in development. Infants of mothers with adequate nutritional status have reserves of some nutrients at birth, but they depend entirely on breast milk for other nutrients. Even in mothers who are well nourished, other physiologic or environmental factors may compromise status and capacity to transfer nutrients via breast milk. This review summarizes the current knowledge on how nutrient concentrations change through the initiation and progression of lactation, and how modifiable and nonmodifiable factors, including interventions, influence breast milk nutrient concentrations (**Table 1**).

Current Status of Knowledge

Thiamin

Thiamin acts as a coenzyme in the metabolism of carbohydrates and BCAAs. Deficiency, a public health problem most common in pregnant women and young children, may cause infantile beriberi and is a leading cause of infant morbidity and mortality in affected populations (11, 12). In breast milk, thiamin is present primarily as thiamin monophosphate (∼60%) and free thiamin (∼30%) (13). Thiamin concentrations in breast milk increase over the first several months of lactation (14–17). Thiamin status is associated with breast milk thiamin concentrations in women with adequate thiamin status (12, 13) but not in women with poor status (18), suggesting preferential transport of thiamin into milk in the case of maternal deficiency. Thiamin intake is positively associated with breast milk thiamin concentrations in both well-nourished and poorly nourished populations (12, 19, 20). Breast milk thiamin concentrations respond rapidly to maternal supplementation in populations where maternal deficiency is prevalent (11, 13) but not in well-nourished women (15, 21). Data on the influence of other maternal factors on thiamin concentrations of breast milk are lacking.

Riboflavin

Riboflavin functions as part of the coenzymes FMN and FAD in redox reactions involved in energy production and activity of glutathione, a free radical scavenger. Deficiency of riboflavin affects multiple metabolic pathways and can cause dermatologic abnormalities, peripheral neuropathy, poor growth, and impaired iron absorption (22). In breast milk, FAD and free riboflavin are the predominant forms of riboflavin (23). One investigator found a peak in breast milk riboflavin at 2–4 mo, with a subsequent reduction at 5–6 mo in lactating low-income Indian women (24), but the

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Abbreviations used: AA, ascorbic acid; BCAA, branched chain amino acid; FAA, free amino acid; TAA, total amino acid; 25(OH)D, 25-hydroxyvitamin D.

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TABLE 1 Summary of BM nutrients[1]

	Infant reliance on BM	Concentrations trend	Affected by maternal status	Affected by maternal diet	Affected by maternal supplementation	Maternal factors influencing BM concentrations	Comments
Thiamin	+	Increases over first several months	−	+	+/− (+ in case of maternal dietary insufficiency)	Insufficient data	The body does not store thiamin so continuous supply is needed to mother and infant
Riboflavin	+	Decreases vs. stable	+/− (mixed evidence)	+	+	Insufficient data	Very limited infant reserves at birth
Vitamin B-6	+/−	Increases during first weeks postpartum, followed by gradual decline	+	+	+	Insufficient data	Gestational reserves help support infant vitamin B-6 needs through first months of lactation; after 6 mo, BM alone may be insufficient to meet infant needs (1)
Vitamin B-12	+	Decreases during first 3–4 mo of lactation	+	+	+/−	Veganism/ vegetarianism/ low consumption of animal source foods (−), pernicious anemia (−)	Limited infant reserves at birth
Folate	+	Peaks at 2–3 mo of lactation	−	−	−	Insufficient data	Supplemental folate may affect BM folate concentrations in undernourished women (2); more data are needed; only severe maternal deficiency compromises BM concentrations
Choline	+	Increases rapidly from 7 to 22 d postpartum and remains stable in mature milk	+	+	+	SNPs in MTHFR (−), preterm delivery (−), inflammation (+), hormones (+/−)	Gene polymorphisms may explain variation in BM choline concentrations in women with similar intakes (3)
Vitamin C	+	Highest in colostrum, decreases with progression of lactation	−	+/−	+/−	Preterm delivery (+), smoking (−), diabetes (−)	Greater effect of diet and supplementation in women with poor status; the body does not store vitamin C so continuous supply is needed to mother and infant
Vitamin A	+	Highest in colostrum, stabilizes in mature milk	− (unless maternal reserves are depleted)	+/− (+ if maternal reserves are inadequate)	+	Preterm delivery (−), adolescence (−), parity (+)	BM vitamin A derived from circulating as well as dietary retinol (4)
Vitamin D	+/− [vitamin D_3, but not active 25(OH)D]	Little 25(OH)D in BM	+/− (conflicting data)	+/− [diet may affect BM vitamin D_3, but not active 25(OH)D]	+	Season, sun exposure (+), obesity (−)	Primary form passed from maternal circulation to BM is vitamin D_3, the biological precursor of 25(OH)D (5, 6)
Vitamin E	+	Decreases from colostrum to mature milk, then stable	−	−	+	Preterm delivery (−)	Limited infant reserves at birth; Greater increase in BM vitamin E concentrations with natural (RRR-α-tocopherol) vs. synthetic all-rac-α-tocopherol) supplementation (7)

(*Continued*)

TABLE 1 (*Continued*)

	Infant reliance on BM	Concentrations trend	Affected by maternal status	Affected by maternal diet	Affected by maternal supplementation	Maternal factors influencing BM concentrations	Comments
Vitamin K	—	Low concentrations in BM	–	–	+	Insufficient data	—
Iron	—	Low concentrations in BM, declines through first year of lactation	–	–	–	No consistent evidence	Infants depend on hepatic reserves to meet iron needs (8)
Copper	—	Low concentrations in BM, declines as lactation progresses	–	–	–	BM selenium concentrations (+)	Hepatic reserves protect infants from deficiency in early infancy (9)
Zinc	+/– (+ in early lactation)	Sharp initial decrease followed by gradual decline	–	–	–	Age (–), parity (–), iron deficiency (–)	Infant zinc stores are limited (9)
Calcium	+	Increases in first week, subsequent gradual decline for duration of lactation	–	+/– (+ where habitual calcium intake is low)	–	Adolescence (–), iron deficiency anemia (–)	—
Phosphorus	+	Increases in first week, subsequent gradual decline for duration of lactation	+/– (+ only in case of genetic anomalies)	–	No data	Familial hypophosphatemia (–), hyperparathyroidism (–)	BM phosphorus is tightly regulated (10)
Magnesium	+	Stable during lactation	–	–	–	Adolescence (–)	—
Iodine	+	Initial decline, stable after 1 mo	–	+	+	Smoking (–)	Influenced by environment (soil iodine, salt iodization, etc.); infants are born with limited reserves
Selenium	+	Decreases throughout lactation	+/– (weak correlation, if present)	+	+	No consistent evidence	Influenced by environment (soil selenium); infants are born with limited reserves
Protein	+	Brief, sharp decrease, then stable from 2 to 6 mo until weaning	–	+/– (amino acid composition varies by maternal intake)	N/A	Milk volume (–)	Similar concentrations in BM of well-nourished and undernourished mothers
Lipids	+	Sharp increase in first week, then stable	+	+/– (FA composition varies by maternal intake)	N/A	%IBW (+), milk volume (–)	Large intraindividual CV
Carbohydrates	+	Lactose is lowest in colostrum, stabilizes as milk matures	–	–	N/A	BMI (–), milk volume (+), preterm delivery (–)	Non-nutritive HMOs decrease from colostrum to mature milk

[1] BM, breast milk; HMO, human-milk oligosaccharide; IBW, ideal body weight; MTHFR, methylenetetrahydrofolate reductase; N/A, Not available; SNP, single nucleotide polymorphism; 25(OH)D, 25-hydroxyvitamin D; +, Yes; –, No.

breast milk riboflavin concentrations was stable for the first 3 mo of lactation in well-nourished mothers (14, 15).

Riboflavin in breast milk is positively correlated with maternal dietary intake (19, 20). There is conflicting evidence on the correlation between maternal riboflavin status and breast milk riboflavin. In well-nourished mothers, investigators found a positive correlation between status and milk riboflavin (20). Although studies in The Gambia, India, and Malawi reported lower breast milk concentrations than the Institute of Medicine and WHO means of 0.35–0.39 mg/L (25–27), another study in India showed comparable breast milk riboflavin concentrations between Indian women with marked deficiency and well-nourished Western women (28). Supplementation has a positive effect on milk riboflavin concentrations (15, 26, 27) that may decrease over time (21). Maternal parity does not affect breast milk riboflavin concentrations (29). Riboflavin in stored milk is highly susceptible to photodegradation upon exposure to sunlight (30) but is stable with refrigeration of $\leq$2 wk (29).

Vitamin B-6

Vitamin B-6 acts as a cofactor for >100 enzymes involved in amino acid metabolism, glycolysis, and gluconeogenesis (22). In infants, vitamin B-6 deficiency is associated with neurological and behavior abnormalities, including irritability, increased startle response, and seizures (31). Pyridoxal is the predominant form of vitamin B-6 in breast milk, which also contains smaller amounts of pyridoxal phosphate, pyridoxamine, and pyridoxine (31–34). Vitamin B-6 concentrations in breast milk increase 3- to 4-fold in the first few weeks postpartum, followed by a gradual decline in late lactation (14, 29, 35, 36). After 6 mo, breast milk alone may be insufficient to meet an infant's vitamin B-6 requirements (1).

Plasma pyridoxal 5′-phosphate, the primary biomarker of vitamin B-6 status, is positively correlated with breast milk vitamin B-6 concentrations (37). Maternal vitamin B-6 intake is a strong determinant of breast milk concentrations (31, 38), with rapid changes in breast milk concentrations observed in response to changes in intake (39). Supplementation of lactating mothers with vitamin B-6 vitamers led to an increase in milk concentrations that could be measured within several hours (2, 40). In a study that provided pyridoxine hydrochloride supplementation to groups of lactating women at different amounts, breast milk vitamin B-6 concentrations paralleled the amount of supplementation (41). There are conflicting data on the effect of premature delivery on early breast milk vitamin B-6 concentrations, with reported concentrations in preterm milk being either higher (36) or lower (42) than in term milk. Data on the influence of other maternal factors on the vitamin B-6 concentrations of breast milk are lacking.

Vitamin B-12

Vitamin B-12 acts as a cofactor in 2 key enzymatic reactions essential for folate metabolism and DNA synthesis, with deficiency during infancy resulting in a cluster of neurologic symptoms and developmental regression (43). Compared with infants who consume formula or bovine milk, exclusively breastfed infants have poorer vitamin B-12 status at 4–6 mo of age, possibly reflecting an altered but appropriate cobalamin profile associated with breastfeeding (44). However, exclusively breastfed infants of mothers with chronic dietary or malabsorptive depletion of vitamin B-12 may suffer consequences of deficiency (43).

In human milk, vitamin B-12 is tightly bound to apo-haptocorrin, a cobalamin-binding protein (45). Binding by apo-haptocorrin has been shown to interfere with the measurement of cobalamin, leading to over- or underestimation depending on the methods used for pretreatment and subsequent assay of the vitamin (46). With the use of a new and more accurate method for pretreatment and measurement of cobalamin in breast milk (47), investigators studying vitamin B-12–replete Danish mothers found a significant decline in both breast milk and infant plasma cobalamin from birth to age 4 mo, with a subsequent increase in both markers at 9 mo (48). Other studies that used older methods found that vitamin B-12 in breast milk declines in early lactation (14, 49), remains stable until 12 wk and declines to a low at 35 wk postpartum (50), or remains stable in early lactation (51).

In the Danish cohort, significant positive correlations were found between breast milk, maternal plasma, and infant plasma cobalamin concentrations at 4 mo but not at birth or at 9 mo, by which point infants were consuming a mixed diet of breast milk and complementary foods (48). In multiple regression analysis of a Guatemalan cohort that used similar analytical techniques, breast milk cobalamin concentrations were significantly associated with maternal, but not infant, serum cobalamin at 12 mo postpartum, possibly indicating the strong influence of maternal status during pregnancy on infant stores at birth (52).

Maternal intake of vitamin B-12 has been associated with breast milk cobalamin concentrations at 1, 6, and 12 mo postpartum in studies in Kenyan and Guatemalan lactating women (52, 53). Several studies found lower concentrations of breast milk vitamin B-12 in macrobiotic or vegetarian mothers than in omnivorous mothers (54–56). Other maternal factors that influence vitamin B-12 in breast milk include conditions such as pernicious anemia or malabsorption that impair maternal vitamin B-12 status (43). Cobalamin concentrations are similar in fore- and hindmilk (48, 57).

Supplementation of women with oral vitamin B-12 during pregnancy (50 μg/d) and lactation (3–1000 μg/d) has resulted in moderate and, at times, significant increases in breast milk vitamin B-12 concentrations at 1–6 mo postpartum compared with placebo or nonplacebo controls (2, 21, 45, 46, 58). However, the biological significance of such findings is difficult to interpret given the paucity of data and questionable analytical methods used to derive reference concentrations for vitamin B-12 in breast milk (46). Existing protocols rely on the treatment of mother and infant with therapeutic doses of intramuscular vitamin B-12 once symptoms are apparent, which may be too late for reversal (43).

Vitamin B-12 concentrations in colostrum, transitional, and mature milk did not differ significantly between women who gave birth to term or preterm infants in 2 studies (14, 59). Other factors, such as maternal age, parity, BMI, smoking status, or oral contraceptive use, have not been investigated in relation to breast milk vitamin B-12 concentrations.

Folate

Folate and its coenzymatic forms are necessary for protein, DNA, and RNA biosynthesis, and as such are in greatest need during periods of growth, development, and reproduction (60). The predominant form of folate in human milk is 5-methyltetrahydrofolate (46). Breast milk folate concentrations are low in colostrum and increase in the weeks after delivery (14), peaking at 2–3 mo (61, 62), decreasing slightly from 3 to 6 mo (60, 61, 62), and remaining stable into late lactation (35). Folate is preferentially taken up by secretory mammary glands, maintaining milk folate concentrations at the expense of maternal stores except in cases of frank maternal deficiency (60). As a result of homeostatic control, milk folate concentrations are unrelated to maternal folate status or intake (46).

Supplementation of US lactating women with folic acid (750 μg/d) and natural food folate (400 μg/d) for 10–12 d did not change breast milk folate concentrations but did significantly increase milk folic acid (63). That folate or folic acid supplementation does not alter breast milk folate concentrations agrees with the results of most other studies (21, 64, 65). However, supplementation with 1 mg folic acid/d prevented the decline in milk folate from 3 to 6 mo postpartum in the treatment group of one study (60), and breast milk folate was significantly increased in a small trial in low-income women who received a multivitamin supplement containing folate when compared with controls (2). Furthermore, maternal supplementation with synthetic folic acid leads to the appearance of unmetabolized folic acid in milk, with unknown downstream effects on the bioavailability of milk folate to infants (65). Milk folate concentrations are similar in preterm and term milk (42) but are higher in the afternoon and evening than in the morning (66). Diurnal variations in folate concentrations decrease as lactation progresses (66).

Choline

Choline is a vital amine involved in numerous physiological processes, including structural integrity of cell membranes, transmembrane signaling, lipid-cholesterol transport and metabolism, methyl group metabolism, and brain development (67, 68). Choline adequacy is particularly important during the rapid growth associated with perinatal development (69). Because betaine, the irreversible oxidation product of choline, is excreted by human infants in large amounts during the first year of life, it is assumed that the supply of dietary choline via breast milk is critical to normal development (70). In young children, choline inadequacy has been correlated with stunting (71), which suggests that adequate breast milk choline may be necessary for proper growth in infancy. In breast milk, choline is found primarily as phosphocholine and glycerophosphocholine, with lower concentrations of free choline, phosphatidylcholine, and sphingomyelin (70, 72). Total breast milk choline concentrations increase rapidly between 7 and 22 d postpartum and remains relatively stable in mature milk, although free choline concentrations decline from 12 to 180 d postpartum (69, 72).

Breast milk total choline is positively correlated with maternal serum phospholipid-bound choline concentrations, whereas breast milk free choline is positively correlated with maternal serum free choline, phospholipid-bound choline, and glycerophosphocholine (69). The increase in maternal serum free and phospholipid-bound choline that occurs during lactation is likely an adaptation to maintain high concentrations of choline in breast milk and is explained by increased hepatic synthesis (69). A significant correlation has been found between dietary intakes and breast milk concentrations of total choline, phosphocholine, and phosphatidylcholine, although this relation is mediated by single nucleotide polymorphisms in genes that code for the enzymes of choline and folate metabolism (3). Supplementation with phosphatidylcholine is effective at increasing free choline concentrations in maternal plasma and breast milk as well as phosphocholine concentrations in breast milk (3). Choline concentrations are lower in preterm than in term breast milk (73) and are influenced by maternal inflammation and hormone concentrations (74, 75).

Vitamin C

Antioxidant vitamins in human milk play an important role in immunomodulation. Vitamin C stimulates leukocytes, augments antibody production, and enhances the synthesis of interferons (76). Breast milk ascorbic acid (AA) is highest in colostrum and decreases over the course of lactation (35, 76). There is wide variability in the AA concentrations of breast milk, in large part due to differences in maternal status and dietary intake (77). In resource-poor settings, breast milk AA concentrations parallel seasonal variations in the consumption of fruit and vegetables rich in vitamin C (78–81), whereas in well-nourished women, dietary intake or supplementation has much less influence on breast milk concentrations (2, 21, 77, 82, 83). Vitamin C is more concentrated in preterm than in term milk (84) and is lower in the milk of mothers who smoke (85, 86) or have diabetes (85).

Vitamin A

Because infants are born with meager vitamin A reserves regardless of maternal nutritional status, adequate retinol in breast milk is critical for ensuring healthy infant growth and development and accumulating liver stores needed after weaning. Expressed either as a concentrations or relative to fat, retinol is highest in colostrum and reaches stability in mature milk. Breast milk vitamin A is present almost exclusively as retinyl esters, mainly retinyl palmitate, in the lipid fraction of the milk (4, 87). Given adequate liver reserves, circulating retinol-binding protein–retinol is stable over a wide range of vitamin A intake (87). Although much of vitamin A in breast milk is derived from serum retinol, which is esterified in the mammary gland, newly absorbed dietary retinol converted to retinyl palmitate is postulated to pass directly into milk via chylomicrons, bypassing regulation by the liver (4). Because maternal liver reserves are drawn upon to compensate for dietary intake inadequacy and retinol is allocated preferentially to breast milk (88, 89), a low breast milk vitamin A concentrations suggests insufficient liver reserves in addition to inadequate intake.

Maternal supplementation with megadoses of 200,000–400,000 IU vitamin A in the first week after birth resulted in an increase in breast milk retinol concentrations compared with baseline or control groups that were sustained for 1–6 mo (90–92). In rural communities of low to middle socioeconomic class in Indonesia and Vietnam, daily supplementation of lactating mothers with 4–6 mg β-carotene for 10–12 wk increased breast milk retinol concentrations significantly compared with controls (93, 94). However, neither a single 60-mg dose nor 4 wk of daily supplementation with 30 mg β-carotene/d increased breast milk retinol concentrations in well-nourished US women (95, 96). In a group of well-nourished Brazilian women, regular intake during pregnancy of a multivitamin containing preformed retinol was more effective at preventing low colostral retinol ($<$2.1 μmol/L) than the intake of a multivitamin containing an equivalent quantity of β-carotene (97).

The influence of a number of maternal factors on breast milk retinol concentrations has been investigated; for most factors, results are mixed. There is a suggestion of higher retinol concentrations after full-term delivery than after preterm delivery (98–101) and in multiparous mothers than in primiparous mothers (99, 102, 103). There is no strong evidence of an association between breast milk retinol concentrations and socioeconomic status (102, 104), maternal age (105–108), maternal anthropometric measurements (103, 106–108), or inflammation (106, 109, 110). Vitamin A in breast milk is susceptible to photodegradation, with $\leq$70% loss reported upon controlled exposure of the breast milk sample to sunlight (30).

Vitamin D

Vitamin D plays an important role in infant bone growth, immune system development, and brain development, but is present in low concentrations in breast milk (111). The primary form of vitamin D passed from maternal circulation to breast milk is cholecalciferol, the biological precursor of 25-hydroxyvitamin D [25(OH)D] (5, 6). However, cholecalciferol is rapidly converted to 25(OH)D in the mother, resulting in limited uptake of vitamin D into breast milk (5). The average total vitamin D activity of breast milk in the first 6 mo of lactation is 544 pg/mL, which provides the exclusively breastfed infant with $\sim$15 IU/d (112). To our knowledge, no studies have measured breast milk vitamin D concentrations longitudinally in unsupplemented women. There is a significant positive correlation between maternal plasma or serum and breast milk cholecalciferol concentrations (113, 114), but results for the correlation between circulating and breast milk 25(OH)D are conflicting (113–116). Similarly, total vitamin D but not 25(OH)D concentrations in breast milk is correlated with maternal dietary intake (114). As a whole, evidence supports an increase in breast milk vitamin D and 25(OH)D concentrations with maternal supplementation of 1,000–6,400 IU/d during lactation (117–123). Vitamin D concentrations vary seasonally and are higher in hindmilk than in foremilk (117). There is some evidence that maternal sunlight or UV-B exposure increases breast milk 25(OH)D (117, 124). Maternal obesity is associated with lower breast milk 25(OH)D concentrations (125).

Vitamin E

During gestation and the postnatal period, vitamin E provides essential antioxidant protection to the fetus and newborn and stimulates immune system development (126). Despite increasing vitamin E concentrations in maternal circulation during pregnancy, placental transfer is limited (127). A very high concentrations of vitamin E in colostrum enables infants to increase circulating vitamin E concentrations from one-third that of their mothers to normal adult concentrations within 4–6 d of breastfeeding initiation (128). The concentrations of vitamin E in breast milk decreases as the milk matures (98, 129–132) and stabilizes after the first month of lactation (133, 134). It has been hypothesized that the decrease in vitamin E from colostrum to mature milk is related to an increase in the diameter of the fat globules, with a proportional decrease in tocopherol and other components of the fat-soluble membrane (126).

The majority of studies did not find a correlation of breast milk tocopherol with maternal plasma or serum concentrations (135, 136) or with maternal dietary intake (98, 133, 134, 137). Maternal supplementation with α-tocopherol, both natural and synthetic, immediately after delivery significantly increased the α-tocopherol concentrations in colostrum 24 h later (7, 138). Supplementation with natural RRR-α-tocopherol (the naturally occurring stereoisomer, indicating that the 3 chiral carbons are in the R conformation) increased colostrum α-tocopherol concentrations more than did synthetic all-rac-α-tocopherol, although the supplementation doses were not reported (7).

The vitamin E concentrations of breast milk are not associated with maternal parity, BMI, or socioeconomic status (127). One study found that breast milk tocopherol concentrations were lower in female adolescents than in women (135), but this association was not confirmed in a second study (139). There is limited evidence that vitamin E concentrations are lower in preterm milk than in term milk (140) and in foremilk than in hindmilk (137).

Vitamin K

Vitamin K traverses the placenta poorly and is present in low concentrations in breast milk (141). As a result, breastfed infants who do not receive a prophylactic dose of vitamin K at birth are at risk of hemorrhagic disease of the newborn (142). Phylloquinone, or vitamin K-1, is the primary form of circulating vitamin K and has been considered the essential form for mothers and infants (142). However, menaquinone-4, a form of vitamin K-2 (menaquinone), is also found in human milk (143). Vitamin K is localized in the lipid core of the milk-fat globule (144).

In a small longitudinal study in 10 mothers, phylloquinone concentrations were found to increase from colostrum to mature milk (145). However, no significant differences were found between the vitamin K concentrations of colostrum or mature milk measured at 1, 3, or 6 mo of lactation in 4 cross-sectional groups of 15 women (144), nor were significant changes in breast milk vitamin K concentrations noted in 23 US women followed longitudinally from 6 to 26 wk of lactation (146).

Breast milk concentrations of phylloquinone do not correlate with maternal plasma concentrations (143) or maternal dietary intake over a wide range of intake amounts, but are at least transiently affected by pharmacologic supplemental doses (146, 147). In a single study in 22 exclusively breastfeeding women, maternal supplementation with 5 mg oral phylloquinone/d (compared with an adequate intake during lactation of 90 μg/d) from delivery through 12 wk resulted in significantly higher maternal serum, breast milk, and infant plasma phylloquinone concentrations at 2, 6, and 12 wk in the intervention group compared with placebo controls (148, 149). There is a lack of published data on the impact of maternal constitutional variables on breast milk vitamin K, likely because concentrations are very low in general (141).

Iron

In addition to its role as a part of hemoglobin, iron is a structural component of a variety of enzymes necessary for a range of metabolic processes. Infants are particularly susceptible to the consequences of iron deficiency due to rapid growth and brain development (150). Newborn needs for iron are met through the utilization of hepatic reserves accumulated mainly during the final trimester of gestation (8). In milk, iron is bound primarily to low-molecular-weight peptides, fat globules, and lactoferrin, with the mean iron saturation of lactoferrin varying from 2.2% to 12% (151). Milk iron concentrations reach a maximum in colostrum and subsequently decline through the first year of lactation (152–157), with reported median values of 0.04–1.92 mg/L (151). Despite an increase in the volume of milk consumed, the total daily intake of iron decreases from birth to 4 mo postpartum (158). The iron concentrations in human milk are insufficient to meet infant requirements (151) and supplementation may be indicated after 6 mo of age (159). Breast milk iron concentrations are not associated with maternal dietary intake (156, 160–162) and are generally refractory to maternal status (156, 163). Iron supplementation of anemic (151) and nonanemic (164, 165) mothers does not improve breast milk iron concentrations.

Few maternal factors influence breast milk iron concentrations. There is no evidence that oral contraceptive use, infection, or β-thalassemia major affect iron concentrations in breast milk despite their role in altering iron metabolism (151). There is inconclusive evidence that breast milk iron concentrations are associated with parity (166), milk vitamin A concentrations, and smoking (167). A single study found higher iron concentrations in hindmilk and in samples collected during the night (166).

Copper

Copper, an essential cofactor for enzymes involved in cellular respiration, iron metabolism, and connective tissue synthesis, is accrued in the fetal liver during gestation and mobilized in the early neonatal period (156). Longitudinal studies of copper concentrations in breast milk have found a decrease over time, at least for the first 6 mo of lactation (153–156, 168–171). While in serum the majority of copper (83–100%) is bound to ceruloplasmin (172); in breast milk, ceruloplasmin carries only 20–25% of copper (173). Breast milk ceruloplasmin decreases in the first month of lactation, but this has not been linked directly with the decrease in milk copper concentrations (174, 175). The copper concentrations in breast milk are not associated with maternal status (156, 163), dietary intake (155, 156, 160, 162, 163), or supplementation (176, 177). Maternal age, parity, smoking, iron supplementation, oral contraceptive use, and infection do not influence breast milk copper concentrations (166, 178), nor is there a difference in concentrations between fore- and hindmilk (151). Breast milk copper concentrations are directly correlated with selenium concentrations (154), and there is some evidence that an increase in soil selenium content may indirectly increase breast milk copper concentrations (179).

Zinc

Zinc deficiency in infants results in stunted growth and compromised immune function, with increased morbidity and mortality from diarrhea and respiratory infections (163, 180). Breast milk zinc concentrations decrease sharply from colostrum to transitional milk (170), followed by a gradual decline throughout lactation (171). It is estimated that the mean daily zinc transfer to the infant via breast milk is 4 mg in colostrum, 1.75 mg at 1 mo, and 0.7 mg at 6 mo (181). Breast milk zinc concentrations are refractory to maternal status (157, 164), intake (156, 160, 161, 182, 183), and supplementation (166, 176). Lower concentrations of breast milk zinc have been observed in older (155, 166), multiparous (156), and iron-deficient (184) women. No relation has been found between breast milk zinc concentrations and maternal smoking, iron or multivitamin/mineral supplementation including zinc, or length of gestation (166, 178).

Calcium

Calcium is an important constituent of bone and plays a critical role as a messenger in cell-signaling pathways. Despite speculation that low breast milk calcium concentrations may contribute to infantile rickets (185), research indicates that breast milk concentrations are tightly linked to casein and citrate in the milk (186, 187). Breast milk total calcium concentrations increase sharply in the first 5 d of lactation (188), followed by a gradual decline for the duration of lactation (186). In contrast, ionized calcium concentrations in breast milk are stable throughout lactation, which suggests a homeostasis similar to that in blood (186). In a review of numerous studies conducted between 1940 and 1990, the median concentrations of calcium measured in breast milk was 252 mg/L, with most samples collected between 1 and 6 mo of lactation having a concentrations between 100 and 300 mg/L (189).

Dietary intake alone is insufficient to explain between-country differences in breast milk calcium concentrations (189), which is consistent with a majority of studies that found no association between maternal dietary calcium intake and breast milk calcium concentrations (168, 190–192). However, in geographic areas where habitual intake of calcium is low, dietary calcium may influence breast milk concentrations (193–196). Neither maternal status (196–198) nor interventions with dietary calcium or vitamin D have shown an effect on breast milk calcium concentrations (118, 185, 199–201). Breast milk calcium concentrations are lower in lactating adolescents (202, 203) and in women with iron deficiency anemia (184). Other variables, such as length of gestation, sampling techniques (time of day, fore- compared with hindmilk, drip compared with expression), maternal age, parity, race, lactation history, smoking, and oral contraceptive use, are not associated with breast milk calcium concentrations (189, 190).

Phosphorus

Phosphorus is a structural component of cell membranes and nucleic acids and is involved in multiple biological processes, including bone mineralization, cell signaling, energy production, and acid-base balance. Although the milk secretion of calcium and phosphorus is independently regulated, the median ratio of calcium to phosphorus is 1.7 in both preterm and term breast milk (189). Like calcium, the concentrations of phosphorus are highest in early transitional milk and decrease gradually as lactation progresses (190, 204). The phosphorus concentrations of human milk are low compared with milk of other mammals, possibly as a mechanism to inhibit the growth of fecal pathogens, to protect the immature newborn renal system from calcium-metabolism disturbance, or to prevent metabolic acidosis (205). Breast milk phosphorus is tightly regulated (10) and does not appear to be influenced by maternal intake, age, parity, race, lactation history, sampling techniques, smoking, or oral contraceptive use (189, 190). Only in the case of maternal familial hypophosphatemia (206, 207) or hyperparathyroidism (208) are breast milk phosphorus concentrations significantly decreased.

Magnesium

Magnesium plays a structural role in bone and is involved in >300 essential metabolic reactions (209). Magnesium from maternal bone is mobilized during lactation, adding stored magnesium to the mineral pool that supplies the mammary gland. The median magnesium concentrations in breast milk is 31 mg/L, with most reported means within the range of 20–40 mg/L (210). Despite interindividual variation, breast milk magnesium concentrations in the same woman are fairly stable during the course of lactation, although various researchers have reported slight increasing or decreasing trends during the first 6 mo (10, 210). Breast milk magnesium concentrations are not affected by maternal intake or supplementation, nor do they vary with length of gestation, maternal metabolic disorders, parity, race, lactation history, smoking, or oral contraceptive use (190, 210). There is some evidence of lower breast milk magnesium concentrations in lactating adolescents (211). Because most of the magnesium in breast milk is bound to low-molecular-weight fractions and proteins (212), there is little difference between its concentrations in fore- and hindmilk (213, 214).

Iodine

Iodine is necessary for infant growth, mental development, and survival (215). Breast-milk iodine concentrations are maximal in colostrum, decrease over the next few weeks, and remain stable at 100–150 μg/L in mature milk of iodine-replete women (216). Most studies have not found an association between milk iodine concentrations and stages of lactation after 1 mo in non–iodine-deficient mothers (217).

The iodine concentrations of human milk vary widely, mainly due to soil iodine content, salt or oil iodization, and maternal intake (217, 218). Although maternal iodine intake and status are closely related given the geographic region, breast-milk iodine concentrations are associated with current maternal intake rather than status (218). Breast-milk iodine concentrations are higher in nonendemic than in endemic goiter regions (219–222), in areas where iodophores are used for sanitizing in dairy farming (223, 224), and in countries with salt iodization (224, 225). In areas where maternal iodine intake is exceptionally high due to the consumption of seaweed and algae, breast-milk iodine concentrations are as much as 10 times higher than that reported in other regions (226, 227). Maternal iodine supplementation is also effective at increasing breast-milk iodine concentrations (228, 229).

Milk iodine concentrations are not affected by sampling time of day (230) and do not differ significantly between fore- and hindmilk (231). Smoking is inversely associated with breast-milk iodine (232).

Selenium

Selenium is an essential component of a number of selenoproteins. These include the potent antioxidant glutathione peroxidases and deiodinases that function in thyroid hormone metabolism, both of which are critical for early-life development (233). In breast milk, selenium is present as a component of the potent antioxidant glutathione peroxidase and to a lesser extent as selenocystamine, selenocystine, and selenomethionine (234). Human infants are born with selenium reserves but also depend on the selenium supplied by their mothers' milk (235). Selenium concentrations are high in colostrum and decrease as lactation progresses (153, 236–239), parallel with the trend for the milk proteins into which selenium is incorporated (235).

Dietary intake of organic selenium, which reflects the selenium content of soils where the foods are grown (240), is a key determinant of breast milk selenium concentrations and explains the wide range of breast milk selenium concentrations across geographic regions (218, 235). Many studies have found a significant, albeit weak, correlation between serum or plasma and breast milk selenium concentrations (153, 241–245). However, others have not found a significant correlation (236, 246, 247). Prophylaxis via soil treatment or maternal supplementation with selenomethionine or sodium selenate is effective at increasing the selenium concentrations in breast milk (248, 249).

Maternal age, BMI, iron supplementation, and smoking do not affect breast milk selenium concentrations (165, 239, 247, 250). One study found an inverse correlation between maternal parity and breast milk selenium in late lactation (251), although a similar association was not found in other studies (239, 250). The difference in selenium concentrations between fore- and hindmilk reported by some researchers but not others may be a statistical artifact due to variability in milk selenium, because <5% of selenium is found in milk fat (235).

Amino acids

Total amino acids (TAAs) in breast milk include protein-bound amino acids as well as free amino acid (FAAs) belonging to the nonprotein nitrogen fraction of milk. FAAs account for 8–22% of nonprotein nitrogen and 5–10% of TAAs (252–254). TAA concentrations decrease from colostrum to mature milk and remains stable from 4 mo of lactation, which corresponds to the changing protein needs of the infant (255, 256). The pattern and composition of FAAs over the course of lactation differ from TAAs, which reflects the functional role of FAAs in early postnatal growth and development (253, 257, 258). FAAs are more readily absorbed than protein-derived amino acids and are credited with the initial change in infant plasma amino acids after a feeding (256, 259). FAAs are not influenced by maternal or gestational age (256, 260, 261), but show large interindividual variability (259, 262, 263) and are modified by recent and habitual maternal intakes (264–267).

Glutamate is the most abundant FAA at all measured stages of lactation, with concentrations in breast milk ranging from 960 to 1529 μmol/L compared with 4–453 μmol/L for other individual FAAs (256). Glutamine, which can be synthesized from glutamate but is conditionally essential (261), increases by ~20-fold from colostrum to 3 mo lactation, such that glutamate and glutamine combined represent ~50% of FAAs in breast milk (252, 253, 254, 260). It has been speculated that glutamate and glutamine supply functional substrates to nervous tissue, protect intestinal growth and integrity, and are essential for immune development (252, 268–271). Free glutamate may have a downregulating effect on infant appetite and growth (272), although additional research is needed to confirm this (262). In a recent Danish study, the glutamine concentrations of breast milk were positively correlated with infant length at 4 mo, although the association was attenuated when controlling for birth length (262).

Taurine is the second most abundant FAA at all stages of lactation (256). Taurine is present in breast milk only as an FAA (253). Because humans have a relatively low capacity to synthesize taurine, it is considered essential to normal perinatal development (273). Taurine is involved in bile acid conjugation, structure and function of retinal photoreceptors, and neurodevelopment (274–276). Compared with formula-fed infants, the presence of the more acidic taurine bile acid conjugates in the intestine may favor colonization by Lactobacillus and Bifidobacteria (277).

Lipids

Compared with the other macronutrients, fat is the most variable component of breast milk, with an estimated CV of 47% over 24 h in mature milk (278). A large part of the fluctuation in milk-fat concentrations within an individual can be accounted for by breast fullness at the point of sampling, which is related to, but may not completely explain, variability due to time of day, interfeeding interval, point of sampling during a feeding, and difference between breasts (4, 279). It is well recognized that the lipid concentrations increases as the breast is emptied, with ~50% of fat present in the 20% of milk that remains in the mammary gland after a typical infant feeding (280). However, milk-fat concentrations are also affected by nontransient factors, including stage of lactation, maternal weight or BMI (281, 282), and general maternal nutritional status (102, 282).

The concentrations of TGs and medium-chain FAs and the size of the milk-fat globule increase from colostrum to mature milk, whereas cholesterol and esterified cholesterol concentrations decrease (132, 204, 283). Fat concentrations remain stable in mature milk (204, 284), although the FA composition depends on the nutritional intake and status of the mother (274, 285, 286). Across countries, breast milk concentrations of PUFAs, especially DHA, vary more widely than the concentrations of SFAs and MUFAs (287, 288).

Carbohydrates

The disaccharide lactose is the principal carbohydrate found in breast milk, with concentrations in the range of 67–78 g/L (289). Lactose concentrations are lowest in colostrum and increases through the first 4 mo of lactation (290). Unlike the other macronutrients, lactose concentrations are fairly consistent across the milk of different mothers, with a CV of 2–4% independent of maternal diet and nutritional status (281, 291–293). Lactose concentrations are not influenced by maternal weight or parity (281). There is some evidence that breast milk lactose concentrations are lower in preterm milk (294–296), higher with advanced maternal age (297), and transiently lower before and after ovulation once menses has resumed (298). Lactose concentrations are correlated with milk volume, possibly related to altered secretion rates of electrolytes contributing to osmolarity (281).

Oligosaccharides, non-nutritive carbohydrates that selectively encourage the growth of beneficial intestinal Bifidobacteria and act as soluble "decoy" receptors for pathogens, contribute substantially to the carbohydrate fraction of human milk (299, 300). Colostrum contains 20–25 g human-milk oligosaccharides/L, decreasing to 5–20 g/L as milk matures (301). Nearly 200 human-milk oligosaccharides have been identified (302), with the distribution depending on the stage of lactation as well as maternal genetic factors (303).

Conclusions

With respect to many nutrients, breast milk is a changing medium that satisfies infant needs at various stages of growth. In some cases, breast milk nutrient concentrations are resilient to changes in maternal status, although maintaining the supply to the growing infant may be at the expense of maternal reserves. In other cases, suboptimal nutrition and nutrient status are reflected in the breast milk, compromising infant development. Infant supplementation with vitamin K, vitamin D, and vitamin B-12 early in lactation and with iron after 6 mo of age may be indicated to buffer for insufficient reserves and inadequate transfer via breast milk. For many nutrients, the effect of maternal factors on breast milk concentrations has been investigated, but for several of the B-vitamins, including thiamin, riboflavin, and vitamin B-6, additional data are needed. Because exclusive breastfeeding is recommended through 6 mo of age, it is critical to understand which factors influence breast milk nutrient concentrations and whether intervention is possible to protect both mother and infant from deficiency. Although substantial progress has been made in elucidating the regulatory factors for each nutrient in breast milk, additional research is needed to clarify normative values in relation to infant developmental outcomes and to better understand how sampling techniques and analytical methods contribute to inter- and intraindividual variability.

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