REVIEW ARTICLE

Fats in Human Milk: 2022 Updates on Chemical Composition

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Abstract

Human milk (HM) feedings are important for all newborn infants. Healthy term infants grow well with the mother's own milk (MOM), be it in direct breastfeeding or when fed expressed breastmilk. Premature and ill infants being treated/monitored in neonatal intensive care units (NICUs) also recover better when fed with HM diets, which can include MOM, donor milk (DM), or a combination of both. In terms of chemical composition, it contains 3–5% fat, 0.8–0.9% protein, 6.9–7.2% carbohydrates (calculated as lactose), and 0.2% mineral constituents. In this review, we present the latest information on HM fats, including triglycerides, phospholipids, triglycerides, cholesterol, glycoproteins, and enzymes. This article is intended to initiate a series of periodic updates on the scientific information available on HM fats. It contains some of our own research findings with an extensive review of the literature. To avoid bias in the identification of studies, keywords were short-listed *a priori* from anecdotal experience and from PubMed's Medical Subject Heading (MeSH) thesaurus. We then searched the databases PubMed, EMBASE, and Science Direct.

Keywords: Donor milk, Infants, Mother's own milk, Neonate, Neonatal intensive care unit, Newborn, Premature, Triglycerides.

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Key Points

- Human milk feedings are important for all newborn infants. Healthy term infants grow well with MOM, be it in direct breastfeeding or when fed expressed breastmilk. Premature and ill infants being treated/monitored in NICUs recover better when fed with HM diets, which can include MOM, DM, or a combination of both.
- Fats in HM are an important source of energy for enterally fed growing term and premature infants. Human milk fats, including triglycerides, phospholipids, triglycerides, cholesterol, glycoproteins, and enzymes may facilitate recovery in ill neonates.
- Fats account for nearly 3–5% of HM and add up to nearly 25 grams/day during the first few months after birth. The amounts are sufficient to cover the physiological needs of newborn infants of about 4.8–6.6 grams/kg per day.
- Increasing information on various types of milk fats, including triacylglycerols, phospholipids, and saturated and unsaturated fatty acids, has improved our understanding of the roles of these lipids in development and disease.
- Docosahexaenoic acid (DHA, C22:6n-3) is a particularly important polyunsaturated FA. It is highly enriched in the brain and is being recognized for its role in neurodevelopment and retinal maturation.

Introduction

Human milk feedings are important for all newborn infants.[1–3] Healthy term infants grow well with MOM, be it in direct breastfeeding or when fed expressed breastmilk.[4] Premature and ill infants being treated/monitored in NICUs also recover better when fed with HM diets, which can include MOM, DM, or a combination of both.[5] For these infants, milk may need appropriate fortification with bovine or HM-derived fortifiers.[6] The use of donor HM, not formula, is also preferred to treat term infants with transient conditions such as hypoglycemia.[7] The Joint Commission PC-05 and Baby-Friendly Hospital Initiative (BFHI) metrics include the exclusive use of HM throughout the initial newborn hospitalization.[8,9] Human milk-derived fortifiers engineered from donated HM are also becoming popular in US NICUs, and are now used exclusively in 1/3rd or more of level-3–4 NICUs.[10] The combination of HM-derived fortifiers with either DM or MOM, excluding any products cow's milk-containing products, has been labeled as exclusive HM diet.[11]

Fat in HM is an important energy source for enterally fed growing term and premature infants.[12] Infants may have developmental limitations in utilizing milk-borne fats in the first few weeks after birth.[13] The expression of many digestive enzymes and the transport of absorbed fats may be low.[14] Maternal milk also shows changes in its fat composition during this period; the carbon chain length and the degree of unsaturation show maturational changes and are important determinants of absorption.[15] The concentrations of major nutritional, immunological, and hormonal components in HM change over the course of lactation and differ between preterm and term populations.[15] These components also vary based on the infant's birth order, gender, gestational age, and postnatal chronological age.[16] Immunological factors are frequently influenced by infant's illness.[16] Some HM hormones show diurnal variations in concentration.[17] The long-term benefits of HM are promising for infants; there is a gut–lung and a gut–brain axis that

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links the intestinal microenvironment in early infancy with gut/lung maturation and neurodevelopmental outcomes.[18,19]

In this review, we present the latest information on HM fats, including triglycerides, phospholipids, triglycerides, cholesterol, glycoproteins, and enzymes. All medical professionals involved in newborn care have long sought a comprehensive source of information on this very important topic, and after serial discussions in a subcommittee at the Global Newborn Society (GNS), we decided to collaborate across the organization to develop articles to cover various aspects of HM feedings ranging from clinical practice to its biochemistry. This article is intended to initiate a series of annual updates on the scientific information on HM. We searched extensively in the databases PubMed, EMBASE, and Scopus after short-listing keywords focused on the biochemistry and clinical relevance of these lipids.

Fats in HM

Fats (lipids) account for nearly 3–5% of HM, and are sufficient to cover the physiological needs of newborn infants of about 4.8–6.6 grams/kg per day.[20,21] About 98% are triacylglycerols (TAGs) that carry nearly 88% of fatty acids (FAs).[1,12] Small amounts of cholesterol esters (CEs) and phospholipids (PLs) are also seen.[22] Table 1 summarizes these data. Overall, TAGs, FAs, CEs, and PLs comprise the four most important classes of lipids in HM and provide 50–60% of the total HM energy content.[23] Milk fats are important vehicles for the transport of many lipid-soluble hormones and vitamins A, D, E, and K.[12] Many of these components play important roles in the development of cognitive function and visual acuity.[24]

Fats make HM energy dense without an inappropriate increase in osmotic load.[4] The highest concentrations are seen in colostrum and then decrease gradually in the postnatal period. This inverse correlation with rising milk volumes keeps the total daily ingested amounts of fats at a consistent level. The fat content shows considerable inter- and intra-individual variation.[25]

Table 1: Types of fats in HM

Type of fats	*Approximate percentages as constituents of the total fat*
Triacylglycerols	98%
Diacylglycerols	Up to 1%
Monoacylglycerols	Traces
Nonesterified FAs	Up to 0.5%
Phospholipids	Up to 1%
Cholesterol	Up to 0.5%

The percentages are rounded-off figures from our own data

There is a rise in fat content each time a mother feeds her baby; hindmilk may contain up to 6% fats, which is more than the 2% seen in foremilk.[26] There is also a diurnal variation with higher fat contents during the day and lower during the night.[17] All these variations contrast with the relatively constant concentrations of protein and lactose.

Triacylglycerols in HM

Triacylglycerols consist of a glycerol molecule that can be esterified in 3 FAs occupying segments, the sn (stereospecific numbering)-1, sn-2 (central position), and sn-3 (Flowchart 1).[20,27] In this notation, the letter C and the following numerical modifier indicates the number of carbon atoms in the FA, and the numeral after the colon is the number of double bonds in the carbon chain.[28]

Human milk contains at least 170 different types of TAGs, of which the 30 most abundant ones comprise 70% of the total milk-borne fats.[29,30] In HM, 60–86% of the TAGs are esterified and these have a unique molecular structure compared to those seen in plasma and other tissues.[31]

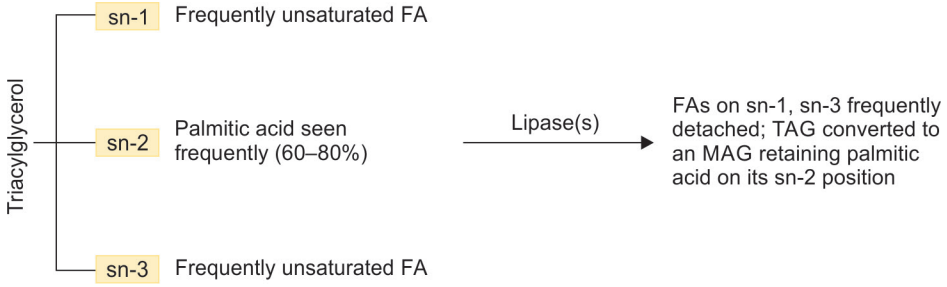
Palmitic acid (hexadecanoic, C16:0) is the most frequently seen saturated FA in HM. It is usually located on the sn-2 position and accounts for 20–25% of the total FA content.[32–34] This location is more conducive for absorption of lipids and calcium, bone health, intestinal flora, and overall comfort.[35–37] Oleic acid (18:1 ω-9) is the most frequently seen unsaturated FA in HM.[33] Fatty acids are described by the ω- or the Δ-nomenclature; the ω names show the carbons counted from the methyl end, whereas the Δ nomenclature shows enumeration from the carboxylic acid.[38] Docosahexaenoic acid (cervonic; C22:3 ω-3) is also seen frequently, located on upto 50% of the sn-2 and 42% of the sn-3 positions.[39–41] During digestion, pancreatic and gastric lipases may selectively hydrolyze FAs at the sn-1 and sn-3 positions, producing two free FAs and a 2-monoacylglycerol containing palmitic acid.[42]

Monoacylglycerols containing palmitic acid are absorbed more efficiently, even more than free palmitic acid.[35] This is because palmitic acid has a melting point (61–65°C) that is higher than the body temperature, and because it forms insoluble soaps with calcium and magnesium in the intestine.[43,44] In contrast, SFAs and 18-carbon FFAs such as oleic and linoleic acid are well-absorbed.[45] Details of various FAs seen in TAGs in HM are provided in the following sections:

Synthesis of TAGs Seen in HM

Mammary epithelial cells (MECs) contain large amounts of TAGs, most of which are synthesized locally.[46] Mammary epithelial cells contain the largest pool of FAs, nearly 95%, in the body[47]; these are acquired via two processes:

Flowchart 1: Schematic showing the structure of triacylglycerols detectable in HM



FA, fatty acid; MAG, monoacylglycerol; sn, stereospecific numbering; TAG, triacylglycerol

- Fatty acids synthesized within MECs from glucose in the endoplasmic reticulum (ER).[48] The rate-limiting step is the conversion of acetyl-CoA to malonyl-CoA, and the FA chains formed in this process grow via stepwise addition of 2-carbon units.[48] Fatty acid synthase is a key enzyme in this process.[49] Unlike in most other tissues where FA synthesis is terminated after a 16-carbon chain has been built, MECs contain an acyl thioester-hydrolase (thioesterase II) that can terminate FA synthesis at shorter lengths of 8–14 carbons to express medium- and intermediate-chain FAs.[50] These evolutionary adaptations can explain the high total FA content in milk.[51]

  Alterations in maternal diet can change the FA composition of HM.[52] Maternal diets low in fat and high in carbohydrates lead to *de novo* synthesis of FAs within the mammary gland, resulting in high concentrations of FAs of less than 16 carbons.[48] Therefore, although the total amount of fat present in the milk remains in the normal range, the fat is more saturated.

- Long-chain FAs (LCFAs; details in Table 1) imported from plasma, which are released from the digestion of TAGs (Flowchart 1) and are carried in circulating chylomicrons or very low-density lipoproteins (VLDLs).[53] These LCFAs in the bloodstream are bound to FA-binding proteins, or alternatively, combine first with CoA and then with an acyl-CoA-binding protein.[54,55]

FAs formed in these two processes bind glycerol-3-phosphate to form TAGs, and these get incorporated into microlipid droplets.[56] These droplets coalesce and move outward toward the cell membrane, where those are pinched-off into the circulation.[56,57]

Several technologies are now available to produce specifically tailored TAGs.[58] Biomimetic infant formulas containing TAG structures similar to those in HM may promote positive outcomes such as metabolic programming.[59] Lipid structures similar to those seen in HM can be produced *in vitro* by using specific lipases for interesterification.[60,61] Several types of oils and fats, such as tripalmitin, lard fat, bovine milk fat, soybean oil, canola oil, borage oil, sunflower oil, and safflower oil, have been used to produce lipid structures resembling HM fat.[62,63]

Digestion of HM-borne Saturated Fats

Neonates are developmentally deficient in many aspects of fat digestion because of low expression of lingual lipase, bile acids, and pancreatic lipase.[64] These enzymes may take a few days or more to be expressed at mature levels. Intragastric lipolysis by lingual and gastric lipases can partially compensate for the deficiency of pancreatic lipase.[64] Lingual lipase, secreted by the serous glands of the tongue, is detectable by 25 weeks' gestation.[65] Gastric lipase is secreted from the *chief (zymogen) cells* in the fundic gastric mucosa.[66] These can penetrate the milk lipid globules and hydrolyze the TAGs inside the core.[67] Fatty acids and monoglycerides resulting from intragastric lipolysis can compensate for low levels of bile acids by emulsifying lipid mixtures.[65]

Human milk feedings can cover for many deficiencies in neonatal digestion as it carries many lipases, including lipoprotein lipase, bile salt esterase, and other nonactivated lipases.[8,68,69] The composition of dietary fat should also be noted; the length of the carbon chain and the degree of unsaturation are important determinants of absorption.[70] Human milk supplies 8–12% of fat as medium-chain triglycerides (MCTs, chain length of 6–12 carbon atoms), which are hydrolyzed easier than long-chain triglycerides. In some cases, MCTs provide upto 40% of the total fat intake.[71]

Table 2: Phospholipids in human milk

	Mean (min–max) mg/100 g
Total phospholipids	25 (10–40)
Phosphatidylinositol	1 (1–2.5)
Phosphatidylserine	1.5 (1–2)
Phosphatidylethanolamine	7 (2–12)
Phosphatidylcholine	6 (2–10)
Sphingomyelin	9 (3–15)

Lipid digestion and absorption are also affected by dietary fat composition.[72] Fatty acids with shorter chain length and higher degrees of unsaturation are absorbed more efficiently without the need for lipase or bile salts.[73] Therefore, commercial formulas are often designed to contain fats with more MCTs.[71] These MCTs get digested and the FAs are transported directly to the liver via the portal vein. These MCTs can also enter mitochondria and be oxidized without the need for carnitine-mediated transport through mitochondrial membranes, and might even play a role in mitochondrial kinetics.[74,75] However, further research is needed to understand the determinants of fat absorption or improved growth in preterm infants.

Phospholipids in HM

Human milk contains traces (<1%) of phospholipids, which interact with and form a protective membrane-like covering around bioactive components such as long-chain polyunsaturated FAs and choline.[76] We have provided some of our own data in Table 2 below.

Nonesterified Fatty Acids in HM

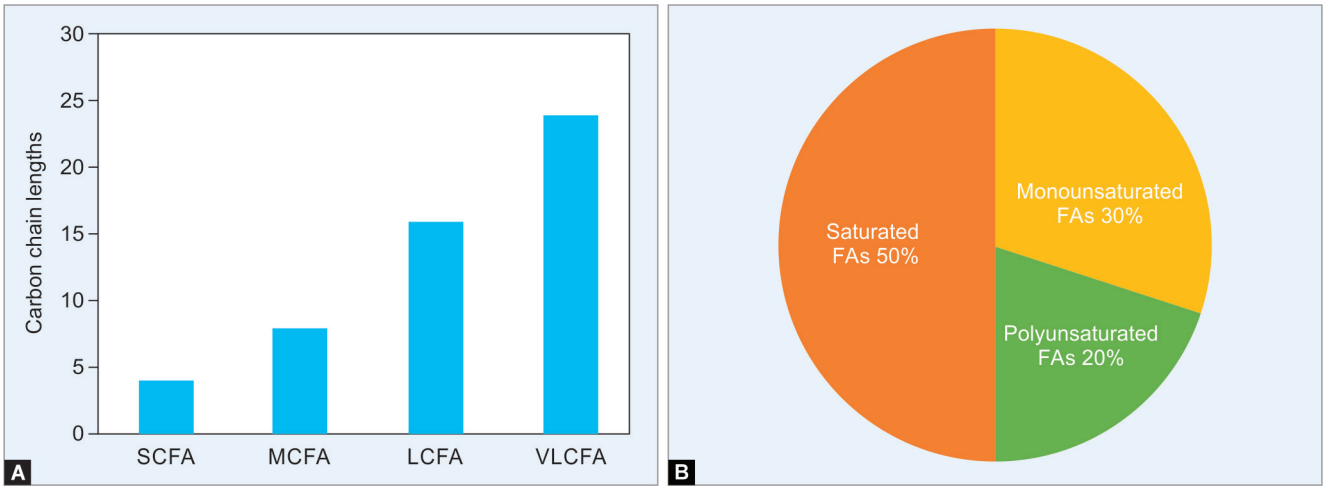
Fatty acids represent about 85% of the TAGs.[31] As shown in Figure 1A, FAs are usually classified either by (a) the number of carbon atoms, into short-chain FAs (3–5 carbons in the longest chain), medium-chain (6–12 carbons), long-chain (13–22 carbons), and very-long-chain FAs (23–27 carbons);[77] or (b) the degree of saturation into saturated, monounsaturated, and polyunsaturated categories (Fig. 1).[78] Table 3 enlists various FAs in the three categories shown in Figure 1B.

Saturated FAs in HM

About 45–50% of all FAs in HM are saturated, and these provide ≥10–15% of the dietary energy content.[79] There are small amounts of short-chain (3–5 carbons long) saturated FAs and 8–10% are medium-chain (6–12 carbons long) FAs. Triacylglycerols containing these FAs are hydrolyzed by gut lipases without the need for bile salts, and the digested products are efficiently absorbed.[80]

Besides known roles in nutrition, many saturated medium-chain FAs also perform important developmental functions.[81,82] Caprylic (octanoic acid, C8:0) and capric (decanoic or decylic acid, C10:0) promote fat absorption.[83] Capric acid also exhibits bactericidal effects.[84] The LCFAs, including myristic (tetradecanoic, C14:0), palmitic (hexadecanoic, C16:0), arachidic (icosanoic acid, C20:0), and behenic (C22:0) acids, have immunomodulatory effects.[73] Palmitic acid may alter protein acylation.[85] It is also a key component of pulmonary surfactant.[86] In HM, palmitic acid is seen in more than half of all TAGs. Oleic acid is seen in 10–12%.[1]

In HM, saturated FAs of carbon chain lengths 12, 14, 16, and 18 are seen in the highest concentrations.[1] The longer ones are a critical source of energy supply, and show dynamic plasticity.[87] Circulating stearic acid (octadecanoic, C18:0) is frequently interconverted



Figs 1A and B: (A) Structural classification of FAs based on lengths of the carbon chain (SCFA, short-chain FA; MCFA, medium-chain FA; LCFA, long-chain FA; VLCFA, very long-chain FA); (B) Classification of FAs based on saturation of carbon bonds in the fatty acid. The percentages show rounded-off data from our own laboratory

Table 3: Most frequently seen FAs in HM

Saturated FAs		*Mono-unsaturated FAs*		*Polyunsaturated FAs*	
C8:0		C14:1 ω-5		C14:2 ω-6	
C10:0	Also called capric, decanoic, or decylic acid	C16:1 ω-9		C16:2 ω-6	
C12:0	Also called lauric, or dodecanoic acid	C16:1 ω-7	Also called palmitoleic acid	C18:2 ω-6	Also called linoleic acid
C13:0		C16:1 ω-5		cis, trans-C18:2 ω-6	
C14:0	Also called myristic, or tetradecanoic acid	C16:1 ω-3		CLA c9, t11	
C15:0		C17:1 ω-7		CLA c10, t11	
C16:0	Also called palmitic acid	C18:1 ω-9	Also called oleic acid	C18:3 ω-3	Also called α-linolenic acid
C17:0		C18:1 ω-7	A C18:1 (n-7) isomer of oleic acid. Also called cis-vaccenic or cis-11-octadecenoic acid.	C20:2 ω-6	
C18:0	Also called stearic acid	C18:1 ω-5		C20:3 ω-6	
C20:0		C20:1 ω-11		C20:4 ω-6	Also called arachidonic acid
C22:0		C20:1 ω-9		C22:2 ω-6	
C24:0		C22:1 ω-9		C22:4 ω-6	
				C22:5 ω-6	

Deep shading in the box indicates levels >10%, light shading indicates 1–10%, and no shading indicates <1%

with its monounsaturated counterpart, oleic acid.[88] Such transformations can be beneficial for preterm infants who may have limitations in absorbing fats. Although there is no demonstrated benefit for energy balance or growth in growing preterm infants, there is some evidence that many saturated medium-chain FAs can be beneficial in fat malabsorption due to short-bowel syndrome and severe cholestatic liver disease.[70]

In humans, palmitic acid attached on the sn-2 position[35] renders it resistant to human lipases that can target sn-1,3 positions but not sn-2.[89] Consequently, lipase action leaves the TAGs only partially digested as sn-2 palmitate monoacylglycerols,[37,90] which have these monoacylglycerols in digested HM, are better tolerated than free palmitic acid, augment fat and mineral absorption, and may also improve bone density in the medium term.[31,37]

Litmanovitz et al.[91] used ultrasound bone sonometry for longitudinal assessment of bone density in term and preterm infants. They performed a double-blinded, randomized controlled study of bone parameters in 3-month-old term infants fed formula containing triglycerides with *sn*-2 16:0 or standard vegetable oil blends and compared those to a nonrandomized group of breast-fed infants. Infants in the intervention group had significantly higher bone density. These data were consistent with a previous report of Kennedy et al.,[92] who had used dual-energy X-ray absorptiometry and shown higher bone mass in 3-month-old infants who were fed

either formula containing structured triglycerides enriched in *sn*-2 16:0 or a conventional formula.

Palmitic acid in HM is important for lipoprotein and nonesterified FA metabolism when compared to that in TAGs sourced from plant oils.[31] In the first few days after birth, HM contains lauric (dodecanoic, C12) and myristic (tetradecanoic acid, C14) saturated FAs in low concentrations.[93] As the concentrations of these two FAs rise, that of the longer FAs decreases.[94] Early FAs may also be derived from extramammary sources, but the breast then quickly begins to synthesize these.[95] The total fat content in milk may have a predictive value; 90% of the women whose milk contained ≥20 grams fat per feeding on postnatal day 7 were successfully breastfeeding 3 months later.[96] Women with lower milk fat content had lower rates of success.[97]

Mono- and Polyunsaturated Fatty Acids in HM

Monounsaturated FAs are an important component of HM and infant formulae.[98,99] Oleic acid (OA, 18C:1 ω-9) is by far the most abundant monounsaturated FA.[99] In HM from Mediterranean regions, where consumption of olive oil is high, the concentrations of oleic acid and its congeners may exceed 40%, and the total content of monounsaturated FAs may exceed 45% of total FA in HM.[100,101] These esterified FAs in TAGs interact extensively with the polyunsaturated FAs (PUFAs).[102] We have described the interactions in the following sections:

The most frequently seen PUFAs in HM are listed in Table 1. These are derived from maternal diet, *de novo* synthesis in the mammary glands, and by mobilization from fat stores.[36] The FA composition of HM is influenced by many factors, including maternal diet, duration of pregnancy, maternal parity, and the stage of lactation.[103] Typically, the most abundant FAs are oleic (30%), palmitic (18%), linoleic (12%), myristic (6%), and stearic acids (8%).[1,104,105] Interestingly, the concentrations of palmitoleic acid (an ω-7 monounsaturated FA, 16:1 ω-7) appear to mirror those in myristic acid.93 In preterm infants, HM may not always be adequate as a source of nutrients.8

Long-chain polyunsaturated FAs play an important role in the development of the infant's brain during the last trimester of pregnancy and during the first months after birth.[106] The precursor C18 fatty acids for the n-6 and n-3 LC-PUFAs are linoleic (C18:2 ω-6) and α-linolenic acid (C18:3 ω-3).[107] These are further elongated and desaturated to form other FAs, of which arachidonic acid (AA) and DHA are essential for normal growth and development.[108] Although the LC-PUFAs are synthesized from precursor FAs in both preterm and term infants, the capacity to produce DHA and AA is not known.[109] In the first week after birth, the levels of DHA and AA might drop due to the lack of adipose reserves and insufficient FA intake by the mother.[110] The LC-PUFA content in HM in the United States, Europe, and Africa is similar, except for higher amounts of ω-3 LC-PUFAs in the milk of women whose diets contain a large quantity of fish.[111,112] Arachidonic acid (C20:4 ω-6) is an important LC-PUFA in HM.[113] Eicosapentaenoic acid (EPA, C20:5 ω-3) is seen in relatively smaller quantities.[113,114]

Polyunsaturated Essential FAs in HM

Human milk usually contains PUFAs such as linoleic acid (LA, 18:2 ω-6) and in adequate amounts.[115] These FAs promote brain growth and retinal maturation, and influence metabolism such as by reducing plasma cholesterol.[116] Human milk content of LA and

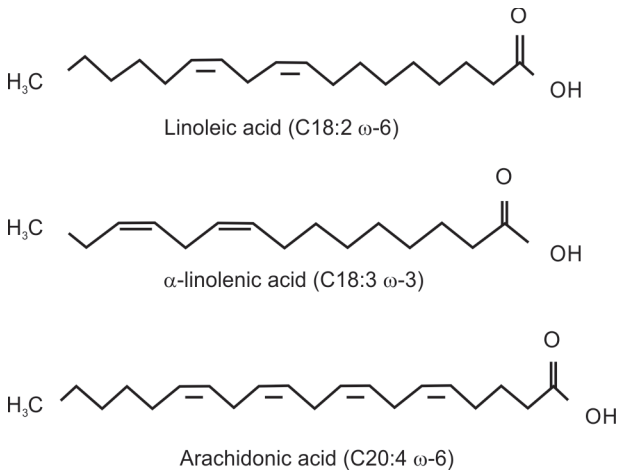


Fig. 2: The three essential FAs

alpha-linoleic acid (ALA) is known to vary according to maternal intake of these FAs.[36] The European Food Safety Authority (EFSA) recommends that infant formula should contain LA and ALA equivalent to 4.5–10.8% and 0.5–0.9% of the energy content.[117] These are precursors of LC-PUFAs such as arachidonic acid and DHA.[118]

Linoleic acid, ALA, and ARA have been recognized as "essential fatty acids (EFAs)" as these cannot be synthesized endogenously and therefore, need to be acquired from diet in adequate amounts (Fig. 1).[118] These FAs cannot be synthesized because the desaturases needed for introducing a double bond at carbons 3 and 6 (counted from the methyl end) are not expressed.[8] Linoleic acid provides nearly 10% of the calories derived from the lipid fraction.[98] In preterm infants, biochemical evidence of EFA deficiency can be detected as early as 72 hours after birth.[119]

Long-chain Polyunsaturated FAs in HM

Increasing data now show that the capacity of young infants to synthesize LC-PUFAs might also be limited.[120] Hence, there may be a justification to supplement infant formulas with LC-PUFAs to bring the levels to resemble HM.[121] The most frequently seen LC-PUFAs are shown in Figure 2. Maternal diet can alter the EFA and LC-PUFA content in HM. Several different elongases and desaturases transform EFAs to LC-PUFAs, such as arachidonic acid, DHA, and EPA, which then serve as substrates for bioactive metabolites such as eicosanoids, lipoxins, resolvins, and protectins.[122,123] Fatty acids are also potential substrates for many elongases and desaturases for the formation of downstream metabolites.[124] In addition to these short-term changes, dietary changes can also change the lipids stored in her adipose tissues and consequently change the lipid composition of her milk.[125] Studies have shown a high correlation between the mother's fish intake and the DHA levels in her plasma and breast milk.[48] Therefore, maternal diet should receive special attention in lactating mothers.

There are some data that show a possible need for supplementing infant formula with monounsaturated FAs such as oleic (C18:1n-9) and palmitoleic acid (C16:1n-7, a product of palmitic acid metabolism).[98] These are normally secreted in HM in adequate amounts.[36] Oleic acid lowers the melting point of TAGs to enhance liquidity required for the formation, transport, and metabolism of milk fat.[126]

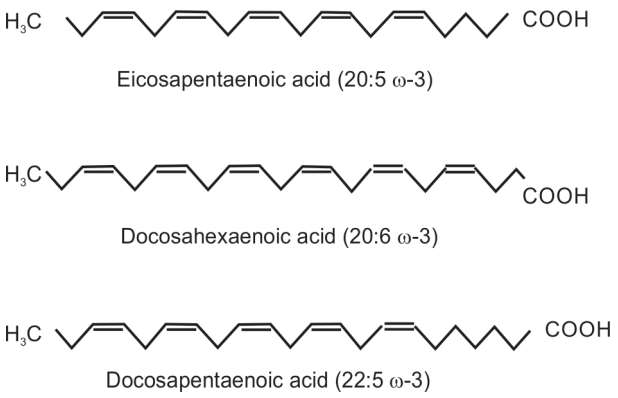


Fig. 3: The most frequently seen LC-PUFAs in human milk

Long-chain polyunsaturated FAs in HM may be derived from diet or drawn from FA storage pools in her own adipose tissue or the liver[107,127] (Fig. 3). Dietary EFA and ω-3 FAs are also known to influence the LC-PUFA content in HM.[36] However, the effects of diet are relatively transient compared with the longer-term changes seen with FAs drawn from body's internal pools.[128] Fatty acids that are synthesized, elongated, or desaturated in the liver or peripheral tissues are more likely to be incorporated into milk fat.[128] Most studies on these changes have focused on the linoleic acid, α-linolenic acid EFAs. A review of 65 studies showed lower variation of ARA compared with DHA between populations with different dietary habits.[129]

The perinatal period is a period of intensive growth of the brain, which contains large amounts of ARA and DHA.[130] There is a likely need for LC-PUFAs in larger amounts for the development of neurological and cognitive functions.[131] Long-chain polyunsaturated FAs are also involved in inflammatory and immunological processes, suggesting a need in optimal maturation of the immune system.[132–134] Long-chain polyunsaturated FAs might also influence adipocyte differentiation and consequently, the risk of obesity in childhood or later.[120]

Carnitine promotes the transport of LC-PUFAs into the mitochondria for oxidation and removal of short-chain FAs that accumulate in mitochondria.[135] Preterm infants are at risk for relative deficiency of carnitine because of their dependence on lipids as an energy source and limited endogenous synthetic ability, although the clinical need is still unproven.[136] Carnitine is detectable in HM and is currently added to standard term and preterm formulas.[137] In preterm infants not receiving supplemental carnitine, plasma and tissue carnitine levels may fall even in the presence of adequate precursor amino acid concentrations.[136,138]

Yaron et al.[139] showed that infants fed with a formula supplemented with β-16:0 for 6 weeks showed more *Lactobacillus* and *Bifidobacterium* genera in their stools than a control group that received formula containing vegetable-sourced 16:0. The mechanisms are unclear, but there is a possibility that the position of palmitic acid on the TAGs may have influenced that gut microbiome.[140] Current infant formulas typically include palm, coconut, soybean, and sunflower oils as the primary lipid sources.[98] The development of structured lipids that resemble HM fat may improve the safety of formula feedings.[73]

The synthesis for LC-PUFAs in HM has severe unique patterns. Similar to the desaturases and elongases seen in plasma, red blood cells, and the adipose tissue, the efficacy of similar enzymes seen in HM in conversion of EFAs into LC-PUFAs may determine the relative concentrations of various FAs in milk.[132] However, there may be subtle differences between individual FAs. Alpha-linolenic acid, the precursor of the n-3 series LC-PUFAs, is processed differently than LA.[36] Nearly 65% of milk ALA seems to be directly derived from maternal diet, not from the body stores.[36,141] The association of maternal DHA intake (fish oil or other sources of ω-3 LC-PUFAs) with milk DHA levels is stronger than that of maternal ARA intake.[142] There are a few studies that tested the effects of n-3 supplementation on milk fat composition in combination with ARA supplementation.[36] In a Dutch study, 88 breastfeeding women received DHA (220 mg/day), with milk samples collected in the second and 12th week of lactation.[143,144] Docosahexaenoic acid percentages were significantly higher than in the placebo group. In the supplemented group, the addition of ARA led to higher median ARA percentages in milk. As the supplementation had started already mid-pregnancy, the findings suggested that increased ARA excretion with milk could be the result of increased direct transfer from the diet and increased ARA contribution to the flux of fatty acids into milk passing maternal storage pools. Several other studies have shown similar findings.[145–147] There is a need to re-evaluate current beliefs that only 10% of milk ARA is directly derived from the diet.

DHA in HM

Docosahexaenoic acid is an important LC-PUFA in HM, most of it *is* derived from its precursor, α-linolenic acid (18:3 ω-3).[148,149] It is highly enriched in the brain and is important for neurodevelopment.[131] Infants, particularly those born preterm, can develop LC-PUFA deficiencies because of their limited ability to synthesize these FAs.[110] Here, an important adaptation in the mother–infant axis is that preterm milk contains more C8–C14 FAs and LC-PUFAs than term milk, and the LC-PUFA content gradually decreases with increasing postnatal age.[115] These developmental adaptations may be helpful as shorter FAs might be easier to digest, and LC-PUFAs are important for brain and retinal development.[80]

Docosahexaenoic acid is important for neurologic development and advancement of visual acuity.[116] Lipids are an important constituent of brain matter, and DHA constitutes 30–40% of the fatty acids in the gray matter and the synaptic membranes.[150] The retina, particularly its outer rod segment, also has a high DHA content.[151] Fatty acids are known to alter gene expression in the developing brain, and hence, are likely to alter long-term neurodevelopment and metabolism.[152] These effects are most likely to be seen in the fetus/premature infants, who may not yet have the capacity to absorb/synthesize specific FAs such as the LC-PUFAs.[153]

Western diets may not always provide appropriate amounts of DHA for lactating mothers, and DHA levels may fall by 40% in preterm infants during the first week after birth.[154] Many studies have measured the effects of DHA supplementation in lactating mothers on the FA composition in HM and infant plasma.[113,155–157] Maternal daily supplementation of 1200 mg of DHA can increase HM and infant plasma DHA concentrations to almost 12 and 2–3 times higher than in controls.[158] These higher levels remained elevated even after 6 weeks of maternal supplementation of DHA at 400 mg/day.[159,160] Current evidence suggests that DHA supplementation to lactating mothers is safe and effective in increasing DHA levels in HM.[161]

Some infant formulas are now being supplemented with these FAs.[162,163] In preterm infants, raising the DHA levels by 2–3 times may have improved neurodevelopmental and cognitive outcomes such as information processing.[164,165] In term infants, LC-PUFA supplementation may improve visual acuity by 12 months of age.[166] Cholesterol is another small (9–12 mg/dL), but an important lipid constituent of HM.[167] Breastfed infants may receive more cholesterol per kg body weight in feedings than adults but have better lipid profiles.[168] There is a possibility that early breastfeeding associated with high measured total blood serum cholesterol may prevent, not raise, some of the risks of developing cardiovascular diseases later in life.[169]

In preterm infants, DHA and its downstream metabolites, the oxylipins, are important regulators of inflammatory responses.[170] The deficiency of DHA after birth can augment inflammation, particularly in preterm infants.[171,172] Infants with higher mean DHA levels may be less likely to develop chronic lung disease (CLD).[173] Docosahexaenoic acid supplementation may also be protective against necrotizing enterocolitis (NEC).[174] The mechanisms by which DHA supplementation to lactating mothers or to infants attenuates inflammation are still not clear; one possibility is that N-docosahexaenoylethanolamine (synaptamide), a neurogenic and synaptogenic metabolite of DHA, may mediate some of these anti-inflammatory effects.[175,176] Maternal diet high in ω-3 fatty acids upregulates genes involved in neurotrophin signaling in fetal brain during pregnancy in C57BL/6 mice.[177] The mechanisms of DHA effects in humans are not clear.

Docosahexaenoic acid and other LC-PUFAs can be acquired in diet, but humans can also synthesize some small quantities from precursors linoleic acid (18:2 ω-6) and α-linolenic acid (18:3 ω-3).[107] The most important pathways include Δ4-desaturation, β-oxidation, and carbon recycling.[178] The FA desaturase (FADS) gene cluster consists of a family of three genes located on human chromosome 11q12-13.1 that yields enzymes catalyzing the insertion of double bonds in PUFA, monounsaturated FAs and palmitic acid.[179] FADS2 can code for pathways involving Δ6-, Δ8-, and Δ4-desaturation.[180] FADS1 codes for a Δ5-desaturase, leading directly to the signaling precursor ω-6 arachidonic acid (20:4 ω-6) and to ω-3 eicosapentaenoic acid (20:5 ω-3).[162,181] Despite these well-established classical results, substrate competition is known to modulate the relative activity of desaturases that defines total PUFA composition of tissues.[182]

In parenteral nutrition, many lipid preparations now contain DHA and AA.[183,184] However, these preparations may not always correct postnatal FA deficits.[185] Eicosapentaenoic acid levels may be elevated due to the fish oil component in these lipid preparations but the DHA and AA levels may decline.[186–190] Low AA levels could possibly be associated with suboptimal clinical outcomes such as with increased risk of late-onset sepsis and retinopathy of prematurity.[171,191,192]

Docosahexaenoic acid and AA are naturally expressed in HM, and so most infant formulas for term and preterm infants are now supplemented with these FAs.[163] Many RCTs have been conducted to evaluate the addition of DHA and AA to preterm formulas.[109,193] Most studies show positive or no changes in growth, although few show negative effects.[193] Findings of improved visual acuity have been inconsistent. Formula supplemented with DHA and AA seems to improve visual acuity,[166] but the effects on neurodevelopment remain unclear.[193] Current recommendations advocate for VLBW infants to receive 55–60 mg of DHA and 35–45 mg per kg/day of AA.[194,195]

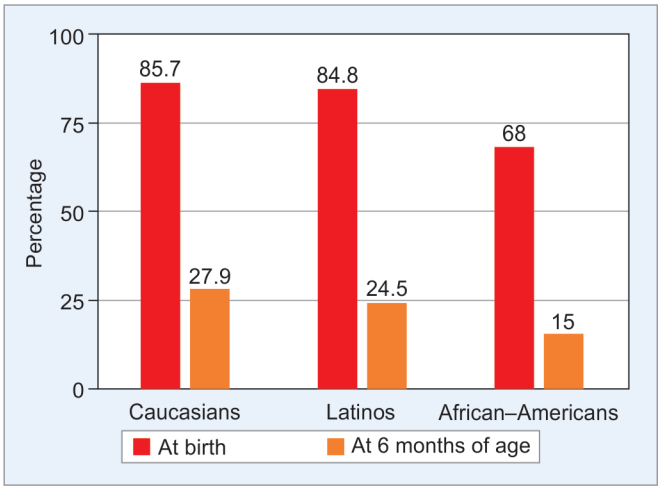


Fig. 4: HM feeding rates by race in the United States (CDC, 2017)

A recent Cochrane review[196] showed that ω-3 LC-PUFA supplementation during pregnancy is effective in reducing the incidence of preterm birth, although it may increase post-term pregnancies. Preterm birth <37 weeks and early preterm birth <34 weeks were reduced in women receiving omega-3 LCPUFA compared with no ω-3.[196] There as a possibility of reduced risk of perinatal death and of neonatal care admission, reduced risk of LBW babies; but a small increased risk of LGA babies with ω-3 LC-PUFAs.[196] For GRADE quality assessments,[197] the conclusions for perinatal outcomes were viewed as high- or moderate-quality evidence.

Conclusion

Human milk is the primary source of nutrients for neonates, and may be the best option from the points of view of nutritional, immunological, food safety, and growth and development.[198] It also improves mother–infant bonding, and facilitates the emotional, cognitive, and nervous system development of the infant.[199] Unfortunately, rapid urbanization and social limitations have been major constraints in promoting HM feedings.[200,201] Worldwide, only 35–40% of infants receive HM from birth to 6 months of age.[202–205] Breastfeeding rates diverge widely along the lines of race, socioeconomic status, and ethnicity (summarized in Figure 4).[206,207]

Despite all the educational and logistical strategies to promote HM feeding, some infants will still continue to need at least some formula feedings because of medical, social, or other reasons.[208] Therefore, there will be a need to develop and improve infant formulas that closely mimic the nutritional and chemical characteristics of HM.[209] Timely delivery of physiologically important lipids will be needed to improve growth and development by optimizing the energy contents, without unduly increasing the osmolar loads.[73,210] We also cannot overemphasize the importance of lipids in neurological development, protection of the gastrointestinal tract, immune defenses, and cholesterol metabolism.[52,154,211,212]

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