Essential fatty acids in mothers and their neonates[1–4]

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ABSTRACT Essential fatty acids (EFAs) and their long-chain polyenes (LCPs) are indispensable for human development and health. Because humans cannot synthesize EFAs and can only ineffectively synthesize LCPs, EFAs need to be consumed as part of the diet. Consequently, the polyunsaturated fatty acid (PUFA) status of the developing fetus depends on that of its mother, as confirmed by the positive relation between maternal PUFA consumption and neonatal PUFA status. Pregnancy is associated with a decrease in the biochemical PUFA status, and normalization after delivery is slow. This is particularly true for docosahexaenoic acid (DHA) because, on the basis of the current habitual diet, birth spacing appeared to be insufficient for the maternal DHA status to normalize completely. Because of the decrease in PUFA status during pregnancy, the neonatal PUFA status may not be optimal. This view is supported by the lower neonatal PUFA status after multiple than after single births. The neonatal PUFA status can be increased by maternal PUFA supplementation during pregnancy. For optimum results, the supplement should contain both n−6 and n−3 PUFAs. The PUFA status of preterm neonates is significantly lower than that of term infants, which is a physiologic condition. Because the neonatal DHA status correlates positively with birth weight, birth length, and head circumference, maternal DHA supplementation during pregnancy may improve the prognosis of preterm infants. In term neonates, maternal linoleic acid consumption correlates negatively with neonatal head circumference. This suggests that the ratio of n−3 to n−6 PUFAs in the maternal diet should be increased. Consumption of *trans* unsaturated fatty acids appeared to be associated with lower maternal and neonatal PUFA status. Therefore, it seems prudent to minimize the consumption of *trans* fatty acids during pregnancy. *Am J Clin Nutr* 2000; 71(suppl):1262S–9S.

KEY WORDS Pregnancy, mother, fetus, hypertension, preterm, neonate, development, essential fatty acids, arachidonic acid, docosahexaenoic acid, linoleic acid, long-chain polyenes, nutrition

INTRODUCTION

Certain fatty acids are indispensable for human development and health, but cannot be synthesized de novo by humans. Therefore, they need to be consumed with the diet. These fatty acids are collectively known as essential polyunsaturated fatty acids (PUFAs) and comprise the parent essential fatty acids (EFAs) and their longer-chain, more unsaturated derivatives, the long-chain polyenes (LCPs). EFAs and LCPs are important structural and functional membrane components. In addition, some LCPs are precursors of the prostanoids (prostaglandins and thromboxanes), a group of local hormone-like substances with important bioregulatory functions (1).

ESSENTIAL FATTY ACIDS AND LONG-CHAIN POLYENES

There are 2 essential PUFA families, the n−6 and n−3 fatty acids. The essentiality of the n−6 family has been recognized for decades (2), but that of the n−3 family has been a matter of debate for some time. However, there is no doubt that n−3 fatty acids are essential for reproductive, brain, and visual functions (3).

The parent EFAs of the n−6 and n−3 families are linoleic acid (LA; 18:2n−6) and α-linolenic acid (ALA; 18:3n−3), respectively. These EFAs can be desaturated and elongated in the human body to a series of longer-chain, more unsaturated derivatives, the LCPs. The most important LA-derived LCPs are dihomo-γ-linolenic acid (20:3n−6) and arachidonic acid (AA; 20:4n−6). These fatty acids are the precursors of the prostanoids of the 1- and 2-series, respectively. In addition, AA is an important structural fatty acid in the brain. The most important LCPs derived from ALA are eicosapentaenoic acid (EPA; 20:5n−3, also known as timnodonic acid) and docosahexaenoic acid (DHA; 22:6n−3, also known as cervonic acid). EPA is the precursor of the prostanoids of the 3-series, whereas DHA, together with AA, the major LCP in the central nervous system, can be converted by a lipoxygenase to form hydroxy fatty acids with biological activity. Most essential PUFAs (EFAs + LCPs) are good lipoxygenase substrates. Many of the resulting hydroxy fatty acids have significant biological functions (1, 4).

ADEQUATE INTAKE OF EFAs AND LCPs IS REQUIRED DURING PREGNANCY AND EARLY DEVELOPMENT

The parent EFAs and their derived LCPs are vitally important structural elements of cell membranes and, therefore, essential for the formation of new tissues, as occurs during pregnancy and

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fetal development. The central nervous system is particularly rich in AA and DHA and the cerebral accretion of these fatty acids may have been decisive in the evolution of *Homo sapiens* (5, 6). The brain has its growth spurt in the third trimester of pregnancy and during early childhood. Therefore, an appropriate pre- and postnatal supply of these LCPs or their precursors is thought essential for normal fetal and neonatal growth (7, 8), neurologic development and function (8–10), and learning and behavior (11, 12). In addition, intrauterine nutrition may influence the adult risk for chronic diseases (13), suggesting that early nutrition has an imprinting effect on later life. This further emphasizes the importance of an adequate supply of essential PUFAs during pregnancy, lactation, and infancy.

Because the parent EFAs cannot be synthesized by humans, they need to be consumed with the diet. LA and ALA are mainly present in seed oils (ALA mainly in green leaves) and can be converted to AA and DHA, respectively. In humans, however, conversion is relatively slow, which is suggested from the observation that AA and DHA concentrations are lower in vegans than in omnivores, whereas EFA intakes are usually higher in vegans than in omnivores (14, 15). Therefore, the diet is also the major source of these LCPs, which are found in egg yolk (AA), lean meat (AA and DHA), and fatty fish (DHA).

For its essential PUFA supply, the developing fetus depends on the availability of maternal EFAs and LCPs. Therefore, the diet of pregnant women should contain sufficient essential PUFAs to meet not only her own requirement, but that of her fetus as well. If the intake of essential PUFAs is too low to meet physiologic requirements, body stores can be used as an additional supply. Considerable amounts of LA are stored in adipose tissue and are readily mobilized. However, adipose tissue contains relatively low amounts of ALA and LCPs. In neonates and in preterm infants in particular, the amount of adipose tissue is rather limited and, therefore, adequate postnatal intakes of EFAs and LCPs are important to guarantee an adequate PUFA status.

ESSENTIAL PUFA STATUS AND FUNCTIONAL STATUS MARKERS

For the assessment of the essential PUFA status of an individual, the total amount of the various EFAs and LCPs in plasma or erythrocyte phospholipids is a useful indicator (16). It should be realized that the plasma content of essential PUFA does not necessarily guarantee the proper use of these fatty acids by cells and tissues. Therefore, additional status markers are required to reliably assess the functional PUFA status of a given individual.

In general, if insufficient essential PUFAs are available to meet PUFA requirements, the body starts to synthesize certain fatty acids that are hardly present if the EFA and PUFA status is adequate. Therefore, these fatty acids can be essential PUFA status markers. The best known marker is Mead acid (20:3n−9). The synthesis of this fatty acid is promoted if there are insufficient concentrations of LA and ALA to meet the need for LCPs. Because LCPs inhibit Mead acid synthesis, the presence of Mead acid indicates a general shortage of all essential PUFAs.

Another suitable indicator of essential PUFA status is the essential PUFA status index, which is the ratio between all essential PUFAs (the sum of all n−3 and n−6 fatty acids) and all nonessential unsaturated fatty acids (the sum of all n−7 and n−9 fatty acids). The higher the essential PUFA status index, the better the essential PUFA status. Finally, if there is a functional shortage of DHA, the body starts to synthesize the most comparable LCP of the n−6 family, osbond acid (22:5n−6; 17). Therefore, under steady state conditions, the ratio between DHA and osbond acid is a reliable indicator of the functional DHA status.

MATERNAL ESSENTIAL FATTY ACID STATUS DECLINES DURING PREGNANCY

Although maternal-fetal differences in blood lipids and essential fatty acid concentrations have been known for decades (18–20), our group was the first to address the maternal essential PUFA status in a longitudinal way (21). From this study it appeared that between early pregnancy (10 wk) and delivery, plasma concentrations (mg/L) of phospholipid-associated essential PUFAs increase on average by ≈40%. For AA and DHA, these values are 23% and 52%, respectively. However, nonessential unsaturated fatty acids increase considerably more (>65%); the general PUFA status marker Mead acid and the specific DHA status marker osbond acid increase by 92% and 125%, respectively. This indicates that under the present dietary conditions, pregnancy is associated with a reduction in the functional PUFA status, particularly that of DHA. After delivery, normalization takes place, but recovery of the functional DHA status, as reflected by the ratio between DHA and its status marker osbond acid, appears to still be incomplete after 6 mo (21).

PREGNANCY MAY CAUSE MATERNAL DHA DEPLETION

The higher circulating LCP concentrations during pregnancy are not associated with a measurable increase in LCP consumption (22) and may, therefore, result from enhanced enzymatic conversion of their precursor fatty acids, LA and ALA. However, both fatty acids compete for the same set of fatty acid–converting enzymes and because the dietary availability of LA surmounts that of ALA, an increased production of DHA is unlikely to occur during pregnancy. Therefore, pregnancy is possibly associated with DHA mobilization from maternal stores, although a metabolic shift from energetic to structural use cannot be excluded.

In a cross-sectional study, we showed that the plasma phospholipid DHA content of primigravidae is significantly higher than that of multigravidae throughout pregnancy. Actually, a significant, negative relation was observed between the plasma phospholipid DHA content at delivery and parity (23). These observations suggest that, in general, the interpregnancy interval may have been too short for a complete replenishment of the maternal DHA stores. Therefore, future studies with respect to the so-called maternal depletion syndrome (24, 25) should include the DHA status.

ESSENTIAL PUFA STATUS OF NEWBORNS IS RESTRICTED BY THAT OF THEIR MOTHERS AND MAY NOT BE OPTIMAL

As mentioned above, EFAs and their LCPs cannot be synthesized de novo by humans and, therefore, the fetal essential PUFA supply strongly depends on maternal essential PUFA consumption and metabolism as well as on the placental transport of these fatty acids. This dependence is convincingly illustrated by the strong, positive maternal-fetal correlations for all EFAs and their LCPs (21, 22). As a consequence, the usually observed decreases in maternal EFA and LCP status occurring during pregnancy (21,

26) may indicate a suboptimal PUFA status in newborns. This view is supported by the following observations:

1) Measurements of fatty acid concentrations indicate that the PUFA concentration of the walls of the umbilical vein is higher than that of the umbilical arteries. In addition, the PUFA concentration of umbilical arterial walls is lower than that of adult arterial tissue (27). The umbilical veins supply blood to the fetus, whereas the umbilical arteries carry the blood away from the fetus back to the placenta. Although direct comparisons with other fetal tissue have not yet been performed, and certain tissues may be preferred sites of EFA and LCP uptake (28), the essential PUFA status of umbilical venous and arterial walls likely reflects the PUFA status of fetal tissue "upstream" and "downstream," respectively. Consequently, the typical fatty acid profiles of umbilical veins and arteries indicate that the EFA status of the developing fetus is relatively low, and is lower in downstream than in upstream areas.

2) A suboptimal neonatal EFA and LCP status is also suggested from our observation of a lower neonatal PUFA status after multiple than after single births (29, 30).

DIETARY *TRANS* UNSATURATED FATTY ACIDS LOWER MATERNAL AND FETAL LCP STATUS AND MAY AFFECT FETAL DEVELOPMENT

Industrial hydrogenation of edible oils is a procedure commonly used to improve the technologic and organoleptic qualities of these oils. However, this process causes the formation of *trans* isomers of unsaturated fatty acids, which are known to interfere with the conversion of parent EFAs into their derived LCPs, especially when the parent EFA concentrations are low (31). Studies by Koletzko (32) showed that *trans* fatty acids can cross the placenta and we showed a highly significant correlation between the relative amounts of *t*-18:1 in maternal plasma and fetal tissue (33). In addition, we showed that the presence of *trans* fatty acids in cord tissue is associated with proportionally lower amounts of essential PUFAs, a reduced birth weight, and a smaller head circumference. However, after correction for gestational age, these latter 2 associations were no longer statistically significant.

Although the consumption of *trans* unsaturated fatty acids is decreasing in most Western countries, the negative association between the intake of these fatty acids and the essential PUFA status was shown to persist at low maternal intakes (RP Mensink, unpublished observations, 1998). Dietary *trans* unsaturated fatty acids were also shown to increase cardiovascular risk as reflected by the plasma lipoprotein profile (34), and cardiovascular risk may be programmed during early development already (13). Therefore, it may be prudent to reduce the maternal intake of *trans* fatty acids as much as possible, even if negative effects of *trans* fatty acids on fetal development cannot yet be ascertained (35).

DIFFERENCES IN MATERNAL AND NEONATAL ESSENTIAL PUFA STATUS BETWEEN COUNTRIES ARE OFTEN LARGER THAN THOSE WITHIN COUNTRIES

To compare maternal and neonatal essential PUFA statuses under different dietary and cultural conditions, samples of plasma from pregnant women and of umbilical material from their neonates were collected in Ecuador, England, Finland, and Hungary and compared with samples from the Netherlands. It then appeared that the differences in maternal PUFA status indexes between countries are often much more pronounced than are differences occurring during pregnancy within a given country (26).. Because the observed differences in maternal essential PUFA status between countries were reflected in those of their infants, the functional implications of the observed decrease in essential PUFA status during pregnancy and of the relatively low PUFA status at birth, if any, are not immediately obvious.

THE LOW ESSENTIAL PUFA STATUS OF PRETERM NEONATES IS PHYSIOLOGIC

Preterm infants were shown to have an essential PUFA status significantly lower than that of term neonates (36). However, EFA and LCP concentrations in cord plasma from preterm infants at birth are not lower than those in cord plasma obtained from fetuses during pregnancy at a comparable gestational age (37). Therefore, the low essential PUFA status of preterm infants is most probably a physiologic situation and not a pathologic condition. These comparative studies also show that the essential PUFA status of the fetus is not stable during its development, but changes with gestational age in a fatty acid–specific way. Thus, LA concentrations, which strongly decrease in fetal tissue during early gestation (38), increase slightly during the second and third trimesters. AA concentrations, however, decrease slowly as pregnancy progresses, whereas DHA concentrations rise strongly during the last 2 mo of gestation (37). Because maternal fatty acid values also change during pregnancy (21, 26), comparative studies in which maternal or perinatal fatty acid data are not corrected for gestational age are difficult to interpret.

In preterm infants, positive relations were observed between the amount of DHA in umbilical artery phospholipids and birth weight, head circumference, and birth length. In addition, the essential PUFA status at birth appeared to be the strongest determinant of the essential PUFA status at the expected date of delivery (39). Therefore, a higher DHA status may benefit preterm neonates, not only in terms of their intrauterine development but also in terms of their postnatal development.

PREGNANCY-INDUCED HYPERTENSION AFFECTS ESSENTIAL PUFA METABOLISM

Inuit women living in seaside settlements are reportedly 2.6 times less likely to develop pregnancy-induced hypertension (PIH) than are Inuit women living in more inland communities. This lower risk of PIH is associated with higher amounts of n−3 LCPs in their plasma phospholipids (40), which indicates that the consumption of n−3 LCPs may prevent PIH. The observation that the risk of preeclampsia is associated with a lower n−3 LCP status (41) is consistent with such a preventive effect. However, in a nested case-control study, no significant association was observed between fish intake and the occurrence of PIH (42). Moreover, Dutch women suffering from PIH have higher amounts of n−6 and n−3 LCPs in their plasma phospholipids at delivery than do women giving birth after an uncomplicated pregnancy (43). Although this finding was not replicated by others (44, 45), we confirmed in a more recent prospective longitudinal study that PIH is associated with higher amounts of n−6 and n−3 LCPs in maternal plasma phospholipids at delivery (46). Because these differences were not observed before the disease became clinically manifest, the altered essential PUFA status in PIH is a late phenomenon and is unlikely to have

contributed to PIH pathogenesis. This view was confirmed by a randomized, double-blind, placebo controlled trial in 233 pregnant women at high risk of developing PIH, in which it was shown that supplementation during pregnancy with 2.7 g n−3 LCPs/d does not lower PIH risk (47).

The higher maternal LCP status at delivery as observed by us in women with PIH was associated with lower amounts of their precursors, LA and ALA (46). Therefore, it seems that PIH is associated with a more active desaturation and elongation of parent EFAs into derived LCPs, possibly to compensate for the compromised placental LCP transport in PIH. This putative compensatory mechanism appeared to be successful because the LCP status of infants born to women with PIH was shown to be slightly higher than that of infants born after an uncomplicated pregnancy (46).

MATERNAL LINOLEATE INTAKE DURING PREGNANCY IS NEGATIVELY RELATED TO NEONATAL HEAD CIRCUMFERENCE

In the course of the prospective, longitudinal study mentioned above (46), dietary intake data were collected by means of the dietary history technique midway through gestation. In addition, the maternal fat and fatty acid consumption was assessed from food-frequency questionnaires filled out during weeks 13, 22, and 32 of gestation (22). Some overall pregnancy-outcome data were collected and the relation between fatty acid intake and pregnancy outcome was evaluated by backwards multiple regression analysis after correction for maternal body weight, height, age, smoking habits, energy intake, education, parity, gestational diabetes, PIH status, neonatal sex, and gestational age. Because of multiple comparisons, the required *P* value for significance was set at 0.005 (48). No significant correlations were observed between any of the dietary PUFAs and birth weight, placental weight/birth weight, and the ponderal index (wt/length^3). A positive relation was observed between the maternal intake of PUFAs without LA and length of the newborn. Maternal LA intake appeared negatively related to neonatal head circumference shortly after birth. Such a negative relation was also observed between the amount of LA in umbilical plasma phospholipids and neonatal head circumference (21). Because head circumference is an excellent predictor of brain weight (49), our finding could imply that the maternal intake of LA during pregnancy affects brain growth. Further studies showed a significant, negative relation between maternal linoleate consumption and maternal as well as fetal amounts of n−3 LCPs (22), the major polyunsaturated building bricks of the brain. This suggests that the ratio between dietary n−3 and n−6 PUFAs is too low and needs readjustment.

MATERNAL PUFA SUPPLEMENTATION DURING PREGNANCY AFFECTS NEONATAL PUFA STATUS

As mentioned before, the essential PUFA status of neonates is strongly correlated with that of their mothers (21). Because the PUFA status of pregnant women appears to be determined by their PUFA intake, it is highly likely that the neonatal EFA status can be altered by nutritional intervention during pregnancy.

From the 2 pilot studies we performed so far, an increase in the neonatal essential PUFA status via the maternal diet appears feasible indeed. Supplementation of pregnant women with 2.7 g fish oil/d from week 31 of gestation and later (50) caused a significantly higher n−3 LCP status in the cord plasma phospholipids of their newborns. This was associated with a comparable reduction in the amount of n−6 LCPs. Changes in the fatty acid compositions of phospholipids isolated from umbilical cord vessel walls were less pronounced. Although n−3 LCPs increased significantly, the decrease in total n−6 fatty acids was not statistically significant. These less-pronounced effects may have been due to a slower turnover of tissue phospholipids than of plasma phospholipids, in combination with the relatively short period of supplementation.

In another pilot study (51), pregnant women with an LA concentration below the 50th percentile were given LA-rich food products beginning at 20 wk of gestation, providing an additional 10 g LA/d. This intervention caused a significant increase in the LA concentration of plasma phospholipids, but the highest values reached remained below the 90th percentile. LA supplementation was associated with a slightly higher neonatal n−6 LCP status, but the neonatal n−3 LCP status became significantly lower than that of a nonsupplemented control group. Therefore, if it were necessary to increase the neonatal essential PUFA status, it would require maternal supplementation with a combination of both n−6 and n−3 PUFAs.

POTENTIAL IMPLICATIONS OF ESSENTIAL PUFA STATUS FOR EARLY AND LATER DEVELOPMENT

Psychomotor, mental, and cognitive development

We have not yet investigated whether our observed changes in the biochemical essential PUFA status have functional consequences. Data from small mammals and nonhuman primates, however, showed that the consumption of adequate amounts of n−3 PUFAs early in life has potentially important long-term effects on behavior and learning (52–55). In addition, Bjerve et al (56) found that the amount of DHA in the plasma phospholipids of 21 low-birth-weight infants at the corrected age of 1 y correlated significantly with Bayley's Psychomotor (PDI) and Mental (MDI) Developmental Indexes. Carlson et al (57) showed that supplementation of preterm infants with a marine oil relatively rich in DHA resulted in a significant improvement in the Bayley MDI score of these infants after 48, but not after 20 wk.. In further randomized, double-blind trials this research group applied the Fagan test of infant intelligence (58). It was then shown that supplementation of preterm infants with a DHA-rich marine oil for 20 wk (until 29 mo past term) was associated with shorter average look duration when tested 10 mo after termination of supplementation (≈12 mo past term; 59). Similar results were obtained in a second study, in which preterm infants were given the DHA-supplemented formula for ≈50 wk (until 9 mo past term) and the test was performed at 6.5, 9, and 12 mo past term (60). Because a shorter look duration is considered to reflect more rapid visual information processing and more mature attention, these observations also point to positive neural outcomes after supplementation with n−3 LCPs.

Willatts et al (61) assessed the cognitive behavior of a group of term infants who, for their first 4 postnatal months had been randomized to receive a formula supplemented or not supplemented with AA and DHA. At 10 mo of age, the LCP-supplemented infants performed significantly better on the means-end problem-solving test used than did infants who had received the nonsupplemented formula.

Human milk contains small but significant amounts of AA and DHA; however, these LCPs are not present in most classic formulas. Preterm infants, when given breast milk for ≥4 wk have, on average, a significantly higher intelligence quotient at 7 y of age than do comparable neonates reared on formula only (62). These results, which were corrected for a large number of possible confounders and confirmed the findings of earlier, longer-term studies (63– 65), were recently confirmed and extended to term infants over an 18-y follow-up period (66). In addition, breast-feeding (as opposed to formula feeding) of term neonates for ≥3 wk has been reported to be associated with significantly less neurologic abnormalities at 9 y of age (67). These results have led to the speculation that the LCPs in breast milk but not in formula at that time, may—at least in part—have been responsible for the differences observed. However, fatty acid measurements made to confirm these findings were not performed.

Recently, Agostoni et al (68) showed that consumption of human milk or an LCP-fortified formula by term infants for 4 mo was associated with a significantly higher developmental quotient (DQ) and higher amounts of AA and DHA in plasma and erythrocyte phospholipids than was the consumption of a classic formula not containing additional LCPs. They, moreover, observed a significant, positive correlation between erythrocyte DHA concentrations and the DQ (69). After 24 mo of follow-up, there were no longer significant differences between feeding groups and the DQ, and DQ values were no longer related to earlier or current DHA concentrations in erythrocyte phosphatidylcholine. However, AA and LA concentrations at the moment of DQ testing were found to correlate positively and negatively with DQ, respectively (70). This study and that of Willatts et al (61) clearly indicate that even in term infants, who have a higher essential PUFA status at birth than do preterm infants (36), the postnatal intake of additional LCP promotes neurodevelopment.

Retinal function

From the phylogenetic point of view, the retina can be considered a part of the central nervous system and, consequently, measures of retinal function can be used to assess the functional maturity of the brain. With use of the Teller acuity card procedure (71), the visual acuity of an infant, which reflects retinal maturity, can be measured by determining the finest grating that can be detected by that infant, as judged from its preferential looking behavior (looking acuity). Visual evoked potential (VEP) acuity can be assessed on the basis of electroencephalograms after a reversing pattern of high contrast black and white squares of ever-smaller sizes or of black and white lines with ever-finer gratings are presented to infants. Preterm infants fed formula with added marine oil rich in n−3 LCPs were shown to have better VEP and looking acuities at 36 and 75 wk postconception than did infants fed a standard formula without added LCP (72). In addition, visual acuity increased as the functional DHA status of the infants' erythrocyte lipids improved. Using the Teller acuity card procedure, Carlson et al (73) obtained results comparable with those of Birch et al (72) at 48 and 57 wk postconception, but not thereafter. In a later study, LCP supplementation improved looking acuity 48 wk postconception. Supplementation was then stopped and no differences were observed thereafter (74). From the results of these studies, it seems that brain maturation in preterm infants, as reflected by retinal function, is promoted by dietary n−3 LCPs.

Results of 4 recent randomized trials in term infants are less consistent. In 2 trials it was found that VEP acuity improved after consumption of a DHA- or DHA+AA–supplemented formula to values reached with breast-feeding (75, 76). In 2 other trials, however, no significant effect of LCP supplementation on VEP, looking acuity, or both was observed, although the LCP-supplemented formula did alter the fatty acid compositions of plasma or erythrocyte phospholipids as expected (77, 78). Enrichment of breast milk with DHA via supplementation of lactating women with a single-cell oil rich in DHA did not affect VEP acuity, nor did it influence Bayley's MDI or PDI scorers (79).

In a series of studies, Innis et al (80–82) found no differences in looking acuity between term infants fed either human milk containing LCPs or a standard formula containing no LCPs. Therefore, they concluded that there is no evidence to suggest that the present formula containing the essential fatty acids LA and ALA, but no LCPs, is inadequate with respect to postnatal brain development of term neonates.

POSSIBLE IMPLICATIONS OF THESE FINDINGS FOR NUTRITION DURING PREGNANCY

Essential fatty acid requirements and genetic constitution of humans

Although the Western diet is under constant criticism for its high amount of fat, its essential PUFA content is usually considered reasonably adequate. However, there are indications that in earlier times, when humans lived as hunter-gatherers, the diet was much richer in n−6 and n−3 LCPs, which came from structural lipids in animal brains and fish (83). Under these conditions, an active enzyme system to desaturate and elongate parent EFAs to derived LCPs was not required because the LCPs were readily available from the daily diet. Consequently, this system was rather inefficient (14, 15). With the introduction of agriculture and animal domestication, however, major changes in the dietary patterns of humans have occurred over the last millennium, leading to the consumption of large amounts of depot fat that are relatively poor in LCPs (83). Thus, a more active system to desaturate and elongate parent EFAs is required, but environmentally driven changes in the genetic constitution of humans occur very slowly. Therefore, the developments described above are likely to have resulted in a situation in which the human desaturation and elongation system is no longer compatible with the dietary fatty acid composition, potentially leading to a relative shortage of LCPs. This requirement (for a more active system to desaturate and elongate parent EFAs) is particularly important under conditions in which the LCP requirement is high, eg, during pregnancy, fetal development, lactation, and neonatal development.

Should the EFA content of the maternal diet be increased?

The results summarized above indicate that it may be necessary to increase the dietary EFA and LCP intakes of pregnant women to prevent a decrease in their essential PUFA concentrations during pregnancy and to optimize the fetal PUFA status, particularly in preterm infants because they have a significantly lower PUFA status than do term neonates (36). In addition, the LCP status of preterm infants drops considerably during the first postnatal weeks, even when infants are fed breast milk (84, 85); however, the EFA status increases considerably during the same

postconceptional period in utero (37). Consequently, during the growth spurt of the brain, the availability of LCPs is much lower in infants born preterm than in intrauterine fetuses of comparable postconceptional age. We also showed in preterm infants that AA and DHA concentrations at birth are positively related to LCP concentrations at the expected date of delivery (39). Therefore, a high intrauterine LCP status would particularly benefit a fetus born preterm because it would result in a higher postnatal LCP status. Because DHA (36) and AA (86, 87) have been shown to be associated with increased prenatal and neonatal growth, our present observations indicate that enhancement of the fetal LCP status may promote fetal and early neonatal development, thereby improving the "starting condition" and general prognosis of infants born preterm.

As mentioned above, the DHA content of maternal plasma phospholipids is significantly lower in multiparous than in primiparous women (23). In this same study it appeared that infants born to multiparous women had significantly less DHA in their umbilical tissue phospholipids than did infants born to primiparous women. Whether this lower DHA content has functional consequences for these infants is not known; however, prenatal and early postnatal DHA status is thought to have important consequences on the growth and function of the central nervous system and, consequently, on neurologic and cognitive development. Therefore, incomplete replenishment of maternal DHA stores after delivery may, at least in part, explain the observation that first-born children generally do better than their younger siblings on several developmental, behavioral, and intelligence tests (62, 63, 88, 89).

Finally, because the 2 PUFA families compete for the same metabolic enzymes (90), the supplement of choice for pregnant women should contain a mixture of n−6 and n−3 PUFAs. Further research is required to find the optimal composition of such a supplement.

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