

Long-chain polyunsaturated fatty acids, pregnancy, and pregnancy outcome¹⁻³

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ABSTRACT During pregnancy, essential long-chain polyunsaturated fatty acids (LCPUFAs) play important roles as precursors of prostaglandins and as structural elements of cell membranes. Throughout gestation, accretion of maternal, placental, and fetal tissue occurs and consequently the LCPUFA requirements of pregnant women and their developing fetuses are high. This is particularly true for docosahexaenoic acid (DHA; 22:6n-3). The ratio of DHA to its status marker, docosapentaenoic acid (22:5n-6), in maternal plasma phospholipids decreases significantly during pregnancy. This suggests that pregnancy is associated with maternal difficulty in coping with the high demand for DHA. The DHA status of newborn multiples is significantly lower than that of singletons; the same is true for infants of multigravidas as compared with those of primigravidas and for preterm compared with term neonates. Because the LCPUFA status at birth seems to have a long-term effect, the fetus should receive an adequate supply of LCPUFAs. Data from an international comparative study indicated that, especially for n-3 LCPUFAs, the fetus is dependent on maternal fatty acid intake; maternal supplementation with LCPUFAs, their precursors, or both increased LCPUFA concentrations in maternal and umbilical plasma phospholipids. However, significant competition between the 2 LCPUFA families was observed, which implies that effective supplementation requires a mixture of n-6 and n-3 fatty acids. Further research is needed to determine whether higher LCPUFA concentrations in plasma phospholipid will have functional benefits for mothers and children. *Am J Clin Nutr* 2000;71(suppl):285S-91S.

KEY WORDS Pregnancy, humans, gestational age, docosahexaenoic acid, nutrition, essential fatty acids, newborn, arachidonic acid, long-chain polyunsaturated fatty acids, n-6 fatty acids, n-3 fatty acids, phospholipids

INTRODUCTION

There are 2 families of essential fatty acids (EFAs), the n-6 and n-3 families. The parent EFA of the n-6 family is linoleic acid (LA; 18:2n-6) and that of the n-3 family is α -linolenic acid (18:3n-3). Both parent EFAs can be desaturated and elongated in the human body to a series of longer-chain, more unsaturated EFAs with 20 or 22 carbon atoms (long-chain polyunsaturated fatty acids; LCPUFAs). Fatty acids of the n-3 and n-6 families play major roles during pregnancy,

providing precursors for the synthesis of eicosanoids and important constituents of cell membrane phospholipids. Two LCPUFAs, arachidonic acid (AA; 20:4n-6) and docosahexaenoic acid (DHA; 22:6n-3), are important structural fatty acids in neural tissue. DHA in particular is found in the membranes of neuronal synapses and of photoreceptor outer segments (1-3), where it performs an array of membrane-associated functions.

During pregnancy, accretion of maternal, placental, and fetal tissue occurs and consequently the EFA requirements of pregnant women and their developing fetuses are high. During the last trimester of pregnancy, fetal requirements for AA and DHA are especially high because of the rapid synthesis of brain tissue (4, 5). To obtain these EFAs, the fetus depends primarily on placental transfer and thus on the EFA status and supply of the mother (6).

MATERNAL AND INFANT LCPUFA STATUS DURING NORMAL PREGNANCY

In a prospective longitudinal study (7), we showed that the total amount (mg/L) of fatty acids in maternal plasma phospholipids increases by \approx 51% during the course of pregnancy. All the individual fatty acids showed similar patterns, although there were some differences in the proportional increments. For instance, the absolute amounts of AA and DHA increased by 23% and 52%, respectively (**Figure 1**). The increases in the total absolute amounts of fatty acids in maternal plasma phospholipids throughout gestation are a direct consequence of the hyperlipidemia of pregnancy (8), but for the individual fatty acids other factors may play a role as well. The increment observed for DHA was one of the highest. In theory, the improved absolute maternal DHA content could result from a change in dietary habits, particularly an increase in fish consumption. However, dietary data for these women did not show changes in fat intake during pregnancy (9). Another explanation could be increased activity of the

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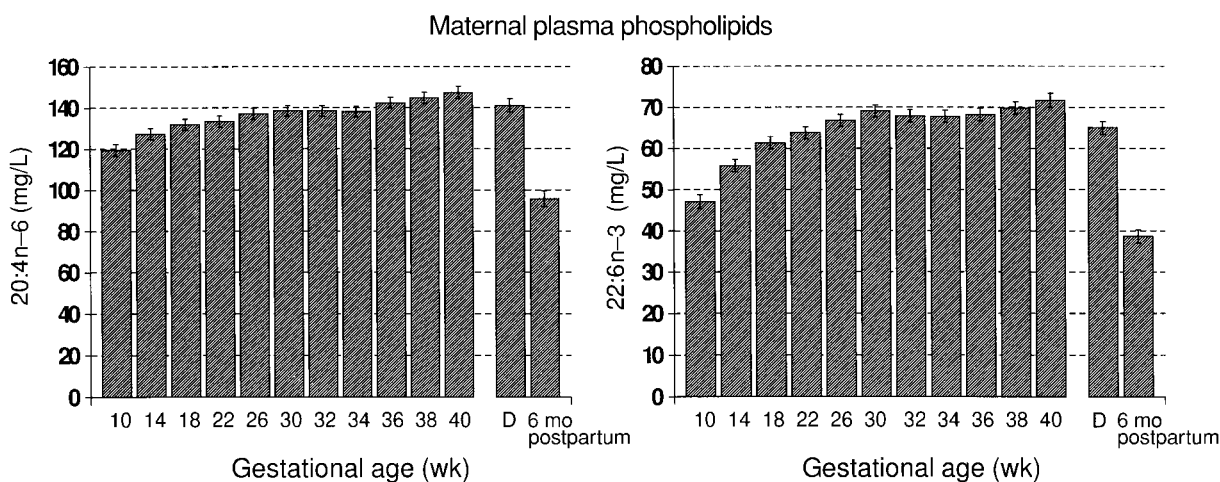


FIGURE 1. Mean (\pm SEM) absolute amount (mg/L) of 20:4n-6 and 22:6n-3 in maternal plasma phospholipids throughout gestation, at delivery (D), and at 6 mo postpartum ($n = 110$).

enzymes involved in the synthesis of DHA from its precursors; however, this process occurs at a low rate only (10). Therefore, it seems more likely that the rise in maternal absolute DHA values during pregnancy is due to increased mobilization from maternal stores, although a metabolic rerouting (from energy substrate to structural use) cannot be excluded.

Despite the increases in absolute fatty acid concentrations, there were continuous declines in the EFA-status index [ratio of ($\Sigma n-3 + \Sigma n-6$) to ($\Sigma n-7 + \Sigma n-9$)] and the ratio of 22:6n-3 to its status marker, 22:5n-6 (Figure 2). These observations suggest that pregnancy is associated with reduced maternal EFA status and, in particular, reduced maternal DHA status. Furthermore, the absolute amounts (mg/L) as well as the relative amounts (% by wt) of DHA in maternal plasma phospholipids were significantly lower in multigravidas than in primigravidas (Figure 3). Although these latter results are based on cross-sectional data and need to be verified by longitudinal studies, the data nonetheless seem to indicate that pregnancy may deplete maternal DHA stores, which may result in a suboptimal DHA supply to the fetus (11).

MATERNAL AND NEONATAL LCPUFA STATUS IN MULTIPLE PREGNANCIES

If the maternal-to-fetal LCPUFA supply is a limiting factor in determining the neonatal LCPUFA status, one might expect that the LCPUFA status of infants born of multiple pregnancies (eg, twins) would be lower than that of infants born of single pregnancies. After correction for differences in gestational age at birth, the fatty acid profiles of umbilical plasma, artery, and vein phospholipids of 94 singletons, 30 pairs of twins, 7 sets of triplets, and 1 set of quintuplets were determined. The data showed that the LCPUFA concentrations in umbilical artery and vein phospholipids were significantly lower in neonates of multiple pregnancies. However, in umbilical plasma phospholipids, most LCPUFA values were not significantly different between multiplets and singletons (12, 13). No significant differences were observed between twins and triplets, but the average phospholipid LCPUFA concentration in the one set of quintuplets was substantially lower than that of the other infants of multiple pregnancies (Figure 4). Hardly any significant differences were

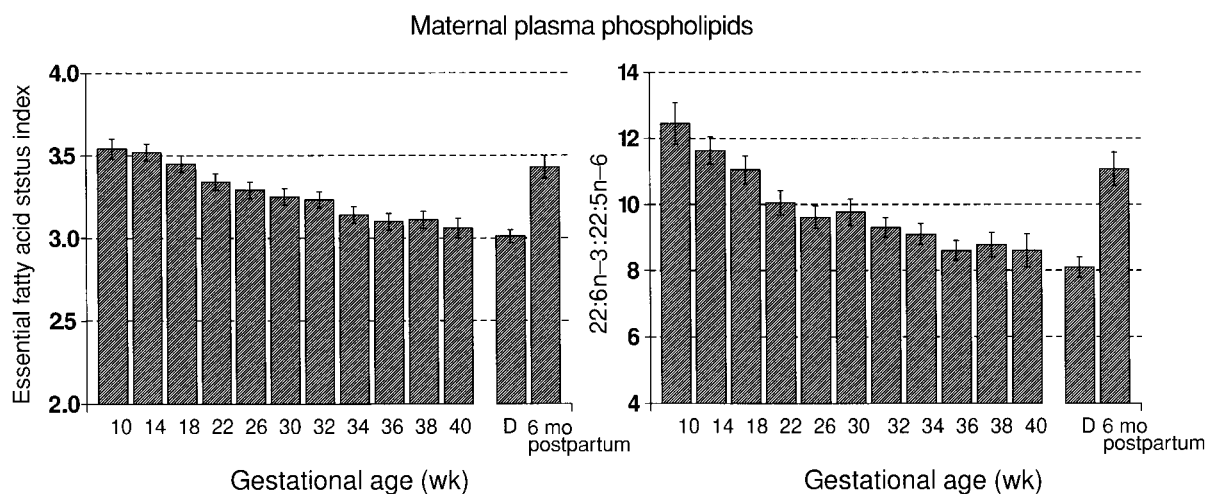


FIGURE 2. Mean (\pm SEM) essential fatty acid status index [ratio of ($\Sigma n-3 + \Sigma n-6$) to ($\Sigma n-7 + \Sigma n-9$)] and ratio of 22:6n-3 to 22:5n-6 in maternal plasma phospholipids throughout gestation, at delivery (D), and at 6 mo postpartum ($n = 110$).

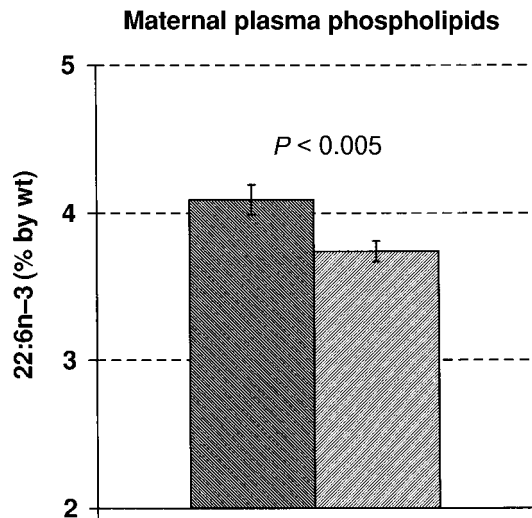


FIGURE 3. Mean (\pm SEM) relative amounts (% by wt) of 22:6n-3 in maternal plasma phospholipids of primigravidas (■, $n = 97$) and multigravidas (▨, $n = 132$) at delivery. P value is based on comparisons between groups (Student's t test).

observed between the LCPUFA concentrations of the lightest and heaviest infants within sets of twins or triplets. This observation is in contrast to those of Crawford et al (14) and Hoving et al (15), who found higher EFA concentrations in the umbilical artery vessel walls of the heaviest infant of one pair of twins and in the umbilical plasma of the heaviest infants of 3 pairs of twins, respectively. Because of the small sample sizes, these data are difficult to interpret.

Fatty acid profiles of maternal plasma phospholipids at delivery showed significantly lower concentrations of 20:4n-6, 20:5n-3, and 22:5n-3 in multiple compared with single pregnancies (13). This could mean that in multiple pregnancies, the LCPUFA composition of the umbilical artery and vein phospholipids may be reduced by a limited transplacental LCPUFA supply.

MATERNAL AND NEONATAL LCPUFA STATUS IN PREGNANCY-INDUCED HYPERTENSION

In situations in which placental function is impaired, the transfer of nutrients from mother to fetus may be compromised. To what extent the maternal-to-neonatal LCPUFA status was affected by such an event was studied in cases of pregnancy-induced hypertension (PIH), which is, in a high percentage of affected women, characterized by reduced uteroplacental perfusion and function (16). The results showed that there were hardly any significant differences between normal and hypertensive pregnancies in the LCPUFA concentrations in umbilical plasma, artery, and vein phospholipids (17, 18). However, fatty acid profiles of maternal plasma phospholipids at delivery showed significantly lower amounts of the parent EFAs 18:2n-6 and 18:3n-3 and significantly higher amounts of Σ n-6 LCPUFAs and 22:6n-3 in cases of PIH compared with normal pregnancies. This suggests that the parent EFAs are more actively desaturated and elongated in PIH than in uncomplicated pregnancies, possibly to guarantee an adequate LCPUFA supply to the fetus in spite of the compromised placental circulation. No significant differences between these 2 groups in maternal plasma concentrations of these fatty acids were observed during the course of pregnancy (at <math>< 16, 22, \text{ and } 32 \text{ wk gestation}</math>). This indicates that the altered fatty acid status at delivery in mothers with PIH is a late phenomenon, occurring after the clinical manifestation of the disease, and therefore is a consequence rather than a cause of this disease (18).

Results from an epidemiologic study performed in northern Canada showed that Inuit women who ate a diet rich in marine foods were 2.6 times less likely to develop PIH than Inuit women whose diets contained a greater proportion of terrestrial foods (19). It has been suggested that supplementing pregnant women with fish oil could correct the imbalance between prostacyclin and thromboxane that occurs in women with PIH (20) and that the supplementation might reduce the occurrence of PIH (21-24). However, in a randomized, double-blind, placebo-controlled trial, fish oil in high-risk pregnancies did not affect the rate of PIH (25).

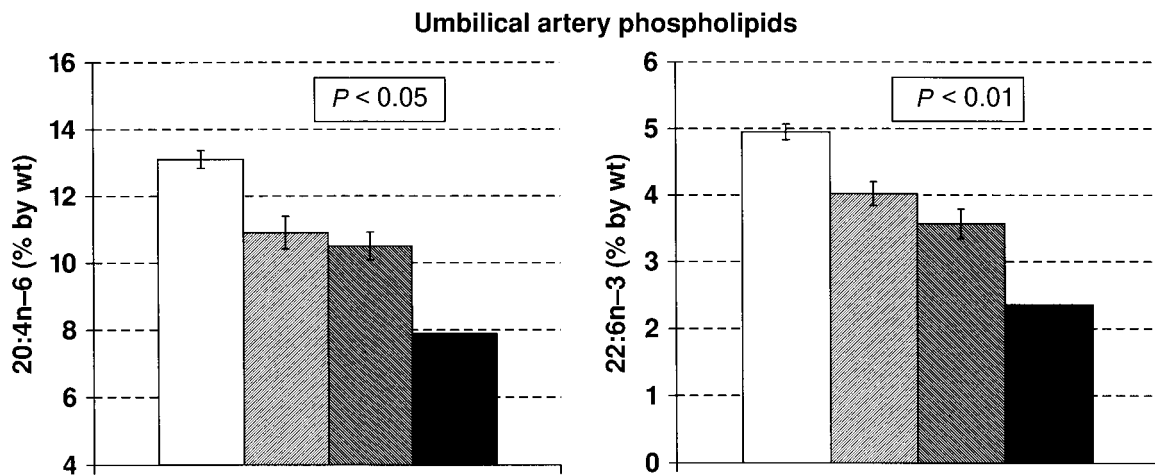


FIGURE 4. Mean (\pm SEM) relative amounts (% by wt) of 20:4n-6 (left) and 22:6n-3 (right) in umbilical artery phospholipids of infants born after single (□, $n = 94$) and multiple [twin (▨, $n = 30$ pairs), triplet (▩, $n = 7$ sets), or quintuplet (■, $n = 1$ set)] pregnancies. Significance level is for difference between infants born after single compared with multiple pregnancies (multiple regression analyses with correction for gestational age at birth).

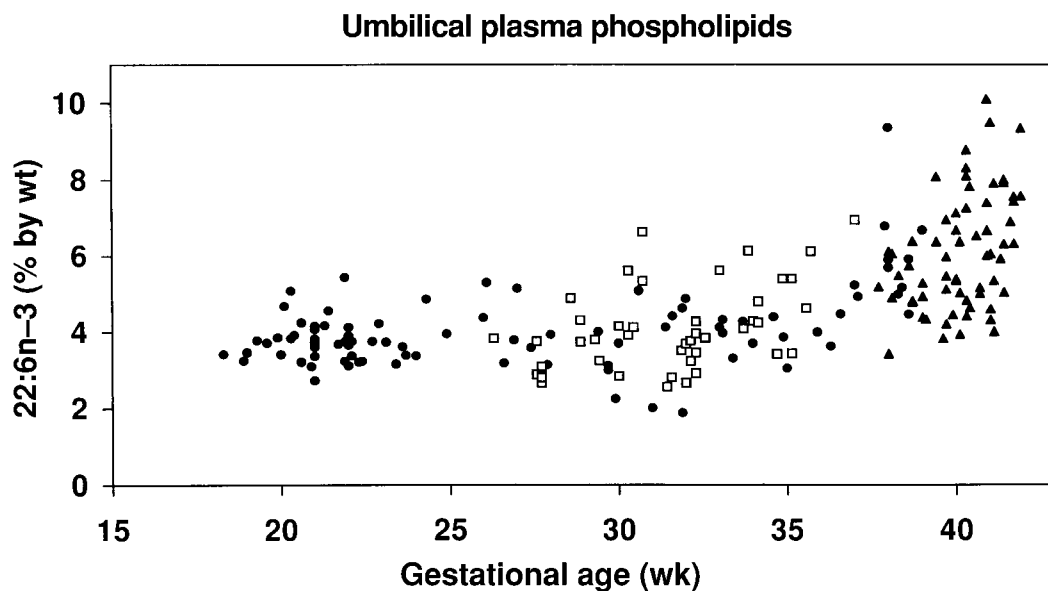


FIGURE 5. Relative amounts (% by wt) of 22:6n-3 in umbilical plasma phospholipids as a function of gestational age. Umbilical plasma samples were obtained by fetal blood sampling of ongoing pregnancies (●, $n = 91$) or were collected from the umbilical vein immediately after delivery in cases of preterm birth (□, $n = 45$) and term birth (▲, $n = 90$); each data point represents an individual value.

NEONATAL LCPUFA STATUS IN RELATION TO GESTATIONAL AGE

Fatty acid profile measurements in umbilical plasma phospholipids showed that the DHA content (% by wt) increases as pregnancy progresses (Figure 5). This strong association between DHA concentrations in umbilical plasma phospholipids and gestational age is probably physiologic rather than pathologic, because DHA concentrations in umbilical plasma samples obtained by fetal blood sampling in ongoing pregnancies were not significantly different from those in umbilical plasma collected after delivery at comparable gestational ages (26).

MATERNAL LCPUFA STATUS AND PREGNANCY DURATION

It has been suggested that maternal dietary intake of n-3 fatty acids may prolong the duration of gestation (27, 28). To test whether the n-3 fatty acid concentrations in maternal plasma phospholipids of women who delivered preterm (<37 wk), at term (37-42 wk), or after a prolonged pregnancy (>42 wk) were indeed significantly different, maternal blood samples were collected longitudinally during pregnancy and after delivery. The n-3 fatty acid contents were not significantly different among the 3 groups during the first, second, and third trimesters of pregnancy and after delivery; the results for DHA are shown in Figure 6. This does not support the opinion of Olsen et al (27, 28) that maternal intake of n-3 fatty acids is an important determinant of the duration of pregnancy. However, in a later study, Olsen et al (29) were also unable to confirm that maternal intake of n-3 fatty acids during pregnancy is a predictor of gestational length. Interestingly, in the present study the n-3 fatty acid content of umbilical plasma phospholipids was positively associated with gestational age (compare Figures 5 and 6). Because mater-

nal n-3 fatty acid values remain fairly constant throughout pregnancy, this observation suggests that the efficiency of the maternal-fetal transfer of n-3 fatty acids improves when pregnancy progresses.

LCPUFA STATUS OF PRETERM INFANTS

The LCPUFA content of umbilical tissue phospholipids of preterm infants is significantly lower than that of term infants (30). These lower LCPUFA concentrations seem to persist over the long term, because significant associations have been observed between fatty acid concentrations at birth and at age 6-8 wk, even when the type of diet and the gestational age at delivery were controlled for (31). Preterm infants are prematurely deprived of their in utero EFA source and are dependent on the fatty acid composition of their postnatal diet for their EFA supply. The observation that the postnatal EFA concentrations of blood phospholipids in preterm infants were higher if their EFA concentrations at birth were higher suggests that not only an adequate postnatal EFA supply, but also an appropriate prenatal EFA supply, may be beneficial.

RELATION BETWEEN MATERNAL AND NEONATAL LCPUFA STATUS

The LCPUFA contents of umbilical plasma phospholipids at birth and those of maternal plasma phospholipids are strongly correlated (7, 9). An international comparative study in which fatty acid data were obtained from pregnant women with a wide range of dietary LCPUFA intakes also showed that the n-3 LCPUFA concentrations in umbilical plasma, vein, and artery phospholipids were the highest in the same country that had the highest maternal plasma n-3 LCPUFA concentrations (32). However, the n-6 LCPUFA concentrations in umbilical material seemed less dependent on the maternal n-6 LCPUFA con-

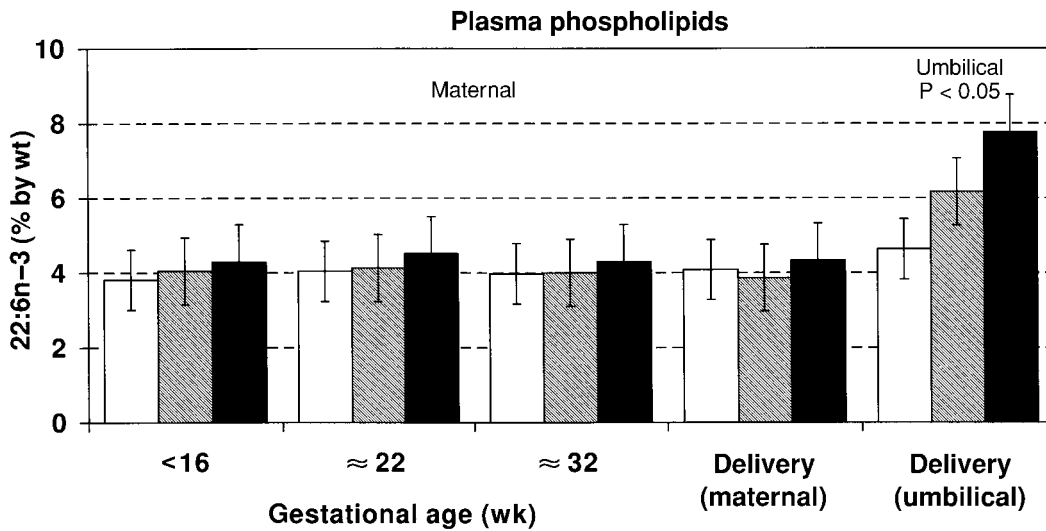


FIGURE 6. Mean (\pm SD) relative amounts (% by wt) of 22:6n-3 in maternal and umbilical plasma phospholipids during gestation and at delivery for women who delivered preterm (\square , $n = 50$), term (\blacksquare , $n = 592$), or after a prolonged pregnancy (\blacksquare , $n = 26$). P value is based on comparisons among groups (Tukey test).

centrations in blood phospholipids. As shown in **Figure 7**, the ratio of umbilical to maternal concentrations of 20:4n-6 (as reflected by the slope of the regression line) was comparable in all 4 countries, although the mean 20:4n-6 concentrations in maternal plasma differed among the countries (32). This suggests some kind of autonomy of the fetus with respect to establishing its 20:4n-6 status. This autonomy seems less pronounced for 22:6n-3 (**Figure 7**); the slope of the regression line is significantly higher in the country with the lowest maternal plasma 22:6n-3 concentration (Hungary) compared with the country with the highest maternal plasma 22:6n-3 concentration (Finland). On the basis of these associations, it seems likely that maternal fatty acid supplementation will alter the neonatal fatty acid status.

EFFECT OF MATERNAL EFA SUPPLEMENTATION ON NEONATAL LCPUFA STATUS

We performed 2 pilot studies to evaluate whether maternal EFA supplementation affects the EFA content of umbilical plasma and tissue phospholipids (33, 34). In one intervention study, supplementation was carried out with 2.7 g fish oil/d from 30 wk gestation until delivery (33). This resulted in significantly increased n-3 LCPUFA concentrations and significantly reduced n-6 LCPUFA concentrations in umbilical plasma phospholipids (**Figure 8**). In the other intervention study, pregnant women were given LA-rich food products (providing 10 g LA/d) from the 20th week of pregnancy until delivery and the opposite results were found; significantly higher n-6 LCPUFA concen-

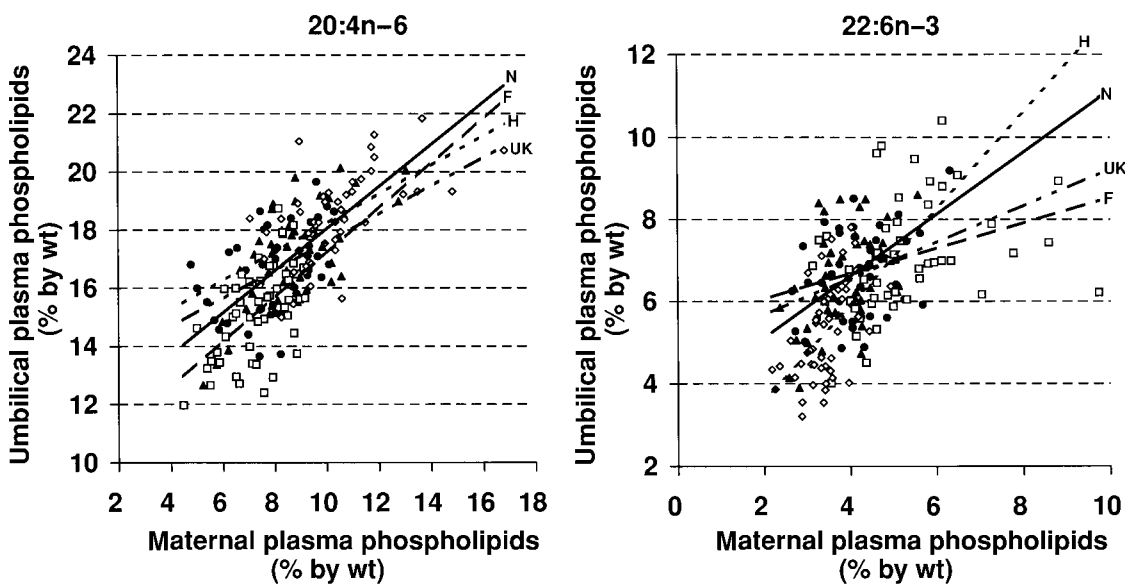


FIGURE 7. Associations between maternal and umbilical plasma concentrations (% by wt) of 20:4n-6 and 22:6n-3 in 4 European countries (32). \blacktriangle , Netherlands (N); \bullet , United Kingdom (UK); \square , Finland (F); \diamond , Hungary (H).

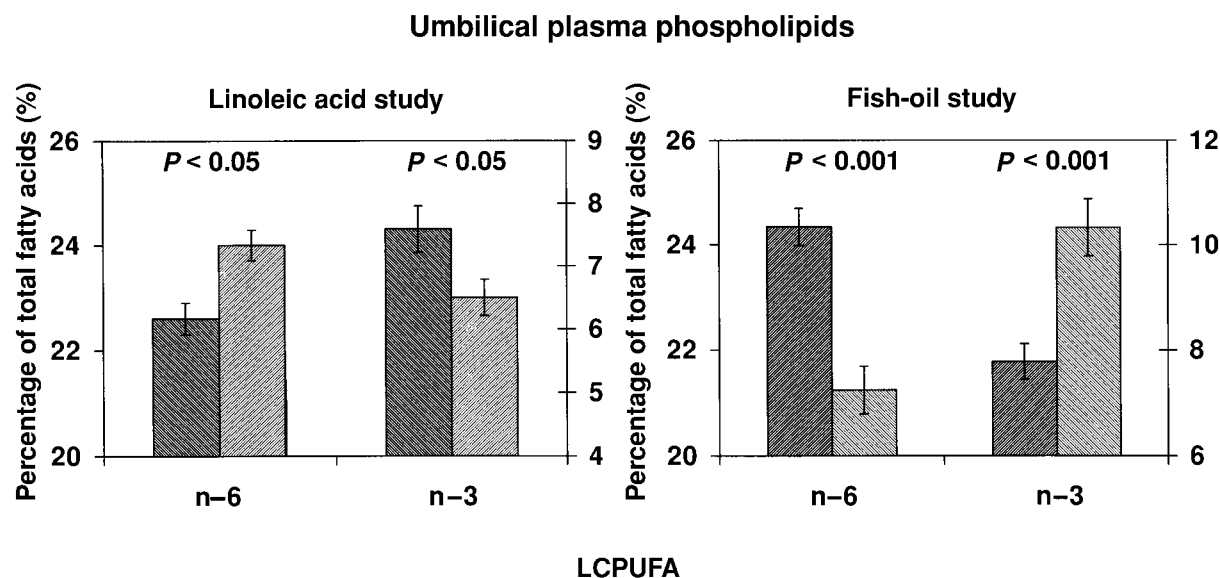


FIGURE 8. Mean (\pm SEM) relative amounts (% of total fatty acids) of n-3 long-chain polyunsaturated fatty acids (LCPUFAs) and n-6 LCPUFAs in umbilical plasma phospholipids of the control (■) and supplemented (▨) groups in the linoleic-acid intervention study (34) and the control (■) and supplemented (▨) groups in the fish-oil intervention study (33). *P* values are based on comparisons between groups (Student's *t* test).

trations were associated with significantly lower n-3 LCPUFA concentrations in umbilical plasma phospholipids (34; Figure 8). Thus, in both studies a competition between fatty acids of the n-3 and n-6 families was evident. Therefore, if it is considered desirable to change the neonatal LCPUFA status at birth, this would require supplementation with a combination of fatty acids from both the n-6 and n-3 families.

Apart from determining the optimal fatty acid mixture, the period of supplementation should also be considered. There is evidence that maternal nutritional status during ovum maturation and early embryonic development has a greater effect on the fetus than maternal nutrition during the last 2 trimesters of pregnancy (35). This may be due, in part, to the development of the placental barrier in early pregnancy. Events occurring at the time of placental implantation play a role in determining the ultimate size attained by the placenta (36). It is thus possible that the nutritional status of the mother during that particular period has a strong influence on the composition and function of the placenta. Therefore, it was interesting to observe that the effect on neonatal LCPUFA status was stronger in the high-LA control group of our LA intervention study (habitual LA intake during pregnancy: 23.5 g/d) (34), than in the intervention group in which LA intake was increased from the habitual value of 14.0 g/d during the first half of pregnancy to 24.7 g/d in the second half of pregnancy. Furthermore, the significant effects of maternal plasma fatty acid concentrations, before supplementation, on the corresponding fatty acids in umbilical plasma and vessel wall phospholipids indicate that preconceptional maternal EFA status does influence neonatal EFA status significantly (34). Therefore, it seems that early intervention may be more effective in altering the neonatal EFA status than supplementation after complete development of the placenta. Thus, if supplementation is indicated, it should begin very early in pregnancy or even before conception.

SHOULD THE LCPUFA CONTENT OF THE MATERNAL DIET BE INCREASED?

The LCPUFA contents in umbilical plasma phospholipids, tissue phospholipids, or both are lower when 1) gestational age at birth is lower, 2) children are born after multiple pregnancies, and 3) birth order is higher. An appropriate prenatal LCPUFA supply is important because neonatal LCPUFA concentrations at birth seem to significantly affect the postnatal LCPUFA content of blood phospholipids (31). We have also shown that the LCPUFA content of umbilical plasma phospholipids can be influenced by maternal dietary intervention. However, we have yet not investigated whether these biochemical differences have functional consequences. Clinical studies with preterm infants have shown that cognitive and neural development is improved if their diet contains LCPUFA, although some of these effects are transitory (37). So far, studies with term infants have yielded inconclusive results (38). Long-term follow-up studies with a large cohort of pregnant women and their infants are needed to investigate whether LCPUFA status during pregnancy, at birth, and in early infancy is associated with functional outcome later in life. Until these data are available, it may be premature to offer recommendations for LCPUFA intake during pregnancy.

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