Essential fatty acids and pregnancy

What are essential fatty acids?
There are two families of essential fatty acids (EFA), the n-6 and n-3 families. They are essential because they are required and cannot be synthesized de novo by humans. Human (and animal) metabolism is unable to introduce a double bond between carbon atoms 3 and 4 (for n-3 fatty acids) or between carbon atoms 6 and 7 (for n-6 fatty acids) proximal to the methyl end of the fatty acid. Linoleic acid (C18:2n-6) and α-linolenic acid (C18:3n-3) can be desaturated and elongated by liver enzymes to form long-chain polyunsaturated fatty acids (PUFA) (Figure 1). Therefore, C18:2n-6 and C18:3n-3 are referred to as the parent FA and need to be present in the diet. Long-chain PUFA play a major role in the development of new life as important structural components of cell membrane phospholipids. In addition, some PUFA (C20:4n-6 and C20:5n-3) are involved in the formation of eicosanoids (prostaglandins, thromboxanes, and leukotrienes), which are hormone-like substances. Arachidonic acid (20:4n-6; AA) and docosahexaenoic acid (22:6n-3; DHA) are important structural fatty acids in neural tissue such as the brain and retina.

EFA deficiency markers
When the diet lacks sufficient EFA to meet the requirements of the body, the human metabolism starts to synthesize fatty acids that normally are present only in trace amounts. Under these conditions, oleic acid (C18:1n-9) will be desaturated and elongated to form Mead acid (C20:3n-9) and dihomo Mead acid (C22:3n-9). The presence of Mead acid is an indication of a deficiency of the parent EFA and their derived long-chain homologs.

The ratio of the sum of all the essential n-3 and n-6 fatty acids over the sum of all the nonessential n-7 and n-9 fatty acids is also an indicator of a generalized EFA shortage. The higher this ratio, the better the EFA status.
An isolated deficiency of DHA stimulates the synthesis of C22:5n-6 from C22:4n-6 (Figure 1); therefore, the ratio between C22:5n-6 and C22:4n-6 is considered to be an indicator of DHA status. The higher this DHA deficiency index, the lower the DHA status.

EFA and pregnancy
During pregnancy, accretion of maternal, placental, and fetal tissue occurs and therefore the EFA requirements of pregnant women and of the developing fetus are high. During the last trimester of pregnancy, the fetal need of AA and DHA are especially high because of rapid synthesis of brain tissue. The desaturation enzyme system in the human fetal liver is immature and unable to supply sufficient long-chain PUFA to meet the high neonatal demand of EFA until 16 weeks after birth. Moreover, the capacity of the placenta to synthesize long-chain PUFA from EFA is very limited.
Thus, to obtain an adequate amount of parent EFA and their long-chain polyunsaturated derivatives, the developing fetus depends on active transport of these fatty acids from the mother across the placenta and thus on the EFA status of the mother. The diet of a pregnant woman should contain sufficient amounts of EFA to cover her own requirement as well as that of her unborn child.

Umbilical cord vessel walls
The umbilical vein (afferent fetal vessel) transports blood and nutrients from the...
mother to the fetus, whereas the blood flows back from the fetus to the mother through the umbilical arteries (efferent fetal vessels). Since umbilical vessel walls do not have a *vasa vasorum* (a fine network of blood vessels for the supply of blood to the vessel walls) to obtain nutrients, they can only obtain their nutrients directly from the blood running through the umbilical vessels. Therefore, the fatty acid composition of the umbilical venous wall is considered to be a long-term reflection of the EFA supply from mother to fetus, whereas the fatty acid composition of the umbilical arterial wall reflects the EFA status of the developing fetus.

It has been shown that the phospholipids of the umbilical arteries contain significantly less C18:2n-6, C20:4n-6, C22:4n-6, C20:5n-3, and C22:5n-3, and significantly more C20:3n-9 and C22:3n-9 than do the phospholipids of the umbilical vein. The presence of high amounts of Mead acid and C22:3n-9 in the umbilical arterial vessel wall has been suggested to be an indication of a marginal EFA status of the newborn. Furthermore, the DHA deficiency index (C22:5n-6/C22:4n-6) has been found to be significantly higher in the phospholipids of the umbilical arteries than the veins. This indicates that the need for DHA by the fetal tissue is not adequately covered (1, 2).

**Maternal and Neonatal EFA Status**

Hyperlipidemia occurs during pregnancy. As a consequence, the absolute...
amounts of all the fatty acids in maternal plasma phospholipids are increased. Longitudinal studies have indicated that the amounts (mg/L) of all the individual fatty acids in the maternal plasma phospholipids increase from the early onset of pregnancy until delivery (3,4). The two most important long-chain PUFA for the newborn, C20:4n-6 and C22:6n-3, increased significantly with progressing gestation. This probably reflects the high requirement of these fatty acids by the developing brain and retina. On the other hand, the nonessential PUFA, especially Mead acid, increased even more significantly.

Proposed explanations for the improved absolute maternal DHA status include changed dietary habits, such as increased fish consumption. But many dietary studies have shown that dietary habits remain unaltered during pregnancy—neither the amount and type of fat nor the fatty acid composition of the maternal diet changed (5,6). Other explanations could be an increase in the activity of the desaturation and elongation system involved in the synthesis of DHA or an increase in the mobilization of DHA from maternal stores.

Although the absolute amounts of fatty acids increase with progressing gestation, the relative EFA concentrations (wt%) decline with progressing gestation. The relative concentration of linoleic acid remains stable, whereas the relative amounts of AA and DHA steadily decline near term. The ratio of the essential n-3 and n-6 fatty acids to the nonessential n-7 and n-9 fatty acids decreases continuously during pregnancy. This suggests that pregnancy is associated with reduced maternal EFA status. In addition, the DHA deficiency index has been found to increase progressively throughout pregnancy (2,3,7).

The absolute amount of fatty acids in umbilical plasma phospholipids is substantially lower than in maternal plasma phospholipids. The relative amounts of AA and DHA, on the other hand, have been found to be significantly higher in umbilical plasma compared to maternal values, whereas the parent EFA are much lower in the neonate than the mother (3,7).

In different study populations, strong positive correlations between postpartum maternal and umbilical plasma phospholipid fatty acids are observed. An international comparative study found strong positive associations between the relative values of AA and DHA in umbilical plasma phospholipids at birth and the maternal AA and DHA status at delivery. The slope of the regression line for AA was comparable in the four countries (Finland, Hungary, The Netherlands, and the United Kingdom). This suggests a possible autonomy of the fetus with respect to establishing its own AA status, whereas the autonomy toward the DHA status is less pronounced. The slope of the regression line for DHA was significantly lower in women from the country with the highest maternal plasma DHA status (Finland) compared to the Hungarian women, who had the lowest maternal plasma DHA status (2).

Researchers at Maastricht University in The Netherlands (8) could not distinguish a difference in n-3 fatty acid concentrations in maternal plasma phospholipids from women who delivered preterm (<37 wk), at term (37–42 wk) and after prolonged gestation (>42 wk).

**Proposed explanations for the improved absolute maternal DHA status include changed dietary habits, such as increased fish consumption.**

But the DHA status (wt%) in umbilical plasma phospholipids significantly increased with progressing gestation. This observation suggests that the efficiency of maternal-fetal transfer of n-3 fatty acids improves with progressing gestation.

During pregnancy, the absolute and relative amounts of DHA in maternal plasma phospholipids of women who were previously pregnant (multigravidae) have been found to be significantly lower than in women who were pregnant for the first time (primigravidae) (9). These observations may indicate that pregnancy depletes maternal DHA stores and that the maternal DHA status may not recover completely to normal after the first pregnancy. On the other hand, in a nonpregnant study population (10), no significant difference in relative DHA concentration was found between nonpregnant nulligravidae and nonpregnant multigravidae nor was there a significant relation between parity and the percentage of DHA in maternal

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plasma phospholipids. The duration between the time of blood sampling and the last partus in the multigravidae was between 1 and 2 years. Thus, these observations indicate that the maternal DHA status after pregnancy normalizes within one year.

The concentrations (wt%) of the long-chain PUFA, C20:4n-6 and C22:6n-3, in the wall of the umbilical artery and vein have been determined to be significantly lower in infants born after a multiple pregnancy (twins and triplets) than in infants born after a singleton pregnancy. The status of Mead acid, on the other hand, is much higher in twins and triplets (11). The observed difference in EFA status between infants born after a singleton and those born after a multiple pregnancy supports the hypothesis that the maternal EFA supply to the developing fetus is limiting. Minor differences occur in the fatty acid composition of maternal plasma phospholipids at delivery between multiplet mothers compared to mothers of singletons.

**Maternal diet and the effect of maternal dietary n-3 fatty acid supplementation**

It has been shown in a Dutch population that dietary habits remained unaltered during pregnancy. Neither the amount and type of fat nor the fatty acid composition of the maternal diet changed from the early onset of pregnancy until delivery (4,5). Our studies with pregnant Belgian women reached similar conclusions (6).

We estimated the dietary fatty acid intake in pregnant Belgian women during the first and third trimester with a food frequency questionnaire. The average intake of C18:2n-6 was 13.3 (SD 5.4) g/d and of C18:3n-3 was 1.4 (SD 0.5) g/d. The daily intake of AA was 130 (SD 30) mg/d and that of EPA and DHA was 20 (SD 7) mg/d. 

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DHA was, respectively, 165 (SD 75) and 300 (SD 140) mg/d. Only 55% of the population had a DHA intake higher than the recommended 250 mg/d. In the pregnant Dutch population only the daily linoleic acid intake was estimated and was on average 14.5 (SD 7.5) g/d.

There is epidemiological evidence that populations with a high fish intake (Faroe Islands and the Inuits) have a longer gestation, larger babies, and reduced incidence of pre-eclampsia (pregnancy-induced hypertension) compared to populations eating less marine food. There is a strong association between gestational age and the DHA concentration (wt%) of umbilical plasma phospholipids. DHA concentration (wt%) increases with progressing gestation. These observations have led to a series of fish oil supplementation studies during pregnancy.

The first studies from Olsen and co-workers at the University of Aarhus (12,13) showed that maternal dietary intake of n-3 fatty acids by supplementation with fish oil from the 30th week of gestation prolonged the duration of pregnancy by four days. The suggested explanation for this delayed delivery was that a high intake of n-3 fatty acids increased the production of n-3-derived eicosanoids (such as prostacyclins PGJ2 and PGJ3, which relax the myometrium) in favor of the n-6-derived eicosanoids (such as prostaglandins F2 and E2, which initiate labor). However, in a later study (14), when the intake of marine n-3 fatty acids was assessed by a semiquantitative questionnaire, no association was found between gestational length and dietary intake of n-3 fatty acids.

Supplementation with fish oil during the last trimester of pregnancy resulted in a significantly higher concentration of n-3 fatty acids and a lower concentration of AA in umbilical plasma phospholipids. As a result of the fish oil supplementation a decrease in n-6 fatty acids (especially linoleic acid but also AA) and a significant increase in C20:3n-3 and C22:6n-3 were observed in maternal plasma phospholipids. In addition, the amount of Mead acid was significantly decreased in maternal plasma phospholipids. Thus, fish oil supplementation improved the maternal EFA status compared to the placebo group. A positive correlation was found between the length of gestation and the DHA status in umbilical plasma (15).

Increased consumption of n-3 fatty acids in the form of sardines and fish oil (16) during the last trimester of pregnancy resulted in significantly higher DHA levels in maternal plasma and red blood cell phospholipids compared to control mothers. Similarly DHA levels increased in the blood of the newborn in both plasma and red blood cells. The length of pregnancy was not affected by this supplementation.

On the other hand, when the diets of pregnant women were supplemented with linoleic acid-rich food products from the 20th week of gestation until delivery, the maternal linoleic acid status in plasma phospholipids significantly increased (17). The neonatal n-6 long-chain PUFA increased, whereas the n-3 long-chain PUFA in umbilical plasma became significantly lower compared to the neonates of the unsupplemented mothers.

The conclusion can be made that the n-3 and n-6 long-chain PUFA levels of newborns are significantly influenced by those of their mothers. The higher the concentration in the maternal diet, the higher the levels of these fatty acids in maternal plasma and in umbilical plasma. Therefore, when one wants to increase the neonatal EFA status by maternal dietary supplementation, it is advisable to increase the intake of both n-6 and n-3 PUFA.

**Conclusion**

It is now well established that adequate fetal accretion of long-chain PUFA is important for the normal neurological development of the fetus. In addition, it is known that the long-chain PUFA concentration in umbilical plasma phospholipids is lower when gestational age at birth is lower, in children born from multiple pregnancies, and when birth order is higher. Many supplementation studies (mainly with fish oil) have shown that it is possible to alter the maternal EFA status as well as that of their neonates. However, it is not yet established whether these biochemical differences have functional consequences.

Further studies are needed to elucidate whether extra n-3 consumption during pregnancy is of functional value for mother and child. Concerning pregnancy complications, such as prematurity and pre-eclampsia, there is conflicting evidence whether dietary supplementation is helpful.

As far as dietary recommendations during pregnancy are concerned, Health Canada has recommended an intake of 1.36 g/d of DHA and 7.9 g/d of n-6 PUFA. Pregnant women should have a minimum DHA intake of at least 250 mg/d (18). Other recommendations for DHA intake of pregnant women are at least 300 mg/d (19).

Readers may contact the author at Ghent University Hospital UZ, Department of Endocrinology, Division of Nutrition 6K12 I.E., De Pintelaan 185, B-9000 Ghent, Belgium (phone: 32-9-240-3939; fax: 32-9-240-3897;
Ms. De Vriese received an AOCS Honored Student Award during the 1998 AOCS Annual Meeting & Expo in Chicago, Illinois. At that time she was preparing her Master's thesis entitled "Experimental Fat Feedings in the Bile Duct Ligated Rat." After graduation, she started research on the evolution of the EFA status during pregnancy as part of the requirements for a Ph.D. degree. The Honored Student Award enabled her to attend the 1998 AOCS meeting in Chicago, and she has since become an active AOCS member, attending all subsequent annual meetings, at which she has given oral presentations on different topics. Together with Dr. A.B. Christophe, her mentor at the University of Ghent, she has edited a book, Fat Digestion and Absorption, published by AOCS Press as well as contributing a chapter as senior author on Fat Absorption and Fatty Acid Composition of Serum Lipids in Cholestatic Bile Duct-Ligated Rats. She also has co-authored a review of this topic (Ann. Nutr. Metab. 45:209-216, 2001). In addition she has two publications in Lipids (36:15-20, 2001; 36:361-366, 2001). She is organizing a session is on Lipid Metabolism and Male Fertility to be held during the AOCS Annual Meeting & Expo on May 5-8, 2002, in Montréal, Canada, which she intends to develop into a second book.

**BIBLIOGRAPHY**


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