



Fatty acids and early human growth¹⁻³

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Infant weight at birth, a major determinant of short- and long-term health, is influenced by genetic factors, maternal body size, and intrauterine substrate supply and metabolism (1). Two articles in this issue of the Journal (2, 3) address intriguing questions about the relation between perinatal fatty acid metabolism, tissue availability of long-chain polyunsaturated fatty acids (LCPUFAs), and early human growth. The underlying hypothesis of a potential causal relation was first raised some 10 y ago when a correlation between the plasma lipid content of the LCPUFA arachidonic acid (AA; 20:4n-6) and birth weight was reported in infants born prematurely (4). Similar associations between LCPUFA status and early growth have since been reported in other clinical studies.

Rump et al (2) report on the analysis of data on a large number of 627 full-term infants and their mothers who participated in different observational studies in the province of Limburg, Netherlands. The SD scores of birth weight for gestational age were inversely related to AA and the major n-3 LCPUFA docosahexaenoic acid (DHA; 22:6n-3) in umbilical cord plasma phospholipids at the time of birth. The authors conclude that these data do not support the previously proposed concept of a growth-enhancing effect of AA and possibly of DHA. In contrast with AA and DHA, the intermediate n-6 metabolite dihomo- γ -linolenic acid (DGLA; 20:3n-6) (Figure 1) was positively correlated with birth weight in this data set. This observation raises the question of whether the different prostaglandins, thromboxanes, and other eicosanoids derived from DGLA and AA, respectively (Figure 1), might have differential effects on cell growth.

Rump et al also observed a trend to lower umbilical cord blood lipid concentrations of linoleic acid (18:2n-6), AA, and n-3 LCPUFAs with increasing birth weights; they consider this a further argument against a growth-promoting effect of PUFAs. However, this relation may in fact reflect reverse causation: a higher fetal weight gain during pregnancy is expected to induce a larger degree of PUFA disappearance from plasma for incorporation into growing tissues, and hence lower plasma concentrations if the placental PUFA supply does not increase proportionally. This interpretation is compatible with the observed relation of birth weight in this cohort to eicosatrienoic acid (20:3n-9), a cell-derived marker of essential fatty acid depletion. These data do not exclude the possibility that LCPUFA availability modulates growth-related processes at the cellular level.

Elias and Innis (3) report somewhat different results in their observational study of a cohort of 84 newborns in Western Canada. Most of these infants were born full term, with a range of birth weights similar to that in the Dutch study. Both gesta-

tional age and birth weight were not related to plasma phospholipid fatty acids, but they correlated positively with AA concentrations in cord blood triacylglycerols and cholesteryl esters. The authors do not report correlations of fatty acid to SD scores of birth weight for gestational age, and it is not clear whether a significant correlation with birth weight persists if one corrects for the relation to length of gestation.

The apparent discrepancies in the results of these 2 studies (2, 3) is not explained by different exposures to n-6 fatty acids. Maternal and umbilical cord plasma lipid concentrations in linoleic acid and its metabolites were similar in these 2 studies and were also similar to those in another study that used comparable methods (5), despite considerable variation in DHA concentrations in the different populations studied.

Elias and Innis also studied maternal and umbilical cord plasma concentrations of *trans* fatty acids and conjugated linoleic acids (CLAs). For the first time they provided evidence of the transport of CLAs across the human placenta. Thus, some of the potent physiologic properties of CLAs (1) might be effective during prenatal development, which deserves further clarification in appropriately designed research studies.

The Canadian authors further report an inverse relation of total *trans* fatty acids to concentrations of various essential fatty acids in plasma lipids of both mothers and infants. These inverse correlations might reflect either potential inverse associations of dietary intakes of *trans* and essential fatty acids in the mothers, reflecting their food choices, or the previously reported metabolic suppression of essential fatty acid desaturation by *trans* isomers (6). Moreover, total *trans* fatty acids in cholesteryl esters, as well as CLAs in cholesteryl esters and triacylglycerols, were inversely correlated with length of gestation but not with birth weight in these full-term infants. In contrast, an inverse relation between *trans* fatty acids and birth weight was previously

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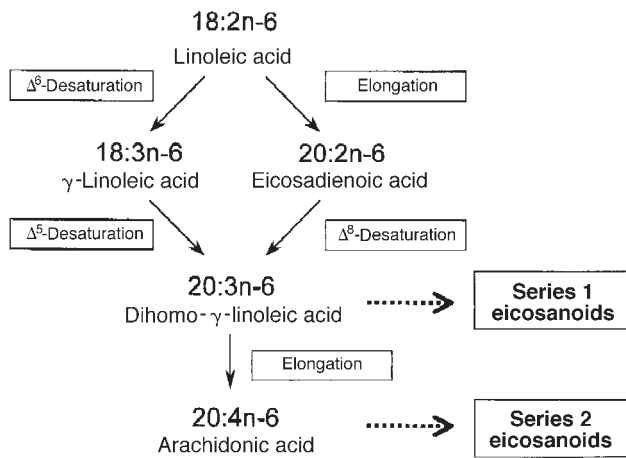


FIGURE 1. Metabolic pathways for the conversion of n-6 polyunsaturated fatty acids.

reported in preterm infants, who might be more susceptible to metabolic perturbations (6).

Firm conclusions on cause and effect cannot be drawn from correlations found in these observational studies because several confounding factors may have influenced the results. Indeed, Rump et al (2) reported that higher infant birth weight is also associated with a trend to increasing maternal height, weight, and weight gain during pregnancy, and to a decreasing rate of smoking. All of these factors might be related to maternal nutrient intakes and metabolism. Other studies also indicated that maternal socioeconomic status and ethnicity are associated with maternal dietary habits and with maternal and infant size. Similarly, maternal consumption, and hence plasma *trans* fatty acid and polyunsaturated fatty acid concentrations, may well be associated with factors that relate to the length of gestation and the risk of premature birth, such as socioeconomic status and the level of health consciousness and education.

Nonetheless, these 2 studies are valuable because they raise important questions of considerable relevance to children's health, that is the possible relations between the supply and metabolism of different fatty acids and early human growth. These hypotheses need to be tested further in experimental studies and intervention trials under controlled conditions. Early results indicate that on a cellular and molecular level, various eicosanoids derived from n-6 LCPUFAs, including prostaglandin E₂, thromboxanes A₂, and prostaglandin F_{2α}, stimulate cell growth. However, prostaglandin I₂, prostaglandin A₂, and prostaglandin E₂ (in some cell lines) inhibited cellular growth (7). The cellular conversion of AA to prostaglandin E₂ induced the mitogenic response in mouse 3T3 fibroblasts, whereas n-3 LCPUFAs antagonized mitogenic stimulation with AA by reducing prostaglandin E₂ formation (7). In premature infants, postnatal growth was reduced by the feeding of formulas supplemented with fish oil rich in the n-3 LCPUFA eicosapentaenoic acid but with no appreciable amount of AA, thus inducing a reduction of plasma AA concentrations (8). In these studies, plasma AA concentrations were positively correlated with postnatal growth. Similarly, a high dietary supply of α-linolenic

acid (18:3n-3), associated with a low dietary ratio of n-6 to n-3 fatty acids, concomitantly reduced both plasma AA and weight gain until the age of 120 d in healthy infants born at term (9). In contrast, the provision of infant formulas with a balanced supply of dietary AA and DHA in reasonable amounts and with adequate antioxidant protection, which is recommended by many experts worldwide, did not lead to poor growth or other adverse effects in several randomized clinical trials (10).

In conclusion, it appears possible that pre- and postnatal essential fatty acid supply and metabolism are related to infant growth. Elias and Innis confirm with their analysis that dietary fatty acid intakes of pregnant women predict maternal plasma concentrations, which in turn are closely related to fatty acid concentrations in infant umbilical cord blood (3). Similarly, the dietary essential fatty acid intakes of lactating women modulate the supply to their breast-fed infants (11). Hence, the quality of maternal dietary fat consumption before and during pregnancy and lactation is of considerable importance for infants. Even though the observations presented by Rump et al and Elias and Innis do not provide conclusive evidence of the causal effects of fatty acids on early growth, they should encourage further experimental and clinical intervention studies under controlled conditions to help elucidate the effects of maternal lipid intakes and metabolism on pre- and postnatal growth and development. 📌

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