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Maternal-Fetal N-6 and N-3 Polyunsaturated Fatty Acids Gradient in Plasma and Red Cell Phospholipids

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Abstract: Fatty acid distribution was investigated in ethnically and economically homogenous Korean mothers (n = 40) and neonates. Venous blood, maternal before delivery and cord, was obtained. Choline (CPG) and ethanolamine (EPG) phosphoglycerides and sphingomyelin (SM) were assayed. Mean arachidonic acid (AA) level was higher in plasma CPG and SM ($p < 0.0001$), and red cell CPG ($p < 0.0001$), EPG ($p < 0.0001$) and SM ($p = 0.005$) of the neonates. Similarly, the neonates had higher proportions of docosahexaenoic acid (DHA) in plasma CPG ($p < 0.0001$) and red cell CPG ($p = 0.001$) and EPG ($p = 0.036$). In contrast, linoleic and alpha-linolenic acids were significantly higher in maternal blood. Mead acid was elevated in plasma CPG ($p < 0.0001$) and red cell CPG and EPG ($p < 0.0001$) of the neonates. Consistent with data from high-fat-intake populations, our subjects, whose traditional diet is low in fat, exhibited maternal-fetal gradient in AA and DHA in plasma and red cell phospholipids. This may be due to an imbalance between supply and maternal and fetal requirements, and/or a physiological response to pregnancy. Prenatal nutritional constraint is associated with impaired development and a risk of chronic diseases in adults. AA and DHA are vital nutrients. Hence, there is a need to investigate whether the discrepancy between maternal and neonatal AA and DHA is a manifestation of nutritional insufficiency.

Key words: Mothers, neonates, plasma, red cell, arachidonic acid, docosahexaenoic acid, choline phosphoglycerides, ethanolamine phosphoglycerides, sphingomyelin

Introduction

Maternal-fetal gradient in n-6 and n-3 fatty acids at birth has been reported in several studies [1, 2, 10, 23, 36]. In fetal plasma and red cells, the relative level of alpha-linolenic acid (ALA, 18:3n-3) is almost undetectable and linoleic acid (LA, 18:2n-6) is nearly half that of the mother. In contrast, the proportions of arachidonic (AA, 20:4n-6) and docosahexaenoic (DHA, 22:6n-3) acids are significantly higher in the fetus. These findings suggest that AA

and DHA are selectively transferred from maternal to fetal circulation to meet the high fetal demand for growth and development. Also, it indicate that there may be a discrepancy between requirement and fetal ability to synthesize these nutrients. Indeed, Koletzko et al [16] have estimated that endogenous synthesis constituted only about 23% of total plasma AA in human infants born at full term. Similarly, Leaf et al [17] have observed a one-third reduction in the relative proportion of AA despite a three-fold increase in the precursor LA in plasma of pre-term neonates between birth and three weeks of age.

Insufficient supply of essential fatty acids during pregnancy would be expected to have a profound adverse effect on fetal growth and development. Intrauterine-growth-restricted neonates [35] and those with low birth weight and small head circumference [6, 17] have reduced levels of AA and DHA at birth. Moreover, Zhang [37] has reported a marked increase in bi-parietal diameter and weight gain in intrauterine-growth-restricted fetuses treated with LA and ALA preparation. In most of the comprehensive studies of fatty acids in pregnancy, the subjects were predominantly Caucasian or non-Caucasian with Western dietary habits – high intake of saturated and total fat. In addition, fatty acid composition of heterogeneous components – total phospholipids or lipids, was assayed. Consequently, it is yet to be established if maternal-fetal gradient in n-6 and n-3 fatty acids is manifested in communities with a distinct ethnic background and dietary habits, and in the different phospholipid classes.

We have investigated relative fatty acid composition of plasma choline phosphoglycerides and sphingomyelin, and red cell choline and ethanolamine phosphoglycerides and sphingomyelin in ethnically and economically homogeneous pregnant Korean women and neonates.

Materials and Methods

Subjects and sample collection: Healthy, non-smoking, middle-class Korean women were recruited (n = 40) between 37 and 42 weeks of gestation on admission for delivery to the Asan Medical Centre, Seoul, South Korea. The women were aged between 23–38 years (mean age = 29.1), had no obstetric complications, and all delivered at term.

Blood specimens, maternal before delivery and cord (venous), were obtained. Plasma and red cells were separated by cold centrifugation at 1000 g for 15 min, stored at –70°C, and subsequently transported to London in dry ice for analysis. Approval was obtained from the Ethics Committee of the Asan Medical Centre.

Fatty acid analysis: Plasma and red cell total lipids were extracted by the method of Folch et al [9] by homogenizing the samples in chloroform and methanol (2:1 v/v) containing 0.01% butylated hydroxytoluene (BHT) under nitrogen. Phospholipids were separated by thin-layer chromatography on silica plates using the developing solvents-chloroform:methanol:water (60:30:4) – containing 0.01% BHT. Bands were detected by spraying with 2,7-dichlorofluoroscein and visualized under ultraviolet (UV) light. Fatty acid methyl esters (FAMEs) were prepared by heating the lipid extract with 4 mL of 15% acetyl chloride in methanol in a sealed tube at 70°C for 3 hours under nitrogen. FAMEs were separated by a gas chromatograph (HRGC MEGA 2 series, Fisons Instruments, Milan, Italy) fitted with a capillary column (25 m $\times$ 0.32 mm ID, 0.25 μ film, BP20). Hydrogen was used as a carrier gas, and the injector, oven and detector temperatures were 235, 210 and 260°C, respectively. The FAMEs were identified by comparison of retention times with authentic standards (Sigma-Aldrich Co. Ltd., UK) and calculation of equivalent chain-length values. Peak areas were quantified by a computer chromatography data system (EZChrom Chromatography Data System, Scientific Software Inc., San Ramon, CA).

Data Analyses: Results are expressed as mean ± standard deviation. The difference in mean fatty acid composition between the mothers and neonates was compared by paired t-test using a statistical computer package, SPSS for Windows, Version 9.

Results

Of the forty babies, twenty-three were boys and seventeen were girls. There was no gender difference in weight, length, head-circumference or blood fatty acid composition ($p > 0.05$).

Mean fatty acid composition of plasma choline (Plasma CPG) and red cell choline (RBC CPG), and ethanolamine (RBC EPG) phosphoglycerides of the neonates, and plasma and red cell sphingomyelin (SM) of the mothers and neonates are shown in Tables I and II respectively. Demographic and anthropometric data, and fatty acids of maternal plasma CPG, and red cell CPG and EPG have been reported previously [11].

Plasma choline phosphoglycerides: The proportions of stearic (18:0), arachidic (20:0), dihomo-gamma-linolenic (DHGLA, 20:3n-6), Mead acid (20:3n-9), AA, adrenic (22:4n-6), DHA, Σ n-6 metabolites, Σ n-3 metabolites ($P < 0.0001$), palmitoleic (16:1n-7) ($p = 0.006$), and Σ n-3 ($p = 0.001$) were significantly higher in the neonates. In contrast, palmitic (16:0), LA, ALA, docosapentaenoic

Table I: Mean (± SD) percent fatty acid composition of plasma choline and red cell choline and ethanolamine phosphoglycerides of neonates (n = 40)

Fatty acids	Plasma CPG	Red cell CPG	Red cell EPG
14:0	0.43 ± 0.26	0.41 ± 0.08	0.23 ± 0.07
16:0	30.1 ± 1.8	29.0 ± 2.3	20.0 ± 1.6
18:0	14.6 ± 0.9	20.3 ± 1.3	5.95 ± 0.86
20:0	0.09 ± 0.04	0.11 ± 0.02	0.07 ± 0.05
22:0	tr	0.11 ± 0.05	0.19 ± 0.08
24:0	tr	0.31 ± 0.23	0.70 ± 0.61
16:1n-7	1.15 ± 0.19	1.15 ± 0.26	0.76 ± 0.47
18:1n-9	10.2 ± 1.1	12.5 ± 1.5	11.5 ± 1.2
20:1n-9	0.09 ± 0.04	0.12 ± 0.05	0.18 ± 0.04
24:1n-9	0.08 ± 0.05	1.15 ± 0.26	0.28 ± 0.18
18:2n-6	8.20 ± 1.3	6.07 ± 0.71	1.88 ± 0.28
18:3n-6	0.12 ± 0.04	0.09 ± 0.02	0.07 ± 0.20
20:2n-6	0.33 ± 0.07	0.28 ± 0.06	0.24 ± 0.20
20:3n-6	5.30 ± 0.79	1.49 ± 0.28	1.61 ± 0.34
20:4n-6	15.6 ± 1.8	13.3 ± 1.7	19.7 ± 1.5
22:4n-6	0.51 ± 0.09	1.58 ± 0.29	5.63 ± 0.82
22:5n-6	0.72 ± 0.30	1.39 ± 0.32	1.72 ± 0.38
18:3n-3	0.06 ± 0.05	0.03 ± 0.02	0.07 ± 0.06
20:5n-3	0.67 ± 0.26	0.34 ± 0.12	0.41 ± 0.15
22:5n-3	0.49 ± 0.17	0.59 ± 0.16	1.15 ± 0.29
22:6n-3	6.80 ± 1.2	6.16 ± 1.31	9.40 ± 1.52
20:3n-9	0.52 ± 0.20	0.39 ± 0.12	1.04 ± 0.24
Σ Saturate	45.2 ± 1.6	50.2 ± 1.9	26.8 ± 2.6
Σ Monoene	11.5 ± 1.2	13.9 ± 1.7	12.6 ± 1.5
Σ n-6	30.9 ± 2.0	26.2 ± 2.0	30.8 ± 1.8
Σ n-3	7.98 ± 1.3	7.08 ± 1.5	11.0 ± 1.7
Σ n-6 metabolites	22.7 ± 1.8	20.2 ± 2.1	28.9 ± 1.8
Σ n-3 metabolites	7.96 ± 1.32	7.08 ± 0.24	11.0 ± 1.7

tr trace

acid (DPA, 22:5n-3), and Σ n-6 were higher ($p < 0.0001$) in the mothers. There were no differences in Σ saturates and monoenes ($p > 0.05$) between the mothers and babies.

Red cell choline phosphoglycerides: In the red cell CPG, the mothers had higher levels of myristic (14:0) ($p = 0.005$), palmitic ($p = 0.012$), oleic (18:1n-9) ($p = 0.003$), behenic (22:0), gondoic (20:1n-9), lignoceric (24:0), nervonic (24:1n-9) acids ($p < 0.0001$) and Σ monoenes ($p = 0.001$), and lower stearic ($p = 0.003$) and Mead acid ($p < 0.0001$) levels compared to their neonates. Of the n-6 family, LA, eicosadienoic acid (20:2n-6), and DHGLA ($p < 0.0001$) were higher and AA, adrenic and osbond (22:5n-6) acids, and Σ n-6 metabolites ($p < 0.0001$) were lower in the mothers. With the exception of DHA ($p = 0.001$) and Σn-3 metabolites ($p = 0.03$), the levels of the other n-3 fatty acids – ALA ($p = 0.001$), eicosapentaenoic acid (EPA, 20:5n-3) ($p = 0.005$) and DPA ($p < 0.0001$) – were higher in the mothers compared to their neonates.

Red cell ethanolamine phosphoglycerides: As with the plasma and red cell CPG, the neonates had reduced levels of LA, ALA, eicosadienoic acid, EPA, and DPA (Pp < 0.0001) and elevated Mead acid, DHGLA, AA, adrenic, osbond, Σn-6, Σn-6 metabolites ($p < 0.0001$), and DHA ($p = 0.036$). In addition, the proportions of myristic ($p = 0.004$), stearic, behenic, oleic, Σ monoenes ($p < 0.0001$), and Σ saturates ($p = 0.008$) were lower in the neonates.

Plasma sphingomyelin: In plasma SM, total saturates and monoenes comprised 68.9 and 17.4%, in the mothers and 68.5 and 16.4%, in the neonates. In contrast, total n-6 and n-3 fatty acids accounted for less than 7% and 1.2% in both groups. The neonates had significantly higher stearic, arachidic, AA ($p < 0.0001$), DHGLA ($p = 0.008$), and lignoceric ($p = 0.001$), and lower palmitic ($p < 0.0001$) and nervonic ($p = 0.001$) acids compared with the mothers.

Red cell sphingomyelin: Similar to the plasma SM, the red cell SM of the mothers and neonates were mainly composed of saturates (71.9 and 81.9%) and monoenes (20.4 and 13.1%), respectively. Total n-6 and n-3 comprised less

Table II: Mean (± SD) percent fatty acid composition of plasma and red cell sphingomyelin of mothers and neonates (n = 40)

	Plasma		Red cell	
Fatty acids	Mothers	Neonates	Mothers	Neonates
14:0	1.44 ± 1.10	0.88 ± 0.30	1.50 ± 0.72	1.12 ± 0.31
16:0	38.9 ± 2.8	30.2 ± 2.9	31.2 ± 3.0	39.9 ±5.2
18:0	10.5 ± 2.4	16.0 ± 2.5	12.4 ± 4.4	16.3 ± 2.8
20:0	3.49 ± 0.56	4.89 ± 0.96	1.44 ± 0.20	2.40 ± 0.26
22:0	8.68 ± 1.61	8.35 ± 1.92	6.82 ± 0.85	5.26 ± 0.86
24:0	5.84 ± 0.98	8.18 ± 2.40	18.6 ± 2.7	16.9 ± 3.7
16:1n-7	0.96 ± 0.72	1.07 ± 0.40	0.33 ± 0.19	tr
18:1n-9	4.39 ± 2.36	5.56 ± 2.03	2.90 ± 1.18	1.55 ± 0.59
24:1n-9	12.1 ± 2.2	9.80 ± 2.32	17.2 ± 3.2	11.4 ± 2.5
18:2n-6	5.29 ± 2.76	3.22 ± 2.12	0.92 ± 0.28	0.53 ± 0.22
20:3n-6	0.40 ± 0.20	0.91 ± 0.43	tr	tr
20:4n-6	1.21 ± 0.41	3.31 ± 1.83	0.64 ± 0.24	087 ± 0.30
22:6n-3	0.88 ± 0.38	1.11 ± 0.50	0.59 ± 0.15	0.70 ± 0.29
Σ Saturate	68.9 ± 5.7	68.5 ± 6.1	71.9 ± 4.4	81.9 ± 3.1
Σ Monoene	17.4 ± 3.3	16.4 ± 3.0	20.4 ± 2.7	13.1 ± 2.3
Σ n-6	6.92 ± 3.0	7.00 ± 4.46	2.19 ± 0.50	1.81 ± 0.51
Σ n-3	0.99 ± 0.48	1.07 ± 0.51	0.63 ± 0.16	0.70 ± 0.29

tr trace

than 3 and 1% in the mothers and neonates. With the exception of palmitic acid, which was higher in the neonates ($p < 0.0001$), the contrast in the levels of the other fatty acids between the mothers and babies was similar to plasma SM.

Discussion

The mothers in this study were ethnically homogenous and their habitual diet was low in fat and high in carbohydrate. According to the Korean National Dietary Survey [19], carbohydrate, fat and protein provide 65, 18 and 16% of the daily energy intake, respectively.

There was maternal-fetal gradient in the relative levels of palmitic, stearic, Mead, and the n-6 and n-3 fatty acids in both plasma and red cell phosphoglycerides. Previous studies [1, 2, 23, 28, 33] have reported higher levels of AA and DHA in neonates compared with their mothers in Caucasians and non-Caucasians with a Western dietary habit. Consistent with these studies, our data reveal a contrasting fatty acid distribution between mothers and neonates in this population with a low-fat diet.

There is evidence that maternal supplementation with fish oil enhances maternal and fetal DHA status [5, 34]. Genetic influence on relative fatty acid levels in neonates has also been postulated [14]. The extent to which maternal-fetal fatty acid gradient is influenced by diet or genetic background is not understood. Low maternal fatty acid status and/or pregnancy-induced physiological response may provide an explanation for the contrast in the levels of the n-6 and n-3 fatty acids between the mothers and neonates.

The maternal-fetal distribution of fatty acids was both fatty acid-specific and phospholipid-specific. Levels of palmitic acid were lower in plasma CPG and SM and red cell CPG, and higher in red cell SM of the neonates. Whereas, the proportion of stearic acid was higher in plasma and red cell CPG and SM and lower in red cell EPG. This may be a reflection of the difference in the incorporation of fatty acids into maternal and neonatal phospholipids.

This study provides an indication that the placenta and/or the fetus may handle the n-6 and n-3 fatty acids differently. Invariably, there were higher levels of DGLA, AA and adrenic and osbond acids in plasma and red cell phosphoglycerides of the neonates. In contrast, with the exception of DHA, the proportions of the n-3 metabolites (EPA and DPA) were consistently lower. The fetal/maternal n-6 metabolite ratios in plasma CPG and red cell CPG and EPG were 1.8, 1.7 and 1.7 and the corresponding values for the n-3 metabolites were 1.1, 1.2 and 1.0, respectively. The fetus and neonate can synthesize DHA [4, 7, 26] and there is a high demand for this fatty acid during the latter part of pregnancy and early infancy. Nevertheless, the higher levels of EPA and DPA in the mothers indicate that these precursors of DHA may not be favorably transferred to the fetus. It is conceivable that the synthesis of DHA from EPA and DPA may be inefficient in the fetus. This would necessitate the retention of both EPA and DPA in maternal circulation for DHA synthesis and subsequent transfer to the fetus.

Mead acid, which is a biochemical marker of a generalized shortage of derived and parent essential fatty acids (EFAs) [13], was consistently higher in plasma and red cell CPG and red cell EPG of the neonates. Also, the neonates had higher levels of total n-6 and n-3 fatty acids in red cell CPG and EPG. There is no obvious explanation for this paradox. However, Holman et al [12] have argued that deficiency of n-6 and n-3 polyunsaturated fatty acids in pregnancy is distinct from a simple nutritional deficiency of essential fatty acids and may not lead to an increase in the level of Mead acid. Ghebremeskel et al [11] have postulated that Mead acid synthesized in response to low maternal EFA status may be transferred to the fetus. If this proposition is correct, the elevated level of Mead acid in cord blood would be indicative of maternal and fetal EFA insufficiency.

A high level of Mead acid has been reported in umbilical artery wall [6, 15, 21]. This was attributed to EFA deficiency of the umbilical vessels [15] and the fetus [6]. However, Sanders and Reddy [30] have stated that the presence of Mead acid in cord artery phospholipids is a manifestation of high activity of the conversion system in the arterial wall rather than EFA deficiency. These authors have not provided evidence for enhanced synthesis of Mead acid in arterial wall.

Although SM constitutes between 25–30% of red cell membrane total phospholipids [32] and about 8% of total myelin lipid [18], there are no published comparative data of SM fatty acid composition of mothers and fetus or of fetal plasma and red cells. Nevertheless, our results were broadly similar to the values reported for adults [8, 24, 27] and pre-term [3] and term [25] neonates.

Nervonic acid level in SM is thought to reflect brain maturation and there is a concordance in the proportions of the fatty acid in red cell and brain SM [3]. In both the brain and red cells, a simultaneous increase in nervonic acid occurs between gestation week 34 and postnatal age year four [3]. This synchrony would not be expected to occur if the fatty acid supply to these tissues originates from different pools. Ruyle et al [28] have postulated that fetal erythrocytes play an important role in the transport of EFA to the developing tissues. If this is the case, red cell SM may be the primary source of long-chain saturates and monounsaturates for the brain during the fetal and neonatal period. This may explain for the higher level of lignoceric and nervonic acids in red cell SM of both the mothers and neonates compared to the values in the corresponding phospholipid in plasma.

The striking finding of the study was the level of AA in the neonates. Compared to that in the mothers, it was higher by 96, 65 and 58% in plasma CPG and red cell CPG and EPG, respectively. The corresponding increase in DHA was only 27, 29 and 14%. From these data, it would be legitimate to suggest that the fetus may a have preferential and enhanced requirement for AA at this stage of its development. This should not be surprising since AA is a major component of the endothelium, and vascular expansion and integrity is a priority for the development and function of tissues including the brain.

The high level of AA in the neonates relative to the mothers raises a pertinent question with regard to maternal supplementation during pregnancy. In both high-risk and healthy pregnancies, the main focus of supplementation has been the n-3 metabolites, specifically DHA [5, 20, 22, 29, 34]. There has not been comparable published data based on AA and DHA supplementation. Sattar et al [31] have remarked that the exclusion of AA in randomized trials during pregnancy may be flawed and that future supplementation regimens should contain higher amounts of DHA relative to EPA and adequate quantities of AA. As supplementation trials that exclude either of the two fatty acid families do not reflect the natural condition, we endorse the view of the above authors.

Conclusions

The present data suggest that lower levels of AA and DHA in maternal blood may not be restricted to any ethnic group or a community with a high intake of saturated fat. This phenomenon could be a physiological response to pregnancy and/or a manifestation of an imbalance between maternal supply, and maternal and fetal requirements. The high level of Mead acid in cord blood points to the latter. Experimental and epidemiological evidence demonstrate that nutritional constraint *in utero* is associated with impaired post-natal development and increased risk of chronic diseases in adults. AA and DHA are vital structural components of the neural, vascular and visual systems. Hence, there is a need to establish whether the discrepancy between maternal and fetal AA and DHA levels is a manifestation of nutritional insufficiency.

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