

The effect of severe pre-eclampsia on maternal and cord erythrocyte membrane essential fatty acid profiles

G F Kirsten, C M Smuts, H Y Tichelaar, J Smith, D Hall, M Faber, M A Dhansay

Objective. To examine the effect of severe pre-eclampsia on maternal and cord erythrocyte membrane essential fatty acid profiles.

Design. Clinical trial.

Setting. Obstetric High Care Unit, Tygerberg Hospital.

Patients. Erythrocyte membrane (EM) essential fatty acid profiles were determined in 17 women with severe pre-eclampsia, in 17 normotensive pregnant women, and in the cord blood of their respective infants.

Results. Pre-eclamptic women had lower EM phosphatidylcholine linoleic acid (C18:2n-6; LA) and α -linolenic acid (C18:3n-3; ALA) levels and lower EM phosphatidylethanolamine ALA levels than the normotensive women with lower cord blood docosahexaenoic acid levels (C22:6n-3; DHA) in both phospholipid fractions. All cord blood arachidonic acid (C20:4n-6; AA) levels were higher than the maternal levels.

Conclusions. Pre-eclamptic women have lower LA and ALA levels than normotensive pregnant women, but AA and DHA levels in the two groups are similar. The cord blood DHA levels of infants of pre-eclamptic women are lower than those of the infants of normotensive women. Infants born to pre-eclamptic women may need dietary DHA to replenish DHA stores. This can be obtained from breast-milk or from a formula enriched with DHA.

S Afr Med J 1998; **88**: 626-629.

Essential fatty acid (EFA) metabolites are transported to fetal tissues by erythrocytes, and their profiles in the erythrocyte membrane (EM) reflect the adequacy of placental transport.¹ In the event of impaired placental function, as occurs in severe pre-eclampsia, the maternal plasma and EM levels of linoleic acid (C18:2n-6; LA) and α -linolenic acid (C18:3n-3; ALA) are reduced.^{2,3} The reason for this is not completely understood. LA and ALA may be more rapidly metabolised through an elongation and desaturation process to ensure an adequate supply of their metabolites to the fetus.^{3,4}

The EFAs LA and ALA are indispensable for optimal fetal brain and retinal development.^{5,6} The fetus is unable to synthesise these fatty acids and depends on maternal intake.^{5,6} Although premature infants are capable of biosynthesising docosahexaenoic acid (C22:6n-3; DHA) from ALA, the amounts of DHA produced may be inadequate for optimal neural development.⁷ ALA in particular is essential for optimal retinal and brain development because of its long-chain polyunsaturated fatty acid metabolite, DHA.^{5,6,8} Selective biomagnification of metabolites from EFAs occurs from the maternal to the fetal circulation, which favours arachidonic acid (C20:4n-6; AA) and DHA.^{1,6} This results in high fetal levels of AA and DHA and low fetal levels of LA and ALA compared with maternal levels.^{6,8} This supply of selected EFA metabolites (namely AA and DHA) to the fetus is necessary for normal brain and retinal development.^{1,5,6,8} Transplacental passage of EFAs and their metabolites occurs mainly during the third trimester.^{6,8,9} Infants born prematurely have higher AA and DHA status when fed human milk.¹⁰ Generally, preterm formulas and parenteral lipid emulsions do not contain AA and DHA.

The objective of this study was to determine the impact of severe pre-eclampsia on the maternal EM EFA and EFA metabolite profiles of affected women and their infants at birth.

Patients and methods

Seventeen infants of women of mixed racial descent with severe pre-eclampsia who delivered before 34 weeks' gestation were matched with infants of 17 normotensive women, also of mixed racial descent and with onset of labour before 34 weeks' gestation. The women were approached regarding participation on admission to hospital but were only included in the study if they delivered between Monday and Friday, because blood samples could not be processed over weekends. Dietary information was not obtained from the women. The diagnosis of severe pre-eclampsia was defined as follows: (i) maternal blood pressure exceeding 180/120 mmHg on at least two occasions at least 30 minutes apart with 2+ or more proteinuria (Multistix; Ames) during the initial 24 hours after admission; or (ii) a blood pressure of 160/110 - 180/120 mmHg on two occasions at least 6 hours apart with 2+ or more proteinuria; or (iii) a blood pressure of 150/100 - 160/110 mmHg on two occasions at least 6 hours apart and 3+ or more proteinuria; or (iv) a blood pressure of 140/90 mmHg or more with proteinuria and clinical signs of imminent eclampsia (epigastric pain, severe headache, visual disturbances, nausea, brisk reflexes) before 34 weeks' pregnancy duration.¹¹

Departments of Paediatrics and Obstetrics and Gynaecology, Tygerberg Hospital, Tygerberg, W Cape

G F Kirsten, MMed (Paed), FCP (SA), MD

J Smith, MMed (Paed)

D Hall, MMed (O&G), MCOG (SA)

National Research Programme for Nutritional Intervention, Medical Research Council, Tygerberg, W Cape

C M Smuts, PhD

H Y Tichelaar, MSc

M Faber, MNutr

M A Dhansay, MMed (Paed), FCP (SA)

The women with pre-eclampsia were monitored in the Obstetric High Care Unit at Tygerberg Hospital until 34 weeks' gestation was reached unless maternal or fetal indications necessitated earlier delivery.

At the time of delivery, 2 ml venous blood was obtained from the mother and cord blood from the umbilical vein immediately after clamping, and the blood was transferred to a tube containing citrate as anticoagulant. Erythrocytes were obtained by centrifugation and then resuspended in 2 ml saline (0.9% sodium chloride) and stored at -70°C for a maximum of 2 weeks until analysis. EMs were prepared by haemolysing erythrocytes with various phosphate buffers.^{12,13} Lipids were extracted from EMs with chloroform/methanol (2:1 v/v), separated by thin-layer chromatography and analysed for fatty acid composition of EM phosphatidylcholine (PC) and phosphatidylethanolamine (PE) by gas-liquid chromatography.^{14,15} A model 3700 Varian gas-liquid chromatograph using fused silica megabore DB-225 columns (J & W Scientific, Cat. No. 125-2232) was used. Gas flow rates were as follows: hydrogen (carrier gas), 5 - 8 ml/min; medical air, 250 ml/min; and hydrogen, 25 ml/min. Temperature programming was linear at $3^{\circ}\text{C}/\text{min}$, initial temperature was 165°C , final temperature was 220°C , injection temperature was 240°C , and detector temperature was 250°C . A fatty acid mixture standard was prepared from individual fatty acids (Sigma, St Louis, Mo., USA). Fatty acid methyl esters of PC and PE were identified by comparison of the retention times with those of the standard mixture of free fatty acids from 14:0 to 22:6 ω 3. The PC fraction may have included some phosphatidylinositol (PI) and phosphatidylserine (PS), because of the close proximity of these two fractions to PC after TLC separation. Gestational age was calculated by using menstrual history, antenatal ultrasound before 20 weeks' gestation or gestational assessment according to the new Ballard score.¹⁶ Informed consent was obtained from each woman on study entry. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Stellenbosch.

All values were expressed as the mean and standard deviation (SD). Statistical differences of the clinical

characteristics and maternal and cord blood fatty acid levels between the normotensive women and the women with pre-eclampsia and their infants were determined using the Wilcoxon two-sample test. The differences between the maternal and cord blood EFA levels within each group (pre-eclamptic and normotensive) were determined using the Wilcoxon sign rank test for paired data. The χ^2 -test was used to determine any difference in the distribution of small-for-gestational-age (SGA) infants between the normotensive and pre-eclamptic groups.

Results

Maternal and infant characteristics are shown in Table I. None of the clinical characteristics were significantly different between the pre-eclamptic and the normotensive women, or between their infants.

Table I. Maternal and infant characteristics (mean (SD))

	Pre-eclampsia (N = 17)	Normotensive (N = 17)	Significance (P-value)*
Maternal characteristics			
Age (yrs)	29.3 (5.1)	28.3 (6.1)	0.6784
Gravidity	2.9 (1.8)	2.2 (0.9)	0.6786
Parity	1.5 (1.2)	1.1 (0.8)	0.4895
Infant characteristics			
Birth weight (g)	1168.8 (236.2)	1450.9 (504.0)	0.0516
Gestation (wks)	29.7 (2.2)	30.9 (2.3)	0.1449
Small for gestational age (%)	58.8	52.9	0.730

*Wilcoxon two-sample test.

Table II compares the EM PC fatty acid composition of the women with pre-eclampsia and the cord blood of their infants with those of the normotensive women and their infants. LA and ALA levels were lower in the EMs of the women with pre-eclampsia ($P < 0.01$). Their metabolic n-6 and n-3 end products were, however, not affected. This was reflected by the higher ($P < 0.05$) indices of n-6 desaturation

Table II. EM PC fatty acid composition (%) of pre-eclamptic and normotensive women and their respective cord bloods at delivery (mean (SD))

	Maternal blood		Cord blood		Maternal v. cord	
	Pre-eclampsia (N = 17)	Normotensive (N = 17)	Pre-eclampsia (N = 17)	Normotensive (N = 17)	Pre-eclampsia P-value	Normotensive P-value
n-6 fatty acids						
LA	14.04 ^a (1.68)	15.46 ^b (1.49)	7.37 (2.74)	6.60 (1.51)	0.0001	0.0001
AA	10.41 (1.51)	9.99 (1.85)	16.12 (2.36)	16.28 (3.09)	0.0001	0.0001
Σ n-6	27.18 (2.03)	28.19 (2.04)	28.00 (2.81)	28.01 (4.44)	0.1594	0.8536
Index of n-6 desaturation*	0.95 ^a (0.19)	0.83 ^a (0.18)	3.01 (0.67)	3.38 (0.95)	0.0001	0.0001
n-3 fatty acids						
ALA	0.68 ^a (0.23)	1.09 ^b (0.05)	0.54 (0.24)	0.80 (0.46)	0.0315	0.0500
EPA	0.29 (0.22)	0.39 (0.39)	0.23 (0.26)	0.20 (0.24)	0.0942	0.0536
DPA	0.99 (0.43)	0.95 (0.49)	0.32 (0.37)	0.12 (0.23)	0.0002	0.0002
DHA	6.49 (1.62)	5.70 (1.29)	5.40 (1.35)	5.55 (1.77)	0.0038	0.5710
Σ n-3	8.45 (2.12)	8.13 (1.61)	6.49 (1.71)	6.67 (1.67)	0.0005	0.0395
Index of n-3 desaturation†	12.73 ^a (5.21)	8.22 ^a (5.03)	13.69 (7.20)	9.91 (5.44)	0.5791	0.3529

Significant difference (Wilcoxon sign rank test for paired data): ^aP < 0.05; ^bP < 0.01.

* Σ n-6/LA.

† Σ n-3/ALA.

(Σ n-6/LA) and n-3 desaturation (Σ n-3/ALA) in EMs of the women with pre-eclampsia compared with the normotensive women. LA levels were lower and AA levels higher ($P = 0.0001$) in the cord blood of all the infants compared with the maternal levels. ALA ($P < 0.05$) and docosapentaenoic acid (C22:5n-3; DPA; $P = 0.0002$) levels were lower in all the infants compared with their maternal bloods. DHA levels were lower only in the cord blood of infants born to the women with pre-eclampsia ($P = 0.0038$).

Table III compares the EM PE fatty acid composition of the women with pre-eclampsia and the cord bloods of their infants with that of the normotensive women and their infants. Maternal ALA was the only fatty acid level that was lower ($P < 0.01$) in the EMs of the women with pre-eclampsia than in the EMs of the normotensive women. This was reflected by the higher n-3 index ($P < 0.05$) of the EMs of the women with pre-eclampsia. LA levels were lower and AA levels higher ($P = 0.0001$) in the cord blood of all the infants when the cord blood and maternal levels were compared. This was also reflected by higher total n-6 fatty acids and the higher n-6 indices. Compared with maternal fatty acids, eicosapentaenoic acid (C20:5n-3; EPA) and DPA levels were lower in the cord blood of all the infants ($P = 0.0001$). DHA levels were lower only in the cord blood of the women with pre-eclampsia ($P = 0.0079$).

Discussion

This study showed that LA and ALA levels in women with pre-eclampsia are lower than in normotensive pregnant women.^{2,4} However, despite the lower levels of LA and ALA in the pre-eclamptic women, the levels of their respective metabolites, AA and DHA, are similar to those of normotensive pregnant women. The findings in pre-eclamptic women reported by Al *et al.*⁵ and Wang *et al.*⁴ of lower EPA and higher DHA levels, respectively, were not confirmed by this study.

Conflicting EFA and EFA metabolite levels have been reported for women with pre-eclampsia. Van der Schouw *et*

*al.*³ reported reduced plasma LA levels but normal ALA levels in pre-eclamptic compared with normotensive pregnant women, while Ogburn *et al.*¹⁷ and Williams *et al.*¹⁸ noted increased plasma and EM AA levels, respectively, in women with pre-eclampsia when compared with normotensive controls.

The reasons for the reduced LA and ALA levels in women with pre-eclampsia are unknown. Wang *et al.*⁴ suggested that LA and ALA are metabolised more rapidly to their metabolites as well as prostanooids and leukotrienes via the cyclo-oxygenase/lipo-oxygenase pathways in pre-eclamptic women. Van der Schouw *et al.*³ argue that a higher fetal demand for n-6 EFA metabolites results in more active elongation and desaturation processes during pre-eclampsia to compensate for a less efficient placental transfer of the n-6 EFA metabolites. The placental infarctions and obliteration of tertiary villi associated with pre-eclampsia may result in a decreased transfer of the EFA metabolites to the fetus.^{19,20} A shortcoming of this study was the unavailability of a dietary history. Van Jaarsveld *et al.*²¹ found low ALA levels in pregnant women with low-birth-weight infants from a mixed racial background in the Western Cape.

The EM LA and AA levels found in women with pre-eclampsia and normotensive women and in cord blood in the present study are consistent with those previously reported, viz. lower LA and higher AA levels in neonates.^{1,6} We did not detect any difference in the AA levels in either normotensive women or those with pre-eclampsia compared with their infants. In both groups the AA levels in the cord EMs were 1.5 times higher than the maternal levels. The n-6 PC desaturase index was, however, significantly higher in the women with pre-eclampsia in the present study. This supports the presence of a more active desaturase process in these women, ensuring an adequate transfer of AA to their fetuses.

In contrast to the high cord EM AA levels, the DHA levels of infants of women with pre-eclampsia were significantly lower than the DHA levels in their mothers, while no significant reduction in EM DHA levels occurred in the normotensive infants compared with those of their mothers.

Table III. EM PE fatty acid composition (%) of pre-eclamptic and normotensive women and their respective cord bloods at delivery (mean (SD))

	Maternal blood		Cord blood		Maternal v. cord	
	Pre-eclampsia (N = 17)	Normotensive (N = 17)	Pre-eclampsia (N = 17)	Normotensive (N = 17)	Pre-eclampsia P-value	Normotensive P-value
n-6 fatty acids						
LA	6.37 (1.41)	6.98 (1.33)	3.37 (1.58)	2.97 (0.65)	0.0001	0.0001
AA	18.02 (2.14)	17.41 (2.08)	25.25 (3.36)	25.83 (3.50)	0.0001	0.0001
Σ n-6	29.78 (3.49)	29.40 (2.99)	36.82 (4.54)	37.36 (4.82)	0.0001	0.0002
Index of n-6 desaturation*	3.87 (1.09)	3.33 (0.78)	11.05 (3.05)	12.09 (2.99)	0.0001	0.0001
n-3 fatty acids						
ALA	1.06 [†] (0.47)	1.74 [‡] (0.80)	1.16 (0.78)	1.64 (1.12)	0.0926	0.7915
EPA	1.16 (0.89)	1.43 (0.80)	0.41 (0.44)	0.24 (0.31)	0.0001	0.0001
DPA	2.67 (1.05)	2.81 (1.05)	0.72 (0.92)	0.50 (0.67)	0.0001	0.0001
DHA	10.30 (2.62)	10.34 (2.07)	8.58 (2.01)	8.77 (2.33)	0.0079	0.0638
Σ n-3	15.19 (3.98)	16.32 (3.02)	10.86 (2.49)	11.15 (2.50)	0.0002	0.0005
Index of n-3 desaturation [†]	15.91 [‡] (7.25)	10.60 [‡] (6.24)	12.42 (8.06)	9.04 (5.99)	0.0638	0.6441

Significant difference (Wilcoxon sign rank test for paired data): * $P < 0.05$; [†] $P < 0.01$.

* Σ n-6/LA.

[†] Σ n-3/ALA.

The significantly higher index of n-3 desaturation of the women with pre-eclampsia compared with the normotensive pregnant women supports the presence of a more active n-3 desaturation process in the presence of pre-eclampsia to compensate for reduced placental transfer of DHA to the fetus. Despite the increased production of DHA, as indicated by the raised index of n-3 desaturation, the DHA levels in cord blood of the infants of the women with pre-eclampsia were significantly lower than the DHA levels in their mothers. Felton *et al.*²⁰ reported decreased DHA but normal AA phospholipid umbilical vein wall levels in growth-retarded small-for-gestational age infants compared with appropriately grown infants; they considered that this was probably due to an impaired placental supply of EFAs.²⁰

DHA is essential for the development and functioning of the retina and central nervous system of the fetus and neonate.^{22,23} The rate of DHA accretion in the fetal brain and retina is very high during the phase of rapid brain growth that occurs from the 26th week of gestation until the first few months after birth.²³⁻²⁵ Preterm infants born during the early third trimester of pregnancy are deprived of EFAs and their metabolites.^{1,9} EM DHA levels also reflect the availability of DHA in neural tissue phospholipids with erythrocyte DHA depletion preceding changes in brain DHA.^{1,22} Infants born to normotensive women before 32 weeks' gestation have lower concentrations of PE DHA in brain, liver and erythrocytes than do infants born at term.^{9,26,27} The infants born to women with pre-eclampsia in the present study were delivered at a mean of 29.7 weeks' gestation. Their low cord EM DHA levels relative to the maternal EM DHA levels imply a reduced EFA metabolite uptake over a period of 2 - 3 months compared with the normotensive infants. The high prevalence of SGA infants in the normotensive group is probably due to the inclusion of constitutionally small infants in this group.

A diet rich in DHA during the first few months after birth may provide for normal brain DHA accumulation in very-low-birth-weight infants born to pre-eclamptic women.^{9,10} This can be achieved by feeding them breast-milk, which contains both AA and DHA.¹ A high dietary intake of DHA in the form of fish by lactating women increases the DHA content of their breast-milk.²⁸⁻³⁰ Preterm formulas are rich in LA and ALA, but preterm infants have a limited ability to transform these substrates into DHA and ALA.^{8,23} If a preterm formula is used, it should be ascertained whether it is enriched with DHA and AA. Currently, parenteral lipid emulsions contain none of the EFA metabolites, underscoring the importance of early enteral intake of DHA and AA.³¹⁻³²

Although preliminary findings on the prevention of severe pre-eclampsia by supplementation with marine oil during pregnancy need to be substantiated,^{33,34} such supplementation could possibly reduce the severity of pre-eclampsia and simultaneously supply DHA to the developing fetal brain and retina.⁶ This supplementation could be continued during lactation.

REFERENCES

- Ruyle M, Connor WE, Anderson GJ, Lowensohn RI. Placental transfer of essential fatty acids in humans: Venous-arterial differences for docosahexaenoic acid in fetal umbilical erythrocytes. *Proc Natl Acad Sci USA* 1990; **87**: 7902-7906.
- Al MD, van Houweling AC, Badart-Smook A, Hasaart TH, Roumen FJ, Hornstra G. The essential fatty acid status of mother and child in pregnancy-induced hypertension: A prospective longitudinal study. *Am J Obstet Gynecol* 1995; **172**: 1605-1614.

- Van der Schouw YT, Al MD, Hornstra G, Bulstra-Ramakers MTEW, Huisjes HJ. Fatty acid composition of serum lipids of mothers and their babies after normal and hypertensive pregnancies. *Prostaglandins Leukot Essent Fatty Acids* 1994; **44**: 247-252.
- Wang Y, Kay MH, Killem AP. Decreased levels of polyunsaturated fatty acids in preeclampsia. *Am J Obstet Gynecol* 1991; **164**: 812-818.
- Crawford MA. The role of essential fatty acids in neural development: implications for perinatal nutrition. *Am J Clin Nutr* 1993; **57**: suppl. 703S-710S.
- Uauy-Dagach R, Mena P. Nutritional role of omega-3 fatty acids during the perinatal period. *Clin Perinatol* 1995; **22**: 157-175.
- Salem N, Wegher B, Mena P, Uauy R. Arachidonic and docosahexaenoic acids are biosynthesized from their 18-carbon precursors in human infants. *Proc Natl Acad Sci USA* 1996; **93**: 49-54.
- Ciandinin MT, Jumpsen J, Sumh M. Relationship between fatty acid accretion, membrane composition, and biologic function. *J Pediatr* 1994; **125**: S25-S33.
- Carlson SE, Rhodes PG, Rao VS, Goldgar DE. Effect of fish oil supplementation on the n-3 fatty acid content of red blood cell membranes in preterm infants. *Pediatr Res* 1987; **21**: 507-510.
- Carlson SE, Rhodes PG, Ferguson MG. Docosahexaenoic acid status of preterm infants at birth and following feeding with human milk or formula. *Am J Clin Nutr* 1986; **44**: 798-804.
- Odendaal HJ, Steyn DW, Norman K, Kirsten GF, Smith J, Theron GB. Improved perinatal mortality rates in 1 001 patients with severe pre-eclampsia. *S Afr Med J* 1995; **85**: 1071-1076.
- Steck TL, Kant JA. *Methods in Enzymology*. New York: Academic Press, 1974: 172-173.
- Burton GW, Ingold KU, Thompson KE. An improved procedure for the isolation of ghost membranes from human red blood cells. *Lipids* 1981; **16**: 946.
- Tichelaar HY, Steyn NP, Nel JH, *et al.* Fatty acid and nutritional status of undernourished rural Pedi children under 6 years of age in Lebowa. *S Afr J Food Sci Nutr* 1995; **7**: 27-32.
- Smuts CM, Tichelaar HY, van Jaarsveld PJ, *et al.* The effect of iron fortification on the fatty acid composition of plasma and erythrocyte membranes in primary school children with and without iron deficiency. *Prostaglandins Leukot Essent Fatty Acids* 1995; **52**: 59-67.
- Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard score, expanded to include extremely premature infants. *J Pediatr* 1991; **119**: 417-423.
- Ogburn PL, Turner SI, Williams PP, Johnson SB, Holman SB. Preeclampsia and essential fatty acid levels. *Prog Lipid Res* 1986; **25**: 417-419.
- Williams MA, Zingheim RW, King IB, Zebelmann AM. Omega-3 fatty acids in maternal erythrocytes and risk of preeclampsia. *Epidemiology* 1995; **6**: 232-237.
- Diaz M, Leal C, Cajal JR, *et al.* Cord blood lipoprotein-cholesterol: relationship to birth-weight and gestational age of newborns. *Metabolism* 1989; **38**: 435-438.
- Felton CV, Chang TC, Crook D, Marsh M, Robson SC, Spencer JA. Umbilical vessel wall fatty acids after normal and retarded growth. *Arch Dis Child* 1994; **70**: F36-F39.
- Van Jaarsveld PJ, Tichelaar HY, Dhansay MA, *et al.* The essential fatty acid status of pregnant women from a community with low socio-economic status. *Med Sci Res* 1994; **22**: 719-721.
- Makrides M, Neumann MA, Byard RW, Simmer K, Gibson RA. Fatty acid composition of brain, retina, and erythrocytes in breast- and formula-fed infants. *Am J Clin Nutr* 1994; **60**: 189-194.
- Ciandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Intrauterine fatty acid accretion rates in human brain: implications for fatty acid requirements. *Early Hum Dev* 1980; **4**: 121-129.
- Martinez M, Ballabriga A. Effect of parenteral nutrition with high doses of linoleate on the developing human liver and brain. *Lipids* 1987; **22**: 133-138.
- Martinez M, Ballabriga A, Gill-Gibernan JJ. Lipids of the developing human retina: I. Total fatty acids, plasmalogens, and fatty acid composition of ethanolamine and choline phosphoglycerides. *J Neurosci Res* 1988; **20**: 484-490.
- Dougherty RM, Galli C, Ferro-Luzzi A, Iacono JM. Lipid and phospholipid fatty acid composition of plasma red blood cells and platelets and how they are affected by dietary lipids: a study of normal subjects from Italy, Finland, and the USA. *Am J Clin Nutr* 1987; **45**: 443-455.
- Ciandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Intrauterine fatty acid accretion rates in human brain: implications for fatty acid requirements. *Early Hum Dev* 1980; **4**: 121-129.
- Hachey DL. Benefits and risks of modifying maternal fat intake in pregnancy and lactation. *Am J Clin Nutr* 1994; **59**: suppl. 454S-464S.
- Hall B. The uniformity of human milk. *Am J Clin Nutr* 1979; **32**: 304-312.
- Finley DC, Lonnerdal B. Fatty acid composition of breast milk from vegetarian and non-vegetarian lactating women. In: Schaub J, ed. *Composition and Physiological Properties of Human Milk*. Amsterdam: Elsevier, 1985.
- Carlson SE, Cooke RJ, Rhodes PG, Peeples JM, Werkman SH. Effect of vegetable and marine oils in preterm infant formulas on blood arachidonic and docosahexaenoic acids. *J Pediatr* 1992; **120**: S159-S167.
- Salem N, Wegher B, Mena P, Uauy R. Arachidonic and docosahexaenoic acids are biosynthesized from their 18-carbon precursors in human infants. *Proc Natl Acad Sci USA* 1996; **93**: 49-54.
- Secher NJ, Olsen SF, Sorensen JD. Fish oil and pre-eclampsia. *Br J Obstet Gynaecol* 1991; **98**: 738-740.
- Olsen SF, Secher NJ. A possible preventive effect of low-dose fish oil on early delivery and pre-eclampsia: indications from a 50-year-old controlled trial. *Br J Nutr* 1990; **64**: 599-609.

Accepted 3 Mar 1998.