Umbilical vessels of preeclamptic women have low contents of both n−3 and n−6 long-chain polyunsaturated fatty acids[1–3]

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ABSTRACT

Background: Preeclampsia is characterized by enhanced platelet aggregation and vasoconstriction and is related to an elevated ratio of thromboxane A_2 to prostacyclin I_2.

Objective: We investigated whether altered eicosanoid production in preeclamptic women could be explained by the fatty acid composition of umbilical vessel walls and platelets.

Design: The fatty acid composition of maternal and umbilical platelets and of umbilical arteries and veins in 27 preeclamptic women and 24 normotensive women was determined. Between-group differences were analyzed with linear discriminant analysis, the Kruskal-Wallis test, or analysis of covariance with gestational age as the covariate.

Results: Platelets of preeclamptic women contained lower amounts of 20:5n−3 and a higher ratio of 20:4n−6 to 20:5n−3 than did platelets of normotensive women. Additionally, linear discriminant analysis revealed higher amounts of 20:4n−6 in platelets of preeclamptic women. Umbilical arteries and veins in preeclamptic women contained lower amounts of long-chain polyunsaturated fatty acids (PUFAs) of the n−3 series, n−6 long-chain PUFAs, and 20:3n−6 than did umbilical arteries and veins of normotensive women. Umbilical arteries also had lower amounts of 20:4n−6, higher amounts of 20:3n−9, and a higher ratio of 20:3n−9 to 20:4n−6.

Conclusions: Low amounts of long-chain n−3 and n−6 PUFAs in umbilical vessels of preeclamptic women with adequate n−6 status may indicate insufficient transplacental transfer of long-chain PUFAs. The low amounts of 20:4n−6, high amounts of 20:3n−9, and high ratio of 20:3n−9 to 20:4n−6 in umbilical arteries may unfavorably affect local prostacyclin production. Low amounts of 20:3n−6 in umbilical arteries and veins and low amounts of 20:5n−3 in maternal platelets may contribute to the dominance of eicosanoids derived from 20:4n−6. *Am J Clin Nutr* 1999;69:293–8.

KEY WORDS Preeclampsia, fatty acids, umbilical vessels, platelets, eicosanoids, long-chain polyunsaturated fatty acids, women, pregnancy, n−3 fatty acids, n−6 fatty acids

INTRODUCTION

The pathogenesis of preeclampsia is unknown, but may involve genetic, immunologic, and dietary factors. Endothelial dysfunction seems to be a common denominator (1). Preeclampsia is characterized by hypertension and proteinuria and is often associated with high perinatal mortality as a result of fetal growth retardation and (induced) early delivery (2). It is also associated with enhanced platelet aggregation and vasoconstriction (3). The ensuing hypertensive and prothrombotic state may at least partly be caused by abnormal eicosanoid production, notably the elevated ratio of thromboxane A_2 (TxA_2) to prostacyclin I_2 (PGI_2) in maternal plasma and placental tissue (4, 5). Dietary influences are therefore conceivable because eicosanoid production is influenced by the type of dietary fat and, more specifically, the status of long-chain polyunsaturated fatty acids (PUFAs).

Long-chain PUFAs are fatty acids with ≥20 carbon atoms and ≥3 double bonds. They are derived from the parent essential fatty acids linoleic (18:2n−6) and α-linolenic (18:3n−3) acids by alternating desaturation and chain elongation (6). Long-chain PUFAs are structural components of membrane phospholipids and are precursors of eicosanoids (prostaglandins, thromboxanes, and leukotrienes). The quantitatively most important long-chain PUFA from 18:2n−6 is arachidonic acid (20:4n−6), whereas 18:3n−3 is converted into eicosapentaenoic (20:5n−3) and docosahexaenoic (22:6n−3) acids. The fatty acids 20:4n−6 and 20:5n−3 are precursors of TxA_2 and TxA_3 in platelets and of PGI_2 and PGI_3 in vascular endothelium, respectively. TxA_2 is a potent vasoconstrictor and platelet aggregator, whereas TxA_3 is less potent (7). PGI_2 and PGI_3 are equipotent vasodilators and inhibitors of platelet aggregation. The dietary intake of n−3 and n−6 fatty acids determines to a large extent the ratio of 20:4n−6 to 20:5n−3, and can thereby influence eicosanoid-mediated vasoactive effects. The present Western diet, characterized by a high intake of n−6 fatty acids (notably 18:2n−6) and a low intake of n−3 fatty acids (from 18:3n−3 and fish), may promote platelet aggregation and vasoconstriction (8).

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[2] Supported by the Netherlands Antilles Foundation for Clinical Higher Education (NASKHO).

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Received November 11, 1997.

Accepted for publication July 6, 1998.

Fetuses have a high long-chain PUFA requirement, eg, for development of the brain. It is widely recognized today that the fetal rate of long-chain PUFA synthesis from the parent essential fatty acids is insufficient to cover the fetus's long-chain PUFA needs (9). A maternal supply is therefore essential; insufficient fetal long-chain PUFA accrual may cause growth retardation and influence gestational age. For instance, prenatal long-chain PUFA status, notably that of 20:4n−6 and 22:6n−3, is related to birth weight (10–12), head circumference (13–16), and abdominal circumference (15) and 22:6n−3 is correlated with length of gestation (11). Studies have shown that umbilical wall 22:6n−3 concentrations correlate with weight, length, and head circumference at birth (16, 17). Fetal long-chain PUFA status seems marginal even under normal conditions because of the lower long-chain PUFA status in umbilical arteries than in umbilical veins (13). It is possible that abnormalities in maternal essential fatty acid status, in transplacental long-chain PUFA transport, or in essential fatty acid handling by the fetus accentuate the already low long-chain PUFA status of the umbilical arteries under normal conditions and thereby induce a local state of platelet aggregation and vasoconstriction.

In the present study, the fatty acid compositions of platelets, umbilical veins, and umbilical arteries of 27 preeclamptic women in Curaçao (Netherlands Antilles) were investigated. Results were compared with those in 24 normotensive, nonproteinuric, pregnant women.

SUBJECTS AND METHODS

Patients and control subjects

Fifty-one pregnant women were included in the study. All women were from Curaçao, a Caribbean island inhabited mostly by people of West African descent. The dietary habits of the people are essentially Western. All women delivered their infants in the main obstetric facilities in Curaçao, ie, the obstetric wards of the St Elisabeth Hospital and the maternity clinic Rio Canario. Preeclampsia was clinically diagnosed in 27 women. Preeclampsia was defined as a diastolic blood pressure ≥90 mm Hg on ≥2 consecutive occasions ≥4 h apart (or as a diastolic blood pressure ≥110 mm Hg on any 1 occasion) in previously normotensive women in combination with proteinuria (one 24-h urine collection with a total protein excretion ≥0.3 g or 2 specimens of urine collected ≥4 h apart with ≥0.3 g albumin/L) (18). Twenty-four normotensive, nonproteinuric pregnant women served as control subjects. The characteristics of the study population are given in **Table 1**. Informed consent was obtained from all participants and the study was conducted in agreement with local ethical standards and the Helsinki Declaration of 1975, as revised in 1989.

Samples, transport, and fatty acid analysis

Maternal venous EDTA-treated blood was collected in an undefined metabolic condition either during delivery or within 2 h after birth. Umbilical EDTA-treated blood was collected immediately after birth. The EDTA-treated blood was subsequently centrifuged at 800 × *g* for 10 min at 4°C and the supernate (platelet-rich plasma) was collected. Platelets were isolated from 2 mL platelet-rich plasma by centrifugation at 2500 × *g* for 10 min at 4°C. The platelet pellet was washed twice, without resuspension, with 5 mL of a 0.9%-NaCl solution. Each wash was followed by centrifugation at 800 × *g* for 10 min at 4°C. Two milliliters of methanol:HCl (5:1, by vol; 6 mol HCl/L) containing 1 mg butylated hydroxytoluene (antioxidant) and 25 μg 17:0 methyl ester (internal quantification standard) was added for immediate preservation and later transmethylation.

TABLE 1
Characteristics of the study population

	Control women (n = 24)	Preeclamptic women (n = 27)
Maternal age (y)	27.8 ± 6.5[1]	27.1 ± 6.0
Nullipara (%)	21 [5][2]	52 [14]
Diastolic blood pressure (max, mm Hg)	74 ± 8	104 ± 10[3]
Cesarean delivery (%)	4 [1]	41 [11][3]
Gestational age (wk)	40 ± 1	36 ± 3[3]
Birth weight (g)	3357 ± 546	2354 ± 932[3]
SGA (%)	21 [5]	33 [9]

[1] $\bar{x}$ ± SD. SGA, small for gestational age: birth weight below the 10th percentile for gestational age, according to Kloosterman (19).
[2] n in brackets.
[3] Significantly different from control women, $P < 0.0001$.

Immediately after delivery, an ≈7-cm sample of the umbilical cord located at the most proximal site to the placenta was removed. The sample was immediately placed in an ice-cold 0.9%-NaCl solution until further processing. The 2 umbilical arteries and the umbilical vein were subsequently dissected from the surrounding tissue, thoroughly washed with an ice-cold 0.9%-NaCl solution, and dried on paper tissue. Umbilical arteries and veins were weighed and subsequently preserved by adding 2 mL methanol:HCl (5:1, by vol; 6 mol HCl/L) that contained 5 mg butylated hydroxytoluene.

All samples were stored at −20°C until transported on dry ice to the Central Laboratory for Clinical Chemistry (University Hospital Groningen). The long-chain fatty acid compositions of platelets, umbilical arteries, and umbilical veins were determined after transmethylation by capillary gas chromatography with split injection and flame-ionization detection (20). Results are expressed as relative amounts (mol%).

Statistics

Between-group comparisons of clinical characteristics were done with Student's t test at $P < 0.05$ (21). Differences in the fatty acid contents of umbilical arteries and veins were tested for both groups with the Kruskal-Wallis test at $P < 0.05$. In the analysis of between-group fatty acid differences, we first tested whether each of the individual fatty acids or ratios correlated with gestational age in preeclamptic women and control women separately by using the Spearman rank coefficient at $P < 0.05$. A finding of insignificant correlations in both subgroups was followed by use of the Kruskal-Wallis test at $P < 0.05$ for analysis of between-group differences. The finding of significant correlations for control women, preeclamptic women, or both was followed by analysis of covariance (ANCOVA) with gestational age as the covariate at $P < 0.05$ (21). Ratios of each of the fatty acids in umbilical arteries to umbilical veins were tested by using the same approach. Between-group comparisons of gestational age and fatty acid data were also investigated with linear discriminant analysis (21) by using the raw data. With stepwise variable selection, this method identified those variables that contributed to the discrimination between preeclamptic and control women.

RESULTS

Study group

Characteristics of the study groups are given in Table 1. Preeclamptic women had higher maximum diastolic blood pressures (by definition) and percentages of cesarean deliveries than did control women. Newborns of preeclamptic women had significantly lower birth weights and gestational ages at delivery. There were no significant differences in the number of small-for-gestational-age infants when birth weights of this mostly Afro-Caribbean study group were evaluated according to Dutch intrauterine growth curves by sex and parity (19).

Fatty acid compositions of maternal and umbilical cord platelets

The fatty acid compositions of maternal and umbilical cord platelets are presented in **Table 2**. The following significant relations were found between the fatty acids and gestational age. There were positive relations with gestational age for 18:1n−9, total n−9 fatty acids, and monounsaturated fatty acids (MUFAs) in maternal platelets of control women and for 20:3n−6 in maternal platelets of preeclamptic women. There were negative relations with gestational age for 18:1n−9, total n−9 fatty acids, and MUFAs in maternal platelets of preeclamptic women. In umbilical platelets of preeclamptic women there were positive relations with gestational age for 18:0, 22:6n−3, 20:4n−6, 22:5n−6, total n−6 fatty acids, long-chain n−6 PUFAs, long-chain n−3 and n−6 PUFAs, saturated fatty acids (SFAs), PUFAs, and the ratios of 20:3n−6 to 18:2n−6, 20:4n−6 to 20:5n−3, and 22:6n−3 to 20:5n−3. In umbilical platelets of preeclamptic women there were negative relations with gestational age for 18:3n−3, 20:5n−3, 18:2n−6, 20:2n−6, 18:1n−9, total n−9 fatty acids, and MUFAs.

Platelets of preeclamptic women contained lower amounts of 20:5n−3, 18:2n−6, and total n−6 fatty acids and higher amounts of 22:5n−6 than did maternal platelets of control women. Ratios of 20:3n−6 to 18:2n−6, 20:4n−6 to 20:5n−3, and 22:6n−3 to 20:5n−3 were higher in platelets of preeclamptic women than in maternal platelets of control women. Umbilical cord platelets of preeclamptic women had higher amounts of 16:0 and SFAs than did those of control women.

TABLE 2
Fatty acid compositions of maternal and umbilical cord platelets from normotensive (control) and preeclamptic women[1]

	Control women (n = 18)		Preeclamptic women (n = 25)	
Fatty acid	Maternal	Umbilical	Maternal	Umbilical
	mol%			
16:0	21.89 ± 1.54	22.04 ± 1.82	22.19 ± 1.13	22.83 ± 1.40[2]
18:0	17.31 ± 1.79	18.99 ± 1.05	17.55 ± 1.20	18.47 ± 1.20
18:3n−3	0.27 ± 0.10	0.14 ± 0.10	0.22 ± 0.11	0.21 ± 0.11
20:5n−3	0.29 ± 0.14	0.16 ± 0.07	0.21 ± 0.07[2]	0.17 ± 0.07
22:5n−3	1.13 ± 0.25	0.45 ± 0.12	1.01 ± 0.31	0.51 ± 0.23
22:6n−3	2.03 ± 0.62	2.33 ± 0.58	2.16 ± 0.93	1.97 ± 0.30
Total n−3	3.70 ± 0.73	3.06 ± 0.71	3.59 ± 1.10	2.77 ± 0.29
LC n−3 PUFAs	3.45 ± 0.72	2.93 ± 0.66	3.37 ± 1.06	2.60 ± 0.30
18:2n−6	9.66 ± 2.75	3.73 ± 0.76	7.02 ± 1.91[3]	4.16 ± 1.51
20:2n−6	0.46 ± 0.08	0.28 ± 0.09	0.47 ± 0.19	0.26 ± 0.10
20:3n−6	1.38 ± 0.26	1.69 ± 0.17	1.33 ± 0.19	1.52 ± 0.37
20:4n−6	19.05 ± 3.12	23.32 ± 2.80	20.48 ± 2.58	22.20 ± 2.66
22:4n−6	1.86 ± 0.42	2.27 ± 0.26	1.97 ± 0.23	2.20 ± 0.29
22:5n−6	0.45 ± 0.11	0.76 ± 0.23	0.56 ± 0.18[2]	0.67 ± 0.29
Total n−6	32.87 ± 1.40	32.02 ± 2.30	31.82 ± 1.52[2]	31.00 ± 2.08
LC n−6 PUFAs	23.21 ± 3.14	28.29 ± 2.56	24.81 ± 2.53	26.84 ± 2.92
LC n−3 + n−6 PUFAs	26.66 ± 2.94	31.22 ± 2.36	28.18 ± 2.34	29.44 ± 2.94
18:1n−9	15.02 ± 1.59	12.46 ± 1.56	15.07 ± 2.35	13.93 ± 2.82
20:3n−9	0.32 ± 0.12	0.53 ± 0.18	0.31 ± 0.10	0.45 ± 0.16
Total n−9	17.32 ± 1.70	15.17 ± 1.91	17.41 ± 2.43	16.33 ± 2.90
SFAs	44.48 ± 1.65	48.01 ± 1.40	45.33 ± 1.86	48.17 ± 2.06[4]
MUFAs	18.59 ± 1.81	16.23 ± 1.98	18.87 ± 2.59	17.54 ± 3.13
PUFAs	36.93 ± 1.17	35.76 ± 1.96	35.81 ± 1.38	34.29 ± 2.11
20:3n−6 to 18:2n−6	0.15 ± 0.03	0.46 ± 0.08	0.21 ± 0.88[5]	0.41 ± 0.15
20:4n−6 to 20:5n−3	78.13 ± 33.1	181.87 ± 91.2	109.13 ± 38.2[2]	163.48 ± 77.5
22:6n−3 to 20:5n−3	7.82 ± 2.89	17.41 ± 8.73	11.00 ± 3.73[5]	14.10 ± 6.85

[1] $\bar{x}$ ± SD. LC, long-chain (≥20 carbon atoms); PUFAs, polyunsaturated fatty acids (≥3 double bonds); SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids.
[2–5] Significantly different from control: [2] $P < 0.05$ (Kruskal-Wallis), [3] $P < 0.001$ (Kruskal-Wallis), [4] $P < 0.05$ (ANCOVA), [5] $P < 0.01$ (Kruskal-Wallis).

Fatty acid compositions of umbilical venous and arterial vessels

The fatty acid compositions of umbilical veins and arteries are presented in **Table 3**. The following significant correlations with gestational age were found. Amounts of 22:6n−3 and 22:5n−6 in umbilical veins and amounts of 18:3n−3 in umbilical arteries were positively correlated with gestational age in control women, whereas amounts of 22:4n−6 in umbilical veins and the ratio of 20:3n−6 to 18:2n−6 in umbilical arteries were positively correlated with gestational age in preeclamptic women. 18:1n−9, total n−9 fatty acids, MUFAs, and the ratio of 20:3n−9 to 20:4n−6 in umbilical veins and amounts of 18:1n−9 and MUFAs in umbilical arteries were negatively correlated with gestational age in preeclamptic women.

All n−6 fatty acids in umbilical arteries of both preeclamptic and control women were significantly lower than in umbilical veins ($P < 0.001$), except for higher amounts of 22:5n−6 in umbilical arteries ($P < 0.01$). Umbilical arteries also contained higher amounts of n−9 fatty acids than did umbilical veins in both groups ($P < 0.0001$). Umbilical arteries contained 4.53 ± 1.62 and 4.68 ± 1.85 times as much 20:3n−9 than did umbilical veins in control and preeclamptic women, respectively ($P < 0.0001$). The umbilical arteries of control women contained higher amounts of 22:6n−3 ($P = 0.0411$) and lower amounts of 22:5n−3 ($P = 0.0045$) than did umbilical veins, whereas in preeclamptic women, only 22:5n−3 was lower in umbilical arteries than in umbilical veins ($P = 0.0023$).

Amounts of 22:5n−3, total n−3 fatty acids, long-chain n−3 PUFAs, 20:3n−6, total n−6 fatty acids, long-chain n−6 PUFAs, long-chain n−3 and n−6 PUFAs, and PUFAs were lower in umbilical arteries and veins of preeclamptic women than in control women. In addition, 20:5n−3, 22:6n−3, 20:4n−6, and 22:4n−6 were lower and 20:3n−9 and total n−9 fatty acids were higher in umbilical arteries of preeclamptic women than in control women; 16:0 was higher in umbilical veins of preeclamptic women than in control women. Ratios of

TABLE 3
Fatty acid compositions of umbilical veins (UV) and umbilical arteries (UA) from normotensive (control) and preeclamptic women[1]

	Control women (n = 22)		Preeclamptic women (n = 27)	
	UV	UA	UV	UA
			mol%	
16:0	24.86 ± 1.25	23.19 ± 0.73	25.98 ± 2.07[2]	23.78 ± 1.79
18:0	19.52 ± 2.40	19.35 ± 1.04	19.67 ± 3.15	20.11 ± 2.67
18:3n−3	0.10 ± 0.05	0.10 ± 0.04	0.11 ± 0.05	0.10 ± 0.06
20:5n−3	0.09 ± 0.04	0.09 ± 0.03	0.07 ± 0.02	0.06 ± 0.03[3]
22:5n−3	0.30 ± 0.11	0.22 ± 0.06	0.23 ± 0.08[2]	0.17 ± 0.06[3]
22:6n−3	4.26 ± 0.85	4.83 ± 0.76	3.35 ± 0.96	3.73 ± 1.03[4]
Total n−3	4.72 ± 0.93	5.23 ± 0.81	3.73 ± 1.00[4]	4.03 ± 1.09[4]
LC n−3 PUFAs	4.62 ± 0.92	5.13 ± 0.81	3.63 ± 1.02[4]	3.94 ± 1.09[4]
18:2n−6	2.69 ± 0.44	1.87 ± 0.39	2.89 ± 0.56	1.74 ± 0.75
20:2n−6	0.42 ± 0.10	0.24 ± 0.06	0.40 ± 0.09	0.21 ± 0.06
20:3n−6	1.94 ± 0.33	1.53 ± 0.36	1.64 ± 0.31[3]	1.25 ± 0.24[3]
20:4n−6	14.67 ± 2.52	12.63 ± 2.49	13.44 ± 3.35	10.38 ± 2.74[3]
22:4n−6	5.09 ± 1.26	2.95 ± 0.77	3.72 ± 1.21	2.16 ± 0.58[3]
22:5n−6	2.58 ± 0.66	3.14 ± 0.57	2.51 ± 0.79	3.22 ± 0.68
Total n−6	27.40 ± 3.85	22.35 ± 3.58	24.84 ± 4.48[2]	18.96 ± 4.08[3]
LC n−6 PUFAs	24.71 ± 3.73	20.48 ± 3.33	21.70 ± 4.77[3]	17.22 ± 3.80[3]
LC n−6 + n−3 PUFAs	29.33 ± 4.38	25.61 ± 3.93	25.33 ± 5.70[3]	21.16 ± 4.78[3]
18:1n−9	11.17 ± 1.15	13.35 ± 2.09	12.52 ± 3.16	15.11 ± 2.29
20:3n−9	0.70 ± 0.39	2.76 ± 1.11	0.85 ± 0.45	3.42 ± 0.96[2]
Total n−9	16.37 ± 1.72	21.60 ± 3.91	18.20 ± 3.35	24.49 ± 3.24[3]
SFAs	48.72 ± 4.20	47.90 ± 1.59	50.38 ± 5.50	49.52 ± 4.57
MUFAs	17.85 ± 1.56	20.40 ± 2.82	19.50 ± 3.28	22.60 ± 2.65
PUFAs	33.42 ± 4.54	31.70 ± 2.96	30.11 ± 5.38[3]	27.89 ± 4.81[3]
20:3n−9 to 20:4n−6	0.05 ± 0.03	0.24 ± 0.15	0.07 ± 0.04	0.37 ± 0.19[3]
20:3n−6 to 18:2n−6	0.73 ± 0.15	0.83 ± 0.15	0.59 ± 0.13[3]	0.78 ± 0.20
22:5n−6 to 22:4n−6	0.54 ± 0.23	1.16 ± 0.44	0.73 ± 0.03[2]	1.58 ± 0.48[3]
20:4n−6 to 22:6n−3	3.50 ± 0.54	2.62 ± 0.40	4.10 ± 0.57[4]	2.81 ± 0.40
22:6n−3 to 22:5n−6	1.72 ± 0.43	1.59 ± 0.16	1.34 ± 0.47[3]	1.20 ± 0.01[3]
n−3 + n−6 to n−7 + n−9	1.71 ± 0.33	1.18 ± 0.34	1.38 ± 0.38[3]	0.87 ± 0.26[3]

[1] $\bar{x}$ ± SD. LC, long chain (≥20 carbon atoms); PUFAs, polyunsaturated fatty acids (≥3 double bonds); SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; ratio of 20:3n−9 to 20:4n−6; essential fatty acid (EFA) deficiency index; ratio of 20:3n−6 to 18:2n−6, expresses Δ6 desaturation and elongation of n−6-series; ratio of 22:5n−6 to 22:4n−6, 22:6n−3 deficiency index; ratio of 20:4n−6 to 22:6n−3, ratio of the major LC PUFAs of the n−6 and n−3 series; ratio of 22:6n−3 to 22:5n−6, 22:6n−3 sufficiency index; ratio of n−3 + n−6 to n−7 + n−9, EFA status index. There were no significant differences by ANCOVA.

[2–4] Significantly different from control (Kruskal-Wallis): [2] $P < 0.05$, [3] $P < 0.01$, [4] $P < 0.001$.

22:5n−6 to 22:4n−6 were higher and ratios of 22:6n−3 to 22:5n−6 and of n−3 + n−6 to n−7 + n−9 fatty acids were lower in umbilical arteries and veins of preeclamptic women than in control women. The ratio of 20:3n−9 to 20:4n−6 was higher in umbilical arteries of preeclamptic women than in control women, whereas the ratio of 20:3n−6 to 18:2n−6 was lower and that of 20:4n−6 to 22:6n−3 was higher in umbilical veins of preeclamptic women than in control women. Only the umbilical artery–to-vein ratio of 18:2n−6 was lower in preeclamptic women than in control women.

Linear discriminant analysis

Linear discriminant analysis revealed that gestational age and amounts of 20:5n−3, 22:4n−6, and 22:5n−3 contributed to the discrimination between preeclamptic and control women for umbilical artery fatty acids. For umbilical vein fatty acids these variables were gestational age and amounts of 22:4n−6, 20:5n−3, 20:3n−6, 22:5n−3, and 22:6n−3; for maternal platelet fatty acids they were gestational age and amounts of 22:5n−6 and 20:4n−6; and for umbilical platelet fatty acids they were gestational age and amounts of 20:2n−6.

DISCUSSION

We studied the fatty acid compositions of maternal and umbilical platelets and umbilical arteries and veins of 27 preeclamptic women and 24 normotensive control women. The women lived on the island of Curaçao; they were mostly of West African descent and their dietary habits were essentially Western. The use of a well-matched control group for preeclamptic women is important because the fatty acid composition of fetal organs, including umbilical vessels (22), is known to be subject to change, especially during the last trimester. Matching for gestational age, however, is virtually impossible because it requires selection of women with uncomplicated pregnancies who deliver before term. We therefore first tested whether the fatty acids or ratios correlated with gestational age. An insignificant finding was tested further by use of the Kruskal-Wallis test, whereas a significant finding was tested further by ANCOVA with gestational age as the covariate. Few differences in maternal and umbilical platelet fatty acid compositions were found by this approach, but striking differences for some fatty acids in umbilical veins and arteries were identified. These results were confirmed and extended by multivariate data analysis. Taken together, our data show that umbili-

cal veins and especially umbilical arteries of preeclamptic women contain lower percentages of essential fatty acids of both the n−3 and n−6 series than do veins and arteries of control women, suggesting that abnormal fetal deposition of these fatty acids is a feature of preeclampsia.

The lower long-chain n−3 and n−6 PUFA status of umbilical arteries especially may reflect impaired fetal long-chain PUFA accrual in preeclampsia, with insufficient amounts of long-chain PUFAs remaining for incorporation into the fetal tissues located most distal from the placental supply. Insufficient fetal long-chain PUFA deposition derives, theoretically, from abnormal fetal handling of essential fatty acids or an insufficient fetal long-chain PUFA supply. An insufficient supply may be the result of marginal maternal long-chain PUFA status, insufficient transplacental transport, or both. From a percentage point of view, the most striking abnormality in preeclampsia seemed to be the lower amounts of long-chain n−3 PUFAs in both umbilical arteries (−23%; Table 3) and umbilical veins (−21%). The quantitatively most important long-chain n−3 PUFA in these compartments is 22:6n−3. Part of the difference in 22:6n−3 between preeclamptic and control women may be explained by the gestational age dependency of 22:6n−3. The marginal 22:6n−3 status in umbilical arteries and veins of preeclamptic women was confirmed by the lower ratio of 22:6n−3 to 22:5n−6 and higher ratio of 22:5n−6 to 22:4n−6, both of which are indicators of functional 22:6n−3 deficiency (23). Note that the dietary intake of n−3 fatty acids (8) from vegetable oils and fish in many Western societies, including Curaçao (24), is low compared with the intake of the competing essential fatty acids of the n−6 series (notably 18:2n−6). On the other hand, amounts of 20:4n−6 in umbilical arteries (−18%) and umbilical veins (−9%; NS) were also low. Lower amounts of 20:4n−6 may be of special interest because this finding is related to lower birth weight (12). Low fetal n−3 and n−6 status in mothers with adequate n−6 status argues in favor of insufficient transplacental transport. Future maternal long-chain PUFA supplementation studies may indicate whether fetal long-chain PUFA shortages are indeed causally related to the pathogenesis of preeclampsia.

Interpreting our findings in terms of eicosanoid production is difficult because our fatty acid data were derived from whole tissue, not from those subcellular compartments and lipid classes that exclusively add to the local production of eicosanoids. Moreover, many factors influence the subsequent relation between eicosanoid production and the long-chain PUFA contents of the subcellular phospholipids that actually serve as eicosanoid precursors. However, preeclamptic women did have lower platelet contents of the precursor of TxA_3 (ie, 20:5n−3) together with unaltered contents of the precursor of TxA_2 (ie, 20:4n−6) and a higher ratio of 20:4n−6 to 20:5n−3 than control women (Table 2). Higher amounts of 20:4n−6 in platelets of preeclamptic women became apparent from the linear discriminant analysis. Taken together, these results may be consistent with TxA_2 dominance, but it must be pointed out that amounts of 20:5n−3 in platelets were extremely low compared with those of 20:4n−6 and that the encountered differences were small.

Fatty acid differences between preeclamptic and control women in the umbilical vessels (Table 3) seemed more pronounced than the differences in platelets. This result may be in line with the finding that umbilical arteries of preeclamptic women produce less prostacyclin (25) than umbilical arteries of normotensive women and that prostacyclin production is inversely related to the ratio of 20:3n−9 to 20:4n−6 in umbilical arteries (26). Umbilical arteries in our study had lower contents of 20:4n−6, higher contents of 20:3n−9, and a higher ratio of 20:3n−9 to 20:4n−6 than did umbilical veins. Crawford et al (14) found that umbilical arteries of babies with the lowest birth weights had the highest 20:3n−9 contents. It is as yet unclear whether the 4 times higher 20:3n−9 content in umbilical arteries than in umbilical veins reflects a local essential fatty acid deficiency. Classically, essential fatty acid deficiency results in the production of 20:3n−9 from 18:1n−9 by Δ6 desaturation and chain elongation because of the local lack of the preferred Δ6 desaturase substrates 18:3n−3 and 18:2n−6. Umbilical arteries and veins do not seem to differ much, however, in the contents of these substrates, which may argue in favor of a derivation of 20:3n−9 from the maternal circulation. Feeding rats with a 20:3n−9-rich oil was found to cause incorporation of this fatty acid into various plasma lipid classes and into the phospholipids of all investigated organs (27). It is possible that 20:3n−9 undergoes similar preferential transplacental transport as long-chain PUFAs of the n−3 and n−6 series by the poorly understood process of biomagnification (10), but is subsequently deposited downstream as a second-choice long-chain PUFA because of the local limited availability of long-chain PUFAs of the n−3 and n−6 series.

The lower amount of 20:3n−6 in umbilical veins and arteries, the lower ratio of 20:3n−6 to 18:2n−6 in umbilical veins (Table 3), and the lower amount of 20:3n−6 in umbilical veins identified by linear discriminant analysis in preeclamptic women might be consistent with lower Δ6 desaturation activity because neither 18:3n−6 (the intermediate Δ6 desaturase product in the conversion of 18:2n−6 to 20:3n−6) nor 20:3n−6 belong to the usual arsenal of dietary fatty acids. Dihomo-γ-linolenic acid (20:3n−6) is the precursor of eicosanoids of the 1-series (28). These eicosanoids share much of the properties of those of the 3-series (ie, from 20:5n−3) and may therefore counteract the vasoconstrictive and platelet-aggregating effects of eicosanoids of the 2-series (from 20:4n−6). Lower amounts of 20:3n−6 and a lower ratio of 20:3n−6 to 18:2n−6 also suggest that the production of 20:3n−9 is unlikely to be by synthesis from 18:1n−9 via Δ6 desaturation.

In conclusion, preeclampsia is characterized by low amounts of long-chain PUFAs of the n−3 and n−6 series in umbilical veins and most notably in umbilical arteries. The underlying cause may be insufficient transplacental transfer of long-chain PUFAs because the women had normal n−6 status. Platelets of preeclamptic women had lower amounts of 20:5n−3 and a higher ratio of 20:4n−6 to 20:5n−3. These differences, however, were small and it is therefore questionable whether they contributed much to the TxA_2 dominance. Umbilical arteries of preeclamptic women had lower amounts of 20:4n−6, higher amounts of 20:3n−9, and a higher ratio of 20:3n−9 to 20:4n−6, which may unfavorably affect local prostacyclin production and cause other adverse effects related to 20:3n−9. It is possible that the high amounts of 20:3n−9 in umbilical arteries were not derived merely from local synthesis, but originated from the maternal circulation. Umbilical veins and arteries of preeclamptic women also had low amounts of 20:3n−6, which together with low 20:5n−3 in maternal platelets may contribute to the dominance of 20:4n−6-derived eicosanoids in preeclampsia.

We thank the medical staff and nurses of the obstetric wards of the St Elisabeth Hospital and the maternity clinic Rio Canario for collecting blood samples, Ingrid Martini and Elly de Hoog for their technical assistance, and Marcel Volmer for his kind support with the statistical analyses.

REFERENCES

1. Ness RB, Roberts JM. Heterogeneous causes constituting the single syndrome of preeclampsia: a hypothesis and its implications. Am J Obstet Gynecol 1996;175:1366–70.
2. Wallenberg HCS. Hypertensive pregnancy syndrome. Unraveling the mystery of preeclampsia: from prostacyclin to cytokines. Orgyn 1995;1:31–5.
3. Walsh SW. Preeclampsia: an imbalance in placental prostacyclin and thromboxane production. Am J Obstet Gynecol 1985;152: 335–40.
4. Wang Y, Walsh SW, Guo J, Zhang J. The imbalance between thromboxane and prostacyclin in preeclampsia is associated with an imbalance between lipid peroxides and vitamin E in maternal blood. Am J Obstet Gynecol 1991;165:1695–700.
5. Walsh SW, Wang Y. Trophoblast and placental villous core production of lipid peroxides, thromboxane and prostacyclin in preeclampsia. J Clin Endocrinol Metab 1995;80:1888–93.
6. Sprecher H. Biochemistry of essential fatty acids. Prog Lipid Res 1981;20:13–22.
7. Sorensen JD, Olsen SF, Pedersen AK, Boris J, Secher NJ, FitzGerald GA. Effects of fish oil supplementation in the third trimester of pregnancy on prostacylin and thromboxane production. Am J Obstet Gynecol 1993;168:915–22.
8. Simopoulos AP. Omega-3 fatty acids in health and disease and in growth and development. Am J Clin Nutr 1991;54:438–63.
9. Clandinin MT, Chappell JE, Heim T. Do low weight infants require nutrition with chain elongation-desaturation products of essential fatty acids? Prog Lipid Res 1981;20:901–4.
10. Innis SM. Essential fatty acids in growth and development. Prog Lipid Res 1991;30:39–103.
11. Leaf LA, Leighfield MJ, Costeloe KL, Crawford MA. Long chain polyunsaturated fatty acids and fetal growth. Early Hum Dev 1992;30:183–91.
12. Koletzko B, Braun M. Arachidonic acid and early human growth: is there a relation? Ann Nutr Metab 1991;35:128–31.
13. Hornstra G, van Houwelingen AC, Simonis M, Gerrard JM. Fatty acid composition of umbilical arteries and veins: possible implications for the fetal EFA-status. Lipids 1989;24:511–7.
14. Crawford MA, Doyle W, Drury P, Lennon A, Costeloe K, Leighfield. N-6 and n-3 fatty acids during early human development. J Intern Med Suppl 1989;225:159–69.
15. Felton CV, Chang TC, Crook D, Marsh M, Robson SC, Spencer JAD. Umbilical vessel wall fatty acids after normal and retarded fetal growth. Arch Dis Child 1994;70:36–9.
16. Foreman-van Drongelen MMHP, van Houwelingen AC, Kester ADM, Hasaart THM, Blanco CE, Hornstra G. Long-chain polyunsaturated fatty acids in preterm infants: status at birth and its influence on postnatal levels. J Pediatr 1995;126:611–8.
17. Robillard P-Y, Christon R. Lipid intake during pregnancy in developing countries: possible effect of essential fatty acid deficiency on fetal growth. Prostaglandins Leukot Essent Fatty Acids 1993;48: 139–42.
18. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. Am J Obstet Gynecol 1988;158:892–8.
19. Kloosterman GJ. Bevruchting en innesteling. In: De Voortplanting van de mens. (Conception and nidation. In: Human Reproduction.) Haarlem, Netherlands: Uitgeversmaatschappij Centen, 1979:81–3 (in Dutch).
20. Muskiet FAJ, van Doormaal JJ, Martini IA, Wolthers BG, van der Slik W. Capillary gas chromatographic profiling of total long-chain fatty acids and cholesterol in biological materials. J Chromatogr 1983;278:231–44.
21. Stevens J. Applied multivariate statistics for the social sciences. New Hillsdale, NJ: LEA, 1986.
22. Hoving EB, van Beusekom CM, Nijeboer HJ, Muskiet FAJ. Gestational age dependency of essential fatty acids in cord plasma cholesterol esters and triglycerides. Pediatr Res 1994;35:461–9.
23. Hornstra G, Al MDM, van Houwelingen AC, Foreman-van Drongelen MMHP. Essential fatty acids in pregnancy and early human development. Eur J Obstet Gynecol Repod Biol 1995;61:57–62.
24. Brouwer DAJ, van der Dijs FPL, Leerink CB, et al. Dietary fatty acids of patients with coronary artery disease in Curaçao. Implications for primary and secondary prevention. West Indian Med J 1997;46:47–52.
25. Downing I, Shepherd GL, Lewis PJ. Kinetics of prostacyclin synthetase in umbilical artery microsomes from normal and preeclamptic pregnancies. Br J Clin Pharmacol 1982;13:195–8.
26. Ongari MA, Ritter JM, Phil D, et al. Correlation of prostacyclin synthesis by human umbilical artery with status of essential fatty acid. Am J Obstet Gynecol 1984;149:455–60.
27. Cleland LG, Neumann MA, Gibson RA, Hamazaki T, Akimoto K, James MJ. Effects of dietary n−9 eicosatrienoic acid on the fatty acid composition of plasma lipid fractions and tissue phospholipids. Lipids 1996;31:829–37.
28. Horrobin DF. Gamma-linolenic acid: an intermediate in essential fatty acid metabolism with potential as an ethical pharmaceutical and as a food. Rev Contemp Pharmacother 1990;1:1–41.