Gestational Diabetes Mellitus Upsets the Proportion of Fatty Acids in Umbilical Arterial but Not Venous Plasma

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OBJECTIVE — Neonates of women with gestational diabetes mellitus (GDM) have reduced levels of arachidonic acid (AA) (20:4 n-6) and docosahexaenoic acid (DHA) (22:6 n-3). To assess whether this is the result of impaired placental transfer or endogenous fetal metabolism, fatty acids in umbilical venous and arterial plasma were analyzed in neonates of GDM women.

RESEARCH DESIGN AND METHODS — Fatty acids were analyzed by gas chromatography in the plasma of 15 subjects with GDM and 30 healthy control subjects undergoing elective cesarean section and in vein and artery cord blood collected separately.

RESULTS — The percentages of AA (20:4 n-6), DHA (22:6 n-3), and total n-6 or n-3 polyunsaturated fatty acids (PUFAs) as well as total PUFAs were lower in umbilical arterial but not in venous plasma of neonates of the GDM versus the control group.

CONCLUSIONS — An altered handling or metabolism of long-chain PUFAs by the fetus rather than impaired placental transfer seems to be responsible for the lower proportion of those fatty acids in the plasma of neonates of GDM mothers.

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Whereas plasma levels of arachidonic acid (AA) and docosahexaenoic acid (DHA) in neonates of women with type 1 diabetes (1), type 2 diabetes (2), or gestational diabetes mellitus (GDM) (3) are low, the levels of AA and DHA in GDM women are normal or even enhanced (4) compared with those of healthy control subjects. Because it is unknown whether this decline in neonates is due to impaired transfer or altered intrauterine fetal metabolism, we analyzed fatty-acid profiles in umbilical venous and arterial plasma and in control and GDM mothers at the time of cesarean delivery.

RESEARCH DESIGN AND METHODS

— Fifteen Caucasian women with GDM (mean ± SD age 32.3 ± 1.0 years) diagnosed by an abnormal 100-g oral glucose tolerance test (5) and 30 healthy control subjects (35.9 ± 1.1 years; $P < 0.05$) were enrolled. The University of Milan Ethical Board approved the protocol, and informed consent was obtained. After diagnosis, patients began a diet together with blood glucose self-monitoring (6). All women underwent elective cesarean after an overnight fast. Pregnancies were singleton, and none of the neonates showed malformations, abnormal karyotypes, or signs of distress. Blood samples from the maternal radial vein and from the umbilical vein and artery were collected in EDTA. The umbilical samples were obtained from a cord segment doubly clamped immediately after fetal extraction, and plasma aliquots were stored at −80°C until analysis.

Sample analysis

Lipids were extracted and put in a 2:1 mixture of chloroform and methanol containing 0.005% butylate hydrotoluene. Fatty acids were transesterified with methanolic hydrochloride, and fatty acid methyl esters were separated and analyzed on a PerkinElmer Autosystem gas chromatograph (Norwalk, CT) (7). Results are expressed as percent (mg/100 mg of fatty acids) of all detected fatty acids with a chain length of 12–24 carbon atoms.

Statistical analysis

Statistical differences were evaluated by one-way ANOVA. When statistically significant differences appeared ($P < 0.05$), they were assessed by Tukey's multiple range comparison test. Student's *t* test was used to compare values between two groups.

RESULTS

— Whereas no major differences were found between the GDM and control groups in the percent of the individual fatty acids analyzed from maternal plasma, umbilical cord plasma values showed interesting differences (Table 1). Palmitic acid values did not differ between umbilical venous or arterial plasma and the plasma of the mothers. However, stearic acid was higher in both umbilical venous and arterial plasma than in maternal plasma. A similar comparison was also found when total saturated fatty acids were estimated, although no difference between the GDM and control groups was found. The percent of palmitoleic acid was slightly higher, whereas that of oleic acid and total monounsaturated fatty acids was lower, in both umbilical venous and arterial plasma than in the mothers' plasma. No differences were found between the GDM and control groups for any of them.

Concerning the n-6 fatty acids, linoleic acid was lower, whereas eicosatrienoic acid (20:3 n-6) was higher, in umbilical venous and arterial plasma than in maternal plasma, with no differences between the GDM and control groups. Also, whereas AA was much higher in umbilical venous and arterial plasma than

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Table 1—*Percent of fatty acids (mg/100 mg fatty acids) in plasma of control (n = 30) and GDM (n = 15) pregnant women at cesarean section delivery and in their respective cord blood*

	Maternal vein	Umbilical vein	Umbilical artery	*P*
Palmitic acid (16:0)				
Control	27.3 ± 0.4	25.4 ± 1.1	26.5 ± 1.6	NS
GDM	27.8 ± 0.5[ab]	25.4 ± 1.7[a]	31.6 ± 2.6[b]	0.0384
Stearic acid (18:0)				
Control	7.00 ± 0.49[a]	19.8 ± 1.9[b]	16.3 ± 2.1[b]	0.0000
GDM	6.83 ± 0.64[a]	19.8 ± 2.9[b]	13.2 ± 2.1[ab]	0.0001
Total SFAs				
Control	36.2 ± 0.5[a]	47.1 ± 1.1[b]	44.7 ± 1.1[b]	0.0000
GDM	36.4 ± 0.7[a]	47.2 ± 2.0[b]	46.6 ± 1.9[b]	0.0000
Palmitoleic acid (16:1 n-7)				
Control	3.24 ± 0.15	3.62 ± 0.29	3.77 ± 0.33	NS
GDM	2.73 ± 0.21[a]	3.93 ± 0.47[ab]	4.04 ± 0.69[b]	0.0026
Oleic acid (18:1 n-9)				
Control	26.6 ± 0.6[a]	19.4 ± 0.5[b]	18.4 ± 0.9[b]	0.0000
GDM	25.9 ± 0.8[a]	20.4 ± 1.0[b]	20.6 ± 1.4[b]	0.0002
Total MUFAs				
Control	30.4 ± 0.6[a]	24.5 ± 0.7[b]	23.4 ± 1.1[b]	0.0000
GDM	29.3 ± 0.9	25.8 ± 1.5	27.5 ± 1.5	NS
Linoleic acid (18:2 n-6)				
Control	22.6 ± 0.7[a]	7.81 ± 0.30[b]	9.32 ± 0.93[b]	0.0000
GDM	23.1 ± 1.0[a]	7.63 ± 0.40[b]	7.73 ± 0.68[b]	0.0000
Eicosatrienoic acid (20:3 n-6)				
Control	1.40 ± 0.12[a]	2.47 ± 0.19[b]	2.39 ± 0.28[b]	0.0001
GDM	1.25 ± 0.13[a]	2.32 ± 0.11[b]	2.11 ± 0.34[b]	0.0002
AA (20:4 n-6)				
Control	5.11 ± 0.20[a]	12.2 ± 0.3[b]	12.3 ± 0.5[b]	0.0000
GDM	5.67 ± 0.20[a]	11.4 ± 0.8[b]	10.2 ± 0.8[b]*	0.0000
Total n-6 fatty acids				
Control	29.7 ± 0.8[a]	23.6 ± 0.6[b]	26.1 ± 0.9[b]	0.0000
GDM	30.6 ± 1.0[a]	22.5 ± 1.2[b]	22.4 ± 1.6[b]*	0.0000
α-linolenic acid (18:3 n-3)				
Control	0.413 ± 0.060	ND	ND	
GDM	0.354 ± 0.064	ND	ND	
DHA (22:6 n-3)				
Control	2.44 ± 0.11[a]	3.99 ± 0.16[b]	4.32 ± 0.19[b]	0.0000
GDM	2.76 ± 0.20[a]	3.96 ± 0.32[b]	3.15 ± 0.31[ab]†	0.0083
Total n-3 fatty acids				
Control	3.64 ± 0.15[a]	5.15 ± 0.43[b]	5.69 ± 0.41[b]	0.0006
GDM	3.94 ± 3.49	4.55 ± 0.37	3.57 ± 0.30†	NS
Total PUFAs				
Control	33.6 ± 0.8[a]	28.8 ± 0.7[b]	31.8 ± 1.1[a]	0.0004
GDM	34.6 ± 0.9[a]	27.1 ± 1.2[b]	25.9 ± 1.7[b]†	0.0000

Data are means ± SEM. Tukey's test was used to determine differences between maternal, umbilical venous, and arterial plasma after one-way ANOVA. Different letters in a row indicate significant differences. The difference between GDM and control values were significantly different at $*P < 0.05$ and $†P < 0.01$ by Student's *t* test. Total SFAs, sum of 12:0, 14:0, 16:0, 18:0, 20:0, 22:0, 23:0, and 24:0. Total MUFAs, sum of 16:1, 18:1, and 20:1. Total n-6 fatty acids, sum of 18:2, 18:3, 20:2, 20:3, 20:4, 22:2, 22:4, and 22:5. Total n-3 fatty acids, sum of 18:3, 20:3, 20:5, 22:3, 22:5, and 22:6. Total PUFAs, sum of total n-6 plus n-3. MUFAs, monounsaturated fatty acids; SFAs, saturated fatty acids.

in maternal plasma, no differences were found between the GDM and control groups in maternal or umbilical venous plasma, although umbilical artery values appeared lower in the GDM than in the control group. A lower percent of n-6 polyunsaturated fatty acids (PUFAs) was found in the umbilical arteries, but not in the umbilical veins, of the GDM group than of the control group.

For n-3 fatty acids, the percent of α-linolenic acid in maternal plasma did not differ between the GDM and control groups, and α-linolenic acid was undetectable in umbilical venous and arterial plasma. The percent of DHA in both the control and GDM groups was higher in umbilical venous and arterial plasma than in maternal plasma, umbilical artery DHA values in the GDM group were lower than those in the control group, and no differences between the two groups were found in either maternal plasma or umbilical venous plasma. Similar intergroup comparisons were found for both n-3 PUFAs and total PUFAs, with values being lower in the umbilical arteries, but not in the umbilical veins, of the GDM than in those of the control group.

CONCLUSIONS — In agreement with previous reports (8), the plasma fatty-acid profile did not differ between GDM and control subjects. However, we show here for the first time that whereas the fatty-acid profile in umbilical venous plasma of GDM subjects does not differ from that of control subjects, a lower percent of both AA and DHA and of n-6 and n-3 PUFAs appears in GDM umbilical arterial plasma than in control umbilical arterial plasma. When the umbilical plasma fatty-acid profile is compared with the maternal plasma profile, there are higher proportions of saturated fatty acids but lower proportions of the two essential n-6 and n-3 fatty acids, linoleic acid and α-linolenic acid, whereas proportions of their respectively derived long-chain PUFAs, AA and DHA, are higher in umbilical plasma. Such enhancement in AA and DHA in fetal circulation is called "magnification" and interpreted as a result of their effective transfer throughout the placenta (9). However, their synthesis by the fetus from their respective precursors cannot be discarded (10,11). Thus, the decreased percent of the long-chain PUFA precursors on the fetal side may only be a reflection of their active conversion rather than a limited placental transfer. In fact, although not directly measured under in vivo conditions, placental transfer of both linoleic and α-linolenic acid has been demonstrated to be even more efficient than that of AA using an ex vivo placental perfusion system (12).

Umbilical artery blood arrives at the placental capillaries from fetal tissues, whereas umbilical vein blood comes from the placental capillaries; its composition is therefore dependent on placental transfer activity. Because the placenta lacks desaturase activity (13), the higher proportions of AA and DHA in umbilical ve-

nous plasma than in maternal plasma would indicate that their placental transfer is unimpaired. However, the decreased proportions of AA, DHA, and total n-6 and n-3 PUFAs in the umbilical arteries of GDM fetuses would indicate their enhanced utilization by fetal tissues. Further studies are needed to establish the mechanism involved and its implications for fetal and postnatal growth.

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