Changes in Serum Lipid Levels During Pregnancy in Type 1 and Type 2 Diabetic Subjects

Christian S. Göbl, MD
Ammon Handisurya, MD
Katharina Klein, MD
Latife Bozkurt, MD

OBJECTIVE — Alterations in maternal lipid metabolism could affect fetal programming and the susceptibility for atherosclerosis in the offspring; therefore, we studied differences in lipid profiles of pregnant women with type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 173 diabetic pregnancies were studied prior to conception (V0), at each trimester (V1–V3), and after delivery and were compared with 137 healthy women at V3.

RESULTS — During gestation, the increase in serum lipid concentrations was less pronounced in type 2 diabetic subjects. At V3, the lipid levels of type 1 diabetic women with normal glucose tolerance were similar but significantly higher then those of type 2 diabetic women. Elevated triglycerides and low HDL cholesterol at V3 were significant predictors for large-for-gestational-age (LGA) newborns.

CONCLUSIONS — Our data suggest smaller changes in serum lipid concentrations during pregnancy in type 2 diabetic mothers. Additionally, we found a positive association between maternal triglycerides and LGA infants independently of chronic glycemic control.

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Decreased HDL cholesterol, elevated triglyceride, and increased LDL cholesterol levels are common features of type 2 diabetes and represent important atherogenic risk factors (1). Non-HDL cholesterol (NHDL-C) (total cholesterol minus HDL cholesterol) comprises further atherogenic lipoproteins and is suggested to be a more reliable predictor of cardiovascular disease (2).

Although mild forms of hyperlipidemias are common during normal pregnancy (3), subtle disturbances of the maternal metabolic milieu could play a key role in the newborns’ later life (4–7).

Currently, data on serum lipid levels in pregnant women affected by different forms of diabetes are scarcely available. Therefore, we evaluated differences in gestational serum lipid profiles of type 1 and type 2 diabetic women as well as the associations of maternal lipid levels with birth weight, ponderal index, and the risk of delivering large-for-gestational-age (LGA) infants.

RESEARCH DESIGN AND METHODS — In this longitudinal study, we consecutively included 173 singleton diabetic pregnancies (109 women with type 1 diabetes and 64 women with type 2 diabetes) attending our diabetes outpatient clinic between January 1995 and January 2006. A total of 137 pregnancies with normal glucose tolerance in the third trimester attending our outpatient clinic between September 2007 and April 2009 served as a control group. Medical records were used to collect data on maternal LDL cholesterol, HDL cholesterol, NHDL-C, triglycerides, and total cholesterol measured at baseline within 6 months prior to conception (V0), at each trimester (V1–V3), and during the first 14 months after delivery (V4) as well as the biometric parameters of the newborns. LGA was defined as birth weight above the 90th percentile, adjusted for sex and age of the Austrian population. The study was approved by the local ethics committee.

Statistical analysis

Univariable cross-sectional comparisons were performed by using the Student t test. Linear mixed-effects models were used to evaluate the changes of lipid levels, as well as to compare differences between type 1 and type 2 diabetic subjects after confounder adjustment (maternal age, BMI, and A1C). The identification number was included as a random effect, and data of all visits were compared with V0. BMI, A1C, and triglyceride levels were log transformed.

At V3, data of type 1 diabetic and type 2 diabetic subjects and subjects with normal glucose tolerance were compared by confounder-adjusted ANCOVA models and contrast analyses, respectively. Pearson correlation was used to evaluate whether maternal lipids in the third trimester of pregnancy are predictive for birth weight or ponderal index (kg/m3), and logistic regression models were used to estimate predictors for having LGA infants.

Statistical analysis was performed using R (version 2.9.0) and SPSS (version 13.0). A two-sided P value ≤0.05 was considered statistically significant. P values and 95% CIs of longitudinal analyses were adjusted using Bonferroni correction.

RESULTS — Table 1 shows the characteristics of the sample and cross-sectional analysis. Univariable longitudinal analysis revealed that LDL cholesterol, NHDL-C,
Lipid levels during diabetic pregnancy

Table 1—Characteristics of the study sample

|                         | n          | Type 1 diabetes | Type 2 diabetes | P      |
|-------------------------|------------|-----------------|-----------------|--------|
|                         | (type 1 diabetes/ type 2 diabetes) |                 |                 |        |
| Age (years)             | 109/64     | 30.2 ± 5.6      | 35.0 ± 5.3      | <0.001 |
| BMI (kg/m²)*            | 101/54     | 24.8 ± 3.8      | 32.0 ± 7.4      | <0.001 |
| A1C (%)**               | 107/64     | 7.2 ± 1.4       | 6.8 ± 1.3       | 0.046  |
| Preecclampsia           | 109/63     | 18 ± 16.5       | 7 ± 10.9        | 0.314  |
| Birth weight (g)        | 109/64     | 3,276 ± 706     | 3,308 ± 826     | 0.789  |
| Birth length (cm)       | 107/64     | 49.7 ± 3.8      | 50.4 ± 3.9      | 0.246  |
| Ponderal index (kg/m³)  | 107/64     | 26.9 ± 9.2      | 25.3 ± 2.7      | 0.187  |
| Small for gestational age | 109/64  | 8 ± 7.3         | 7 ± 10.9        | 0.417  |
| LGA                     | 109/64     | 21 ± 19.3       | 17 ± 26.6       | 0.263  |
| LDL cholesterol V0 (mg/dl) | 61/17       | 111.1 ± 31.3   | 125.7 ± 40.7   | 0.117  |
| LDL cholesterol V1 (mg/dl) | 77/34       | 96.1 ± 28.2   | 97.4 ± 22.1   | 0.809  |
| LDL cholesterol V2 (mg/dl) | 84/26       | 119.3 ± 33.8   | 96.8 ± 29.3   | 0.003  |
| LDL cholesterol V3 (mg/dl) | 81/24       | 146.0 ± 42.3   | 110.7 ± 38.4   | <0.001 |
| LDL cholesterol V4 (mg/dl) | 65/19       | 114.3 ± 30.5   | 113.8 ± 27.5   | 0.949  |
| NHDL-C V0 (mg/dl)       | 64/16      | 129.5 ± 34.8    | 150.9 ± 37.2   | 0.032  |
| NHDL-C V1 (mg/dl)       | 77/34      | 112.5 ± 29.7    | 126.6 ± 26.5   | 0.019  |
| NHDL-C V2 (mg/dl)       | 84/26      | 148.6 ± 37.4    | 144.9 ± 32.1   | 0.651  |
| NHDL-C V3 (mg/dl)       | 81/23      | 193.4 ± 44.5    | 169.0 ± 36.6   | 0.018  |
| NHDL-C V4 (mg/dl)       | 64/19      | 135.2 ± 37.7    | 141.3 ± 28.5   | 0.517  |
| Total cholesterol V0 (mg/dl) | 67/21       | 195.5 ± 36.8   | 202.3 ± 39.6   | 0.470  |
| Total cholesterol V1 (mg/dl) | 77/38       | 181.0 ± 34.0   | 176.2 ± 28.6   | 0.459  |
| Total cholesterol V2 (mg/dl) | 84/29       | 229.7 ± 43.1   | 200.0 ± 39.2   | 0.001  |
| Total cholesterol V3 (mg/dl) | 100/53      | 274.8 ± 50.3   | 220.5 ± 44.5   | <0.001 |
| Total cholesterol V4 (mg/dl) | 71/28       | 204.7 ± 39.2   | 200.9 ± 34.1   | 0.654  |
| HDL cholesterol V0 (mg/dl) | 64/16       | 65.2 ± 16.1    | 54.5 ± 18.7    | 0.024  |
| HDL cholesterol V1 (mg/dl) | 77/34       | 68.2 ± 17.2    | 49.2 ± 12.6    | <0.001 |
| HDL cholesterol V2 (mg/dl) | 84/26       | 80.6 ± 16.3    | 56.3 ± 13.8    | <0.001 |
| HDL cholesterol V3 (mg/dl) | 81/23       | 74.8 ± 16.3    | 62.9 ± 10.0    | <0.001 |
| HDL cholesterol V4 (mg/dl) | 64/19       | 68.0 ± 17.9    | 50.3 ± 14.6    | <0.001 |
| Log triglycerides V0 (mg/dl) | 67/21       | 4.32 ± 0.47    | 4.99 ± 0.58    | <0.001 |
| Log triglycerides V1 (mg/dl) | 77/38       | 4.36 ± 0.39    | 4.97 ± 0.34    | <0.001 |
| Log triglycerides V2 (mg/dl) | 84/28       | 4.96 ± 0.34    | 5.43 ± 0.40    | <0.001 |
| Log triglycerides V3 (mg/dl) | 98/53       | 5.51 ± 0.30    | 5.55 ± 0.39    | 0.466  |
| Log triglycerides V4 (mg/dl) | 71/28       | 4.62 ± 0.62    | 5.02 ± 0.55    | 0.003  |

Data are means ± SD, unless otherwise indicated. V0, prior to conception; V1–V3, first to third trimester; V4, after delivery. *P values are based on log-transformed data.

...and total cholesterol levels were significantly lower at V1 than at V0 and increased later on during gestation. Additionally, LDL cholesterol, NHDL-C, and total cholesterol serum levels were significantly higher at V3 but were comparable to V0 after delivery. Multivariable analysis showed that the increase in LDL cholesterol (B = 47.6 [95% CI 9.6–85.6]; P<0.007), NHDL-C (B = 40.8 [4.4–77.2]; P<0.020), and total cholesterol (B = 48.9 [12.7–85.1]; P<0.003) levels from V0 to V3 was more pronounced in type 1 diabetic women. Also, regarding HDL cholesterol and log-transformed triglyceride concentrations, we found a significant increase at V3. Women with type 1 diabetes showed a more pronounced increase in log-transformed triglyceride levels (B = 0.52 [0.06–0.99]; P<0.02) up to V3.

At V3, total cholesterol ([means ± SD] 271.3 ± 46.5; P = 0.256), LDL cholesterol (156.7 ± 39.7; P = 0.128), HDL cholesterol (78.4 ± 17.8; P = 0.974), and NHDL-C (192.4 ± 41.1; P = 0.431) levels of women with normal glucose tolerance were comparable to type 1 diabetic subjects but significantly higher than those observed in type 2 diabetic subjects. Additionally, women with normal glucose tolerance showed lower log-transformed triglyceride levels (5.17 ± 0.38) than type 1 diabetic (P < 0.001) and type 2 diabetic (P < 0.001) women.

At V3, we found no correlation between lipid parameters and birth weight or ponderal index in diabetic women. However, our data revealed a positive association of log-transformed triglycerides (B = 1.57 [95% CI 0.38–2.92]; P = 0.01) and a negative association of HDL cholesterol (B = −0.07 [−0.12 to −0.03]; P = 0.001) with LGA infants (which remained significant after adjustment for maternal age and A1C).

CONCLUSIONS — Little is known about the dynamic changes of lipid values during pregnancy, as well as the consequences of maternal hyperlipidemia during pregnancy on fetal outcome. In the present study, we investigated the serum lipid parameters of pregnant diabetic and healthy women and their correlation with birth weight and having an LGA infant. Most interestingly, we observed a less pronounced increase in serum lipids of pregnant women with type 2 diabetes. This was unexpected, as insulin resistance and dyslipidemia are commonly related metabolic alterations and components of the metabolic syndrome and type 2 diabetes (1). Our findings are corroborated by another study showing lower LDL cholesterol levels in pregnant insulin-resistant women with gestational diabetes mellitus, compared with women with normal glucose tolerance. The authors hypothesized decreased LDL cholesterol production and increased direct removal of triglyceride-enriched VLDL cholesterol due to insulin resistance and the effect of hyperestrogenemia on LDL cholesterol catabolism (8). However, the results are contradictory (9). In part, such differences might be explained by the fact that the serum lipid levels were measured between the 24th and the 28th week of gestation in one study (9), whereas in our, as well as in another, study (8) the greatest differences were observed in the third trimester.

Recently, Schaefer-Graf et al. (10) found that maternal serum triglyceride levels significantly correlated with abnormal fetal growth in women with gestational diabetes mellitus. This is in agreement with our data for women with type 1 diabetes and furthermore extended to women with type 2 diabetes.

Intrauterine conditions play a key role in programming the susceptibility for atherosclerosis in the newborns later in life (4–7). The relationship found between maternal C-reactive protein levels and plasma cholesterol with the extent of atherogenesis in childhood (5) suggests...
that enhanced oxidative stress induced by inflammation may influence atherosclerosis. Infants of mothers with type 1 diabetes featured increased LDL cholesterol and C-reactive protein levels (11), while antioxidative treatment (e.g., vitamin E supplementation) was reported to prevent fetal programming for atherosclerosis in animal models (7,12).

In summary, we found different changes in gestational lipid profiles in both forms of diabetes. As maternal serum lipids were associated with the risk for LGA infants, further investigations on the effect of maternal metabolism on fetal programming are urgently needed.

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