Fetal macrosomia related to maternal poorly controlled type 1 diabetes strongly impairs serum lipoprotein concentrations and composition

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Abstract

Aims—To determine the effects of fetal macrosomia related to maternal type 1 diabetes on the lipid transport system.

Methods—Serum lipoprotein concentrations and composition and lecithin:cholesterol acyltransferase (LCAT) activity were investigated in macrosomic newborns (mean birth weight, 4650 g; SEM, 90) and their mothers with poorly controlled type 1 diabetes, in appropriate for gestational age newborns (mean birth weight, 3616 g; SEM, 68) and their mothers with well controlled type 1 diabetes, and macroscopic (mean birth weight, 4555 g; SEM, 86) or appropriate for gestational age (mean birth weight, 3290 g; SEM, 45) newborns and their healthy mothers.

Results—In mothers with well controlled type 1 diabetes, serum lipids, apolipoproteins, and lipoproteins were comparable with those of healthy mothers. Similarly, in their infants, these parameters did not differ from those of appropriate for gestational age newborns. Serum triglyceride, very low density lipoprotein (VLDL), apolipoprotein B100 (apo B100), and high density lipoprotein (HDL) triglyceride concentrations were higher, whereas serum apo A-I and HDL concentrations were lower in mothers with diabetes and poor glycaemic control than in healthy mothers. Their macroscopic newborns had higher concentrations in all serum lipids and lipoproteins, with high apo A-I and apo B100 values compared with appropriate for gestational age newborns. In macroscopic infants of healthy mothers, there were no significant differences in lipoprotein profiles compared with those of appropriate for gestational age infants. LCAT activity was similar in both groups of mothers and newborns.

Conclusion—Poorly controlled maternal type 1 diabetes and fetal macrosomia were associated with lipoprotein abnormalities. Macroscopic lipoprotein profiles related to poor metabolic control of type 1 diabetes appear to have implications for later metabolic diseases.

Macrosomia or fetal obesity (birth weight > 4000 g at term) is a frequent complication of pregnancy in diabetes. Maternal hyperglycaemia leads to fetal hyperglycaemia, which stimulates pancreatic islet cells and produces hyperinsulinaemia. This intrauterine hyperinsulinaemic state results in increased fat tissue, liver glycogen content, and total body size. Other maternal fuels such as plasma amino acids and lipids are also thought to be contributors to overgrowth. Disturbances of maternal metabolism are well known factors affecting growth. Because type 1 diabetes mellitus produces changes in maternal metabolic fuels, and because diabetic pregnancy is often associated with macrosomia, the effects of maternal diabetes on lipid metabolism are unclear.

Macrosomic infants of diabetic mothers have been shown to be prone to the development of glucose intolerance, obesity, and diabetes during childhood and adulthood. Obesity and diabetes are associated with lipoprotein abnormalities such as high plasma triglyceride (TG) concentrations and low high density lipoprotein (HDL) cholesterol concentrations. HDL has been shown to protect against the development of atherosclerosis because of the ability of HDL to mediate reverse cholesterol transport from the cell to the liver. Lecithin: cholesterol acyltransferase (LCAT; EC 2.3.1.43), an enzyme produced in the liver, esterifies free cholesterol of the HDL3 subclass, converting it into the HDL2 subclass. This process enables HDL2 to accept a greater amount of cholesterol. LCAT influences not only the metabolism of HDL but also that of other lipoproteins. Early studies showed that HDL2 and HDL3 cholesterol concentrations and LCAT activity are lower at birth in full term infants than in adults. We have reported previously that LCAT activity is low in small for gestational age newborns. However, no information has been provided on HDL2 subfractions and LCAT activity in the sera of macrosomic infants of diabetic mothers. There is increasing interest in the importance of lipoprotein metabolism during life and its implications for later cardiovascular diseases. Because obesity and hyperinsulinaemia begin early in life in macroscopic infants of mothers with type 1 diabetes, it would be interesting to see whether these infants present "at risk" lipoprotein profiles at birth, which would make them prone to later metabolic diseases.
The purpose of our present investigation was to determine whether lipoprotein metabolism is altered in macrosomic newborns of mothers with poorly controlled type 1 diabetes and, if so, to what extent these abnormalities are related to maternal lipid disturbances.

Material and methods

Patients

The subjects for our study were drawn consecutively from women investigated at the Maternity Hospital of Tlemcen, Algeria. Forty pregnant women with type 1 diabetes whose babies were macrosomic or appropriate for gestational age at birth, after term deliveries, were selected. Maternal diabetic status was determined by medical history review. Twenty one mothers had White’s class B (mean duration of diabetes, 4 years; SEM, 0.6) diabetes, and 19 had White’s class C (mean duration of diabetes, 12 years; SEM, 1) diabetes. Table 1 summarises the anthropometric and laboratory characteristics of these mothers. All mothers with diabetes were treated with insulin during pregnancy (multiple injection self administration of short or long acting doses of insulin), but 20 (mothers of macrosomic newborns) were poorly controlled, as shown by their glycosylated haemoglobin concentrations (Hb A1, performed by isolab column chromatography; 24; interassay coefficient of variation (CV) of 7.2%; normal range of Hb A1 was 4–7%) and their fasting glucose concentrations determined by a glucose oxidase procedure (Beckman glucose analyser; Beckman, Palo Alto, California, USA) with a CV less than 4%, during the last term of pregnancy (table 1). Diabetes in mothers of appropriate for gestational age newborns was considered well controlled, with Hb A1 values close to normal reference values. For comparison, 48 healthy pregnant women whose babies were macrosomic or appropriate for gestational age at term were selected after an oral glucose tolerance test within 48 hours of birth. Only women with a normal glucose tolerance test according to the World Health Organisation (WHO) criteria22 were enrolled as control cases. An attempt was made to match these women with those with diabetes, at least with regard to maternal age, height, parity, gestational age, weight gain during pregnancy, and mode of delivery (table 1). No subjects were obese or hypertensive. Newborns with malformations or with intrauterine growth retardation were excluded.

The gestational age of all the neonates was ≥38 weeks. Gestational age was assessed according to the mother’s menstrual history and ultrasonography, and then confirmed by the paediatrician’s assessment of the baby’s maturity. Newborn weight was obtained immediately after delivery. Macrosomia was defined as a birth weight of ≥4000 g at term. The infants belonged to one of the four following groups: (1) Group 1 consisted of 20 pairs of mothers with poorly controlled type 1 diabetes and their macrosomic newborns at term (mean birth weight, 4650 g; SEM, 9). These macrosomic newborns had significantly higher cord serum insulin (measured by radioimmunoassay) values than appropriate for gestational age newborns (table 1). (2) Group 2 comprised 20 pairs of mothers with well controlled type 1 diabetes and their appropriate for gestational age newborns at term (mean birth weight, 3616 g; SEM, 68). (3) Group 3 comprised 18 pairs of healthy mothers and their macrosomic newborns at term (mean birth weight, 4555 g; SEM, 86). In these newborns, insulin concentrations were similar to those found in appropriate for gestational age newborns. (4) Group 4 comprised 30 pairs of healthy mothers and their appropriate for gestational age newborns (mean birth weight, 3290 g; SEM, 45).

We explained the purpose of our study to the mothers and the investigation was carried out with their consent. The experimental protocol was approved by the local human subjects review committee of the University Hospital of Tlemcen, Algeria.

Blood samples

Maternal blood was collected from the arm vein of the mothers within 48 hours of birth under fasting conditions. Cord blood samples were obtained from the umbilical vein immediately after delivery and cutting the umbilical cord. After clotting, sera were separated by centrifugation at 600 g and 4°C. An aliquot of serum was preserved with 0.1% disodium EDTA and 0.02% sodium azide to measure and analyse lipoproteins; another part was used to measure LCAT activity.

Laboratory methods

Lipoprotein isolation

Serum lipoprotein fractions were separated by sequential ultracentrifugation (very low density lipoprotein (VLDL), 1.006 < d < 1.019; low density lipoprotein (LDL), 1.019 < d < 1.063; HDL1, 1.063 < d < 1.21; HDL2, 1.21 < d < 1.21 g/ml) in a Beckman ultracentrifuge (model L5-65, 65 Ti rotor), using sodium bromide for density adjustment, according to Havel et al.23

Chemical analysis

Triglyceride, total cholesterol, and unesterified cholesterol contents of serum and each lipoprotein fraction were measured by means of a Boehringer kit (Mannheim, Germany), using
Table 2  Serum lipid (mmol/litre), apolipoprotein A-I (apo A-I) and apo B100 (both g/litre) values, and LCAT activity of mothers with diabetes, control mothers, and their newborns

<table>
<thead>
<tr>
<th>Group</th>
<th>Mothers</th>
<th>Newborns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Triglycerides</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>4.25 (0.17)*</td>
<td>2.90 (0.2)**</td>
</tr>
<tr>
<td>Group 2</td>
<td>3.54 (0.23)</td>
<td>3.69 (0.20)</td>
</tr>
<tr>
<td>Group 3</td>
<td>1.50 (0.10)</td>
<td>1.52 (0.11)</td>
</tr>
<tr>
<td>Group 4</td>
<td>5.10 (0.40)</td>
<td>4.98 (0.45)</td>
</tr>
<tr>
<td></td>
<td>Phospholipids</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>3.69 (0.20)</td>
<td>3.80 (0.16)</td>
</tr>
<tr>
<td>Group 2</td>
<td>3.01 (0.14)</td>
<td>3.13 (0.12)</td>
</tr>
<tr>
<td>Group 3</td>
<td>1.50 (0.10)</td>
<td>1.52 (0.11)</td>
</tr>
<tr>
<td>Group 4</td>
<td>5.10 (0.40)</td>
<td>4.98 (0.45)</td>
</tr>
<tr>
<td></td>
<td>Unesterified cholesterol</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>1.00 (0.04)</td>
<td>0.71 (0.03)**</td>
</tr>
<tr>
<td>Group 2</td>
<td>1.30 (0.02)**</td>
<td>1.12 (0.03)**</td>
</tr>
<tr>
<td>Group 3</td>
<td>0.30 (0.02)**</td>
<td>0.65 (0.03)**</td>
</tr>
<tr>
<td>Group 4</td>
<td>0.92 (0.03)*</td>
<td>0.65 (0.03)**</td>
</tr>
<tr>
<td></td>
<td>Cholesterol esters</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>1.68 (0.04)**</td>
<td>1.20 (0.06)**</td>
</tr>
<tr>
<td>Group 2</td>
<td>1.10 (0.03)**</td>
<td>1.58 (0.02)**</td>
</tr>
<tr>
<td>Group 3</td>
<td>0.50 (0.0)*</td>
<td>0.20 (0.04)**</td>
</tr>
<tr>
<td>Group 4</td>
<td>0.50 (0.0)*</td>
<td>0.20 (0.04)**</td>
</tr>
<tr>
<td></td>
<td>Apo B100</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>1.68 (0.04)**</td>
<td>1.20 (0.06)**</td>
</tr>
<tr>
<td>Group 2</td>
<td>1.10 (0.03)**</td>
<td>1.58 (0.02)**</td>
</tr>
<tr>
<td>Group 3</td>
<td>0.50 (0.0)*</td>
<td>0.20 (0.04)**</td>
</tr>
<tr>
<td>Group 4</td>
<td>0.50 (0.0)*</td>
<td>0.20 (0.04)**</td>
</tr>
<tr>
<td></td>
<td>LCAT (nmol/ml/h)</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>269 (48)</td>
<td>270 (55)</td>
</tr>
<tr>
<td>Group 2</td>
<td>252 (56)</td>
<td>275 (67)</td>
</tr>
<tr>
<td>Group 3</td>
<td>160 (41)</td>
<td>123 (52)</td>
</tr>
<tr>
<td>Group 4</td>
<td>110 (50)</td>
<td>110 (50)</td>
</tr>
</tbody>
</table>

Values are means (SEM).

Group 1, mothers with poorly controlled diabetes and macrosomic newborns.
Group 2, mothers with well controlled diabetes and appropriate for gestational age newborns.
Group 3, healthy mothers with macrosomic newborns.
Group 4, healthy mothers with appropriate for gestational age newborns.

Values within a row with different numbers of asterisks are significantly different, p < 0.05.

LCAT, lecithin: cholesterol acyltransferase.

Results

Table 2 presents serum lipid, apo A-I and apo B100 concentrations, and LCAT activity in diabetic and healthy mothers, and in their respective newborns. Serum TG and apo B100 values were significantly higher, whereas serum apo A-I was lower in mothers with poorly controlled diabetes (group 1) than in mothers with well controlled diabetes (group 2) and healthy mothers (groups 3 and 4). Apo A-I to apo B100 ratios were lower in group 1 than groups 2–4 (mean, 0.65 (SEM, 0.10) v mean, 1.35 (SEM, 0.08); p < 0.05). No significant differences in serum lipid and apolipoprotein values were detected between mothers with well controlled diabetes and non-diabetic healthy subjects. LCAT activity in mothers with diabetes was similar to that found in healthy mothers.

Table 3 shows the mass and composition of each lipoprotein fraction (VLDL, LDL, HDL\(_2\), and HDL\(_3\)). In mothers with poorly controlled diabetes, VLDL concentrations were higher whereas HDL\(_3\) values were lower when compared with other groups. In addition, these mothers with poorly controlled diabetes had significantly higher VLDL, HDL\(_2\), and HDL\(_3\), TG values and lower HDL\(_2\), cholesterol values than those in other groups. No differences were noted between well controlled diabetic and non-diabetic healthy groups.

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Table 3 Serum lipoprotein concentrations and composition of mothers and their newborns

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass (g/l)</td>
<td>4.92 (0.31)</td>
<td>4.44 (0.43)</td>
<td>4.80 (0.22)</td>
<td>4.62 (0.31)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.91 (0.06)</td>
<td>0.82 (0.06)</td>
<td>0.75 (0.06)</td>
<td>0.70 (0.08)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>4.10 (0.22)</td>
<td>3.89 (0.28)</td>
<td>3.95 (0.15)</td>
<td>3.70 (0.26)</td>
</tr>
</tbody>
</table>

Table 4 presents the apolipoprotein profiles of VLDL, HDL$_2$, and HDL$_3$. VLDL apo B100 and VLDL apo C-III were higher, whereas HDL$_2$, apo A-I and HDL$_3$, apo A-II values were lower in mothers with poorly controlled diabetes compared with the other groups. No significant differences were found in HDL$_2$ apolipoprotein concentrations between all groups.

**LIPROPROTEIN PROFILES IN NEWBORNS**

Macrosomie newborns of mothers with poorly controlled diabetes (group 1) had increased serum TG, phospholipid, unesterified cholesterol, cholesteryl ester, apo A-I, and apo B100 concentrations compared with the other newborn groups. However, the apo A-I to B100 ratio was lower in these newborns than in the other newborn groups (mean, 2.01 (SD, 0.30) vs. mean, 3.50 (SD, 0.10); p < 0.05). In macrosomie newborns of healthy mothers (group 3), serum lipid and apolipoprotein values were similar to those obtained in appropriate for gestational age newborns (groups 2 and 4). LCAT activity tended to be greater in macrosomie than in appropriate for gestational age newborns, but the differences were not significant. In macrosomie newborns of mothers with poorly controlled diabetes, all lipoprotein values (VLDL, LDL, HDL$_2$, and HDL$_3$) were higher than in the other newborn groups. These newborns also had higher HDL$_2$ and HDL$_3$ TG values and lower HDL$_2$ cholesterol concentrations than the other newborn groups. VLDL apo B100, HDL$_2$, apo A-I, HDL$_3$, apo A-II, HDL$_3$, apo A-I, and HDL$_3$, apo A-II values were higher in macrosomie newborns of moth-

Table 4 Serum VLDL, HDL$_2$, and HDL$_3$, apolipoprotein (apo) profiles (AU/L) in mothers and their newborns

<table>
<thead>
<tr>
<th>Lipoprotein</th>
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Values are mean (SEM).

Group 1, mothers with poorly controlled diabetes and macrosomie newborns.

Group 2, mothers with well controlled diabetes and appropriate for gestational age newborns.

Group 3, healthy mothers with macrosomie newborns.

Group 4, healthy mothers with appropriate for gestational age newborns.

Values within a row with different numbers of asterisks are significantly different, p < 0.05.

AU/L, arbitrary unit/litre of serum; on the densitometer tracing obtained after electrophoresis, the concentration of each apolipoprotein was calculated from the percentage of the area for each apolipoprotein relative to the total apolipoprotein concentration of each fraction. HDL$_2$, high density lipoprotein; VLDL, very low density lipoprotein.
Lipoproteins, macrosomia, and maternal diabetes

921

TG. TG and explained 46% of the variation in fetal
respectively, of the variation in fetal TG and
maternal Hb A1 and glucose were associated
diabetes and fetal macrosomia. In this case,
variables can be
not significant predictors of fetal lipids and
values (from 2% to 8%) are small, indicating
that little of the variations in birth weight and
are explained by mater-
between maternal or cord lipoprotein parameters
and birth weight in all groups studied. Taking
newborns of healthy mothers, serum
parameters and insulin values. However, in
were macrosomic at birth, which is an indicator
of macrosomia. In agreement
between maternal Hb A1 and birth
with previous findings, there was no corre-
ation between maternal Hb A1 and birth
weight. In healthy pregnancies, a varying
contribution might be made by the genetic
background of the fetus. In addition, in macro-
somic newborns of healthy mothers, serum
lipid, apolipoprotein, and lipoprotein values
did not differ significantly from those of appro-
imate for gestational age newborns, in agree-
ment with the results of Rovamo et al. On the
other hand, the infants born to mothers with
poorly controlled diabetes might have been
exposed to a hyperglycaemic milieu in utero,
which resulted in macrosomia.

Mothers with poorly controlled diabetes
showed high serum TG, apo B100, and VLDL
values and low serum apo A-I and HDLc,
concentrations when compared with healthy
mothers. These results differ from those of Kilby et
al., who found no significant differences
between serum lipids and apolipoproteins in
pregnant women with type 1 diabetes and nor-
mal pregnant women, despite high Hb A1
values in patients with type 1 diabetes. Monte-
longo and colleagues hypothesised that the
development of excess hyperlipidaemia in dia-
abetic pregnancy depends on the balance
between the degree of glycaemic control and
the plasma sex hormone values during preg-
nancy. Indeed, in our study, all the infants of
these mothers with poorly controlled diabetes
were macrosomic at birth, which is an indicator
of maternal hyperglycaemia in late pregnancy,
and is contrary to the results of previous stud-
ies.9–10

Our results showed that mothers with poorly
controlled diabetes had increased serum TG,
apo B100, and VLDL values, probably as a
result of both overproduction induced by pregnan-
cy and decreased catabolism related to a
failure of lipoprotein lipase (LPL) activity sec-
dary to insulin deficiency. In addition,
VLDL apo C-III, an inhibitor of LPL action,
was increased in the mothers with type 1
diabetes. These mothers also showed several
modifications in HDLc and HDL, composition
and concentration; however, LCAT activity,
which is responsible for cholesterol esterifica-
tion and which modulates HDL composition,
was similar to that found in healthy mothers.
Although HDLc, TG values were increased,
HDLc, apo A-I and HDLc, apo A-II values were
decreased in mothers with type 1 diabetes.
These data suggest a reduction in HDLc, parti-
cle number, with changes in their composition
that could affect reverse cholesterol transport.
Decreased nascent HDL synthesis or reduced
VLDL catabolism could be factors that con-
tribute to low HDLc values in the mothers with
poorly controlled diabetes. In addition, HDLc,
and HDL, particles were TG enriched owing to impaired removal of VLDL TGs or decreased hepatic lipase (HL) activity.

In macrosomic newborns of mothers with poorly controlled diabetes, serum lipid and apolipoprotein values were higher than in control newborns. These data show that fat and protein synthesis was increased in those fetuses with overnutrition, and are in agreement with earlier reports.\(^{35-37}\) In children and adults, obesity is associated with increased concentrations of plasma lipids.\(^{38,39}\) Kilby et al also showed increased serum lipids and apolipoproteins in infants of mothers with type 1 diabetes, despite their normal birth weight.\(^{37}\) Indeed, in that study, mothers with type 1 diabetes had only minor lipoprotein changes, although their Hb A1 values were significantly higher than controls.\(^{35}\) In our study, macrosomic newborns showed higher serum VLDL values accompanied by an increase in serum TG and apo B100 values. An enhancement in glucose and free fatty acid transfer from the mother could explain raised hepatic VLDL secretion and hypertriglyceridaemia, because glucose and free fatty acids are major substrate determinants for hepatic VLDL secretion.\(^{40}\) Indeed, hyperinsulinaemia boosted lipid and protein synthesis. In our study, highly significant positive correlations between (1) maternal Hb A1, glucose, and TG values and neonate TG and VLDL concentrations, and (2) between cord serum insulin values and lipid and apolipoprotein concentrations support these findings. Macrosomic newborns also showed high LDL values, as a result of high concentrations of VLDL, because most LDL particles are derived from VLDL after the action of LPL. Macrosomic newborns had higher HDL and LDL values, which were accompanied by higher HDL apo A-I and HDL apo A-II concentrations, suggesting an increase in the number of HDL particles, probably as a result of their enhanced synthesis. In these newborns, LCAT activity was not significantly different from that found in control newborns, despite high concentrations of apo A-I (its major cofactor). HDL, and HDL, particles were enriched in TGs, whereas amounts of HDL, cholesteryl ester were low. A possible increase in the interchange of lipids between lipoproteins resulting from high cholesteryl ester transfer protein (CETP) activity could contribute to the increase in HDL, and HDL, TGs and the decrease in HDL, cholesteryl ester values. Neary et al showed a reduction in cholesteryl ester transfer activity in the mother during normal pregnancy, with an even greater reduction in the fetus.\(^{41}\) However, plasma CETP values could be enhanced in macrosomic newborns, as is found in obese adults, because adipose tissue is a major source of CETP.\(^{42}\) Further analysis of CETP activity in these macrosomic newborns is needed.

Lipoprotein profiles in macrosomic newborns of mothers with poorly controlled diabetes are consistent with high atherogenic risk. Thus, persisting lipoprotein abnormalities in macrosomic infants could be one of the processes that link macrosomia to adult metabolic diseases.\(^{40}\)

In conclusion, under appropriate metabolic control, type 1 diabetes did not affect maternal and fetal lipid values. In addition, macrosomia in non-diabetic pregnancy was not associated with lipoprotein changes. However, lipoprotein metabolism was altered in mothers with type 1 diabetes and poor glycaemic control, and in their macrosomic newborns. Hypertriglyceridaemia with high VLDL concentrations, TG enrichment in HDL particles, and a low apo A-I to apo B100 ratio were major changes in mothers with type 1 diabetes and in their macrosomic newborns. Persistent macrosomic lipoprotein alterations might be an important risk factor for later metabolic diseases. Macrosomia should be prevented in type 1 diabetic pregnancy to reduce the risk of the later development of metabolic diseases. In addition, special health care for these macrosomic infants should be recommended, including regular examinations and dietary advice.

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