Pregnancy Lipid Profile and Different Lipid Patterns of Gestational Diabetes Treated by Diet Itself

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Summary

The development of gestational diabetes mellitus (GDM) affects lipid metabolism during pregnancy. However, the magnitude of changes in lipid parameters is unclear. In addition, the patterns of these changes may vary based on the criteria selected for making the diagnosis of GDM. Thus, our aim was to compare the anthropometric and laboratory profiles of GDM-associated vs. GDM-free gestation with those of healthy non-pregnant women. We designed a cross-sectional study involving a group of females affected by GDM, a group of healthy pregnant controls and a group of healthy non-pregnant counterparts. GDM patients were divided into 3 subgroups according to the fulfilled diagnostic criteria, that is, those presenting with high fasting plasma glucose in the first trimester (subgroup 1), high fasting plasma glucose in the second trimester (subgroup 2) and high plasma glucose following oral glucose load in the second trimester (subgroup 3). The anthropometric and metabolic profiles of GDM subjects resembled the facets of metabolic syndrome (highest body mass index, waist circumference, C-peptide level, triglycerides) significantly more than the respective profiles of healthy non-pregnant women ($p<0.0001$). While total cholesterol (TC) (together with LDL-C and non-HDL-C) in pregnant women with GDM and without GDM did not differ, both groups had significantly higher levels of triglycerides (TG) than non-pregnant women ($p<0.0001$). Subgroup 1 had the highest fasting glucose level in the second trimester whereas subgroup 3 had the lowest fasting glucose level ($p=0.019$). Concentration of TG increased, being the lowest in subgroup 1 and the highest in subgroup 3 ($p=0.006$). Women with GDM had more pronounced features of metabolic syndrome than pregnant women without GDM. Both groups reached higher levels of TC (LDL-C, non-HDL-C) than non-pregnant controls and did not differ from each other. We found differences in TG and fasting glucose levels among different types of GDM

Key words

Gestational diabetes • Lipids • Triglycerides • Pregnancy

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Introduction

Gestational diabetes mellitus (GDM) is a glucose intolerance disorder with the onset or first recognition during pregnancy, which, however, does not meet the criteria of diabetes mellitus for the general population. GDM diagnostic criteria vary across the world and time. Currently, according to the International Association of Diabetic Pregnancy Study Group (IADPSG), the diagnosis of GDM could be based upon oral glucose tolerance test (oGTT) in the second trimester and upon repetitive measurement of fasting glycaemia during the first trimester [1,20,21]. Some authors postulate that GDM is not a uniform diagnosis [2,3]. Women with GDM respond differently to physiologic challenge of a 400-kcal mixed meal breakfast depending on their body weight [2]. They also react differently to a standard 75-g oGTT test depending on the underlying

defect in insulin sensitivity or secretion defect [3].

Screening for GDM is obligatory in managing pregnant women in many countries. It is a tool for preventing potential negative effects of GDM – maternal or fetal short- and long-term complications, as well as, for example, delivery of large for gestational age (LGA) infants [4]. LGA increases the risk of macrosomia, shoulder dystocia, a cesarean deliveries [21]. GDM is also associated with pregnancy-induced hypertension, preeclampsia and polyhydramnion [21]. Short-term risks for the baby include neonatal hypoglycemia, hyperbilirubinemia, hypocalcemia, respiratory distress syndrome and polycythemia [21]. Shortly after delivery, the glucose values are generally restored to nor-mal, but women with GDM have a sevenfold increased risk of developing type 2 diabetes mellitus after pregnancy [22].

However, there is growing evidence that it is important not only to measure glucose, but also to evaluate the lipid profile during pregnancy, with a particular emphasis on tri-glyceride (TG) levels which rise even in the course of physiological pregnancy. The reason is that even GDM mothers with good blood glucose control are at risk for macrosomia [4].

A pregnancy with GDM is associated with mixed dyslipidemia with predominantly elevated TG concentrations and a shift towards small, dense low-density lipoprotein (LDL) particles (5), as can also be found in other insulin resistance states. However, there are still many controversies and not all studies show the same changes of lipid profiles in pregnant women with or without GDM, as we have recently reviewed (6). Therefore, we have decided to conduct a study comparing lipid profiles of non-pregnant and pregnant women in the second trimester with or without GDM and healthy non-pregnant counter-parts.

Materials and methods

Study design, inclusion, and exclusion criteria

Our study was undertaken as cross-sectional, with women affected by GDM (group 1, n = 43), healthy pregnant (group 2, n = 19) and healthy non-pregnant (group 3, n = 34) controls. It was performed at a tertiary diabetes center and held in accordance with the principles of the Declaration of Helsinki as revised in 2013. It was reviewed and approved by the Faculty of Medicine and Dentistry and University Hospital Olomouc Ethics Committee and informed consent was obtained from all participants.

The diagnosis of GDM was based on any of the following values at any time during pregnancy: fasting plasma glucose 5.1–6.9 mmol/l; 1-h post 75-g oral glucose load ≥ 10.0 mmol/l; 2-h post 75-g oral glucose load ≥ 8.5 mmol/l; according to the IADPSG guidelines [1,20]. Women with GDM were further divided into 3 subgroups according to the diagnostic method: high fasting plasma glucose in the first trimester (subgroup 1), high fasting plasma glucose in the second trimester (subgroup 2) and high plasma glucose post 75-g oral glucose load (subgroup 3). Women treated with insulin were excluded from the study and only women with diet-controlled GDM were included.

Healthy pregnant and healthy non-pregnant controls had no personal history of glucose intolerance or diabetes (including GDM) or history of delivering a high birth weight baby (≥ 4.5 kg).

Participants were asked about their medical history and age. Body mass index (BMI), waist and hip circumference were measured and laboratory tests were performed. BMI was calculated as body weight / body height2 (kg/m2). Waist circumference was measured while standing, in the middle between the anterior iliac crest and the lower border of the ribs. Hip circumference was measured around the widest portion of the buttocks, with the tape parallel to the floor. In pregnant women, all the tests were carried out in the second trimester (between 14 and 26 weeks of gestation).

We have performed the calculation of the sample size (power = 90%, type I error = 0.05) and assumed BMI in groups (gestational diabetes = 30, gravid controls = 26 and healthy non-pregnant controls = 22, sigma = 5). Minimal sample size is 11 patients in each group. Because be assumed use of nonparametric tests, we have increased the sample size by 15 %, which gives the minimum 13 patients in each group, which we have fulfilled.

Laboratory analysis

Venous blood samples were drawn in the morning after a 12-h fast. Routine serum biochemical parameters (lipids, glucose, glycated hemoglobin, C-peptide) were analyzed on Cobas 8000 (Roche, Mannheim, Germany) on the day of blood collection.

Total cholesterol (TC), TG and high-density lipoprotein cholesterol (HDL-C) were determined enzymatically on the Cobas 8000 system. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula (LDL-C = TC – TG*0.4537 –

HDL-C for TG<4.5 mmol/l). Non-HDL-cholesterol (non-HDL-C) was calculated as follows: non-HDL-C = TC – HDL-C. Glucose was determined using the hexokinase method (Roche, Basel, Switzerland). Glycated hemoglobin levels (HbA1c) were measured by ion ex-change chromatography using the Arkray Adams HA-8180V analyzer (Arkray Corporation, Kyoto, Japan). C-peptide was determined with a commercially available kit (Immunotech, Marseille, France) using specific antibodies by the IRMA methods.

Statistical analysis

Certain datasets lacked normal distribution (Shapiro–Wilk test of data distribution) or were of small sizes. Thus, non-parametric statistical methods were employed. Data are expressed as median, minimum and maximum values. Comparison of three independent groups of patients was made by the Kruskal–Wallis tests. If the difference was significant, Dunn's post hoc tests were performed.

Statistical analysis was performed with IBM SPSS Statistics for Windows, version 23.0 (Armonk, NY: IBM Corp.). Probability values of $p<0.05$ were considered statistically significant.

Results

Women were divided into three groups: those with GDM (group 1, n = 43), healthy pregnant (group 2, n = 19) and healthy non-pregnant (group 3, n = 34) controls. Women with GDM had most pronounced patterns indicating the presence of metabolic syndrome (highest BMI, waist circumference, C-peptide level, TG), whereas healthy non-pregnant women had the lowest values. Pregnant women without GDM had also elevated BMI, waist circumference, C-peptide level and TG but not reaching the grade of those with GDM. As for TC (together with LDL-C and non-HDL-C), pregnant women with GDM and without GDM did not differ from each other. On the other hand, both groups had significantly higher levels of TC (together with LDL-C and non-HDL-C) than non-pregnant women.

Healthy pregnant women (group 2) had lower levels of HbA1c in comparison to patients with GDM (group 1) or healthy non-pregnant women (group 3). Further comparisons between these groups and exact values are summarized in Table 1.

Table 1. Comparison of lipid and glucose parameters in patients with GDM, healthy pregnant and non-pregnant women

	Groups			*p*	*p* (Dunn's post hoc test)		
	GDM (group 1)	Healthy pregnant (group 2)	Healthy non-pregnant (group 3)		Group 1 vs. 2	Group 1 vs. 3	Group 2 vs. 3
	Median (range)	Median (range)	Median (range)				
Age (years)	33 (22-44)	31 (23-40)	28.5 (23-39)	0.029	0.548	0.026	1
BMI (kg/m^2)	30.4 (19.6-44.8)	25.6 (21-39.4)	21.7 (18.2-29.1)	<0.0001	0.029	<0.0001	0.019
WC (cm)	99 (82-124)	95 (78-115)	74 (66-90)	<0.0001	0.622	<0.0001	<0.0001
HC (cm)	107.5 (92-137)	104 (93-136)	96 (84-116)	<0.0001	0.677	<0.0001	0.002
Glucose (mmol/l)	4.8 (3.9-5.9)	4.2 (3.4-4.9)		<0.0001			
HbA1c (mmol/mol)	31 (25-38)	29.5 (25-37)	31 (28-36)	0.012	0.026	1	0.014
C-peptide (pmol/l)	660 (411-1191)	552 (495-609)	472 (328-621)	0.001	1	0.001	0.986
TC (mmol/l)	6.1 (4.3-11.4)	6.3 (4.7-8.8)	4.5 (3.2-7.5)	<0.0001	1	<0.0001	<0.0001
TG (mmol/l)	2.2 (0.9-4.2)	1.6 (1-2.8)	0.8 (0.5-1.7)	<0.0001	0.067	<0.0001	0.0002
HDL-C (mmol/l)	2 (1-3.1)	2.2 (1.6-2.7)	1.7 (1.1-2.7)	0.001	0.048	0.196	0.0005
LDL-C (mmol/l)	3.2 (1.7-7.1)	3.2 (1.3-5.6)	2.3 (1.3-5)	<0.0001	1	<0.0001	0.0002
Non-HDL-C (mmol/l)	4.1 (2.7-8.7)	4.2 (2.6-6.5)	2.6 (1.7-5.7)	<0.0001	1	<0.0001	<0.0001

(BMI = body mass index, WC = waist circumference, HC = hip circumference, TC = total cholesterol, TG = triglycerides, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, non-HDL-C = non-HDL-cholesterol)

Table 2. Comparison between patients with GDM in whom diagnosis was made according to method 1, 2 or 3 – high fasting plasma glucose in the first trimester (subgroup 1), high fasting plasma glucose in the second trimester (subgroup 2) and high plasma glucose post 75-g oral glucose load (subgroup 3), respectively

	Patients with GDM			*p*	*p* (Dunn's post hoc test)		
	Diagnosis 1 (n = 22) Median (range)	**Diagnosis 2 (n = 15) Median (range)**	**Diagnosis 3 (n = 6) Median (range)**		**1 vs. 2**	**1 vs. 3**	**2 vs. 3**
Age (years)	32.5 (26-41)	34 (22-44)	34 (27-40)	0.852			
BMI (kg/m2)	31.4 (19.6-39.5)	28 (22.7-44.8)	30.1 (23.7-37.1)	0.286			
WC (cm)	104.5 (90-124)	97 (82-114)	99 (92-116)	0.534			
HC (cm)	109.8 (93-135)	102.5 (92-137)	106.5 (99-120)	0.139			
Glucose (mmol/l)	5 (4.2-5.9)	4.7 (4.3-5.6)	4.4 (3.9-4.9)	0.019	0.854	0.015	0.153
HbA1c (mmol/mol)	31 (26-38)	32 (25-36)	30.5 (27-34)	0.496			
c-peptide (pmol/l)	731 (411-1191)	601 (426-1168)	615 (470-1086)	0.578			
TC (mmol/l)	6.1 (4.4-7.8)	6 (5-9.2)	6 (4.3-11.4)	0.958			
TG (mmol/l)	**1.9** (1.4-3.9)	**2.2** (0.9-3.5)	**3.2** (2.6-4.2)	0.006	1	0.005	0.02
HDL-C (mmol/l)	2 (1.3-3.1)	1.9 (1.3-3)	1.3 (1-2.7)	0.199			
LDL-C (mmol/l)	3.2 (2-4.5)	2.9 (2-5.8)	3.4 (1.7-7.1)	0.874			
Non-HDL-C (mmol/l)	4.2 (2.9-6.3)	4 (2.7-7.3)	5 (3.2-8.7)	0.306			

(BMI = body mass index, WC = waist circumference, HC = hip circumference, TC = total cholesterol, TG = triglycerides, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, non-HDL-C = non-HDL-cholesterol)

Table 3: Multivariate logistic regression (Backward Stepwise method), dependent variable – elevated triglycerides (TG)

Significant predictors:	**OR (95 % CI)**	**p**
Group (healthy non-pregnant as reference):		<0.0001
GDM vs healthy non-pregnant	89.652 (9.184-875.199)	0.0001
Healthy pregnant vs healthy non-pregnant	3.762 (0.289-48.892)	0.311
Cholesterol (per 1 mmol/l)	2.483 (1.112-5.545)	0.027

Multivariate logistic regression (Backward Stepwise method) was performed with dependent variable high TG (above 1.7 mmol/l). Independent predictors were: age of participants, BMI, waist circumference, glycated hemoglobin and cholesterol levels (see Table 3). Patients with GDM had almost 90-times higher chance to have elevated cholesterol levels.

As mentioned in the methods section, women with GDM were further divided into 3 subgroups according to the diagnostic method: high fasting plasma glucose in the first trimester (subgroup 1), high fasting plasma glucose in the second trimester (subgroup 2) and high plasma glucose post 75-g oral glucose load (subgroup 3). Comparison between these GDM subgroups is summarized in Table 2.

Subgroups differed by fasting plasma glucose and triglyceride concentrations. Sub-group 1 (diagnosed by high fasting glucose level in the first trimester) had the highest fasting glucose level also in the second trimester whereas subgroup 3 (diagnosed by high glucose level after glucose load) had the lowest fasting glucose level. We have not found difference in HbA1c in between the subgroups of GDM.

Concentration of triglycerides increased, being the lowest in subgroup 1 and the highest in subgroup 3.

Discussion

Pregnancy lipid profiles in women with and without GDM compared to non-pregnant controls

There is no doubt that hyperglycemia, at levels less than those that occur in overt diabetes, is associated with adverse pregnancy outcomes, such as LGA infants, neonatal hyperinsulinism neonatal hypoglycemia and preeclampsia [7]. Apart from hyperglycemia, also TG levels have an impact on fetal growth and outcome [8,9].

According to our study, women with GDM have higher levels of TG and higher BMI than pregnant women without GDM. Both groups reached higher levels of TC (LDL-C, non-HDL-C) than non-pregnant controls and did not differ from each other.

During pregnancy, lipoprotein metabolism in the liver and adipose tissue changes, altering the serum concentrations of fatty acids, TG, cholesterol and phospholipids. Normal maternal metabolism during pregnancy is characterized by physiological hyperlipidemia [7]. After an initial decrease in the first eight weeks of pregnancy, there is a steady increase in lipoproteins and, especially, in TG levels [10,11]. GDM, however, is often associated with even higher blood lipids than those in normal pregnancy [7,12], although not all studies confirm this [8,13,14]. According to most studies, obese women and women with GDM have abnormal lipid profiles in pregnancy with a pattern of hypertriglyceridemia, elevated very low-density lipoprotein and low HDL-C, in association with hyperinsulinemia [6,15], similar to that in metabolic syndrome. Also in our study, women with GDM had most pronounced patterns indicating the presence of metabolic syndrome (highest BMI, waist circumference, C-peptide level, TG), whereas healthy non-pregnant women had the lowest levels. Pregnant women without diabetes had lower BMI than those with GDM, corresponding with the aforementioned statement. TG levels were also higher in women with GDM than in pregnant women without GDM, but the difference did not reach statistical significance. HDL-C was also lower in pregnant women with GDM compared to those without GDM. This is in concordance with other studies showing lower HDL-C levels throughout pregnancy in women with GDM in comparison with those without GDM [13,14,16]. HDL-C increases significantly during pregnancy with a peak in the second trimester [17].

There are many controversies regarding TC (and, therefore, also LDL-C and non-HDL-C) levels during pregnancy. In our study, pregnant women (both with and without GDM) had higher TC, LDL-C and also non-HDL-C levels in comparison with non-pregnant women. There was no difference between pregnant women with and with-out GDM. A study performed by Koukkou et al. showed that during the third trimester of pregnancy, women with GDM had higher TG, but lower LDL-C concentrations in serum than controls. TC, HDL-C and apolipoprotein concentrations did not differ between women with and without GDM during pregnancy [18]. Similarly, Toescu *et al.* did not find any significant differences between normal and diabetic women although TC and TG increased progressively throughout pregnancy. Unlike the former study, these authors found higher LDL levels in diabetic women in each trimester of pregnancy compared with controls without GDM [5].

Changes in lipid metabolism during pregnancy are important for accumulation of maternal fat stores in early and mid-pregnancy and accelerate fat mobilization in late pregnancy [10]. The anabolic phase of early pregnancy promotes lipogenesis and fat storage. This is important in preparation for the rapid fetal growth in late pregnancy [5]. Lipid deposition and lipolysis inhibition are stimulated by increased estrogen, progesterone and insulin [10]. The placenta needs cholesterol for steroid synthesis, and fatty acids are used for placental oxidation and membrane formation [10].

According to the above studies, it is important not only to measure glucose, but also to evaluate the lipid profile during pregnancy, with a particular emphasis on TG levels. Both have an impact on fetal growth and outcome. It is especially important to advise women to avoid being obese before pregnancy because the presence of subclinical metabolic dysfunction prior to conception leads to the development of GDM during pregnancy.

In our study, we have included only women without insulin treatment of GDM. It is known, that insulin treatment lowers serum concentrations of triglyceride-rich lipoproteins [19].

As we show, healthy pregnant women (group 2) had lower levels of HbA1c in comparison to patients with GDM (group 1) or healthy non-pregnant women (group 3). We anticipate, that the reason for this is the increase of insulin sensitivity in the first part of gravidity in healthy pregnant women.

Different patterns of gestational diabetes

In the literature, only few authors postulate that

GDM is not a uniform diagnosis [2,3]. Cheney *et al.* divided woman with GDM according to their weight (into lean and obese) and found different reaction to load of meal [2]. Obese patients with GDM were more hyperglycemic than lean GDM patients in both the fasting and postprandial periods [2]. Another study, published more recently by Powe *et al.*, divided women with GDM in the second semester into groups depending on their impaired insulin sensitivity or insulin secretion defect [3]. Relative to women with normal glucose tolerance, women with predominant insulin sensitivity defect had higher BMI and fasting glucose and larger infants. Women with predominant insulin secretion defects had BMI, fasting glucose and infant birth weights like those with normal glucose tolerance [3].

We divided women with GDM to 3 subgroups according to the diagnostic method which face the international recommendations (20) and was used in our previous publication (23): high fasting plasma glucose in the first trimester (subgroup 1), high fasting plasma glucose in the second trimester (subgroup 2) and high plasma glucose post 75-g oral glucose load (subgroup 3). Subgroup 2 is comparable with the group with insulin sensitivity defect (GDM sensitivity) from the Powe study and subgroup 3 is comparable with the group with insulin secretion defect (GDM secretion) from the same study. Subgroup 3 had lower fasting plasma glucose than groups 1 and 2, similarly as the GDM secretion group had lower fasting plasma glucose than the GDM sensitivity group (3). Similarly, the GDM subgroups did not differ in age, but we were not able to prove the disparity in BMI, HbA1c or fasting C-peptide, probably because of the small subgroup sizes. Also, Cheney and coworkers did not find any differences in HbA1c in different subgroups of GDM (2).

Interestingly, the subgroups differed in TG concentrations. Subgroup 1 had the lowest TG whereas subgroup 3 had the highest TG level, with the difference being statistically significant. HDL-C levels showed the opposite trend, but without reaching statistical significance. TC and LDL-C levels did not differ among the groups. This finding is quite unique, and we have not found any other study comparing lipid parameters in GDM subgroups. In the study by Cheney *et al*., there was no difference in mean fasting plasma levels of TC and TG among pregnant women, lean and obese GDM patients in the late third trimester [2]. Question arises whether women with GDM could be stratified into low-risk and high-risk groups according to the diagnostic methods and whether differences in TG levels among the subgroups could also play a role in adverse pregnancy out-come. In the future, developing a risk calculator (including glycemic and non-glycemic risk factors) for adverse pregnancy outcomes in GDM women should be considered [7].

A limitation of our study may be the small number of participants, wide margin of data collection and different group sizes. We neither recorded nor accounted for dietary variations between the women.

Conclusions

In view of our study and studies of other authors, it is important to measure both glucose and lipid profiles (with emphasis on TG levels) during pregnancy. GDM is probably not a uniform diagnosis. In the future, we should consider a different approach to GDM patients according to how the diagnosis was made, either based on elevated fasting glucose or elevated glucose level after glucose load. Better risk stratification could contribute to better outcomes.

Conflict of Interest

There is no conflict of interest.

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