Early Pregnancy Maternal Lipid Profiles and the Risk of Gestational Diabetes Mellitus Stratified for Body Mass Index

Reproductive Sciences
2015, Vol. 22(6) 712-717
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DOI: 10.1177/1933719114557896
rs.sagepub.com

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Abstract

Objective: To determine associations between lipid profiles in early pregnancy stratified by body mass index (BMI) and risk of developing gestational diabetes mellitus (GDM). **Study Design:** A total of 2488 healthy pregnant women were enrolled prospectively. Fasting plasma lipid profiles were measured at mean 11 weeks of gestation including triglycerides (TGs), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and cholesterol (CHO). We assessed early pregnancy maternal lipid concentrations in different tertiles in association with the risk of GDM stratified for BMI. Multivariable logistic regression analyses were used to estimate the relative risk of GDM by calculating odds ratios and 95% confidence intervals (CIs). **Results:** In univariate analyses, pregnant women with GDM had significantly increased serum TG, CHO, LDL concentrations, LDL/HDL ratio, and decreased HDL concentrations, compared to control groups, each $P < .01$, respectively. After adjustment for confounders, there was a 1.8-fold increase in risk for GDM in the lean group (95% CI: 1.2-2.7) and 2.7-fold increase in the obese group (95% CI: 1.1-6.6), respectively, if $TG \geq 1.58$ mmol/L. About a 50% decrease in the risk of GDM was observed in lean women with $HDL \geq 2.22$ mmol/L (95% CI: 0.3-0.9). No significant correlations of other lipid profiles with the risk of developing GDM were observed. **Conclusion:** Early pregnancy dyslipidemia is associated with the risk of developing GDM. Lean or obese women with higher TG concentrations are at an increased risk for developing GDM while lean women with high HDL are protected.

Keywords

pregnancy, triglycerides, high-density lipoprotein cholesterol, body mass index, gestational diabetes mellitus

Introduction

There is abundant evidence that gestational diabetes mellitus (GDM) has various adverse effects on maternal and infant outcomes, including increased risk of developing preeclampsia, fetal death, macrosomia, shoulder dystocia, perinatal hypoglycemia, and respiratory distress.^{1,2} Moreover, women with GDM are at increased risk of type 2 diabetes, hypertension, and cardiovascular disease later in life.³ So far, although the etiology of GDM is still unclear, it is thought to share similar pathophysiology with type 2 diabetes, which includes insulin resistance and deficient insulin secretion due to failure of pancreatic β cells.^{4,5} Some studies show that patients with insulin resistance and type 2 diabetes tend to have lipid and lipoprotein abnormalities, including elevated triglycerides (TGs), lower high-density lipoproteins (HDLs), and higher small dense low-density lipoproteins (LDLs). These 3 abnormalities constitute the so-called lipid triad or “atherogenic lipoprotein phenotype”.⁶ A few studies have been carried out to assess associations of lipid profiles in early pregnancy with subsequent risk of GDM.^{3,7,8} However, the results are inconsistent.

Maternal obesity is one of the important high risk factors of GDM that is well known. Moreover, maternal prepregnancy body mass index (pBMI) could affect lipid metabolism and plasma levels.⁹ However, so far few studies have been conducted to assess effects of early pregnancy maternal lipid concentrations stratified for BMI on developing GDM.

The aims of the study were to examine the relationship between serum lipid (maternal TG, TC, HDL, LDL, and HDL/LDL ratios) levels in early pregnancy in pregnant women with different BMI ranges and the risk of GDM.

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Materials and Methods

A prospective cohort study was performed in the Department of Obstetrics, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, one of the tertiary specialized hospitals in Obstetrics and Gynecology. The study protocol was approved by the ethics board of the hospital. All participants provided written informed consent during the initial enrollment.

Study Participants

Pregnant women were recruited for the study at their first prenatal visit between January 2013 and April 2013. Eligibility criteria included a gestational age between 6 and 15 weeks, age ≥ 18 years, a singleton pregnancy, and existence of a complete maternal and infant information record including maternal age, parity, gravity, education, height, pBMI weight, medical histories, disease histories of first-degree family members, and pregnancy outcomes. Exclusion criteria were as follows: the pregnant woman did not plan to deliver at our hospital, gestational age of 16 or more weeks, patient has prediabetes, diabetes, dyslipidemia, hypertension, or thyroid disorder, age < 18 or ≥ 45 years, or patient had no complete maternal and infant record. A total of 3022 pregnant women received a serum lipid test during their first visit, and the data of 2488 women who met the above-mentioned eligibility criteria were enrolled for analysis. To determine impacts of pBMI on the occurrence of GDM in this prospective study, we divided all participants into 2 groups (obese group: BMI ≥ 24 kg/kg² and lean group: BMI < 24 kg/kg²) stratified for BMI and estimated the risk of GDM in lean or obese women with different tertiles of lipid concentration.

Laboratory Analyses

Fasting blood lipid concentrations (more than 10 hours) were measured between 6 and 15 weeks of gestation (11.7 weeks on average). Participants did not need to undergo additional blood drawings for lipid tests because maternal lipid measurements had been one of routine test markers during their first prenatal visits in this hospital since 2011. Maternal TG and cholesterol (CHO) concentrations were determined using end-point colorimetric method by clinical chemistry analyzer (Beckman Coulter China, Inc. SuZhou, Jiangsu Province). The coefficients of variation for TG and CHO were $< 5\%$, respectively. High-density lipoprotein and LDL were tested by direct assay method (Prodia Diagnostics German, Botzingen). Analytical interassay coefficients of variation for LDL and HDL were $< 3\%$, respectively.

Definition

Body mass index was calculated as the weight (in kg) divided by the square of the height (in m²). Four groups were categorized based on the criterion recommended by the Group of China Obesity Task Force of the Chinese Ministry of Health, with the following definitions¹⁰: underweight (BMI < 18.5),

normal weight (BMI 18.5-23.9), overweight (BMI 24-27.9), and obese (BMI ≥ 28). Education level grading was based on the number of school years and was divided into 3 groups: high (> 16), medium (10-16 years), and low (≤ 9 years). A 75-g oral glucose tolerance test (OGTT) was carried out at 24 to 28 weeks of gestation in women not previously diagnosed with overt diabetes. A diagnosis of GDM was made when any one of the following values was met or exceeded in the 75-g OGTT according to American Diabetes Association (ADA) criteria¹¹: 0 hour (fasting), 5.1 mmol/L; 1 hour, 10.0 mmol/L; and 2 hour, 8.5 mmol/L according to ADA criteria.

Statistical Analysis

Statistical analyses were performed using SPSS package version 18.0 (SPSS Inc, Chicago, Illinois). Descriptive information was reported as mean $\pm$ standard deviation for continuous variables. Categorical variables were presented as numbers and percentages and tested with chi-square tests or Fisher exact tests (if the variable contained less than 5 measurements). The distributions of maternal TG, total cholesterol, LDL, HDL, and HDL/LDL were normalized by examination. Demographic variables (age, gravidity, parity, gestational weeks, pBMI, and maternal lipid profiles) were analyzed using the Student's *t* test between 2 groups. Analysis of variance was used to detect the difference between multiple groups followed. To evaluate the associations of maternal lipid concentrations in different BMI ranges with risk of GDM, we calculated different tertiles of the lipid concentrations according to the entire eligible data. We estimated the relative risk of GDM by calculating odds ratios (ORs) and 95% confidence intervals (CIs) in the multivariable logistic regression analyses. In multivariable logistic regression analyses, we adjusted for ages (< 35 , ≥ 35), gravidity (< 2 , ≥ 2), nulliparity (yes, no), first-degree family history of type 2 diabetes (yes, no), BMI (< 24 , ≥ 24), and education level (< 16 , ≥ 16) for ORs. A *P* value $< .05$ was considered statistically significant.

Results

Table 1 showed that GDM women were older, less educated, and had higher gravidity, parity, pBMI, and gestational age at delivery compared with controls. No significant difference was noted between GDM women and controls regarding mean birth weight.

Table 2 demonstrated associations of the unadjusted lipid concentrations with the risk of GDM. Pregnant women with GDM had significantly increased serum TG, CHO, LDL concentrations, LDL/HDL ratios, and decreased HDL concentrations compared to control groups, *P* $< .01$ for each.

Figure 1 displayed maternal lipid levels with different BMI classes in study participants. Maternal TG, LDL concentrations, and LDL/HDL ratios were significantly increased with increasing pBMI, *P* $< .01$. However, HDL concentrations were significantly decreased with elevated BMI, *P* $< .01$. Maternal CHO concentrations in the overweight group (BMI 24-27.9)

Table 1. The Baseline Characteristics and Maternal Lipid Profile of Study Participants.

	GDM (n = 379)	Control Group (n = 2166)	t or χ^2	P Value
Age, years	31.60 ± 4.25	30.40 ± 7.36	3.08	.002
Gravidity	1.97 ± 1.17	1.71 ± 1.00	4.72	.000
Parity	1.12 ± 0.35	1.08 ± 0.30	2.67	.008
Education level (school years) ≥ 16	239 (63.1%)	1574 (71.4%)	10.78	.001
9-16	105 (27.7%)	481 (22.2%)	5.50	.019
≤9	13 (3.4%)	42 (1.9%)	3.39	.066
Family history of diabetes	56 (14.8%)	197 (9.1%)	11.63	.001
Prepregnancy BMI, kg/m ²	22.57 ± 4.75	20.81 ± 5.45	5.86	.000
<18.5	41 (10.8%)	445 (17.3%)	10.20	.001
18.5-23.9	215 (56.7%)	1473 (68.0%)	18.37	.000
24-27.9	76 (20.1%)	204 (9.4%)	37.26	.000
≥28	38 (10.0%)	36 (1.7%)	79.94	.000
Gestational age at delivery, w	38.34 ± 1.27	38.84 ± 1.40	6.53	.000
Birth weight, g	3437.05 ± 480.68	3401.90 ± 442.12	0.09	.159

Abbreviations: GDM, gestational diabetes mellitus; BMI, body mass index.

Table 2. Maternal Serum Lipid Concentrations in GDM Women and Controls in Early Pregnancy.

	GDM (n = 379)	Control Group (n = 2166)	t	P Value
TG (mmol/L)	1.61 ± 0.88	1.26 ± 0.63	9.25	.000
CHO (mmol/L)	4.79 ± 1.08	4.56 ± 0.82	4.81	.000
HDL (mmol/L)	1.84 ± 0.46	1.97 ± 0.50	4.62	.000
LDL (mmol/L)	2.18 ± 0.72	2.09 ± 0.59	3.03	.003
LDL/HDL ratio	1.32 ± 0.61	1.11 ± 0.41	3.18	.002

Abbreviations: GDM, gestational diabetes mellitus; TG, triglyceride; CHO, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

were lower compared to the low-weight group (BMI < 18.5), but the highest CHO concentrations were detected in the highest BMI group, *P* < .05.

Table 3 showed early pregnancy maternal lipid profiles in different tertiles in association with the risk of GDM stratified for BMI. After adjusting for confounders, we found a 1.8-fold in the lean group (BMI < 24) and 2.7-fold increase in the obese group (BMI ≥ 24) in the risk of GDM and, respectively, if TG ≥ 1.58 mmol/L (upper tertile), as compared to peers with the same BMI range whose TG concentrations were < 0.87 mmol/L (lower tertile). As for CHO, after adjusting for potential confounders, lean women in the highest tertile (≥ 5.07mmol/L) had a 1.7-fold increase in the risk of GDM as compared with the corresponding lean women in the lowest tertile, 95% CI: 0.97-3.12. However, the risk of GDM was not different between different tertiles of CHO concentrations in the obese group. Odds ratio for GDM was decreased across increasing tertiles of HDL concentration in the lean group. Lean women in the upper tertile (≥ 2.22 mmol/L) had an almost 50% decreased risk of GDM as compared with lean women in the lower tertile (95% CI: 0.32-0.93). We examined the risk of GDM in relation to maternal LDL/HDL ratio. We noted that the GDM risk increased as the ratio increased in both the lean and obese groups. Women with the highest ratio values

Figure 1. Maternal lipid levels with different body mass index (BMI) classes in study participants.

(upper tertile ≥ 1.37) experienced a 1.9-fold and 2.3-fold increased risk of GDM in the lean and obese groups, respectively (95% CI: 1.31-2.69; 95% CI: 1.08-4.84, respectively) compared with women whose ratio values were < 0.85 (lower tertile). However, the association was attenuated considerably after adjusting for confounders (OR 1.01, 95% CI: 0.52-1.96; OR 2.4, 95% CI: 0.67-8.63, respectively) for the lean and obese groups. No significant associations were noted between the other lipids and the risk of developing GDM after adjustment for confounding factors.

Discussion

The present study showed that women who developed GDM had significantly increased TG, CHO, LDL concentrations, LDL/HDL ratios, and decreased HDL concentrations in early pregnancy, compared to controls in univariate analyses. After adjusting for potential confounders, we found that lean or obese women with higher TG concentrations were at an increased risk of developing GDM while lean women with high HDL were protected.

Table 3. Joint Analysis of Effects of Maternal BMI and Lipid Profile on the Risk of GDM.^a

	BMI	Lipid Level	No. of GDM	No. of Controls	Crude OR (95% CI)	Adjusted OR (95% CI)	χ^2	P
TG	<24 (kg/m ²)	<0.87	56 (22.2%)	518 (27.0%)	1	1	27.82	.000
		0.87-1.57	96 (38.1%)	1018 (53.1%)	0.82 (0.58-1.15)	0.74 (0.52-1.06)		
		≥1.58	100 (39.7%)	381 (19.9%)	2.27 (1.61-3.21)	1.813 (1.22-2.69)		
	≥24 (kg/m ²)	<0.87	8 (7.0%)	36 (15.0%)	1	1	11.85	.001
		0.87-1.57	43 (37.7%)	116 (48.3%)	1.67 (0.72-3.87)	1.59 (0.67-3.81)		
		≥1.58	63 (55.3%)	88 (36.7%)	3.22 (1.40-7.40)	2.703 (1.11-6.57)		
CHO	<24 (kg/m ²)	<4.04	55 (21.8%)	498 (26.0%)	1	1	7.99	.005
		4.04-5.06	115 (45.6%)	972 (50.7%)	1.00 (0.72-1.40)	1.13 (0.74-1.72)		
		≥5.07	82 (32.5%)	447 (23.3%)	1.55 (1.08-2.22)	1.74 (0.97-3.12)		
	≥24 (kg/m ²)	<4.04	24 (21.0%)	52 (21.7%)	1	1	1.51	.219
		4.04-5.06	50 (43.9%)	126 (52.5%)	0.86 (0.48-1.54)	0.58 (0.27-1.25)		
		≥5.07	40 (35.1%)	62 (25.8%)	1.40 (0.75-2.61)	0.69 (0.26-1.81)		
HDL	<24 (kg/m ²)	<1.66	77 (30.6%)	389 (20.4%)	1	1	7.67	.006
		1.66-2.19	113 (44.8%)	1005 (52.4%)	0.54 (0.40-0.74)	0.55 (0.37-0.80)		
		≥2.20	62 (24.6%)	522 (27.2%)	0.57 (0.40-0.82)	0.54 (0.32-0.93)		
	≥24 (kg/m ²)	<1.66	54 (47.4%)	89 (37.1%)	1	1	3.94	.047
		1.66-2.19	48 (42.1%)	113 (47.1%)	0.70 (0.43-1.13)	1.111 (0.60-2.05)		
		≥2.20	12 (10.5%)	38 (15.8%)	0.52 (0.25-1.08)	1.230 (0.41-3.61)		
LDL	<24 (kg/m ²)	<1.71	54 (21.5%)	516 (27.2%)	1	1	8.02	.005
		1.71-2.44	122 (48.6%)	975 (50.8%)	1.107 (0.80-1.54)	1.06 (0.66-1.70)		
		≥2.45	75 (29.9%)	421 (22.0%)	1.58 (1.10-2.27)	0.94 (0.47-1.85)		
	≥24 (kg/m ²)	<1.71	14 (12.5%)	42 (17.5%)	1	1	8.11	.004
		1.71-2.44	40 (35.7%)	117 (48.8%)	0.90 (0.46-1.75)	0.88 (0.33-2.33)		
		≥2.45	58 (51.8%)	81 (33.7%)	1.88 (0.96-3.66)	1.04 (0.32-3.410)		
LDL/HDL	<24 (kg/m ²)	<0.85	56 (22.3%)	512 (27.0%)	1	1	14.82	.000
		0.85-1.36	111 (44.2%)	1015 (52.9%)	0.94 (0.67-1.29)	0.74 (0.47-1.16)		
		≥1.37	84 (33.5%)	384 (20.1%)	1.86 (1.31-2.66)	1.01 (0.52-1.96)		
	≥24 (kg/m ²)	<0.85	9 (8.0%)	32 (13.3%)	1	1	16.59	.000
		0.85-1.36	30 (26.8%)	115 (47.9%)	0.76 (0.34-1.68)	0.84 (0.32-2.24)		
		≥1.37	73 (65.2%)	93 (38.8%)	2.28 (1.08-4.84)	2.40 (0.67-8.63)		

Abbreviations: BMI, body mass index; pBMI, prepregnancy body mass index; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GDM, gestational diabetes mellitus; CI, confidence interval; OR, odds ratio; CHO, cholesterol.

^aOR and 95% CI adjusted for age, gravidity, parity, first-degree family history of diabetes, and pBMI, and education degree.

Similar to our results, the study by Savvidou et al found women who developed GDM had higher TG, CHO, LDL levels, and lower levels of HDL in univariate analyses. However, only low HDL levels among lipid profiles were identified as significant independent predictors of GDM in stepwise analyses ($P \leq .015$).¹² Bower et al¹³ noted a high-TG and low-HDL pattern in women with GDM. The investigators thought it was reasonable due to the inverse association between HDL and TG. Emet et al did not observe positive associations between GDM and any lipid profile changes, but in patients with glucose intolerance, decreased CHO and LDL concentrations and increased TG concentrations were detected.⁷

With regard to each lipid marker, some studies from case-control studies^{13,14} or prospective studies^{3,12,15,16} suggested associations between higher TG concentrations and increased GDM risk, but other studies had different findings.^{7,17-20} Maternal CHO levels were found either unchanged in the first trimester^{7,17-19} or higher.^{12,16} Maternal LDL concentrations were also reported to be unchanged^{7,18} or increased.^{12,16} Rizzo et al²⁰ did not find any differences in the concentration of any of the plasma lipids between GDM women and controls but detected significantly increased levels of small-size dense LDL

particles in GDM women. Meanwhile, HDL was shown to be lower,¹² unchanged,⁷ or even higher.¹⁷

After we performed subgroup analyses stratified for BMI, we found that strong associations of increased maternal TG with the risk of developing GDM still remained in each subgroup (both obese and lean groups), independent of their pBMI. It implicated that special attention should be paid by health care providers to women with higher TG concentrations regardless of whether they are lean or obese. In addition, a trend toward increasing incidence of GDM was only noted in lean women with elevated CHO concentrations and not in obese women. It seems to suggest that maternal CHO concentrations play varied roles on the occurrence of GDM in different pBMI classes, and higher CHO by itself does not increase the risk of GDM in obese women. Notably, the protective effects of high HDL concentrations on GDM were seen only in lean women. Interestingly, we observed a trend toward the increased incidence of GDM at elevated tertiles of HDL concentrations in obese women. The mechanisms by which obesity partially offsets the protective effects of HDL on GDM are unclear.

Conflicts in findings among the studies mentioned earlier may be due to a variety of reasons, including study design,

sample size, confounders, variations in population characteristics, and diagnosis criteria of GDM. For instance, in this study, we adopted the latest ADA criteria for GDM which had by far the lowest diagnosis cut-offs.¹¹

To our knowledge, this is the only study in the literature to perform joint analysis of effects of maternal BMI and lipid profile on the occurrence of GDM. Our prospective study was unique in its design. First, to exclude possible effects of pBMI on GDM risk, maternal lipid profiles in association with adjusted risks of GDM stratified for BMI were determined. Second, we adjusted for a great number of potential confounders in multiple logistic regression analysis. Third, we had adequate numbers of patients with GDM and controls to evaluate a statistically significant difference. Fourth, blood samples were tested at 11 weeks of gestation on average, which is an earlier record in previous prospective studies. Moreover, maternal lipid concentrations were determined by testing morning fasting blood samples and were measured 1 to 2 hours after the blood was drawn, which was different from previous studies.³ This not only avoided concerns regarding possible effects of nonfasting condition on lipid concentrations, but it alleviated issues regarding storage and thawing effects.

Nevertheless, our study had some potential limitations. Although we adjusted for various potential confounders, we cannot exclude the possible impacts of other unmeasured covariates such as dietary factors, settlements, genotype, and race on lipid profiles since we did not collect these data in this study. Moreover, maternal pBMI was self-reported. Earlier studies showed that heavier women have a tendency to underreported their weight and underestimate their BMI.²¹ Self-reporting may have led us to misclassify some overweight/obese women as normal women, but the same underreporting would have appeared equally in controls.

So far, the mechanisms for associations between early pregnancy maternal dyslipidemia and GDM risk are unknown. Some investigators have hypothesized a few possible etiologies to explain these associations.

The TG concentrations were negatively correlated with LDL size,¹³ and small dense LDL particles are reported to be more susceptible to lipid oxidation than larger particles.²² Therefore, some researchers postulated that oxidative stress, secondary to dyslipidemia, may ultimately cause decreased insulin gene expression and impairment of insulin secretion.²³ Some studies have also suggested that chronic hyperglycemia may impair β -cell function and cause β -cell apoptosis.²⁴⁻²⁷ Kelley and Goodpasture assumed that excess TG storage, particularly in skeletal muscles, may lead to increased insulin resistance.²⁸

Several studies implicate that CHO metabolism/lipoprotein fractions may play key roles in the progression of β -cell failure. It is likely that these effects are mediated by c-Jun N-terminal kinase and caspase-3 pathways.²⁹

Some investigators assumed that dyslipidemia, which leads to increased TG and small density LDL, may contribute to the elevated oxidative stress and endothelial failure that occurs in preeclampsia and also insulin resistance.³⁰ Endothelial

dysfunction is the most accepted theory for the etiology of preeclampsia that is possibly associated with metabolic syndrome. Our findings regarding correlations of dyslipidemia with the risk of developing GDM risk further support the theory that relates GDM to metabolic syndrome.

Maternal lipid concentrations in the first trimester are concordant with nonpregnant women and are significantly different from nonpregnant levels mainly beginning from 12 weeks of gestation.³¹ Further studies are needed to determine whether interventions for dyslipidemia prior to pregnancy or in early pregnancy are helpful to prevent GDM.

Acknowledgments

We thank the participants for their participation and medical staff involved in this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This project was supported by “Capital Health industry special funds” from Beijing Health Bureau and Beijing Science Committee (Grant number 2011-2011-02) and “Capital Clinical Characteristic Research” from Beijing Science Committee China (Grant number Z121107001012166).

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