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Maternal gestational diabetes and childhood hyperlipidemia

Xiaoyun Yang[1,2], **Junhong Leng**[3], **Huikun Liu**[3], **Leishen Wang**[3], **Weiqin Li**[3], **Wei Li**[3], **Xilin Yang**[4], **Ming Liu**[2], **Gang Hu**[1]

[1]Chronic Disease Epidemiology Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA

[2]Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital, Tianjin, China

[3]Tianjin Women's and Children's Health Center, Tianjin, China

[4]Department of Epidemiology, School of Public Health, Tianjin Medical University, Tianjin, China

Abstract

Aims: To assess dyslipidemia risk between children exposed to maternal gestational diabetes mellitus (GDM) and those not exposed.

Methods: We recruited 1144 mother-child pairs (572 GDM and 572 non-GDM women matched by their offspring's age and sex). The age of offspring ranged from 3 to 9 years old. We used general linear models to compare mean values of different lipid profiles among children born to mothers with and without GDM. Logistic regression models were used to assess associations of maternal GDM with abnormal lipid profiles in offspring.

Results: After adjustment for maternal and children's characteristics, children born to mothers with GDM had lower mean values of high-density-lipoprotein (HDL) cholesterol (1.40±0.01 vs 1.50±0.01; P <0.001) and higher mean levels of triglycerides/HDL cholesterol ratio (0.37±0.01 vs 0.35±0.01; P <0.05) in comparison with their counterparts born to mothers without GDM. Multivariate-adjusted odds ratios among children exposed to mothers with GDM compared with the counterparts were 2.11 (95% confidence interval [CI 1.15–3.88]) for low HDL cholesterol and 1.35 (95% CI 1.00–1.81) for high triglycerides/HDL cholesterol ratio, respectively.

Conclusions: Maternal GDM was associated with an increased risk of hyperlipidemia in the offspring during early childhood aged from 3 to 9 years old.

Keywords

Gestational diabetes mellitus; children; lipid profile

Corresponding author: Gang Hu, Chronic Disease Epidemiology Laboratory, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808, Tel: 225-763-3053, Fax: 225-763-3009, gang.hu@pbrc.edu.

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Introduction

With rapid economic development, cardiovascular disease (CVD) has become one of the leading causes for death among Chinese adults (1). However, autopsy studies showed that the pathological progress of atherosclerosis began with aortic fatty streak and fibrous plaques in childhood, which were associated with dyslipidemia (2–4). Meanwhile, the abnormal serum lipid concentration can be tracked from childhood into adulthood, which had an adverse effect on CVD (5–7). Data from the National Health and Nutrition Examination Survey showed that from 2011 to 2012 approximately one in five US children and adolescents aged 8–17 years had an adverse concentration of total cholesterol, low-density-lipoprotein cholesterol (LDL-C) or non-high-density-lipoprotein cholesterol (non-HDL-C) (8). A meta-analysis from China indicated that the pooled prevalence of dyslipidemia including high total cholesterol, high triglyceride, high LDL-C or low HDL-C among Chinese children and adolescents was estimated as 25.3% (9). The high prevalence of dyslipidemia in children is likely to be an important predictor of subsequent CVD risk in adults. Thus, prevention of dyslipidemia in early childhood might prevent the atherosclerosis process and ultimately the incidence of CVD in adults (10).

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first recognition during pregnancy (11), is continued to increase in coming years due to the unhealthy dietary pattern, sedentary lifestyle, increase of elderly pregnant women and prevalence of obesity (12). The presence of GDM has adverse future health effects not only in mothers, but also in offspring including occurrence of obesity, high blood pressure, insulin resistance, diabetes, dyslipidemia, metabolic syndrome, and CVD (13) (14). As CVD incidence may be traced back to the maternal GDM (15) and has an association with dyslipidemia in childhood, more investigations have focused on the impact of maternal GDM on lipid profiles of the offspring. However, the results of previous studies were inconsistent (16–19). Until now, very few studies have assessed the impact of maternal GDM on lipid profiles in the offspring in mainland China. Thus, the objective of the present study was to evaluate the lipid profile in 3 to 9 years old children who were born to mothers with and without a history of GDM.

Participants and Methods

Tianjin GDM screening project

Tianjin is the fourth largest city in China with more than 12 million residents. There are six central urban districts with more than 4.3 million permanent residents. Since 1999, all pregnant women who lived in the six central districts have participated in the universal GDM screening launched by the Tianjin Women’s and Children’s Health Center. The average screening proportion of pregnancies was >91% during 1999 – 2008 (20). All pregnancies at 26–30 gestational weeks were enrolled in a one-hour oral glucose tolerance test (OGTT) with 50-g glucose load. Women with a glucose reading ≥7.8 mmol/L were invited to the Tianjin Women’s and Children’s Health Center to undergo a two-hour OGTT with 75-g glucose load. According to the 1999 World Health Organization (WHO)’s criteria, either diabetes (fasting glucose ≥7.0 mmol/L or 2-hour glucose ≥11.1 mmol/L) or impaired

glucose tolerance (2-hour glucose ≥7.8 mmol/L and <11.1 mmol/L) would be diagnosed as GDM (21).

Study population

Totally 76,325 women were screened from 2005 to 2009, among whom 4644 women were diagnosed as GDM and 71,681 were free of GDM. We invited all 4644 women with GDM to participate in the Tianjin Gestational Diabetes Mellitus Prevention Program. From August 2009 to July 2011, a total of 1263 GDM women finished the baseline survey. We randomly selected 572 GDM mother-child pairs who finished the Year 1 or 2 follow-up survey and also had blood samples as the GDM case group. No differences at baseline age (32.3 compared with 32.4 years), BMI (23.9 compared with 24.0 kg/m^2), fasting glucose (5.21 compared with 5.23 mmol/L), and 2-h glucose (6.57 compared with 6.59 mmol/L) were found between GDM women who were selected and those not selected as the case group. We simultaneously and randomly recruited 572 non-GDM mother–child pairs from 71,681 non-GDM women who finished the GDM screening at the same period with children's age (±1 month) and sex frequency-matched to 572 children of GDM mothers. The clinical examination's procedure, items, and timing for non-GDM mother-child pairs were almost the same as the GDM mother-child pairs. We collected written informed consents from all participants. This study was approved by the Human Subjects Committee of the Tianjin Women's and Children's Health Center.

Questionnaires and measurements

At the baseline survey, every mother completed a self-administered questionnaire including socio-demographic characteristics (age, marital status, education, income, and occupation); family history of diabetes; pregnancy outcomes (pre-pregnancy weight, weight gain during pregnancy and number of children); lifestyle in the past year including smoking habits (non-smoking, former smoking, current smoking), passive smoking status and alcohol intake; physical activity (0 min/day, <30 min/day, ≥ 30 min/day). Children's information was collected by another questionnaire completed by their mothers including children's general information, such as gender, birth date, age, birth weight, birth length, lactation (exclusive formula, mixed or exclusive breast), lactation duration, dietary habits (using a validated food frequency questionnaire), daily energy intake, sleeping time (≤ 8 hours/day, 9–10 hours/day, ≥ 11 hours/day), screen watching time, and outdoor physical activity time.

All mother-child pairs underwent physical examination including body weight (wearing light clothes), height (without shoes) by specially trained doctors using standardized protocols. Body weight and height were measured to the nearest 0.1kg and 0.1cm. Body mass index (BMI) was obtained by dividing weight in kilograms by the square of height in meters. All mothers' pre-pregnancy BMI calculation used their self-reported pre-pregnancy weight and their height. Children's BMI calculation used their body weight and height in the study visit. Children's Z scores for BMI-for-age were calculated according to the WHO growth reference and children's BMI was classified as normal weight (BMI<85^{th} percentiles, Z-score<1.035), overweight (85^{th} percentile ≤ BMI <95^{th} percentile, 1.035≤ Z-score <1.645), and obesity (BMI ≥ 95^{th} percentile, Z-score ≥ 1.645) according to the WHO age- and gender-specific growth reference (22, 23).

All children provided a 0.5-mL peripheral blood sample from the ring finger after at least 8 hours of fasting. The blood samples were immediately centrifuged and processed with an automatic device. Serum levels of total cholesterol, LDL-C, HDL-C, and triglyceride were measured enzymatically using Toshiba Automatic Chemistry Analyzer TBA-120FR (Toshiba Medical Systems Corporation) (24). We calculated the triglycerides to HDL-C ratio, as well as non-HDL-C levels using total cholesterol minus HDL-C. Childhood dyslipidemia was defined as total cholesterol ≥5.18 mmol/L, LDL-C ≥3.37 mmol/L, HDL-C <1.04 mmol/L, non-HDL-C ≥3.76 mmol/L or triglycerides ≥1.13 mmol/L (children aged from 0 to 9 years old) according to Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents in 2011 (25).

Statistical analysis

Demographic and lifestyle data of mothers and children were revealed according to maternal GDM status. Chi-square tests and T-test were used to assess the differences in categorical and continuous variables. General linear models were applied to assess the differences in childhood total cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides, and the triglycerides/HDL-C ratio according to maternal GDM status. Logistic regression was used to estimate the odds ratios (ORs) and 95% confidential intervals (CIs) of abnormal lipid profiles or upper quartile of the triglycerides/HDL-C ratio by maternal GDM status. All analyses were first adjusted for maternal age, gestational age at delivery, education, and smoking status (Model 1); then for children's birth weight, outdoor physical activity time, daily energy intake, screen watching time, sleeping time, and Z-score for BMI for age (Model 2); and further for maternal pre-pregnancy BMI, gestational weight gain and history of hypercholesterolemia (Model 3). All the statistical analyses were performed with SPSS statistics V.25.0 for Windows software package (IBM). Two-sided $P < 0.05$ was considered statistically significant.

Results

Mothers with GDM were older at delivery, had a higher pre-pregnancy BMI and less weight gain during pregnancy compared with women without GDM (Table 1). The mean value of age among children was 5.88 years old (age range from 3.15 to 9.96 years old). Boys accounted for 52.4%. Children of GDM mothers had higher birth weight and Z score for BMI for age, longer screen watching time and outdoor activity time, less sleeping time, and higher prevalence of overweight or obesity than offspring of non-GDM mothers (Table 1).

After adjustment of maternal delivery age, gestational age, education, smoking and children's birth weight, outdoor physical activity time, daily energy intake, screen watching time, sleeping time, and Z-score for BMI for age (multivariable-adjusted Model 2), children born to mothers with GDM had significant higher mean values of triglycerides (0.80 vs 0.76), non-HDL-C (3.01 vs 2.92), triglycerides/HDL-C ratio (0.38 vs 0.35) and lower mean values of HDL-C (1.39 vs 1.50) than children of non-GDM mothers (Table 2). After additional adjustment of maternal pre-pregnancy BMI, gestational weight gain and history of hypercholesterolemia (Model 3), differences of HDL-C and triglycerides/HDL-C ratio

between the two groups were still significant, but differences of triglycerides and non-HDL-C between the two groups disappeared.

Multivariable-adjusted (maternal delivery age, gestational age, education, and smoking, Model 1) odds ratios among children of GDM mothers compared with children of non-GDM mothers were 2.12 (95% CI 1.19–3.78) for low HDL-C, 1.32 (95%CI 1.01–1.73) for dyslipidemia, and 1.44 (95% CI 1.09–1.90) for high triglycerides/HDL-C ratio, respectively (Table 3). After further adjustment for children's birth weight, outdoor physical activity time, daily energy intake, screen watching time, sleeping time, Z-score for BMI for age, maternal pre-pregnancy BMI, gestational weight gain, and history of hypercholesterolemia (Model 3), associations of maternal GDM with the risk of children's low HDL-C and high triglycerides/HDL-C ratio were still significant, but the significant association between maternal GDM and offspring's dyslipidemia disappeared.

Discussion

The present study indicated that maternal GDM was associated with an increased risk of dyslipidemia in offspring during early childhood aged from 3 to 9 years old. The most obvious impacts on the lipid profile were increased risks of low HDL-C and high triglycerides/HDL-C ratio among children born to GDM mothers.

Several studies have found that maternal GDM increased the risks of obesity and insulin resistance in offspring (26, 27), and these two factors also increased the risk of dyslipidemia in children (28, 29). With the remarkable rise of the prevalence of dyslipidemia in children and adolescents in China (30, S1), it is important for early prevention of children's dyslipidemia especially among children born to GDM mothers. Several studies have assessed the association between maternal GDM and children's lipid profile, however results were inconsistent. A Polish case-control study consisted of 50 children exposed to GDM mothers and 46 control subjects detected high values of total and LDL-C among GDM-exposed children (19). Another study including 597 children indicated that maternal GDM exposure was associated with high levels of total and LDL-C only in girls, but not in boys (S2). The Danish National Birth Cohort of 561 offspring of GDM mothers and 597 control offspring aged 9 to 16 years found that children of GDM mothers displayed high levels of triglycerides and low levels of HDL-C (S3). A Chinese case-control study showed low levels of HDL-C among children born to GDM mothers compared with children of non-GDM mothers (18). Several other studies found no associations of maternal GDM with offspring's abnormal lipid profile. The major reasons for the inconsistency of these previous studies were small sample sizes, different ethnicities, and different age ranges of the children. The present study including 572 GDM and 572 non-GDM mother-child pairs demonstrated that children born to mothers with GDM had significantly higher mean values of triglycerides, non-HDL-C, triglycerides/HDL-C ratio and lower mean values of HDL-C than children of non-GDM mothers; and children of GDM mothers showed increased risks of low HDL-C and high triglycerides/HDL-C ratio compared with children of non-GDM mothers; and most of these associations were independent of major risk factors including maternal pre-pregnancy BMI and history of hypercholesterolemia. It has long been known that low level of HDL-C was a risk factor for CVD (S4). Recently, the triglycerides/HDL-C

ratio was suggested as a novel marker of endothelial dysfunction in obese children and was correlated with carotid artery intima-media thickness (IMT) (S5), which was considered to be a potential marker of preclinical atherosclerosis in children (S6), The present study indicated that maternal GDM was not only a risk factor for short-term dyslipidemia in offspring during childhood, but also might have an adverse effect on the long-term CVD risk during adulthood. Since non-HDL-C level has been identified as a significant predictor of the presence of atherosclerosis as powerful as any other lipoprotein cholesterol in children and adolescents (S7), the present study also assessed this marker and found an elevated value of non-HDL-C in children of GDM mothers than those of non-GDM mothers, however, this difference was not independent of maternal pre-pregnancy BMI, gestational weight gain and history of hypercholesterolemia.

The mechanisms underlying how GDM impacted lipid profiles of offspring are few and pathogenesis is not confirmed till now. There are different views. First, it is likely related to occurrence of the perturbed maternal lipid metabolism in the context of gestational hyperglycemia, which may affect offspring's lipid metabolism (S8). Second, some researchers thought dyslipidemia as secondary to hyperinsulinemia, which has been confirmed previously (S9), and the low HDL-C level may be associated with the inhibition of HDL-C biosynthesis by the direct effect of insulin (S10). Third, animal experiments indicated the impact of maternal hyperglycemia on hepatic lipid content and metabolism through oxidative stress and inflammatory pathways, which was associated with children's dyslipidemia (S11).

Our study has several strengths. First, our study recruited a larger number of GDM and non-GDM mother-child pairs matched by children's age and sex, which are more powerful to explore the association between maternal GDM and the risk of dyslipidemia of the offspring. Second, the present data included a variety of confounder risk factors that might obviously influence the children's lipid profile, such as children's birth weight, outdoor physical activity time, daily energy intake, screen watching time, sleeping time, z-score for BMI for age, and maternal pre-pregnancy BMI, gestational weight gain and history of hypercholesterolemia. Third, lipid profiles including total cholesterol, LDL-C, and HDL-C, and triglycerides were completely detected, and we also calculated the level of non-HDL-C and triglycerides/HDL-C ratio that could evaluate the lipid metabolism more comprehensively. There are also some limitations in our study. First, all the participants were Chinese and the conclusion can only represent a single ethnic group, thus larger surveys including disparate–ethnicities should be conducted in the future. Second, children in our study were all at pre-pubertal stage under 10 years old and the results were only fit for children at this certain age. After puberty, the change of hormone in vivo may alter the lipid profile, so future regular follow-ups are imperative. Finally, other confounders, such as maternal glucose control throughout pregnancy, and fathers' factors including history of hypercholesterolemia were not available in the present study.

Conclusion

Maternal GDM increased the risk for dyslipidemia among offspring, especially for low HDL-C and high triglycerides/HDL-C ratio, which may have an adverse effect on the

atherosclerosis early in the childhood. Strengthen screening and controlling dyslipidemia among children are very important, in particular for the children born to GDM mothers.

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Novelty statement

What's already known?

Maternal gestational diabetes (GDM) may have an influence on dyslipidemia of offspring, but the results were inconsistent.

What this study has found?

The odds ratios of low high-density-lipoprotein (HDL) cholesterol and high triglycerides/HDL cholesterol ratio were 2.07 and 1.36 among children of mothers with GDM compared with children of mothers without GDM.

What are the clinical implications of the study?

Maternal GDM is associated with an increased risk of hyperlipidemia in the offspring during early childhood aged from 3 to 9 years old.

Table 1.

Maternal and children's characteristic according to maternal gestational diabetes status

	Non-GDM	GDM	P value
No. of subjects (N)	572	572	
Maternal characteristics			
Age at delivery, years	29.7 (2.92)	30.5 (3.59)	<0.001
Pre-pregnancy body mass index, kg/m^2	21.4 (2.94)	22.9 (3.06)	<0.001
Gestational weight gain, kg	18.2 (6.72)	16.6 (5.86)	<0.001
Gestational age at delivery, weeks	39.1 (1.53)	39.1 (1.32)	0.76
Education, %			<0.001
≤12 years	10.9%	19.9%	
13–15 years	75.3%	73.1%	
≥16 years	13.8%	7.0%	
Gestational hypertension, %	3.3%	4.9%	0.18
History of hypercholesterolemia, %	9.6%	12.6%	0.11
Current smokers, %	3.7%	1.7%	0.06
Child characteristics			
Boys, %	52.4%	52.4%	1.00
Age, years	5.88 (1.23)	5.87 (1.24)	0.98
Birth weight, gram	3404 (455)	3538 (504)	<0.001
Energy intake, kcal/day	1404 (405)	1390 (465)	0.58
Outdoor activity, hours/day	3.1 (1.4)	3.3 (1.5)	<0.001
Sleeping time, %			<0.001
≤ 8 hours/day	11.1%	15.2%	
9–10 hours/day	67.0%	71.5%	
≥ 11hours/day	21.9%	13.3%	
Screen watching time, hours/day	0.95 (0.76)	1.17 (0.83)	<0.001
Body mass index, kg/m^2	15.7 (2.30)	16.2 (2.54)	<0.001
Z score for BMI-for-age	0.02 (1.28)	0.33 (1.33)	<0.001

Values are means (SD). unless otherwise specified.

GDM, gestational diabetes mellitus.

Table 2.

Comparison of children's different lipids measures according to maternal gestational diabetes status

	Non-GDM (n=572)	GDM (n=572)	P value
Total cholesterol, mmol/L			
Model 1	4.42 (0.03)	4.40 (0.03)	0.64
Model 2	4.42 (0.03)	4.41 (0.03)	0.77
Model 3	4.43 (0.03)	4.40 (0.03)	0.57
High-density lipoprotein cholesterol, mmol/L			
Model 1	1.50 (0.01)	1.39 (0.01)	<0.001
Model 2	1.50 (0.01)	1.39 (0.01)	<0.001
Model 3	1.50 (0.01)	1.40 (0.01)	<0.001
Low-density lipoprotein cholesterol, mmol/L			
Model 1	2.26 (0.03)	2.24 (0.03)	0.65
Model 2	2.26 (0.03)	2.25 (0.03)	0.78
Model 3	2.26 (0.03)	2.24 (0.03)	0.55
Triglycerides, mmol/L			
Model 1	0.76 (0.01)	0.81 (0.01)	0.010
Model 2	0.76 (0.01)	0.80 (0.01)	0.048
Model 3	0.76 (0.01)	0.80 (0.01)	0.11
Non-high-density lipoprotein cholesterol, mmol/L			
Model 1	2.92 (0.03)	3.01 (0.03)	0.034
Model 2	2.92 (0.03)	3.01 (0.03)	0.027
Model 3	2.93 (0.03)	3.00 (0.03)	0.070
Triglycerides/high-density lipoprotein cholesterol			
Model 1	0.35 (0.01)	0.38 (0.01)	0.006
Model 2	0.35 (0.01)	0.38 (0.01)	0.025
Model 3	0.35 (0.01)	0.37 (0.01)	0.048

Data are means (SE).

Model 1 adjusted for maternal age at delivery, gestational age at delivery, education, and current smoking. Model 2 adjusted for covariates in model 1 and also for children's birth weight, outdoor physical activity, daily energy intake, screen watching time, sleeping time, and z score for BMI-for-age. Model 3 adjusted for covariates in model 2 and also for maternal pre-pregnancy BMI, gestational weight gain, and history of hypercholesterolemia.

GDM, gestational diabetes mellitus.

Table 3.

Odds ratios for children's dyslipidemia according to maternal gestational diabetes status

	Non-GDM	GDM	P values
No. of subjects	572	572	
Total cholesterol ≥5.18 mmol/L			
No of cases	74	73	
Odds ratios (95% confidence intervals)			
Model 1	1	1.09 (0.77–1.56)	0.62
Model 2	1	1.11 (0.76–1.60)	0.59
Model 3	1	1.03 (0.70–1.50)	0.90
High-density lipoprotein cholesterol <1.04 mmol/L			
No of cases	19	38	
Odds ratios (95% confidence intervals)			
Model 1	1	2.12 (1.19–3.78)	0.011
Model 2	1	2.33 (1.28–4.24)	0.005
Model 3	1	2.11 (1.15–3.88)	0.016
Low-density lipoprotein cholesterol ≥3.37 mmol/L			
No of cases	26	18	
Odds ratios (95% confidence intervals)			
Model 1	1	0.77 (0.41–1.45)	0.42
Model 2	1	0.71 (0.37–1.38)	0.32
Model 3	1	0.65 (0.33–1.28)	0.21
Triglycerides ≥1.13 mmol/L			
No of cases	62	84	
Odds ratios (95% confidence intervals)			
Model 1	1	1.42 (0.99–2.03)	0.055
Model 2	1	1.26 (0.87–1.83)	0.23
Model 3	1	1.14 (0.78–1.68)	0.50
Non-high-density lipoprotein cholesterol ≥3.76 mmol/L			
No of cases	51	59	
Odds ratios (95% confidence intervals)			
Model 1	1	1.31 (0.87, 1.96)	0.20
Model 2	1	1.37 (0.90, 2.09)	0.14
Model 3	1	1.25 (0.81, 1.93)	0.31
Dyslipidemia (any one of above five)			
No of cases	140	166	
Odds ratios (95% confidence intervals)			
Model 1	1	1.32 (1.01, 1.73)	0.045
Model 2	1	1.27 (0.96, 1.68)	0.095
Model 3	1	1.18 (0.88, 1.57)	0.27
High quartile of triglycerides/high-density lipoprotein cholesterol			
No of cases	121	165	

	Non-GDM	GDM	P values
Odds ratios (95% confidence intervals)			
Model 1	1	1.44 (1.09, 1.90)	0.010
Model 2	1	1.32 (0.99, 1.76)	0.057
Model 3	1	1.35 (1.00, 1.81)	0.047

Model 1 adjusted for maternal age at delivery, gestational age at delivery, education, and current smoking. Model 2 adjusted for covariates in model 1 and also for children's birth weight, outdoor physical activity, daily energy intake, screen watching time, sleeping time, and z score for BMI-for-age. Model 3 adjusted for covariates in model 2 and also for maternal pre-pregnancy BMI, gestational weight gain, and history of hypercholesterolemia.

GDM, gestational diabetes mellitus.