e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(5); 2176-2183

Original Research Article

A Longitudinal Study of Lipid Concentrations in Pregnancy and the Risk of Gestational Diabetes Mellitus

Ankit Abhishek[1], Swastika Jayaswal[2], Ajay Kumar Sinha[3]

[1]Postgraduate, Department of Medicine, Nalanda Medical College, Patna, Bihar, India
[2]Senior Resident, Department of Obstetrics and Gynaecology, Nalanda Medical College, Patna, Bihar, India
[3]HOD & Associate Professor, Department of Medicine, Nalanda Medical College, Patna, Bihar, India

Received: 17-03-2023 / Revised: 18-04-2023 / Accepted: 24-05-2023
Corresponding author: Ankit Abhishek
Conflict of interest: Nil

Abstract

Objective: Few studies use longitudinal measurements of lipids during pregnancy, even though abnormal lipid profiles have been linked to gestational diabetes mellitus (GDM). The goals of this study were to describe the long-term changes in lipid profiles throughout pregnancy and to prospectively look at the relationships between plasma lipid levels and the risk of GDM.

Method: 105 GDM cases and 215 matched non-GDM controls from patients at the Nalanda Medical College, Patna participated in this nested case-control research over the course of a year. At gestational weeks 11–13, 14–25 (fasting sample), 22–30, and 32–37, blood samples were longitudinally taken. Enzymatic assays were used to determine the levels of triglycerides, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) in the plasma. The Friedewald formula was used to compute low-density lipoprotein cholesterol (LDL-C).

Results: As the pregnancy went on, plasma levels of triglycerides, total cholesterol, and LDL-C rose. The adjusted odds ratios (ORs) of GDM at gestational weeks 11–13 comparing the highest with lowest quartile for triglycerides and HDL–C, respectively, were 3.14 (95% confidence interval [CI] 1.37–7.14; P = 0.001) and 0.43 (95% CI 0.17–1.08; P for trend = 0.044). The corresponding ORs for triglycerides and HDL-C were 6.56 (95% CI 2.24-19.16; P for trend = 0.002) and 0.22 (95% CI 0.07-0.62; P = 0.004), respectively, during gestational weeks 14 to 25. We found no conclusive links between total cholesterol or LDL-C levels and the incidence of GDM.

Conclusion: In early and mid-pregnancy, higher plasma triglyceride and lower HDL-C concentrations were substantially related to an increased risk of GDM. Pregnancy LDL-C and total cholesterol levels were not substantially linked to the risk of GDM.

Keywords: Pregnancy; Longitudinal; Lipids; Triglycerides; Cholesterol; Gestational Diabetes.

Introduction

The most prevalent metabolic disorder during pregnancy is gestational diabetes mellitus (GDM), which is defined as glucose intolerance with onset or first

detection during pregnancy [Figure 1; 1]. GDM is linked to detrimental consequences for women and their children in the short- and long-term [1]. The developing fetus needs a constant supply of nutrients during pregnancy, independent of the mother's inconsistent food intake. As a result, metabolic alterations in lipid and carbohydrate metabolism are common in pregnant women [2]. Negative pregnancy and newborn outcomes may be linked to changes in maternal lipid metabolism [2].

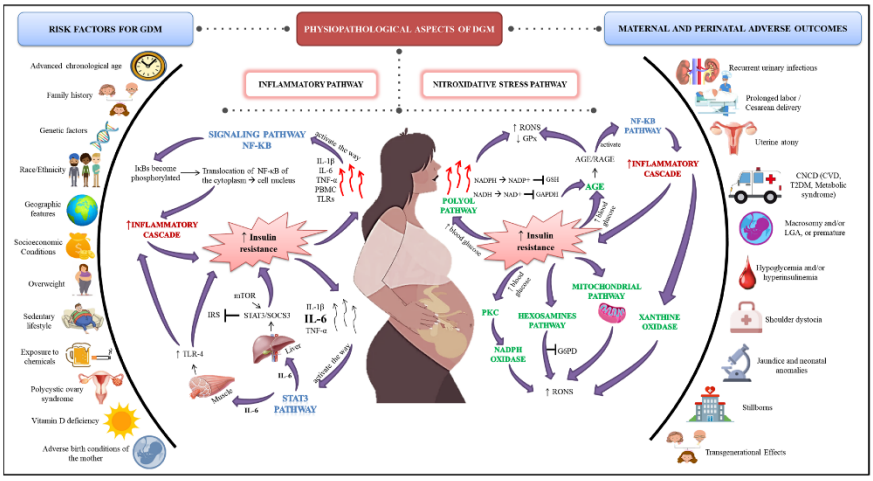

Figure 1: Gestational Diabetes Mellitus Linked with Pregnancy.

However, prior research on the correlations between circulating lipid patterns during pregnancy and the risk of GDM has produced conflicting results [3]. The bulk of earlier investigations used blood samples taken in the late second or even third trimester, when GDM may have already been identified, and were structured as cross-sectional comparisons between women with GDM and those with normal pregnancies [4]. Such studies thus lack an understanding of the temporal relationships between lipid disturbance and the incidence of GDM. Numerous prospective cohort studies have examined the relationship between circulating lipids at a certain period of early pregnancy and the risk of developing gestational diabetes. However, little is known about how circulating lipid changes throughout time during pregnancy relate to the risk of GDM.

This study's main goal was to prospectively investigate the relationships between maternal plasma lipid levels in the first and second trimesters and the later risk of GDM. Additionally, we sought to assess the longitudinal trend of plasma lipids during several pregnant trimesters.

Methods

Study Design: This was a nested case-control study conducted at Nalanda Medical College, Patna for one year.

Methodology: Sonograms, anthropometric measures, and questionnaires were used to track the progress of the women from the time they signed up until delivery. Maternal venous blood samples were longitudinally obtained across four chosen research visits, which were planned at 7–12, 15–21, 23–28, and 33–36 weeks of pregnancy. The blood sample from the second visit was taken while the mother was fasting. The participants were randomized to various follow-up plans within each study visit time window to acquire weekly biomarker data. The actual gestational weeks during blood collection, which ranged from 11-13, 14-25, 24-30, and 32-38 weeks, accordingly, went a little beyond the predetermined time frames due

to a few participants arriving after the scheduled appointment had already begun. Following collection, plasma samples were processed right away and kept at 80 °C till analysis.

Enzymatic tests were used to determine the levels of triglycerides, high-density lipoprotein cholesterol (HDL-C), and total cholesterol in the maternal plasma. Triglycerides, HDL-C, and total cholesterol each had analytical inter-assay coefficients of variation of 2.1%, 3.1%, and 2.2%, respectively. Friedewald's formula, which reads LDL-C = total cholesterol - HDL-C - triglycerides/5, was used to compute low-density lipoprotein cholesterol (LDL-C) [5]. All plasma lipid measurements were given in milligrams per liter (mg/dl). The status of GDM was not known before any of the tests were run. Plasma lipid levels were evaluated during the first two visits before the diagnosis of GDM in both GDM patients and controls. Plasma lipid measures were taken for the two visits before or after the diagnosis of GDM in each patient and one of the matched controls.

Maternal demographic, lifestyle, and health data were gathered using questionnaires or by consulting medical records. We included pre-pregnancy body mass index (BMI), which is derived from measured height and self-reported pre-pregnancy weight, and family history of diabetes, both of which are traditional risk factors for GDM. Maternal age and gestational age at blood collection were two matching parameters that could only be matched within a particular range to get conservative risk estimations.

Sample Size: This study comprised 215 matched non-GDM patient controls and 105 GDM cases.

Inclusion criteria: The pre-pregnancy body mass index (BMI) ranged from 18–45 kg/m^2 in the 19–41 age group with a singleton pregnancy.

Exclusion criteria: Women with HIV or serious chronic illnesses such as pre-existing diabetes, cancer, autoimmune, renal, or mental problems were not included.

Statistical analysis: For continuous data, descriptive statistics were presented as mean ± standard deviation (SD), or for categorical variables, as frequencies. Mixed-effect linear regression models for continuous variables and binomial/multinomial logistic regression with generalized estimating equations for binary/multilevel categorical variables, accounting for matched case-control pairs, were used to compare participant characteristics between GDM cases and controls.

Women were divided into quartiles based on the distribution of each plasma lipid variable among controls, with the lowest quartile serving as the referent group, to analyze the relationship between each plasma lipid variable and the risk of GDM. To determine if pre-pregnancy body weight status and family history of diabetes affected the correlations of maternal plasma lipids with GDM risk, we conducted interaction tests with multiplicative factors. The mean levels and standard errors (SE) of each biomarker were plotted against gestational-age intervals of 2-3 weeks to visualize the longitudinal changes in plasma lipid levels during pregnancy in GDM patients and controls. Using matched case-control pairs as input, mixed-effect linear regression models were used to compare the longitudinal changes between GDM patients and controls.

The SAS software program, version 9.4, was used to conduct all statistical analyses. Statistical significance was defined as a P-value of less than 0.04.

Results

In summary, women with GDM had higher pre-pregnancy BMIs than controls and were more likely to have a family

history of diabetes. There were no statistically significant differences seen in terms of education, health insurance type, marital status, parity, smoking, or alcohol intake [Table 1].

Table 1:

Criteria	GDM Case *n*	Control *n*	Crude model	Multivariable model*
Gestational weeks 11–13				
Total cholesterol, mg/dL				
Q1: 109.1–158.1	20	52	1.01	1.01
Q2: 159.1–179.1	24	53	1.15 (0.58, 2.27)	1.22 (0.58, 2.55)
Q3: 180.1–199.1	33	51	1.82 (0.91, 3.63)	2.30 (1.05, 5.02)
Q4: 200.1–289.1	21	52	1.01 (0.48, 2.04)	0.95 (0.43, 2.10)
P-for-trend			0.791	0.790
HDL–C, mg/dL				
Q1: 17–54.8	41	52	1.01	1.01
Q2: 55.0–63.5	25	52	0.62 (0.33, 1.14)	0.60 (0.30, 1.18)
Q3: 63.6–72.5	15	52	0.37 (0.17, 0.79)	0.45 (0.21, 1.06)
Q4: 73.2–125.4	17	52	0.41 (0.21, 0.86)	0.43 (0.17, 1.08)
P-for-trend			0.010	0.044
LDL–C, mg/dL				
Q1: 1.3–70.3	22	52	1.01	1.01
Q2: 70.4–88.1	24	52	1.11 (0.55, 2.15)	1.42 (0.65, 3.08)
Q3: 88.3–105.3	27	52	1.25 (0.65, 2.42)	1.62 (0.78, 3.32)
Q4: 105.8–170.2	23	52	1.03 (0.53, 2.02)	1.04 (0.48, 2.22)
P-for-trend			0.828	0.725
Triglycerides, mg/dL				
Q1: 56.1–93.1	13	52	1.01	1.01
Q2: 94.1–119.1	14	53	0.95 (0.42, 2.16)	0.94 (0.37, 2.33)
Q3: 120.1–155.1	24	52	1.71 (0.78, 3.63)	1.91 (0.81, 4.48)
Q4: 157.1–389.1	45	51	3.21 (1.53, 6.65)	3.14 (1.37, 7.14)
P-for-trend			<0.002	0.001
Gestational weeks 14–25				
Total cholesterol, mg/dL				
Q1: 118.1–177.1	23	53	1.01	1.00
Q2: 178.1–207.1	34	52	1.30 (0.67, 2.50)	1.28 (0.62, 2.67)
Q3: 209.1–230.1	16	54	0.60 (0.28, 1.25)	0.63 (0.28, 1.39)
Q4: 231.1–358.1	16	50	0.65 (0.30, 1.41)	0.77 (0.34, 1.76)
P-for-trend			0.098	0.298
HDL–C, mg/dL				
Q1: 12.2–58.0	31	53	1.01	1.01
Q2: 58.2–70.0	27	52	0.83 (0.41, 1.66)	0.95 (0.43, 2.11)
Q3: 70.1–82.6	23	52	0.72 (0.32, 1.51)	0.72 (0.31, 1.76)
Q4: 83.1–124.2	8	52	0.24 (0.11, 0.58)	0.23 (0.08, 0.63)
P-for-trend			0.001	0.004
LDL–C, mg/dL				
Q1: 11.5–82.6	23	53	1.01	1.01
Q2: 82.8–104.3	30	52	1.22 (0.60, 2.51)	1.11 (0.51, 2.47)

Q3: 104.3–125.3	17	52	0.81 (0.38, 1.65)	0.86 (0.38, 1.92)
Q4: 125.8–214.3	21	52	0.77 (0.37, 1.58)	0.80 (0.36, 1.75)
P-for-trend			0.325	0.485
Triglycerides, mg/dL				
Q1: 64.1–104.1	8	56	1.01	1.01
Q2: 105.1–134.1	16	51	1.88(0.75, 4.72)	2.91 (0.97, 8.74)
Q3: 136.1–170.1	31	52	3.52 (1.51, 8.22)	5.31 (1.83, 15.38)
Q4: 171.1–378.1	34	52	3.92 (1.67, 9.24)	6.56 (2.24, 19.16)
P-for-trend			0.002	0.002

Women who developed GDM exhibited decreased HDL-C levels and increased triglyceride levels in their plasma. The likelihood of developing gestational diabetes mellitus was strongly correlated with plasma levels of triglycerides and HDL-C at both 11–13 and 14–25 weeks of gestation (Table 1).

At gestational weeks 11–13, the adjusted ORs of GDM for triglycerides and HDL-C across increasing quartiles in the multivariable model were 1.01 (reference), 0.94, 1.91, and 3.14 (P for trend = 0.001) and 0.60, 0.45, and 0.43 (P for trend = 0.044), respectively. The corresponding ORs for triglycerides and HDL-C were 1.01 (reference), 2.91, 5.31, and 6.56 (P for trend = 0.002) and 1.01 (reference), 0.96, 0.72, and 0.22 (P for trend = 0.004), respectively, during gestational weeks 14 to 25. The observed relationships were only slightly diminished by further correction for other lipid components. For instance, after further adjusting for various lipid fractions, during gestational weeks 11–15, the ORs of GDM comparing the highest with the lowest quartile for triglycerides were 2.71 (1.14-6.34) and for HDL-C were 0.70 (0.27-1.80). The corresponding ORs were 6.74 (2.05-22.0) for triglycerides and 0.48 (0.14-1.58) for HDL-C during gestational weeks 14 to 25. We found no conclusive links between plasma LDL-C and total cholesterol levels and the risk of GDM. There was no discernible difference in the effects of a family history of diabetes or prepregnancy body weight.

We found that GDM patients continually had lower levels of HDL-C than controls in assessments of longitudinal trends of plasma lipids throughout pregnancy, with significant differences at gestational weeks 12–14, 21–22, 23–26, and 31–34. In the first and second trimesters, GDM patients had an average triglyceride level that was higher than controls, but there was no longer a discernible difference. Between GDM patients and controls during pregnancy, longitudinal increases in total cholesterol and LDL-C did not substantially vary from each other.

Discussion

We found an inverse relationship between plasma HDL-C levels and the risk of GDM among women who were longitudinally monitored from early pregnancy to delivery and a positive correlation between plasma triglyceride levels and future risk of GDM. Women who developed GDM and those who did not were compared for the longitudinal trends in their plasma lipid levels over the course of their pregnancies. We discovered that the plasma HDL-C levels in GDM cases were consistently lower from early to late pregnancy and that the plasma triglyceride levels among GDM cases were higher in the first and second trimesters than in controls.

Only two prior studies [6, 7] that tracked longitudinal changes in circulating lipid levels in pregnant women with and without GDM have been found to far. The statistical power needed to detect significant relationships between plasma lipids and GDM risk, however, may be

compromised by the fact that both earlier investigations relied on small sample sizes (one with 9 and the other with 12 GDM patients). In the research, which only included 9 GDM patients and 12 healthy controls, it was shown that GDM cases had considerably lower levels of HDL-C than controls, but that there was no discernible difference in triglyceride levels between cases and controls [6]. 12 of the 50 high-risk pregnant participants in the research went on to develop GDM [7]. While there were no significant correlations between plasma lipid levels and risk of GDM during the first trimester, higher levels of triglycerides and LDL cholesterol were linked to a considerably increased risk of GDM in the second and third trimesters, respectively [7].

Our findings on the potential correlations between plasma lipid concentrations in the first and second trimesters and risk of gestational diabetes mellitus were generally in agreement with some but not all prior prospective studies. A research [8] found a favourable correlation between triglyceride levels at around 13 weeks of gestation and likelihood of developing GDM, which is consistent with our findings. For other lipids, they did not discover a significant connection. According to two studies [9,10], women who developed GDM had lower levels of HDL-C and higher levels of triglycerides in the first trimester. According to a study, GDM development was linked to decreased HDL-C levels and higher triglyceride levels at 20 weeks of gestation [11]. There were no statistically significant correlations between lipids in the first and early second trimesters and GDM in a prior study that included exclusively obese pregnant women [12]. A favourable correlation between plasma triglyceride levels at gestational weeks 11–13 and the probability of developing gestational diabetes mellitus was discovered in our subgroup study of obese women. Other studies [13,14] found that in the univariate analysis, women who acquired GDM had higher levels of triglycerides than controls, but the link was not significant in the multivariable analysis.

The disparity in these studies' results may be at least partially attributable to heterogeneity in the study's methods and design, including variations in population characteristics, gestational age at blood collection, fasting status, and diagnostic criteria for gestational diabetes. According to a recent meta-analysis, which supports our findings, women who acquired GDM had greater triglycerides during all three trimesters of pregnancy than women who did not have insulin resistance throughout pregnancy [10]. Women with GDM had considerably lower HDL-C levels than women who were pregnant normally, however this difference was not seen in the first trimester [10]. It is necessary to conduct studies with a large sample size to determine how lipid metabolism contributes to the development of GDM.

Although specific mechanisms need to be clarified, the reported relationships of plasma lipids with GDM in this investigation are physiologically feasible. Significant physiological changes in lipid and glucose metabolism occur during pregnancy. Increased levels of maternal hormones and other maternal variables, such as pre-pregnancy BMI and gestational weight gain, may lead to changes in lipids and lipoproteins [15]. According to one research, triglycerides increased at the fastest rate during a typical pregnancy, whereas HDL-C increased at the slowest rate [16]. Although not all triglyceride levels in our study were measured in fasting samples, [17] we observed an initial slow slope in the increase of triglyceride levels in the first trimester, followed by a large increase towards the second trimester and doubled levels in the third trimester. Human studies show a connection between excessive skeletal muscle triglyceride buildup and impaired insulin sensitivity [18], which

may therefore play a role in the development of GDM.

Limitations

First, due to practicality concerns and the fact that it can be particularly challenging for pregnant women to fast, we were unable to obtain fasting samples during study visits outside of those between 14 and 25 weeks of gestation. As a result, care should be used when interpreting the longitudinal patterns of plasma lipid levels throughout pregnancy in this research. The observed connection, however, is not expected to be significantly influenced by fasting state.

Second, although this study is prospective and longitudinal, it cannot completely rule out the potential of reverse causality. Additionally, it should be highlighted that this study purposefully did not recruit women who had serious chronic illnesses like diabetes or cardiovascular disorders, which decreases the likelihood of reverse causation.

Third, even though we took into account significant confounders in the study, we were unable to completely rule out the possibility of residual confounding. For instance, even after adjusting for pre-pregnancy BMI, there may still be residual confounding from maternal obesity, which is a shared risk factor for lipid diseases and GDM.

Conclusion

In a longitudinal study of pregnant women of different races and ethnicities, we found a strong correlation between higher plasma triglyceride levels and lower HDL-C levels in the early and middle stages of pregnancy with a higher risk of developing gestational diabetes. Future studies are necessary to examine the interactions between dyslipidemia and biomarkers in additional pathways in the etiology of GDM.

Funding

No outside funding was used for this study.

References

1. American Diabetes Association. Gestational diabetes mellitus. Diabetes Care. 2004; 27:S88–90.
2. DeSisto CL, Kim SY, Sharma AJ. Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007–2010. Preventing chronic disease. 2014; 11:E104.
3. Ferrara A. Increasing prevalence of gestational diabetes mellitus: a public health perspective. Diabetes Care. 2007; 30:S141–6.
4. Zhu Y, Zhang C. Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. Current diabetes reports. 2016; 16:7.
5. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18: 499–502.
6. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 200 9; 373:1773–9.
7. Butte NF. Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. Am J Clin Nutr. 2000; 71: 12 56S–61S.
8. Alvarez JJ, Montelongo A, Iglesias A, Lasuncion MA, Herrera E. Longitudinal study on lipoprotein profile, high density lipoprotein subclass, and postheparin lipases during gestation in women. Journal of lipid research. 1996; 37:299–308.
9. Herrera E, Ortega-Senovilla H. Disturbances in lipid metabolism in

diabetic pregnancy - Are these the cause of the problem? Best Pract Res Clin Endocrinol Metab. 2010; 24:515–25.
10. Barrett HL, Dekker Nitert M, McIntyre HD, Callaway LK. Normalizing metabolism in diabetic pregnancy: is it time to target lipids? Diabetes Care. 2014; 37:1484–93.
11. Ryckman KK, Spracklen CN, Smith CJ, Robinson JG, Saftlas AF. Maternal lipid levels during pregnancy and gestational diabetes: a systematic review and meta-analysis. BJOG. 2015; 122:643– 51.
12. Montelongo A, Lasuncion MA, Pallardo LF, Herrera E. Longitudinal study of plasma lipoproteins and hormones during pregnancy in normal and diabetic women. Diabetes. 1992; 41:1651–9.
13. Paradisi G, Ianniello F, Tomei C, et al. Longitudinal changes of adiponectin, carbohydrate and lipid metabolism in pregnant women at high risk for gestational diabetes. Gynecol Endocrinol. 2010; 26:539–45.
14. Enquobahrie DA, Williams MA, Qiu C, Luthy DA. Early pregnancy lipid concentrations and the risk of gestational diabetes mellitus. Diabetes research and clinical practice. 2005; 70:134–42.
15. Savvidou M, Nelson SM, Makgoba M, Messow CM, Sattar N, Nicolaides K. First-trimester prediction of gestational diabetes mellitus: examining the potential of combining maternal characteristics and laboratory measures. Diabetes. 2010; 59:3017–22.
16. Makgoba M, Nelson SM, Savvidou M, Messow CM, Nicolaides K, Sattar N. First-trimester circulating 25-hydroxyvitamin D levels and development of gestational diabetes mellitus. Diabetes Care. 2011; 34:10 9 1–3.
17. Zhou J, Zhao X, Wang Z, Hu Y. Combination of lipids and uric acid in mid-second trimester can be used to predict adverse pregnancy outcomes. J Matern Fetal Neonatal Med. 2012; 25: 2633–8.
18. Maitland RA, Seed PT, Briley AL, et al. Prediction of gestational diabetes in obese pregnant women from the UK Pregnancies Better Eating and Activity (UPBEAT) pilot trial. Diabet Med. 2014; 31:963–70.