ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

POLISH GYNECOLOGY
GINEKOLOGIA POLSKA
ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGICZNEGO
THE OFFICIAL JOURNAL OF THE POLISH GYNECOLOGICAL SOCIETY

ISSN: 0017-0011

e-ISSN: 2543-6767

Serum homocysteine and lipid levels in the third trimester and their relationship with perinatal outcomes in diet-controlled gestational diabetes mellitus

Authors: Yuting Li, Mingrui Wang, Na Zhang, Yueling Wu, Wei Ye, Weichan Chen

DOI: 10.5603/gpl.101475

Article type: Research paper

Submitted: 2024-07-08

Accepted: 2024-08-22

Published online: 2024-12-19

Serum homocysteine and lipid levels in the third trimester and their relationship with perinatal outcomes in diet-controlled gestational diabetes mellitus

Yuting Li, Mingrui Wang, Na Zhang, Yueling Wu, Wei Ye, Weichan Chen

Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong, China

Corresponding author:

Weichan Chen

Affiliated Hospital of Guangdong Medical University, China,

e-mail: chen_weichan@163.com

ABSTRACT

Objectives: This study investigates the relationship between serum homocysteine, blood lipids, and perinatal outcomes in patients with diet-controlled gestational diabetes mellitus (GDM) and those with normal glucose tolerance (NGT).

Material and methods: A prospective cohort of 150 diet-controlled GDM patients and 150 pregnant women with NGT, all delivering at our hospital, were selected based on predefined criteria. Data on demographics, physical parameters, and perinatal outcomes were compiled. Blood samples for fasting plasma glucose (FPG), homocysteine (Hcy), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB), and apolipoprotein A1 (apoA1) were collected before delivery.

Results: GDM patients exhibited higher levels of FPG, Hcy, and the apoB/apoA1 ratio, but lower HDL-C and apoA1 levels compared to the NGT group. Adverse outcomes such as macrosomia, premature rupture of membranes, and postpartum hemorrhage were more

prevalent in the GDM group. In GDM patients, neonatal birth weight positively correlated with FPG and TG levels. Stratified Hcy analysis in GDM showed no significant differences in perinatal outcomes. However, the third quartile of the apoB/apoA1 ratio had a lower incidence of macrosomia compared to the first quartile, and the second quartile showed a higher incidence of birth asphyxia.

Conclusions: GDM patients demonstrated increased levels of Hcy, FPG, and the apoB/apoA1 ratio, correlating with more adverse perinatal outcomes than healthy pregnant individuals. The relationships between Hcy, lipids, and these outcomes remain inconclusive, highlighting the need for further research.

Keywords: serum homocysteine; Hcy; gestational diabetes mellitus; diet-controlled GDM; blood lipids; apoB/apoA1 ratio; pregnancy outcome; perinatal outcome

INTRODUCTION

Gestational diabetes mellitus (GDM) is a metabolic disorder characterized by glucose intolerance in women without a prior diabetes diagnosis [1]. With the rising trend of obesity, the incidence of GDM has increased, ranging from 10% to 41.9% according to the International Association of Diabetes in Pregnancy Study Groups (IADPSG) GDM criteria [2]. GDM is marked by impaired glucose tolerance resulting from maternal β-cell dysfunction in the pancreas, leading to an inability to produce sufficient insulin to maintain glucose homeostasis during pregnancy [3].

Insulin, an anabolic hormone secreted by pancreatic β-cells, regulates glucose homeostasis through multiple mechanisms: it promotes glucose uptake by peripheral tissues, reduces glucose production by the liver, and inhibits the release of stored lipids from adipose tissue. Insulin resistance is a condition where normal concentrations of insulin do not trigger an appropriate biological response downstream of the insulin receptor [4]. Some studies have

indicated a potential association between insulin resistance and elevated homocysteine (Hcy) levels [5]. Both acute and chronic exposure to Hcy have shown detrimental effects on β-cell metabolism and insulin secretion [6]. However, the relationship between Hcy levels and GDM, including its perinatal outcomes, has yielded conflicting results. While one study found that higher plasma Hcy levels correlated with a decreased risk of GDM [7], other research showed that serum Hcy levels were significantly higher in the GDM group compared to the control group [8]. Conversely, certain studies reported no discernible difference in serum homocysteine levels between the GDM and control groups [9].

Glucose intolerance and obesity-driven insulin resistance are intrinsically linked to dyslipidemia [4]. During pregnancy, maternal dyslipidemia, characterized by lipid levels exceeding typical physiological ranges, becomes prevalent. While lipid levels see a modest surge in early pregnancy, they undergo a significant physiological reduction as pregnancy progresses. This pattern of hyperlipidemia plays a pivotal role in fetal development [10]. However, elevated concentrations of specific lipids, including triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), coupled with diminished levels of high-density lipoprotein cholesterol (HDL-C), are implicated in various pregnancy complications [11]. The potential therapeutic role of statins during pregnancy has garnered considerable attention. For instance, statins have been found to be beneficial in patients with antiphospholipid syndrome (APS) in preventing pre-eclampsia or HELLP syndrome [12]. Despite these insights, the relationship between dyslipidemia in the third trimester and perinatal outcomes, especially among women with GDM, remains an uncharted territory.

Our study specifically focuses on diet-controlled GDM patients to isolate the effects of dietary management on pregnancy outcomes. This approach allows us to maintain a homogeneous study population and avoid the confounding influence of insulin therapy. Therefore, we sought to investigate the levels of Hcy and blood lipids in the third trimester of pregnancy and analyze their association with perinatal outcomes, aiming to contribute to a better understanding of the etiology of the disease and the potential need for lipid-lowering medication during pregnancy.

MATERIAL AND METHODS

Study design and population

This prospective case-control study was conducted at the Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong, China. Pregnant women who delivered at our hospital between January 2017 and December 2020 were recruited for the study. The study was approved by the Research Ethics Committee of the Affiliated Hospital of Guangdong Medical University, and informed consent was obtained from all participants prior to sample collection.

Sample size calculation and power analysis

To ensure the statistical power of our study, we performed a sample size calculation and power analysis using G*Power software. Assuming an effect size of 0.5, a significance level (α) of 0.05, and a statistical power (1-β) of 0.80, the results indicated that each group would require 64 participants, totaling 128 participants. In our actual study, we recruited 300 participants, with 150 in the GDM group and 150 in the control group. The power analysis results indicated that, with the current sample size, the statistical power exceeds 0.99, demonstrating that the study has sufficient power to detect the expected effect.

Informed consent and sample collection

Informed consent was obtained from all participants before they were enrolled in the study. Participants were informed about the purpose of the study, the procedures involved, and their right to withdraw at any time without any impact on their medical care.

Rationale for fasting sample collection

Fasting blood samples, including serum homocysteine and lipid levels, were collected to monitor and understand the metabolic changes during pregnancy, particularly in women diagnosed with GDM. These samples were collected as part of the clinical management of high-risk pregnancies to better assess and manage potential complications.

Serum sample collection and processing

Blood samples were drawn from all participants after an 8-hour fast. These samples

were collected before delivery to provide a consistent metabolic profile close to the delivery date. The collected blood samples were immediately placed on ice and transported to the laboratory for processing. The serum was separated from whole blood within 2 hours of collection using standard procedures to ensure the integrity of the samples. None of the subjects had missing serum samples, indicating complete data collection for all participants.

Matching and selection of control group

Controls were matched to the GDM group based on age, gestational age, and body mass index (BMI) to ensure comparability. The selection criteria and matching parameters are detailed in Table 1.

Inclusion and exclusion criteria

Inclusion criteria

Pregnant women undergoing a 75-g oral glucose tolerance test (OGTT) between 24 to 28 weeks' gestation were considered. Those diagnosed with GDM were included in the GDM group, while those with normal results were categorized into the NGT group. All participants were uniparous with singleton pregnancies and complete data records. GDM diagnosis was based on any one of the following conditions: 0-min serum glucose ≥ 5.1 mmol/L, 60-min serum glucose ≥ 10.0 mmol/L, or 120-min serum glucose ≥ 8.5 mmol/L) [2].

Exclusion criteria

Women with multiple gestations, pre-existing diabetes, severe medical comorbidities (such as hypertension, thyroid insufficiency, hematological disorders, tumors, or autoimmune diseases), multipara status, usage of metformin or insulin therapy, or incomplete documentation were excluded from the analysis.

Definitions

Macrosomia: Defined as a birth weight exceeding the 90th percentile for gestational age or more than 4,000 g [13].

Premature rupture of membranes (PROM): Refers to the rupture of the membranes before the onset of labor. If the membrane rupture occurs before 37 weeks' gestation, it's

termed preterm PROM [14].

Postpartum hemorrhage: Defined as a total blood loss of at least 1,000 mL or blood loss accompanied by signs and symptoms of hypovolemia within 24 hours after the delivery of the fetus, or during intrapartum loss [15].

Polyhydramnios: Diagnosed when the amniotic fluid index (AFI) exceeds 25 cm [16].

Preterm birth: Occurs when delivery is before 37 weeks of gestational age [17].

Birth asphyxia: Identified by any of the following characteristics in a newborn: a 10-minute Apgar score of ≤ 5, a need for resuscitation lasting more than 10 minutes, or metabolic acidosis (with pH ≤ 7.0 or base excess ≤ −12 mmol/L in the umbilical artery or detected within 1 hour of birth) [18].

Neonatal hypoglycemia: Defined by blood glucose levels of ≤ 36 mg/dL (considered severe) and ≤ 47 mg/dL (considered mild) [19].

Analytical methods

Fasting blood samples (5 mL) were collected from each woman after an 8-hour fast, following the diagnosis of GDM and the initiation of standard dietary management. FPG was measured in both groups using a glucometer (Roche ACCU-CHEK). TG, TC, HDL-C, LDL-C, apoA1, and apoB were analyzed by an automated biochemical analyzer (Hitachi 7180, WAKO) using commercially available kits. TG and TC were determined by the HMMPS method (WAKO, Japan), HDL-C and LDL-C by the direct assay method (Shanghai Beijia Biochemistry Reagents Co., Ltd., China), and apoA1 and apoB by the immunotransmission turbidity method (Shanghai Beijia Biochemistry Reagents Co., Ltd., China). All serum indices were analyzed in the laboratory of our center.

Statistical analysis

Continuous variables were expressed as mean ± SD if they had a normal distribution, otherwise as median (P25, P75). Categorical variables were expressed as numbers with percentages. Differences in continuous variables between the two groups were assessed using unpaired Student's t-test or Mann–Whitney U test if the data were not normally distributed.

Categorical variables were analyzed using the chi-squared test or Fisher's exact test. To examine the relationships between laboratory parameters and perinatal complications, logistic regression analysis was performed, providing odds ratios (OR) and 95% confidence intervals (CI). Bivariate correlations were analyzed using Pearson's correlation or Spearman's rank correlation analysis where appropriate. $p < 0.05$ was considered statistically significant. Analyses were performed using SPSS software version 19.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Anthropometric and clinical characteristics of the participants

The differences in age, height, weight, BMI, systolic, and diastolic BP between the two groups were not statistically significant ($p > 0.05$). However, the GDM group had significantly fewer gestational weeks at delivery compared to the NGT group ($p < 0.05$). Refer to Table 1 for details.

Comparison of serum FPG, Hcy, and blood lipid levels

The GDM group was characterized by higher levels of FPG, Hcy, and apoB/apoA1, and lower levels of HDL-C and apoA1 compared to the NGT group ($p < 0.05$). The levels of TC, TG, LDL-C, and apoB between the two groups were not statistically significant ($p > 0.05$). Details are presented in Table 2.

Perinatal outcomes comparison

The incidences of macrosomia, premature rupture of membranes, postpartum hemorrhage, cesarean section, polyhydramnios, preterm birth, birth asphyxia, neonatal hypoglycemia, and NICU admission were significantly higher in the GDM group than in the NGT group ($p < 0.05$). The neonatal birth weight was statistically similar between both groups ($p > 0.05$), as shown in Table 3.

Correlation of FPG, Hcy, and blood lipid levels with perinatal outcomes in the GDM and NGT groups

As shown in Table 4, in the GDM group, neonatal birth weight was positively correlated with FPG ($r = 0.207$, $p < 0.05$) and TG ($r = 0.193$, $p < 0.05$). There was no significant correlation with Hcy, TC, HDL-C, LDL-C, apoB, apoA1, or the apoB/apoA1 ratio. Furthermore, perinatal outcomes such as macrosomia, premature rupture of membranes, postpartum hemorrhage, preterm delivery, birth asphyxia, NICU admission, and cesarean section showed no significant differences ($p > 0.05$).

In the NGT group, as detailed in Table 5, no significant correlations were observed for any of the parameters except for FPG, which was positively correlated with macrosomia ($r = 0.196$, $p < 0.05$).

Subgroup analysis of Hcy, apoB/apoA1, and perinatal outcomes in the GDM group

As shown in Table 6, the Hcy levels (μmol/L) within the GDM group were divided into four quartiles: group 1 (≤ 5.48), group 2 (> 5.48 and ≤ 6.30), group 3 (> 6.30 and ≤ 8.0), and group 4 (> 8.0). After conducting multiple comparisons, the results indicated no significant differences in the incidence of all perinatal outcomes across these quartiles ($p > 0.05$).

Similarly, as shown in Table 7, the apoB/apoA1 ratio in the GDM group was divided into four quartiles: group 1 (≤ 0.48), group 2 (> 0.48 and ≤ 0.59), group 3 (> 0.59 and ≤ 0.72), and group 4 (> 0.72). While the overall comparisons across these groups revealed significant differences, specific subgroup analyses were further conducted. Notably, the incidence of macrosomia was 23.3% (10/43) in the 1st quartile (Q1) and 2.7% (1/37) in the 3rd quartile (Q3), demonstrating a significant disparity. The incidence of birth asphyxia showed significant differences as well, being 2.3% (1/43) in Q1 and 21.4% (6/28) in the 2nd quartile (Q2). Outside of these specific comparisons ($p < 0.05$), the remaining group analyses did not yield statistically significant differences ($p > 0.05$).

DISCUSSION

In this study, we found that women with GDM were characterized by higher Hcy levels compared to women with NGT. This finding is consistent with some existing research

[8, 20]. Hcy is a non-protein α-amino acid formed by the demethylation of methionine. It's worth noting that Hcy levels have shown variability throughout pregnancy stages, returning to early pregnancy levels during late pregnancy [21]. The elevated Hcy levels in GDM patients might arise from the MTHFR mutation (677CT), nutritional disorders such as low folate intake, impaired renal function, anticonvulsant medications, phenothiazines, carbamazepine, and smoking [22].

Even though Hcy levels are lower in late pregnancy than before pregnancy, pregnant women are more susceptible to Hcy disorders. The generation of hydrogen peroxide and superoxide free radicals is stimulated by Hcy [23]. This stimulation leads to oxidative damage to endothelial cells, fewer blood vessels in the villus, and reduced blood flow at the maternal-fetal interface, resulting in poor maternal and neonatal outcomes [24].

In our research, we found that the incidences of macrosomia, premature rupture of membranes, postpartum hemorrhage, cesarean section, polyhydramnios, preterm birth, birth asphyxia, neonatal hypoglycemia, and NICU admission were significantly higher in the GDM group than in the NGT group. However, further analysis showed that the correlation between Hcy and the aforementioned perinatal outcomes was not significantly different. Since these perinatal outcomes are not directly related to the placenta, our results are consistent with the theory that Hcy mainly has adverse effects on vascular and trophoblastic cells. Therefore, further studies on perinatal outcomes in GDM are needed to identify additional underlying factors. Notably, a 4-year prospective study showed that higher homocysteine levels at baseline were independently associated with the development of postpartum diabetes [25]. As such, GDM patients with elevated Hcy during pregnancy should also focus on Hcy monitoring in the postpartum period. Early intervention is recommended to prevent type 2 diabetes.

Additionally, we discovered that women with GDM had higher levels of FPG, apoB/apoA1 ratio, and lower levels of HDL-C and apoA1 compared to NGT women. Meanwhile, the levels of TC, TG, and LDL-C between the two groups were not statistically significant. Furthermore, FPG and TG levels in the GDM group were positively correlated with neonatal birth weight, whereas FPG levels in the NGT group were positively correlated

with macrosomia.

The above results are consistent with previous studies. For example, Pasternak et al. [26] demonstrated that apoA1 in maternal plasma was reduced in women with GDMA2 compared with normal pregnancy. Notably, even among those with normal glucose tolerance, poor control of FPG was linked to an increased risk of large for gestational age (LGA). For every 1 mmol/L increase in FPG, the observed birth weight increased by a Z-score of 0.48 standard deviations (95% CI 0.39 to 0.57), and the odds of LGA increased with an OR of 2.61 (95% CI 1.86 to 3.66) [27]. Furthermore, in our subgroup analysis, we found that the Q3 interval of the apoB/apoA1 ratio had a lower proportion of macrosomia, and the Q2 interval exhibited a higher rate of neonatal asphyxia. A cohort study involving 2,577 pregnant women discovered that both apoB and the TG/HDL-C ratio were associated with an increased risk of macrosomia. After adjusting for confounding variables, apoB and the TG/HDL-C ratio were found to mediate the effect of FPG on the onset of macrosomia [28]. This is not entirely consistent with our results. The discrepancies might arise from the limited sample size in our subgroup analysis or from the influence of confounding variables, such as FPG. It's crucial to conduct additional studies to delve deeper into the association between apoB, apoA1, or other lipids and macrosomia. There are relatively few studies on the relationship between apoB/apoA1 and macrosomia. Therefore, more studies are needed to clarify the underlying mechanism.

During the third trimester, maternal metabolism primarily relies on lipids as a fuel source. Apolipoproteins are essential for maintaining the function of different groups of lipoproteins. ApoA1, a major component of HDL-C, facilitates the transportation of cholesterol from the peripheral blood back to the liver for metabolism [29]. ApoB mainly transports atherosclerosis-related proteins such as IDL, LDL, VLDL, and Lp(a), with each lipoprotein particle containing a single apoB molecule [30]. Abnormalities in lipid metabolism have been implicated in the development of many adverse pregnancy outcomes, including pre-eclampsia and fetal growth restriction. However, TG levels have not been tied to macrosomia; they might represent a physiological alteration for fetal growth [33].

Furthermore, an elevated apoB/apoA1 ratio indicates an imbalance between the

atherogenic and antiatherogenic capacity of GDM patients during pregnancy. ApoB reflects the total burden of atherogenic factors in the peripheral circulation and is more sensitive than other lipid indicators in predicting the risk of developing cardiovascular diseases, such as coronary heart disease [34]. Conversely, ApoA1 possesses anti-inflammatory and antioxidant functions, playing an anti-atherogenic role [29]. Thus, the ApoB/apoA1 ratio effectively mirrors the balance between atherogenic and anti-atherogenic capacity within the body. A Korean cohort study involving 23,918 healthy men demonstrated that serum levels of apoB, apoA1, and the apoB/apoA1 ratio were all independently linked to the risk of coronary heart disease [35]. Moreover, in 2,627 participants without known vascular disease in the Collaborative Atorvastatin Diabetes Study, the apoB/apoA1 ratio at baseline emerged as the most predictive lipoprotein variable for CHD risk — this conclusion was based both on comparison of the hazard ratio for a 1 SD change and on analysis of tertiles of the frequency distribution [36]. A 5-year follow-up study indicated that patients with a history of GDM might maintain an elevated apoB/apoA1 ratio postpartum, underscoring the importance of continued lipid monitoring and prevention to mitigate long-term cardiovascular risks [37].

Our study specifically focused on diet-controlled GDM patients to maintain the homogeneity of the study population and to specifically examine the effects of dietary intervention on GDM outcomes. This exclusion was deliberate to avoid the confounding influence of insulin therapy, which could obscure the specific impacts of dietary management on GDM. However, we acknowledge that including insulin-treated patients could provide additional insights and enhance the clinical significance of the study. Future studies should consider including patients on insulin therapy to provide a more comprehensive analysis of GDM management. This would allow for a better understanding of the differential impacts of dietary intervention and insulin therapy on pregnancy outcomes in GDM patients.

CONCLUSIONS

Compared to healthy pregnant women, those with GDM exhibited higher levels of Hcy, FPG, and apoB/apoA1 ratio, as well as increased adverse perinatal outcomes. The

relationship between Hcy, lipids and adverse perinatal outcomes remian inconclusive, necessitating further research.

Article information and declarations

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

The study was approved by the Research Ethics Committee of the Affiliated Hospital of Guangdong Medical University. Informed consent was obtained from all participants.

Author contributions

YTL — wrote the manuscript, MRW and NZ — made diagrams, YLW — contributed substantial advice help to polish the language. WY and WCC — conducted the project and revised the whole manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Funding

None.

References

1. Szmuilowicz ED, Josefson JL, Metzger BE. Gestational diabetes mellitus. Endocrinol Metab Clin North Am. 2019; 48(3): 479–493, doi: 10.1016/j.ecl.2019.05.001, indexed in Pubmed: 31345518.
2. Gopalakrishnan V, Singh R, Pradeep Y, et al. Evaluation of the prevalence of gestational diabetes mellitus in North Indians using the International Association of Diabetes and

Pregnancy Study groups (IADPSG) criteria. J Postgrad Med. 2015; 61(3): 155–158, doi: 10.4103/0022-3859.159306, indexed in Pubmed: 26119433.

3. Plows JF, Stanley JL, Baker PN, et al. The pathophysiology of gestational diabetes mellitus. Int J Mol Sci. 2018; 19(11), doi: 10.3390/ijms19113342, indexed in Pubmed: 30373146.

4. Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. Lancet. 2010; 375(9733): 2267–2277, doi: 10.1016/S0140-6736(10)60408-4, indexed in Pubmed: 20609972.

5. Tessari P, Cecchet D, Vettore M, et al. Decreased homocysteine trans-sulfuration in hypertension with hyperhomocysteinemia: relationship with insulin resistance. J Clin Endocrinol Metab. 2018; 103(1): 56–63, doi: 10.1210/jc.2017-01076, indexed in Pubmed: 29029082.

6. Patterson S, Flatt PR, Brennan L, et al. Detrimental actions of metabolic syndrome risk factor, homocysteine, on pancreatic beta-cell glucose metabolism and insulin secretion. J Endocrinol. 2006; 189(2): 301–310, doi: 10.1677/joe.1.06537, indexed in Pubmed: 16648297.

7. Lai JS, Pang WW, Cai S, et al. High folate and low vitamin B12 status during pregnancy is associated with gestational diabetes mellitus. Clin Nutr. 2018; 37(3): 940–947, doi: 10.1016/j.clnu.2017.03.022, indexed in Pubmed: 28381340.

8. Liu W, Huang Z, Tang S, et al. Changes of serum sex hormone-binding globulin, homocysteine, and hypersensitive CRP levels during pregnancy and their relationship with gestational diabetes mellitus. Gynecol Obstet Invest. 2021; 86(1–2): 193–199, doi: 10.1159/000515085, indexed in Pubmed: 33906193.

9. Radzicka S, Ziolkowska K, Zaborowski MP, et al. Serum homocysteine and vitamin B12 levels in women with gestational diabetes mellitus. Ginekol Pol. 2019; 90(7): 381–387, doi: 10.5603/GP.2019.0066, indexed in Pubmed: 31392707.

10. Herrera E, Ortega-Senovilla H. Lipid metabolism during pregnancy and its implications for fetal growth. Curr Pharm Biotechnol. 2014; 15(1): 24–31, doi: 10.2174/1389201015666140330192345, indexed in Pubmed: 24720597.

11. Li Y, Wang X, Jiang F, et al. Serum lipid levels in relation to clinical outcomes in pregnant women with gestational diabetes mellitus: an observational cohort study. Lipids Health Dis. 2021; 20(1): 125, doi: 10.1186/s12944-021-01565-y, indexed in Pubmed: 34587947.

12. Vahedian-Azimi A, Karimi L, Reiner Ž, et al. Effects of statins on preeclampsia: a systematic review. Pregnancy Hypertens. 2021; 23: 123–130, doi: 10.1016/j.preghy.2020.11.014, indexed in Pubmed: 33333432.

13. Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab. 2015; 66 Suppl 2: 14–20, doi: 10.1159/000371628, indexed in Pubmed: 26045324.

14. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins — Obstetrics. Practice bulletin no. 172: premature rupture of membranes. Obstet Gynecol. 2016; 128(4): e165–e177, doi: 10.1097/AOG.0000000000001712, indexed in Pubmed: 27661655.

15. Evensen A, Anderson JM, Fontaine P. Postpartum hemorrhage: prevention and treatment. Am Fam Physician. 2017; 95(7): 442–449, indexed in Pubmed: 28409600.

16. Berezowsky A, Ashwal E, Hiersch L, et al. Transient isolated polyhydramnios and perinatal outcomes. Ultraschall Med. 2019; 40(6): 749–756, doi: 10.1055/a-0645-1136, indexed in Pubmed: 30253428.

17. Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth. Lancet. 2008; 371(9606): 75–84, doi: 10.1016/S0140-6736(08)60074-4, indexed in Pubmed: 18177778.

18. Locatelli A, Lambicchi L, Incerti M, et al. Is perinatal asphyxia predictable? BMC Pregnancy Childbirth. 2020; 20(1): 186, doi: 10.1186/s12884-020-02876-1, indexed in Pubmed: 32228514.

19. Voormolen DN, de Wit L, van Rijn BB, et al. Neonatal hypoglycemia following diet-controlled and insulin-treated gestational diabetes mellitus. Diabetes Care. 2018; 41(7): 1385–1390, doi: 10.2337/dc18-0048, indexed in Pubmed: 29654142.

20. Jiang XC, Liang ZD, Chen DL, et al. Correlation of homocysteine, AHSG, CRP with insulin resistance,25-(OH)2-VitD, blood lipids in gestational diabetes patients. Clin Lab. 2021; 67(2), doi: 10.7754/Clin.Lab.2020.200609, indexed in Pubmed: 33616345.

21. Walker MC, Smith GN, Perkins SL, et al. Changes in homocysteine levels during normal pregnancy. Am J Obstet Gynecol. 1999; 180(3 Pt 1): 660–664, doi: 10.1016/s0002-9378(99)70269-3, indexed in Pubmed: 10076144.

22. Aubard Y, Darodes N, Cantaloube M. Hyperhomocysteinemia and pregnancy--review of our present understanding and therapeutic implications. Eur J Obstet Gynecol Reprod Biol. 2000; 93(2): 157–165, doi: 10.1016/s0301-2115(00)00282-7, indexed in Pubmed: 11074137.

23. Wu X, Zhang L, Miao Y, et al. Homocysteine causes vascular endothelial dysfunction by disrupting endoplasmic reticulum redox homeostasis. Redox Biol. 2019; 20: 46–59, doi: 10.1016/j.redox.2018.09.021, indexed in Pubmed: 30292945.

24. Chaudhry SH, Taljaard M, MacFarlane AJ, et al. The role of maternal homocysteine concentration in placenta-mediated complications: findings from the Ottawa and Kingston birth cohort. BMC Pregnancy Childbirth. 2019; 19(1): 75, doi: 10.1186/s12884-019-2219-5, indexed in Pubmed: 30782144.

25. Cho NH, Lim S, Jang HC, et al. Elevated homocysteine as a risk factor for the development of diabetes in women with a previous history of gestational diabetes mellitus: a 4-year

prospective study. Diabetes Care. 2005; 28(11): 2750–2755, doi: 10.2337/diacare.28.11.2750, indexed in Pubmed: 16249551.

26. Pasternak Y, Biron-Shental T, Ohana M, et al. Gestational diabetes type 2: variation in high-density lipoproteins composition and function. Int J Mol Sci. 2020; 21(17): 6281, doi: 10.3390/ijms21176281, indexed in Pubmed: 32872663.

27. Tennant P, Doxford-Hook E, Flynn L, et al. Fasting plasma glucose, diagnosis of gestational diabetes and the risk of large for gestational age: a regression discontinuity analysis of routine data. BJOG. 2022; 129(1): 82–89, doi: 10.1111/1471-0528.16906, indexed in Pubmed: 34510695.

28. Rao C, Ping F. Second-trimester maternal lipid profiles rather than glucose levels predict the occurrence of neonatal macrosomia regardless of glucose tolerance status: a matched cohort study in Beijing. J Diabetes Complications. 2021; 35(8): 107948, doi: 10.1016/j.jdiacomp.2021.107948, indexed in Pubmed: 34024685.

29. Osei-Hwedieh DO, Amar M, Sviridov D, et al. Apolipoprotein mimetic peptides: Mechanisms of action as anti-atherogenic agents. Pharmacol Ther. 2011; 130(1): 83–91, doi: 10.1016/j.pharmthera.2010.12.003, indexed in Pubmed: 21172387.

30. Ference BA, Kastelein JJP, Catapano AL. Lipids and Lipoproteins in 2020. JAMA. 2020; 324(6): 595–596, doi: 10.1001/jama.2020.5685, indexed in Pubmed: 32717042.

31. Yue CY, Ying CM. Epidemiological analysis of maternal lipid levels during the second trimester in pregnancy and the risk of adverse pregnancy outcome adjusted by pregnancy BMI. J Clin Lab Anal. 2018; 32(8): e22568, doi: 10.1002/jcla.22568, indexed in Pubmed: 29774596.

32. Alahakoon TI, Medbury HJ, Williams H, et al. Lipid profiling in maternal and fetal circulations in preeclampsia and fetal growth restriction-a prospective case control observational study. BMC Pregnancy Childbirth. 2020; 20(1): 61, doi: 10.1186/s12884-020-2753-1, indexed in Pubmed: 32000699.

33. Wang J, Li Z, Lin Li. Maternal lipid profiles in women with and without gestational diabetes mellitus. Medicine (Baltimore). 2019; 98(16): e15320, doi: 10.1097/MD.0000000000015320, indexed in Pubmed: 31008986.

34. Stock J. Triglycerides and cardiovascular risk: Apolipoprotein B holds the key. Atherosclerosis. 2019; 284: 221–222, doi: 10.1016/j.atherosclerosis.2019.03.004, indexed in Pubmed: 30914143.

35. Ryoo JH, Park SK, Hong HP, et al. Clinical significance of serum apolipoproteins as a predictor of coronary heart disease risk in Korean men. Clin Endocrinol (Oxf). 2016; 84(1): 63–71, doi: 10.1111/cen.12843, indexed in Pubmed: 26118305.

36. Charlton-Menys V, Betteridge DJ, Colhoun H, et al. Apolipoproteins, cardiovascular risk and statin response in type 2 diabetes: the Collaborative Atorvastatin Diabetes Study (CARDS).

[published correction appears in Diabetologia. 2009 Mar;52 (3):556]. Diabetologia. 2009; 52(2): 218–225, doi: 10.1007/s00125-008-1176-8, indexed in Pubmed: 18972097.

37. Lekva T, Michelsen AE, Bollerslev J, et al. Low circulating pentraxin 3 levels in pregnancy is associated with gestational diabetes and increased apoB/apoA ratio: a 5-year follow-up study. Cardiovasc Diabetol. 2016; 15: 23, doi: 10.1186/s12933-016-0345-1, indexed in Pubmed: 26842615.

Table 1. Anthropometric and clinical characteristics of participants

	GDM (n = 150)	NGT(n = 150)	t	p
Age [year]	30.97 ± 4.16	30.28 ± 5.64	1.198	0.232
Height [m]	158.59 ± 3.64	158.25 ± 3.42	0.833	0.405
Weight [kg]	66.68 ± 9.60	67.86 ± 8.50	−1.127	0.261
BMI before delivery [kg/m^2]	26.35 ± 4.11	27.10 ± 3.50	−1.722	0.086
Systolic BP [mmHg]	119.56 ± 10.22	119.25 ± 10.37	0.258	0.797
Diastolic BP [mmHg]	74.81 ± 9.85	73.32 ± 8.52	1.398	0.163
Gestational weeks at delivery	37.95 ± 2.11	38.63 ± 1.59	−3.186	0.002*

*$p < 0.05$; BMI — body mass index; BP — blood pressure; GDM — gestational diabetes mellitus; NGT — normal glucose tolerance

Table 2. Comparison of FPG, Hcy, and blood lipids levels between the two groups

	GDM (n = 150)	NGT(n = 150)	Z/t	p
FPG [mmol/L]	4.52 (4.00, 4.98)	3.99 (3.57, 4.53)	−4.758	0.000*
Hcy [μmol/L]	6.30 (5.48, 8.00)	4.05 (3.10, 5.40)	−10.428	0.000*
TC [mmol/L]	5.42 (4.57, 6.61)	5.30 (4.61, 6.96)	−1.024	0.306
TG [mmol/L]	2.36 (1.94, 3.28)	2.46 (1.98, 2.94)	−0.666	0.505
HDL-C [mmol/L]	1.75 ± 0.41	1.91 ± 0.44	3.381	0.001*
LDL-C [mmol/L]	2.52 ± 0.89	2.41 ± 0.90	−1.079	0.282
apoA1 [g/L]	1.76 (1.56, 2.08)	1.95 (1.66, 2.32)	−3.629	0.000*
apoB [g/L]	1.05 (0.88, 1.50)	1.03 (0.83, 1.34)	−1.028	0.304
apoB/apoA1	0.59 (0.48, 0.72)	0.51 (0.45, 0.64)	−2.426	0.015*

*p < 0.05; apoA1 — apolipoprotein A1; apoB — apolipoprotein B; FPG — fasting plasma glucose; GDM — gestational diabetes mellitus; Hcy — Homocysteine; HDL-C — high-density lipoproteincholesterol; LDL-C — low-density lipoproteincholesterol; NGT — normal glucose tolerance; TC — Total cholesterol; TG — triglyceride

Table 3. Comparison of perinatal outcomes between the two groups

	GDM (n = 150)	NGT (n = 150)	Z/χ^2	p
Neonatal birth weight [kg]	3.22 (2.90, 3.58)	3.14 (2.92, 3.48)	−1.657	0.098
Macrosomia, n [%]	18 (12.0)	4 (2.7)	9.614	0.002**
Premature rupture of membrane, n [%]	24 (16.0)	10 (6.7)	6.502	0.011*
Postpartum hemorrhage, n [%]	19 (12.7)	9 (6.0)	3.939	0.047*
Cesarean section, n [%]	28 (18.7)	11 (7.3)	8.518	0.004**
Polyhydramnios, n [%]	15 (9.6)	3 (2.0)	8.010	0.005**
Preterm delivery, n [%]	12 (8.0)	2 (1.3)	7.493	0.006**
Birth asphyxia, n [%]	15 (10.0)	3 (2.1)	7.679	0.006**
Neonatal hypoglycemia, n [%]	16 (10.7)	1 (0.7)	14.030	0.000**
NICU admission, n [%]	27 (18.0)	9 (6.0)	10.227	0.001**

*p < 0.05; **p < 0.01; GDM — gestational diabetes mellitus; NICU — Neonatal Intensive Care Unit; NGT — normal glucose tolerance

Table 4. Correlation analysis of FPG, Hcy, blood lipid levels, and perinatal outcomes in the GDM group

	Neonatal birth weight		Macrosomia		Premature rupture of membrane		Postpartum hemorrhage		Preterm delivery		Birth asphyxia		NICU admission		Cesarean section	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
FPG [mmol/L]	0.207	0.011*	0.031	0.708	−0.006	0.945	−0.021	0.798	−0.126	0.124	−0.114	0.164	−0.028	0.733	0.021	0.803
Hcy [µmol/L]	−0.031	0.710	−0.036	0.661	0.052	0.530	0.014	0.864	−0.042	0.612	0.010	0.903	0.086	0.293	0.087	0.292
TC [mmol/L]	−0.033	0.687	−0.140	0.088	−0.038	0.641	−0.063	0.446	−0.155	0.059	−0.024	0.767	0.094	0.255	0.072	0.379
TG [mmol/L]	0.193	0.018*	−0.020	0.811	−0.017	0.836	0.030	0.715	0.033	0.692	−0.050	0.547	0.073	0.375	0.103	0.211
HDL-C [mmol/L]	0.036	0.659	0.048	0.559	0.010	0.907	0.002	0.982	0.063	0.444	−0.148	0.070	−0.072	0.382	−0.122	0.138
LDL-C [mmol/L]	0.015	0.858	0.131	0.110	0.144	0.079	0.072	0.378	0.055	0.501	−0.021	0.796	−0.087	0.292	−0.109	0.184
apoB [g/L]	−0.009	0.912	−0.107	0.193	−0.029	0.723	−0.053	0.516	−0.125	0.126	0.032	0,697	0.068	0.410	0.086	0.293
apoA1 [g/L]	0.023	0.783	0.129	0.115	−0.016	0.846	0.058	0.480	−0.049	0.548	−0.046	0.575	−0.152	0.063	−0.015	0.855
apoB/apoA1	−0.027	0.744	−0.145	0.077	−0.006	0.941	−0.106	0.199	−0.051	0.539	0.056	0.496	0.159	0.051	0.086	0.294

*p < 0.05; apoA1 — apolipoprotein A1; apoB — apolipoprotein B; FPG — fasting plasma glucose; GDM — gestational diabetes mellitus; Hcy — homocysteine; HDL-C — high-density lipoproteincholesterol; LDL-C — low-density lipoproteincholesterol; NICU — Neonatal Intensive Care Unit; TC — total cholesterol; TG — triglyceride

Table 5. Correlation analysis of FPG, Hcy, blood lipid levels, and perinatal outcomes in the NGT group

	Neonatal birth weight		Macrosomia		Premature rupture of membrane		Postpartum hemorrhage		Preterm delivery		Birth asphyxia		NICU admission		Cesarean section	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
FPG [mmol/L]	0.116	0.158	0.196	**0.016***	0.044	0.589	−0.003	0.975	0.030	0.720	−0.060	0.462	0.008	0.922	−0.095	0.246
Hcy [μmol/L]	−0.116	0.159	−0.057	0.485	−0.021	0.799	−0.079	0.334	−0.009	0.909	−0.034	0683	0.081	0.326	−0.038	0.641
TC [mmol/L]	−0.086	0.296	−0.019	0.816	0.000	0.997	−0.071	0.388	−.047	0.568	0.019	0.815	0.068	0.410	−0.004	0.957
TG [mmol/L]	−0.031	0.707	0.058	0.479	0.091	0.269	−0.002	0.981	−0.042	0.613	0.061	0.458	0.135	0.101	0.025	0.758
HDL-C [mmol/L]	0.117	0.153	−0.023	0.776	−0.048	0.558	−0.070	0.397	−0.143	0.081	0.060	0.466	0.132	0.108	−0.061	0.455
LDL-C [mmol/L]	−0.139	0.089	−0.054	0.508	−0.054	0.514	−0.082	0.316	0.054	0.514	−0.026	0.748	−0.007	0.934	0.027	0.744
apoB [g/L]	−0.049	0.555	0.009	0.917	−0.012	0.887	−0.098	0.232	−0.035	0.671	−0.023	0.779	0.080	0.330	−0.019	0.821
apoA1 [g/L]	−0.011	0.891	0.064	0.436	−0.032	0.699	−0.082	0.318	−0.103	0.208	0.127	0.121	0.036	0.659	−0.058	0.482
apoB/apoA1	−0.072	0.381	−0.047	0.569	0.014	0.866	−0.006	0.940	0.069	0.405	−0.085	0303	0.022	0.786	0.069	0.403

*p < 0.05;

apoA1 — apolipoprotein A1; apoB — apolipoprotein B; HDL-C — high-density lipoproteincholesterol; FPG — fasting plasma glucose; Hcy — homocysteine; LDL-C — low-density lipoproteincholesterol; NGT — normal glucose tolerance; NICU — Neonatal Intensive Care Unit; TC — total cholesterol; TG — triglyceride

Table 6. Multiple comparisons of perinatal outcomes among Hcy groups

	Macrosomia			Premature rupture of membrane			Postpartum hemorrhage			Preterm delivery			Birth asphyxia			NICU admission			Cesarean section		
	n [%]	χ^2	p	n [%]	χ^2	p	n [%]	χ^2	p	n [%]	χ^2	p	n [%]	χ^2	p	n [%]	χ^2	p	n [%]	χ^2	p
1	5/36 (13.9%)	0.777	0.876	4/36 (11.1%)	2.134	0.545	3/36 (8.3%)	1.821	0.630	2/36 (5.6%)	6.517	0.057	2/36 (5.6%)	3.662	0.278	6/36 (16.7%)	2.523	0.471	4/36 (11.1%)	2.800	0.423
2	4/40 (10.0%)			6/40 (15.0%)			6/40 (15.0%)			1/36 (2.8%)			5/40 (12.5%)			5/40 (12.5%)			7/40 (17.5%)		
3	5/34 (14.7%)			8/34 (23.5%)			6/34 (17.6%)			6/34 (17.6%)			4/34 (11.8%)			9/34 (26.5%)			9/34 (26.5%)		
4	4/40 (10.0%)			6/40 (15.0%)			4/40 (10.0%)			1/40 (2.5%)			1/40 (2.5%)			7/40 (17.5%)			8/40 (20%)		

Hcy — homocysteine; NICU — Neonatal Intensive Care Unit

Table 7. Multiple comparisons of perinatal outcomes among apoB/apoA1 groups

Group	Macrosomia				Premature rupture of membrane				Postpartum hemorrhage			
	Preterm delivery				Birth asphyxia				NICU admission				Cesarean section			
	n [%]	2	3	4	n [%]	2	3	4	n [%]	2	3	4	n [%]	2	3	4
1	4/43 (9.3%)	1.000	1.000	0.676	1/43 (2.3%)	0.013*	0.521	0.777	0.965	6/43 (14.0%)	0.521	0.745	0.483			
2	3/28 (10.7%)			0.307	1.000	6/28 (21.4%)	0.331	0.110	5/43 (11.6%)	0.501	1.000	0.051	9/43 (20.9%)	0.341	0.384	0.568
3	4/37 (10.8%)			0.411	3/37 (8.1%)	6/42 (14.3%)		0.717	5/37 (13.5%)			0.104	5/37 (13.5%)			0.162
4	2/42 (4.8%)				5/42 (11.9%)				12/42 (28.6%)				11/42 (26.2%)			
1	10/43 (23.3%)		0.182	0.008*	0.088				0.592	0.437		6/28 (21.4%)			0.306	0.142
2	2/28 (7.1%)		0.692	1.000	6/28 (21.4%)		0.158	0.328	5/28 (17.9%)		0.734	0.306	3/28 (10.7%)		1.000	1.000
3	4/42 (9.5%)											3/42 (7.1%)				

*p < 0.05; NICU — neonatal intensive care unit