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Mini review article

ASSOCIATION OF LIPID LEVELS DURING GESTATION COMPLICATED WITH GESTATIONAL DIABETES MELLITUS AND EARLY PREDICTION OF GESTATIONAL DIABETES MELLITUS BY FIRST TRIMESTER LIPID VALUES

POVEZANOST NIVOA LIPIDA TOKOM TRUDNOĆE KOMPLIKOVANE GESTACIJSKIM DIJABETESOM I RANO PREDVIĐANJE GESTACIJSKOG DIJABETESA MELITUSA KORIŠĆENJEM VREDNOSTI LIPIDA U PRVOM TROMESEČJU

Miloš Milinčić[1,2], Miroslava Gojnić Dugalić[1,2]

[1] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija
[2] Univerzitetski klinički centar Srbije, Klinika za ginekologiju i akušerstvo, Beograd, Srbija

Correspondence: milosmilincic@gmail.com

Abstract

Pregnancy induces intricate physiological changes, including alterations in lipid profiles crucial for fetal development. The transition from an anabolic to a catabolic phase in the third trimester reflects increasing insulin resistance, facilitating lipid breakdown for fetal energy. Physiological pregnancy exhibits significant lipid profile changes, with dyslipidemia linked to negative effects on maternal and fetal health. Dyslipidemia in pregnancy correlates strongly with cases of pregnancy-related high blood pressure and diabetes. Gestational diabetes mellitus (GDM) introduces distinctive lipid alterations, including elevated triglycerides (TG) and low-density lipoprotein particles. Mixed dyslipidemia in GDM, exceptionally high TG, and reduced levels of high-density lipoprotein cholesterol (HDL-C) are linked to negative perinatal outcomes, emphasizing the importance of lipid profile assessment. Evaluating lipid profiles, especially TG levels, in early pregnancy proves valuable in predicting GDM. The ratio of triglycerides to high-density lipoprotein cholesterol (TG/HDL-C) shows potential as a predictive marker for GDM, demonstrating commendable sensitivity and specificity. Elevated TG levels, even before 28 weeks, increase GDM risk, emphasizing the role of lipid markers in early detection. Early predictions of GDM through plasma lipid profiling offer a promising avenue for enhancing antenatal care. While standardized markers and thresholds require further research, integrating lipid profiles into routine screenings may optimize GDM management, ultimately benefiting both the mother and fetus.

Keywords:
pregnancy,
gestational diabetes mellitus,
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Sažetak

Trudnoća izaziva složene fiziološke promene, uključujući promene u lipidnim profilima koji su ključni za razvoj fetusa. Prelazak sa anaboličke na kataboličku fazu u trećem trimestru odražava povećanje insulinske rezistencije, olakšavajući razgradnju lipida za fetalnu energiju. Fiziološka trudnoća pokazuje značajne promene lipidnog profila, pri čemu je dislipidemija povezana sa nepovoljnim ishodom kod majke i fetusa. Dislipidemija u trudnoći snažno korelira sa hipertenzivnim poremećajima i gestacijskim dijabetesom. Gestacijski dijabetes melitus (GDM) uvodi karakteristične promene lipida, uključujući povišene trigliceride (TG) i pomeranje ka malim, gustim česticama lipoproteina niske gustine. Mešovita dislipidemija kod GDM, posebno visoki TG i nizak HDL-C, povezana je sa nepovoljnim perinatalnim ishodima, naglašavajući važnost procene lipidnog profila. Procena profila lipida, posebno nivoa TG, u ranoj trudnoći pokazuje se vrednim u predviđanju GDM. Odnos TG/HDL-C javlja se kao prospektivni indikator za GDM, pokazujući hvale vrednu osetljivost i specifičnost. Povišeni nivoi TG, čak i pre 28. nedelje, povećavaju rizik od GDM, naglašavajući ulogu lipidnih markera u ranom otkrivanju. Rana predviđanja GDM kroz profilisanje lipida u plazmi nude obećavajući put za poboljšanje prenatalne nege. Dok standardizovani markeri i pragovi zahtevaju dalja istraživanja, integrisanje lipidnih profila u rutinske skrininge može optimizovati upravljanje GDM, što na kraju ima korist za ishod majke i fetusa.

Ključne reči:
trudnoća,
gestacijski dijabetes melitus,
rana predikcija,
lipidi,
lipidni profil

Introduction

Pregnancy induces numerous physiological changes, among which alterations in lipid profiles play a vital role in supporting fetal development. The course of lipid metabolism in pregnancy begins with an anabolic phase characterized by enhanced lipid production and accumulation of fat reserves, which are essential in supporting the rising energy requirements of the fetus during the later stages of pregnancy. Later, the shift to the catabolic phase promotes the degradation of fat reserves, supplying critical nutrients necessary for fetal development (1). These alterations reflect insulin resistance in the mother, ensuring a harmonious balance to nourish the developing fetus. Insulin resistance must occur in the 3rd trimester of pregnancy to catabolize lipids as a fetal growth and development. In a physiological pregnancy, lipid profiles undergo significant changes (1,2). Total cholesterol (TC) levels increase by 50%, low-density lipoprotein cholesterol (LDL-C) by 30 - 40%, high-density lipoprotein cholesterol (HDL-C) by 25%, and triglycerides (TG) by 2.7-fold (3). Abnormal lipid levels during pregnancy are closely linked to negative outcomes, affecting the health of both the mother and fetus. It is essential to understand the complex connections between dyslipidemia and other co-occurring conditions intra-utero (4). The implications of dyslipidemia in pregnancy extend beyond the immediate perinatal period, influencing developmental programming and predisposing offspring to chronic diseases later in life. Recognizing these implications, screening for lipid disorders is imperative, preferably before conception or during the first prenatal appointment for those not screened pre-pregnancy (5). Abnormal lipids should be monitored throughout pregnancy, with multifactorial treatment strategies, including diet, exercise, and weight management.

Dyslipidemia in pregnancy exhibits profound associations with hypertensive disorders and GDM (6). The effect of elevated lipid levels on the epigenetic development of the fetus is concerning, as it may increase future atherogenesis risks for both the mother and child. The unique role of HDL in fetal circulation and its contribution to fetal neurodevelopment further highlight the complex interplay of lipids during pregnancy (5).

Understanding clinical management is crucial, with normal pregnancy-associated lipid levels not exceeding 6.45 mmol/L for TC. If the concentrations of TC are over 7.7 mmol/L, the concern for abnormality rises (7). The LDL/HDL ratio, which indicates atherogenic risk, stays stable throughout pregnancy, emphasizing the even distribution of cholesterol-containing lipoprotein fractions despite overall lipid level increases. Normal increases in lipids during pregnancy are characterized by a simultaneous rise in HDL-C, differentiating them from abnormal lipid imbalances seen in pathological conditions (8).

During the initial and early middle stages of pregnancy, there is an upsurge in the production of lipids driven by maternal hyperphagia, increased insulin sensitivity, and the production of progesterone, cortisol, leptin, and prolactin (9). Insulin sensitivity fosters fatty acid synthesis in adipocytes, while lipoprotein lipase (LPL) expression promotes the uptake of fatty acids. Simultaneously, the elevated levels of leptin, cortisol, prolactin, and progesterone play a role in enhancing the accumulation of fat reserves, creating a favorable environment for the growing fetus (1,2). As pregnancy progresses into the third trimester, a net breakdown phase begins, marked by decreased insulin sensitivity or resistance. This shift prompts enhanced lipolysis of stored triglycerides in adipocytes, driven by factors such as human placental lactogen (HPL) and reduced LPL activity (10). The interplay of hormonal signals orchestrates a decrease in fat stored in fat cells occurs in accordance with the evolving metabolic requirements of the growing fetus.

The liver responds to the increased free fatty acids

transported from adipocytes (11). This triggers the production of lipoproteins high in triglycerides, particularly very low-density lipoproteins (VLDL), which are subsequently secreted. A unique condition in the liver is characterized as selective insulin resistance. Increased glucose production occurs despite accelerated lipid synthesis. This leads to hyperglycemia and hyperlipidemia simultaneously (12). Increased levels of estrogen in the later stages of pregnancy promote liver fat synthesis and the generation of VLDL, creating a complex interplay between hormonal signals and hepatic lipid metabolism (13, 14).

Estrogen, a key player in the hormonal orchestra, suppresses hepatic lipase activity, encourages the production of VLDL, and enhances fat synthesis in the liver. Human placental lactogen (HPL) triggers insulin resistance, boosts the breakdown of fats, and contributes to altered lipid dynamics. Insulin resistance itself affects lipolysis, lipoprotein lipase function, and boosts the action of cholesterol ester transfer protein (CETP), resulting in the accumulation of triglycerides in LDL and HDL (10).

Maternal dyslipidemia, mainly characterized by elevated TG and reduced HDL-C levels, is linked to negative perinatal outcomes. However, establishing causation requires intervention studies demonstrating reduced adverse outcomes through lipid level management (15).

This review aims to discover the possibility of early prediction of diabetes mellitus, which will develop later in pregnancy and manifest itself clinically through specific alterations in lipid metabolism and altered lipidogram in the early pregnancy.

Specific lipid changes in GDM patients

Gestational diabetes mellitus is confirmed when an Oral Glucose Tolerance Test (OGTT) is done in women without pre-existing diabetes and who have not had previous GDM (16). The relative complexity of this test and the frequent side effects on patients open up the possibility of another type of detection of insulin metabolism disorders in pregnancy, which, among other things, are included in this review paper. The increasing importance of screening for dyslipidemia in assessing the risk of developing GDM is being recognized. Research on GDM reveals mixed findings regarding lipid changes. Women with GDM during the third trimester have elevated serum TG levels but reduced LDL-C levels compared to controls (17). Interestingly, other studies documented elevated levels of TG in the blood plasma and VLDL in GDM, while LDL-C levels were lower. The lipid parameters exhibited a parallel decrease post-pregnancy in both groups, except for LDL cholesterol, which did not decrease in GDM patients (18, 19). A review of 60 studies confirmed this finding, demonstrating notably higher TG levels and lower HDL-C levels in women with GDM. Nonetheless, there were no consistent variations in TC or LDL-C levels between insulin-resistant patients and healthy participants (20).

The link between GDM and abnormal lipid levels may be influenced by high maternal body mass index (BMI). Their research indicates that after accounting for BMI, the tendency for elevated TG was mainly seen in obese women. This underscores the need to account for maternal obesity as a potential confounding variable when examining the connection between GDM and changes in lipid levels (18).

Pregnancies complicated by GDM often exhibit mixed dyslipidemia, primarily marked by elevated triglyceride (TG) concentrations and a transition towards small, dense, low-density lipoprotein particles (sdLDL) (21). There is evidence that sdLDL particles are significantly more atherogenic than standard LDL particles; this should be taken into account when we know that in diabetic patients, there is a larger fraction of these sdLDL lipids (21, 22). Comparable lipid imbalances are seen in conditions such as type 2 diabetes mellitus. Women with GDM exhibit notably elevated triglyceride levels and reduced HDL levels during the first trimester. Both low and high BMI patients with higher TG levels have a greater risk of acquiring GDM, with maternal obesity influencing the link between GDM and abnormal lipid levels (23).

On the other hand, women with a healthy pregnancy experience a unique pattern of lipid imbalance, with plasma TC levels much higher compared to levels before pregnancy and TG levels nearly doubling. Nonetheless, it is important to note that TC levels should stay below 6.5 mmol/L during a normal pregnancy. Interestingly, normal pregnancy lipid changes differ from the pathological lipid changes observed in GDM by a concurrent rise in HDL-C concentrations, while the atherogenic index (LDL-C/HDL-C) remains largely stable. In contrast, the ratio of triglycerides to HDL-C increases (24).

In GDM, elevated plasma insulin can inhibit fatty acid oxidation, resulting in reduced metabolism of dietary TG. This situation increases the TG presented to the fetus and placenta, which can contribute to fetal macrosomia. High maternal TG and low HDL cholesterol levels during pregnancy are linked to fetal macrosomia, increased birth weight, and a higher likelihood of LGA infants. This correlation is especially strong in patients with high pre-pregnancy BMI (25).

These results highlight the significance of assessing the lipid profile during pregnancy, especially TG levels, as a valuable tool in identifying metabolic abnormalities in GDM and predicting fetal outcomes. This approach aligns with the recommendation to measure glucose and lipid profiles during pregnancy.

Early predictions of GDM through plasma lipid profile

Using OGTT in early pregnancy can be problematic due to gastrointestinal side effects in pregnant women and the need to repeat the test. In this review, growing data about the possibility of using lipids in the prediction of GDM will be presented. Early identification of GDM allows healthcare providers to implement timely interventions to

manage blood glucose levels. This, in turn, reduces the risk of maternal complications such as preeclampsia, hypertension, and the onset of diabetes in later years (26). Pregnancy triggers a substantial metabolic makeover of the lipid profile that is particularly pronounced in the early stages of gestation (1, 2, 7, 15). Understanding the nuances of these changes has prompted researchers to investigate whether specific lipid markers can act as early indicators of GDM. Forecasting GDM is most critical during the initial phases of pregnancy (1st or early 2nd trimester). The predictive value of lipid status was tested in the study by Zheng et al. at 11 - 13 weeks of gestation. They showed increases in concentrations of GDM vs. average pregnancy lipid profiles that manifested as statistically significant increases of TC, TG, and LDL-C. No significant statistical association was found between Lp(a) and HDL-C. Compared to the group without GDM, age, pre-pregnancy BMI, lipid profile, apolipoprotein B (APOB), and apolipoprotein E (APOE) were significantly higher in the GDM group. Conversely, coagulation factors were significantly lower in the non-GDM group. The area under the curve (AUC) of the existing GDM risk prediction model was 0.892 (27).

One of the possibilities for predicting GDM is using the TG/HDL-C ratio (28). Although the TG/HDL-C ratio correlates with insulin resistance and cardiovascular disease, a TG/HDL-C ratio of 3.0 or higher serves as a potential marker for prediabetes and insulin resistance in women (29). Guided by this, You et al. have performed a prospective cohort study involving pregnant women with GDM at 10 - 14 weeks and found that the TG/HDL-C ratio was positively correlated with the occurrence of GDM OR = 1.77. Upon accounting for potential confounding factors, an affirmative correlation emerged between the TG/HDL-C ratio and the onset of GDM. Demonstrating efficacy as a GDM predictor, the TG/HDL-C ratio yielded a commendable AUC of 0.7863. The prime TG/HDL-C ratio threshold for GDM detection was established at 2.2684, boasting a sensitivity of 72.97% and a specificity of 75.05% (30). In other similar studies, the TG/HDL-C ratio's ability to predict GDM pregnancies showed an AUC of 0.886 (31-33).

However, it was shown that the high value of TG showed a higher association with GDM and preeclampsia compared to low values of HDL-C. Wiznitzer et al. have demonstrated that the prevalence of the composite endpoint increased with escalating TG levels, ranging from 7.2% in the low TG group (< 25th percentile adjusted for gestational month) to 19.8% in the high TG group (> 75th percentile). However, this association was not linked to HDL-C levels. Multivariate analysis underscored that higher TG levels, rather than LDL-C, were explicitly associated with the primary endpoint. Moreover, the study observed significant alterations in lipid profiles from preconception to gestation, with TC levels rising from 4.251 to 6.17 mmol/L and TGs increasing from 1.0455 to 2.6915 mmol/L. The association extended to clinical outcomes, with women having high TG levels demonstrating much higher blood glucose levels (≥ 5.6 mmol/L). Interestingly, the study indicates that high levels of LDL-C did not show a significant association with a composite endpoint, preeclampsia, or GDM (3). Furthermore, with high TG values before 28 weeks, there was a heightened risk of GDM, with an OR of 1.67 and mean level of TG by trimesters 1.54 mmol/L, 2.64 mmol/L, 3.23 mmol/L, respectively (34).

Benhalima et al. showed a difference in dyslipidemia between subtypes of impaired glucose metabolism in pregnancy in an interesting prospective cohort study. The group with more pronounced insulin resistance and more severe forms of GDM had significantly higher values of BMI, systolic blood pressure, free plasma glucose (FPG), TC, LDL-C, and TC levels (35). The prediction of a 2018 case-control study was of great importance, as it demonstrated that women who eventually developed GDM exhibited specific metabolic changes in the first trimester when compared to the healthy control group. In the GDM group, a statistically significant elevation was observed in the median concentrations of TC, TG, insulin, tissue plasminogen activator (tPA), and HOMA index, along with an elevated average level of LDL-C were observed when compared to the control group. These differences indicate a broad metabolic shift that occurs before the clinical onset of GDM. The analysis of AUC revealed a strong performance of 0.870, showing a sensitivity and specificity of > 80%, which indicates the potential utility of these blood-borne biomarkers in identifying individuals at risk for GDM during the first trimester (36).

Other lipid markers that can contribute to understanding models of GDM prediction are lipoprotein(a) (Lp(a)), APOA-1, APOE, and APOB (37). Elevated Lp(a) levels may contribute to atherogenic processes, potentially influencing the cardiovascular health of women with GDM during pregnancy and in the postpartum period. Elevated Lp(a) levels were associated with an increased risk of cardiovascular diseases (38). Notably, few researchers have used these parameters, which leaves room for future research.

Table 1 summarizes lipid levels in studies that were measured between 11 - 14 weeks of pregnancy, with notable studies on the subject not discussed in the text (39-43).

Elevated triglyceride levels in early pregnancy have been consistently associated with an increased risk of GDM. Research by Zhu et al. indicated that higher maternal TG levels can induce insulin resistance, a hallmark of GDM. Women in the highest quartile of TG levels in early pregnancy had a significantly higher risk of developing GDM compared to those in the lowest quartile (adjusted odds ratio [OR] 2.15, 95% confidence interval [CI] 1.53 – 3.02). Increased levels of TC and LDL-C have also been linked with GDM, though the evidence is less consistent than for TG. Higher TC and LDL-C levels measured before 20 weeks of gestation were associated with a greater risk of GDM (44). Women with LDL-C levels in the highest quartile had an adjusted OR of 1.63 (95% CI 1.13 - 2.35) for GDM. The relationship between HDL-C and GDM is more complex. Some studies suggest that lower HDL-C levels in early pregnancy are associated with GDM risk,

Table 1. Comparison of lipid profile in non-GDM vs. GDM patient in first trimester of pregnancy

	TG (mmol/L)			TC (mmol/L)			LDL-C (mmol/L)			HDL-C (mmol/L)		
	non-GDM	GDM	P value	non-GDM	GDM	P value	non-GDM	GDM	P value	non-GDM	GDM	P value
Zheng et al.	1.55	1.91	< 0.001	4.85	5.31	< 0.001	2.61	2.85	< 0.001	1.73	1.70	0.634
Shen et al.	1.31	1.54	< 0.001	4.93	5.08	0.008	3.34	3.47	0.179	1.65	1.69	0.710
Benhalima et al.	0.9	1.2	< 0.001	4.5	4.9	0.008	2.3	2.5	0.012	1.8	1.7	0.318
Ye et al.	1.44	1.67	0.002	4.6	4.71	0.009	ND	ND	/	1.05	1.08	0.450
Wu et al.	1.68	1.97	< 0.001	5.43	5.46	0.210	2.90	2.93	0.450	2.95	2.61	0.002
Correa et al.	1.08	1.55	0.003	4.28	5.01	0.04	2.37	3.01	0.009	1.70	155	0.176
Shen et al.	1.33	1.47	< 0.001	4.94	5.11	0.014	2.75	2.88	0.004	1.79	1.78	0.939
Wang et al.	0.91	1.08	0.017	4.04	4.07	0.066	2.14	2.21	0.310	1.43	1.37	0.426
Kumru et al.	1.18	1.62	0.001	4.42	5.01	< 0.001	2.24	2.76	0.001	1.75	1.62	0.078

TG – Triglicerides; TC – total cholesterol; LDL-C – low-density-lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol

while others do not find a significant correlation. A meta-analysis by Ryckman et al. found that lower HDL-C levels in the first trimester were significantly associated with GDM, with an adjusted OR of 1.58 (95% CI 1.19 - 2.10) for women in the lowest quartile compared to those in the highest quartile (20).

Suggested Lipid Thresholds for GDM Prediction

Based on current research, the following lipid thresholds in early pregnancy may serve as indicators of increased GDM risk:

- Triglycerides (TG): > 1.7 mmol/L;
- Total Cholesterol (TC): > 5.01 mmol/L;
- Low-Density Lipoprotein Cholesterol (LDL-C): > 3.4 mmol/L;
- High-Density Lipoprotein Cholesterol (HDL-C): < 1.3 mmol/L.

These values are indicative and should be interpreted in the context of other clinical factors and the overall risk profile of the patient.

Occurrence of dyslipidemia after pregnancies complicated by GDM

The occurrence of dyslipidemia following pregnancies complicated by GDM is a topic of substantial clinical interest and research. Research indicates an increased frequency of lipid imbalances in women who have experienced GDM during pregnancy (45). Post-GDM, there is often a notable persistence of adverse lipid alterations. Elevated TG levels and decreased HDL-C are commonly observed, contributing to an atherogenic lipid profile. This pattern may persist even in the absence of overt diabetes postpartum. The study, encompassing a cohort of 4,693 patients, showed that women who have had GDM often face dyslipidemias after childbirth. The OR of 1.63 for TC ≥ 5.17 mmol/L and LDL-C ≥ 3.36 mmol/L underscores a substantial and statistically significant increased likelihood of these dyslipidemic conditions in women with a history of GDM compared to those without. Moreover, the persistence of these associations with slightly attenuated odds ratios (1.55 for TC ≥ 5.17 mmol/L and 1.56 for LDL-C ≥ 3.36 mmol/L) in the absence of type 2 diabetes further emphasizes the independent impact of GDM on lipid metabolism (45).

In most studies, the association of high LDL-C values with the prediction of GDM has not been demonstrated. Pei et al. demonstrated that an LDL-C level of 3.56 mmol/L in 2nd trimester serves as the threshold for ongoing dyslipidemia postpartum for women who had GDM (46).

The continuation of dyslipidemia after GDM presents long-term cardiovascular risks for those affected. High TG and irregular cholesterol levels are known risk factors for atherosclerosis and heart disease. Women who have experienced GDM have higher chances of type 2 diabetes in life (47). Abnormal lipid levels play a role, with insulin resistance and disrupted lipid metabolism working together to heighten the risk.

Conclusion

Gestational diabetes mellitus and dyslipidemia represent intertwined facets of pregnancy-associated metabolic changes, impacting both maternal and fetal health. Understanding their interplay is crucial for comprehensive antenatal care. Early predictions of GDM through plasma lipid profiling represent a promising avenue for improving antenatal care. While further research is needed to establish standardized markers and thresholds, the evolving understanding of the intricate interplay between lipid metabolism and GDM offers new perspectives on early detection and targeted intervention strategies. The great importance of researching possibilities for treating dyslipidemia during pregnancy and breastfeeding are also pointed out. Integrating lipid profiles into routine antenatal screenings may pave the way for personalized approaches to GDM management, ultimately optimizing maternal and fetal outcomes.

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