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Роль дислипидемии в патогенезе перинатальных осложнений при сахарном диабете у матери

© Р.В. Капустин[1, 2], Е.М. Цыбук[2], Е.Н. Алексеенкова[1], Е.В. Коптеева[2], О.Н. Аржанова[1, 2], Т.И. Опарина[1], Ж.Н. Тумасова[1]

[1] Научно-исследовательский институт акушерства, гинекологии и репродуктологии им. Д.О. Отта, Санкт-Петербург, Россия;
[2] Санкт-Петербургский государственный университет, Санкт-Петербург, Россия

Актуальность. Заболеваемость сахарным диабетом среди беременных растет. Физиологическая гиперлипидемия, характерная для поздних сроков гестации, усиливается во время беременности, осложненной сахарным диабетом. Изменения липидного профиля неразрывно связаны с неблагоприятными перинатальными исходами. Однако исследований, направленных на изучение взаимосвязи липидного обмена у женщин с различными типами сахарного диабета и развитием акушерских осложнений, недостаточно.

Цель — оценить липидный профиль у женщин с различными типами сахарного диабета (1-й, 2-й типы и гестационный сахарный диабет) с учетом метода его коррекции в III триместре беременности, выявить взаимосвязь липидов с перинатальными осложнениями, а также определить их возможную прогностическую значимость в развитии неблагоприятных исходов беременности.

Материалы и методы исследования. В исследование включено 277 женщин, которые составили несколько групп сравнения в зависимости от типа сахарного диабета и метода его коррекции, группу женщин с преэклампсией и группу условно здоровых. Анализировали клинические и лабораторные данные амбулаторных и стационарных карт беременных, находящихся на диспансерном учете в период с 2010 по 2017 г. Для исследования использовали периферическую венозную кровь, взятую у беременных натощак при сроке 28–32 нед. За первичную точку исследования принимали показатели содержания триглицеридов, холестерина, липопротеинов высокой, низкой и очень низкой плотности, коэффициент атерогенности. Дополнительно оценивали частоту гестационной артериальной гипертензии, преэклампсии, задержки развития плода, преждевременных родов.

Результаты исследования. Для беременных с различными типами сахарного диабета характерно преобладание в сыворотке крови атерогенных липидов (триглицериды, липопротеины очень низкой плотности), повышение индекса атерогенности и снижение содержания антиатерогенных липопротеинов высокой плотности. Эти изменения наиболее выражены у беременных с прегестационными типами сахарного диабета и в группах пациентов, получающих инсулинотерапию. При проведении корреляционного анализа выявлена слабая прямая связь между уровнем триглицеридов и макросомией (r = 0,26) и между значением индекса атерогенности и развитием тяжелой преэклампсии (r = 0,26). Анализ ROC-кривой показал, что триглицериды, липопротеины очень низкой плотности, индекс атерогенности являются предикторами развития тяжелой преэклампсии.

Заключение. Сахарный диабет усиливает состояние дислипидемии у беременных, что играет важную роль в патогенезе многих перинатальных осложнений. Оценка маркеров липидного профиля у женщин с различными типами сахарного диабета в III триместре беременности может являться валидным методом предикции тяжелой преэклампсии.

Ключевые слова: сахарный диабет; гестационный сахарный диабет; дислипидемия; макросомия; преэклампсия.

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The role of dyslipidemia in the pathogenesis of perinatal complications in pregnant women with diabetes mellitus

© Roman V. Kapustin[1, 2], Elizaveta M. Tsybuk[2], Elena N. Alexeyenkova[1], Ekaterina V. Kopteyeva[2], Olga N. Arzhanova[1, 2], Tatyana I. Oparina[1], Zhanna N. Tumasova[1]

[1] The Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia;
[2] Saint Petersburg State University, Saint Petersburg, Russia

HYPOTHESIS/AIMS OF STUDY: The prevalence of diabetes mellitus in pregnant women is increasing. Physiological hyperlipidemia is usually developed during the last third of gestation, increases during pregnancies complicated by diabetes mellitus. Abnormal lipid profiles are associated with adverse perinatal outcomes. However, the associations between maternal dyslipidemia and pregnancy complications in women with different diabetes mellitus types remain unclear. The aim of this study was to assess the lipid profile in women with different types of diabetes mellitus (Type 1, Type 2, and gestational diabetes) based on the therapy in the third trimester of pregnancy, to investigate the associations between serum lipid profile and perinatal complications, and to determine possible prognostic value of lipids in the development of adverse pregnancy outcomes.

STUDY DESIGN, MATERIALS AND METHODS: The study included 277 women who were divided into several groups depending on the type of diabetes mellitus and its therapy method, a group of patients with preeclampsia, and the control group. We analyzed the clinical and laboratory data of outpatient and inpatient cards of pregnant women in the period between 2010 and 2017. Maternal blood samples were collected between 28 and 32 weeks of gestation. The samples were assayed for fasting triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and very-low-density lipoprotein cholesterol concentrations, as well as the atherogenic index of plasma. We also assessed the incidence of gestational arterial hypertension, preeclampsia, intrauterine growth restriction, and preterm birth.

RESULTS: Pregnant women with various types of diabetes mellitus were characterized by a significant rise in serum triglycerides and very-low-density lipoprotein cholesterol levels, an increase in the atherogenic index of plasma, and a significant decrease in antiatherogenic, high-density lipoprotein cholesterol levels. These changes were most pronounced in pregnant women with pregestational diabetes mellitus types and in groups receiving insulin therapy. Correlation analysis revealed weak positive correlations between serum triglycerides concentrations and macrosomia ($r = 0.26$) and between the atherogenic index of plasma and severe preeclampsia ($r = 0.26$). The analysis of the ROC curve showed that triglycerides, very-low-density lipoprotein cholesterol, and the atherogenic index of plasma are predictors of severe preeclampsia.

CONCLUSION: Diabetic pregnancies are associated with increased dyslipidemia, which plays an essential role in the pathogenesis of perinatal complications. Evaluating lipid profile markers in the third trimester of diabetic pregnancy may be valid predictors of severe preeclampsia.

Keywords: diabetes mellitus; gestational diabetes; dyslipidemia; macrosomia; preeclampsia.

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INTRODUCTION

Currently, a steady increase in diabetes mellitus (DM) incidence among pregnant women was reported [1]. In 2019, hyperglycemia was concomitant with every sixth pregnancy. A lesser proportion of these cases were represented by pregestational DM (16%), and gestational DM (GDM) was diagnosed in 84% of cases [2]. This pathology is associated with a high risk of perinatal complications, such as, fetal macrosomia, preterm delivery, and preeclampsia (PE) [1]. Nowadays, the study of maternal lipid profile and its relationship with unfavorable pregnancy outcomes is of great interest for researchers [3]. Impaired lipid metabolism in women with DM is assumed to be no less significant in the pathogenesis of these complications than hyperglycemia [4].

During pregnancy, significant changes occur in the lipid profile of female patients. The first two trimesters correspond to the anabolic phase when the adipogenesis processes are enhanced and fat accumulates in the depot [5]. This is due to the action of insulin high concentrations and increased activity of lipoprotein lipase (LPL) of the adipose tissue. By the third trimester of pregnancy, hormonal changes lead to an increase in the lipolytic activity of the adipose tissue. The lipolysis products are re-etherified for triglyceride (TG) synthesis and are released into the bloodstream in the form of very low density lipoproteins (VLDL) [6]. The increased activity of the cholesterol ester transfer protein (CETP) promotes the accumulation of TGs not only in VLDL, but also in low density lipoproteins (LDL) and high density lipoproteins (HDL) [6]. These processes correspond to the peak of physiological insulin resistance in late pregnancy. At the same time, LPL activity decreases, causing maternal hyperlipidemia [5].

Numerous studies showed that characteristics of the lipid profile at different stages of pregnancy are inextricably related with various obstetric complications [7–12]. According to recent studies, in the first trimester of pregnancy, an increase in total cholesterol (TC), TG, and LDL and a decrease in HDL may precede unfavorable perinatal outcomes [3]. Hypertriglyceridemia in the first trimester is noted in women with further development of PE; and in cases of severe PE, more significant deviations from the norm are recorded [3, 7]. The endothelial dysfunction and activation of oxidative stress may cause changes in the lipid profile [7]. An increased LDL, TC, and TG levels in early pregnancy is significantly associated with preterm birth [3, 8]. Similar results were obtained in the study of lipid levels in the third trimester of pregnancy, namely low HDL and high TG values, are associated with a high risk of PE, intrahepatic cholestasis in pregnant women, and macrosomia [9]. The latter complication is given special attention from the perspective of its relation with lipid metabolism. Hypertriglyceridemia and a decrease in HDL levels has been established to be independent predictors of macrosomia in women without DM [10], but earlier studies indicate the presence of this relationship only in overweight women [11, 12].

Physiological hyperlipidemia increases during pregnancy complicated by DM [13]. No definitive explanation for dyslipidemia in this condition is reported. Under conditions of insulin resistance, insulin signal transduction is impaired, which suppresses the expression of LPL mRNA. Subsequently, the activity of this enzyme is further reduced through post-transcriptional and post-translational mechanisms. Thus, the elimination of VLDL from the plasma slows down, and hyperlipidemia increases [4]. In female patients with DM type 1, the activity of the placental LPL is increased, which is relative to healthy patients, but the expression of LPL mRNA remains unchanged. This indicates that LPL activity is modulated at the post-transcriptional level [14]. One of the possible mechanisms of placental LPL activation in pregnant women with DM may be a decrease in the concentration of angiopoietin-like protein 4 (ANGPTL-4) in the third trimester, which is an irreversible inhibitor of LPL. Its occurrence is believed to be compensatory, promoting intensive transfer of fatty acids across the placenta to the fetus. However, low concentrations of ANGPTL-4 have no significant effect on the LPL activity of the adipose tissue [15].

In the early trimester of pregnancy in women, the plasma TG level is known to increase with the further development of GDM, indicating the presence of dyslipidemia even before the manifestation of insulin resistance [3]. At later stages of pregnancy in patients with GDM, in addition to hypertriglyceridemia, HDL levels significantly decrease compared to that of healthy women [16]. Other researchers noted an increase in LDL values in pregnant women with various types of DM throughout pregnancy, but no difference was found between groups of different types of DM [17]. Some studies found no significant differences in lipid concentrations in pregnant women with and without GDM [18].

A number of studies examined the relationship between lipid metabolism disorders in female patients with DM and the development of perinatal complications. Such studies are rare and were mainly performed in patients with GDM. In women with well-controlled GDM, the glucose level does not correlate with the weight of the newborn, but a direct relationship is present between the child's body weight and the TG level, free fatty acids in the mother's plasma in the third trimester of pregnancy [4, 19]. Women with type 1 DM with the further development of PE are also characterized by a change in the lipid profile; and significant differences in lipid concentration were determined only in early terms of pregnancy [20].

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This study aimed to assess the lipid profile in women with various types of DM (DM1, DM2, and GDM) in the third trimester of pregnancy and to identify the relationship of lipids with perinatal complications due to insufficient amount of data on this issue and conflicting results of previous studies.

MATERIALS AND METHODS

Study design

An observational single-center retrospective cohort study was performed in the Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott. Clinical and laboratory data of the outpatient and inpatient records of pregnant women, who were registered at the dispensary at the Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott at a term of 28–32 weeks in the period from 2010 to 2017, were analyzed. The DM type was verified and corrected based on clinical guidelines [21].

In this study, inclusion criteria include DM and singleton pregnancy; and exclusion criteria include an indication of taking ursodeoxycholic acid drugs, as well as ademetionine or essential phospholipids before weeks 28–30 of gestation, diseases that determine symptomatic DM, namely thyrotoxicosis, hyperadrenocorticism, somatotropinoma, and pheochromocytoma, severe somatic pathology, oncological diseases, and multifetal pregnancy.

Based on the inclusion criteria, the study included 277 women who were distributed into several comparison groups depending on the DM type and method of its correction (method of continuous subcutaneous insulin infusion [CSII], multiple insulin injections [MII], and diet), a group of female patients with PE, and conditionally healthy women.

Type 1 DM (CSII) — $n = 20$;
Type 1 DM (MII) — $n = 22$;
Type 2 DM (diet) — $n = 17$;
Type 2 DM (insulin) — $n = 26$;
GDM (diet) — $n = 88$; and
GDM (insulin) — $n = 42$.
Comparison group: PE — $n = 24$.
Control group: $n = 38$.

The glycemic level was determined using a BIOSEN C-line EKF analyzer (Germany), and the glycated hemoglobin (HbA1c) level was determined using a Bio-Rad D-10 analyzer (USA). A comprehensive study of blood lipid metabolism was performed on an automatic biochemical analyzer, Furuno CA-90 (Japan), using test systems of Thermo Scientific (Finland) and Diasys (Germany). Peripheral venous blood was used for the study, taken from pregnant women in the fasted state at a term of 28–32 weeks.

The lipid profile analysis included cholesterol, cholesterol–HDL, cholesterol–LDL, and TGs. Based on these tests results, the concentration of cholesterol–VLDL, Klimov atherogenic index (AI), and atherogenic index of plasma were calculated. TG, cholesterol, HDL, LDL, and VLDL were determined in the blood serum.

Main study outcome

The primary point was taken as indicators of the levels of TG, cholesterol, HDL, LDL and VLDL, and AI.

Additional study outcomes

The incidence of gestational arterial hypertension, PE, fetal growth retardation, and preterm delivery was assessed.

Statistical methods

Statistical data processing was performed using Statistical Package for the Social Sciences (SPSS) V. 23.0 software (USA). The distribution parameters of the sample were assessed using the Kolmogorov–Smirnov test. To determine the statistical significance of differences between the quantitative parameters of the normally distributed data of the study groups, analysis of variance was performed, and Fisher's test (LSD) was used. The Kruskal–Wallis test, median test, and Dann method were used for nonparametric distribution of data. Statistical processing of qualitative traits was performed using the χ^2 criterion. Correlation analysis was performed using Pearson's coefficient for normally distributed data and Spearman's coefficient for nonparametric distribution of attributes. To assess indicators as predictors of obstetric complications, ROC analysis was performed and areas under the curves (AUC) were calculated. The equality hypothesis of mean values in the studied groups was rejected at a significance level of $p < 0.05$.

RESULTS

Clinical characteristics of study groups

Table 1 presents the characteristics of the studied groups. Female patients with type 2 DM and GDM were older compared to patients from other groups ($p < 0.001$). The maximum values of the pregestational body mass index (BMI) were registered in patients with type 2 DM (33.7 kg/m^2 in those on a diet and 34.6 kg/m^2 in those on insulin therapy), which significantly exceeded the values from other groups. The average HbA1c level was higher in pregnant women with DM1, as well as in patients with DM2 and GDM who received insulin therapy. In the oral glucose tolerance test (OGTT), the highest glycemic values were recorded in patients with diagnosed GDM, who were subsequently

Table 1. Clinical characteristics of the study groups

Indicators	Type 1 DM		Type 2 DM		GDM		PE *n* = 24	Control *n* = 38	*F*	*p*-level
	CSII *n* = 20	MII *n* = 22	diet *n* = 17	insulin *n* = 26	diet *n* = 88	insulin *n* = 42				
Age, years (95% CI)	28.1 (26.2–30)	27.9 (26.1–29.7)	32.9 (30.2–35.7)	33.5 (31.7–35.4)	32 (31.2–33)	31.1 (30.2–32)	26.9 (24.1–30)	30.1 (29–32)	10.7	0.0001
BMI, kg/m^2 (95% CI)	27.4 (26–28.8)	26.9 (24.1–30.0)	33.7 (31.6–35.8)	34.6 (32.5–36.8)	29.7 (28.3–31)	29.1 (27.5–30.6)	27.6 (26–29.2)	26 (25.2–26.8)	11.5	0.0001
HbA1c in the trimester III, % (95% CI)	6.31 (6.0–6.5)	6.73 (6.2–6.9)	5.71 (5.4–6.0)	6.17 (5.8–6.4)	5.52 (5.1–5.6)	6.0 (5.5–6.2)	–	4.75 (4.5–5.1)	13.6	0.0001
OGTT, mmol/l										
Fasting (95% CI)	–	–	–	–	4.9 (4.8–5.0)	5.2 (5.1–5.3)	4.6 (4.4–4.8)	4.1 (3.6–4.4)	8.5	0.01
1 h (95% CI)	–	–	–	–	9.8 (9.5–10.2)	10.1 (9.9–10.4)	7.9 (7.3–8.6)	6.4 (5.9–6.7)	7.7	0.01
2 h (95% CI)	–	–	–	–	8.6 (8.4–9.0)	9.0 (8.5–9.5)	7.5 (6.3–8.1)	5.9 (5.4–6.1)	14.2	0.0001
Concomitant somatic pathology									χ^2	
Varicose veins (*n*, %)	3 (15)	2 (9.1)	4 (23.5)	7 (26.9)	15 (17)	9 (21.4)	2 (8.3)	4 (10.5)	37.4	0.0001
Chronic AH (*n*, %)	0 (0)	2 (9.1)	3 (17.6)	6 (23.1)	4 (4.5)	2 (4.8)	4 (16.7)	0 (0)	83.7	0.0001
Hepatic steatosis (*n*, %)	0 (0)	0 (0)	3 (17.6)	5 (19.2)	3 (3.4)	3 (7.1)	0 (0)	0 (0)	53.4	0.0001
BD (*n*, %)	0 (0)	0 (0)	1 (5.9)	0 (0)	5 (5.6)	0 (0)	1 (4.2)	2 (5.3)	4.5	0.72
Excess body weight (*n*, %)	11 (55)	10 (45.5)	5 (31.3)	4 (15.4)	27 (31.8)	19 (46.3)	14 (58.3)	22 (57.9)	20.4	0.005
Obesity degree I (*n*, %)	4 (20)	1 (4.5)	1 (6.3)	6 (23.1)	26 (30.6)	8 (19.5)	3 (12.5)	2 (5.3)	17.9	0.013
Obesity degree II (*n*, %)	0 (0)	2 (9.1)	5 (31.3)	12 (46.5)	7 (8.2)	5 (12.2)	2 (8.3)	0 (0)	43.5	0.0001
Obesity degree III (*n*, %)	0 (0)	0 (0)	5 (31.3)	2 (7.7)	8 (9.4)	1 (2.4)	0 (0)	0 (0)	28.0	0.0001
Gestational complications										
Preterm delivery (*n*, %)	4 (20)	5 (22.7)	2 (11.8)	5 (19.2)	6 (6.8)	4 (9.5)	5 (20.8)	1 (2.6)	38.9	0.0001
Gestational AH (*n*, %)	1 (5)	1 (4.5)	0 (0)	2 (7.7)	5 (5.6)	3 (7.1)	0 (0)	1 (2.6)	6.8	0.01
Moderate PE (*n*, %)	3 (15)	3 (13.6)	3 (17.6)	5 (19.2)	8 (10.2)	4 (9.5)	9 (37.5)	0 (0)	52.7	0.001
Severe PE (*n*, %)	1 (5)	2 (9.1)	2 (11.8)	4 (15.3)	4 (4.5)	2 (4.8)	15 (62.5)	0 (0)	73.6	0.0001
Fetal growth retardation (*n*, %)	0 (0)	1 (4.5)	1 (5.9)	3 (11.5)	5 (5.6)	3 (7.1)	5 (20.8)	0 (0)	43.8	0.0001

Note. CSII: continuous subcutaneous insulin infusion; MII: multiple insulin injections; DM: diabetes mellitus; GDM: gestational diabetes mellitus; PE: preeclampsia; BD: biliary dyskinesia; OGTT: oral glucose tolerance test; AH: arterial hypertension; BMI: body mass index; HbA1c: glycated hemoglobin; CI: confidence interval.

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Table 2. Indicators of lipid profile in women in the third trimester of pregnancy

Group	TG, mmol/L	CS, mmol/L	HDL, mmol/L	LDL, mmol/L	VLDL, mmol/L	AI
Type 1 DM, CSII	4.42 (3.13–6.21)	6.63 (6.11–7.14)	1.11 (1.1–1.89)	3.3 (3.12–4.89)	1.31 (0.99–1.74)	3.23 (3.02–3.73)
Type 2 DM, MII	4.02 (3.03–5.01)	6.67 (6.39–6.94)	1.49 (1.35–1.63)	3.8 (3.36–4.24)	1.41 (0.98–1.84)	3.57 (3.15–3.98)
Type 2 DM, diet	5.84 (3.36–8.31)	6.45 (5.97–6.92)	1.5 (1.27–1.74)	3.26 (2.83–3.68)	1.06 (0.79–1.33)	3.38 (2.23–4.52)
Type 2 DM, insulin	5.42 (1.9–8.97)	6.45 (5.97–6.71)	1.23 (0.92–1.53)	3.41 (2.86–3.97)	1.43 (1.05–1.8)	3.96 (2.79–5.12)
GDM, diet	2.9 (2.64–3.17)	6.6 (6.4–6.81)	1.78 (1.68–1.88)	3.39 (3.19–3.6)	1.12 (1.03–1.21)	2.38 (2.21–2.56)
GDM, insulin	3.41 (2.86–3.95)	6.32 (5.92–6.72)	1.55 (1.44–1.66)	3.22 (2.98–3.46)	1.42 (1.15–1.68)	2.62 (2.3–2.93)
PE	3.3 (2.52–4.08)	6.48 (5.75–7.21)	1.83 (1.74–1.92)	3.27 (2.76–3.79)	1.51 (1.19–1.83)	2.58 (2.18–2.97)
Control	2.78 (2.54–3.02)	6.53 (6.27–6.79)	2.04 (1.66–2.44)	3.27 (3.1–3.44)	1.06 (0.98–1.14)	2.4 (2.27–2.53)
F	8.3	0.48	5.94	1.26	4.23	11
p	<0.001*	0.851	<0.001*	0.274	<0.001*	<0.001*

Note. DM: diabetes mellitus; GDM: gestational diabetes mellitus; PE: preeclampsia, CSII: continuous subcutaneous insulin infusion; MII: multiple insulin injections; TG: triglycerides; CS: cholesterol; HDL: high density lipoproteins; LDL: low density lipoproteins; VLDL: very low density lipoproteins; and AI: atherogenic index. * Statistically significant differences.

treated with insulin. In addition, the glycemic parameters in OGTT in pregnant women with GDM and PE were relatively higher compared to the control group (Table 1).

The incidence analysis of somatic pathology revealed that pregnant women with type 2 DM and GDM had the highest frequency of concomitant diseases, namely varicose veins, obesity, hepatic steatosis, and chronic arterial hypertension (Table 1).

Assessment of primary study outcomes

The lipid profile study revealed that TG level was significantly higher in female patients with carbohydrate metabolism disorders and PE compared to that of the control group ($p < 0.001$). The most pronounced changes in this indicator of the lipid profile were registered in pregnant women with type 2 DM (5.42–5.84 mmol/l). A similar tendency was noted when assessing the VLDL and AI levels. VLDL concentrations were highest in pregnant women with severe metabolic disorders (receiving insulin therapy) and with PE ($p < 0.001$). The increase in AI was maximal in patients with pregestational types of DM (3.23–3.96). The antiatherogenic HDL level, on the contrary, was significantly lower in DM groups under study compared to healthy pregnant women, especially in patients with type 1 and 2 DM ($p < 0.001$). No significant differences were found in assessing the TC and LDL concentrations (Table 2).

Evaluation of additional study outcomes

Preterm delivery are complicated every fifth pregnancy in patients with type 1 DM (20.5%), with type 2 DM receiving insulin therapy (19.2%), and with PE (20.8%). In the groups of patients with GDM, the prevalence of preterm birth was also slightly higher (7.7%) than in the control group (Table 1).

Hypertensive complications during pregnancy were significantly more frequent in women with various types of DM (Table 1). However, the development of severe forms of PE was typical for groups with more pronounced metabolic disorders (who received insulin therapy). Fetal growth retardation was most often noted in pregnant women with PE (20.8%) and with type 2 DM with insulin therapy (11.5%). Pregnancy was not complicated by either PE or fetal growth retardation in any patients from the control group.

Additional research findings

Correlation analysis revealed a weak direct relationship between the TG level and the development of macrosomia ($r = 0.26$; $p = 0.001$) and between the AI value and severe PE ($r = 0.26$; $p < 0.001$). A less pronounced correlation with the development of severe PE was established for such indicators as TG ($r = 0.2$; $p < 0.001$) and VLDL ($r = 0.22$; $p < 0.001$). Any other significant correlations in this study were not revealed (Table 3). According to the ROC analysis results, the values

Table 3. Correlation analysis

Indicator	TG (*r*)	CS (*r*)	HDL (*r*)	LDL (*r*)	VLDL (*r*)	AI (*r*)
Macrosomia	**0.26 (*p* = 0.001)**	0.02 (*p* = 0.3)	0.07 (*p* = 0.1)	0.04 (*p* = 0.26)	0.03 (*p* = 0.29)	–0.01 (*p* = 0.12)
Baby weight	0.08 (*p* = 0.09)	–0.02 (*p* = 0.32)	**–0.12 (*p* = 0.03)**	0 (*p* = 0.49)	0.04 (*p* = 0.27)	0.01 (*p* = 0.46)
HbA1c	0.05 (*p* = 0.39)	0.1 (*p* = 0.12)	0.17 (*p* = 0.16)	0.28 (*p* = 0.06)	0.14 (*p* = 0.25)	0.06 (*p* = 0.37)
Gestational AH	**0.15 (*p* = 0.004)**	–0.05 (*p* = 0.12)	–0.08 (*p* = 0.1)	0.07 (*p* = 0.11)	**0.11 (*p* = 0.041)**	**0.12 (*p* = 0.016)**
Moderate PE	0.06 (*p* = 0.17)	0.01 (*p* = 0.44)	–0.004 (*p* = 0.47)	–0.05 (*p* = 0.19)	0.06 (*p* = 0.15)	0.05 (*p* = 0.22)
Severe PE	**0.2 (*p* = 0.00)**	–0.004 (*p* = 0.46)	**–0.18 (*p* = 0.001)**	0.08 (*p* = 0.1)	**0.22 (*p* = 0.00)**	**0.26 (*p* = 0.00)**
Preterm delivery	**0.12 (*p* = 0.016)**	–0.01 (*p* = 0.41)	**–0.13 (*p* = 0.012)**	**0.097 (*p* = 0.05)**	**0.1 (*p* = 0.04)**	**0.127 (*p* = 0.015)**
BMI	**0.33 (*p* = 0.00)**	**0.13 (*p* = 0.002)**	–0.09 (*p* = 0.15)	–0.06 (*p* = 0.26)	**0.27 (*p* = 0.003)**	0.08 (*p* = 0.18)

Note. AH: arterial hypertension; PE: preeclampsia, TG: triglycerides; CS: cholesterol; HDL: high density lipoproteins; LDL: low density lipoproteins; VLDL: very low density lipoproteins; AI: atherogenic index; HbA1c: glycated hemoglobin; and BMI: body mass index. Statistically significant results are presented in bold.

Table 4. ROC analysis, AUC

Indicator	TG	CS	HDL	LDL	VLDL	AI
Macrosomia	0.54 (0.44–0.65) *p* = 0.42	0.53 (0.42–0.64) *p* = 0.61	0.59 (0.48–0.69) *p* = 0.12	0.52 (0.43–0.62) *p* = 0.68	0.53 (0.41–0.65) *p* = 0.58	0.49 (0.39–0.59) *p* = 0.83
Moderate PE	0.52 (0.43–0.61) *p* = 0.63	0.53 (0.43–0.63) *p* = 0.58	0.5 (0.41–0.6) *p* = 0.94	0.45 (0.35–0.54) *p* = 0.26	0.55 (0.45–0.64) *p* = 0.31	0.52 (0.42–0.61) *p* = 0.76
Severe PE	0.64 (0.54–0.73) **p = 0.003**	0.51 (0.42–0.6) *p* = 0.9	0.39 (0.3–0.48) **p = 0.02**	0.56 (0.48–0.65) *p* = 0.19	0.66 (0.58–0.75) **p < 0.001**	0.69 (0.6–0.77) **p < 0.001**

Note. PE: preeclampsia, TG: triglycerides; CS: cholesterol; HDL: high density lipoproteins; LDL: low density lipoproteins; VLDL: very low density lipoproteins; AI: atherogenic index. Statistically significant results are presented in bold.

of TG, VLDL, and AI can be used to predict the development of severe PE. AUC for these indicators is 0.64 ($p = 0.003$), 0.66 ($p < 0.001$), and 0.69 ($p < 0.001$), respectively (Table 4).

DISCUSSION

The study demonstrates that pregnancy proceeding in presence of DM is associated with a high incidence of adverse perinatal complications, such as birth of a large fetus, preterm delivery, and PE.

A change in the lipid pattern in pregnant women with various types of DM in late pregnancy was confirmed relative to the control group, characterized by atherogenic lipids (TG and VLDL) predominance in the plasma, increase in AI, and decrease in the level of anti-atherogenic HDL. However, significant differences in the TC and LDL concentrations were not detected. Similar results were obtained by K. Ryckman et al. (2015), who studied lipid levels in women with GDM throughout pregnancy [16]. In an earlier study, the lipid profile in women with different types of DM (types 1, 2, and GDM) has no difference in TG and TC levels compared to that of healthy women, but the LDL value was significantly higher in all trimesters, which differs from our data obtained [17]. C. Göbl et al. (2010) found that concentrations of TC, LDL, and HDL in the plasma of female patients in the third trimester with type 1 DM was significantly higher compared to patients with type 2 DM [22]. Considering our results in conjunction with the type of DM correction, we did not reveal a significant advantage of insulin therapy in assessing the lipid profile. However, according to P. Olmos et al. (2017), only the basal-bolus regimen of insulin therapy in women with well-controlled GDM reduces the plasma TG

concentration, while the AI was within the normal range both in the group of patients receiving insulin therapy and in the control group. This was due to the ability of insulin to reduce the production of VLDL by the liver and activate maternal LPL, without affecting CETP [23].

A comparison group (patients with developed PE) was added to our study. They were diagnosed with dyslipidemia, with values registered close in pregnant women with DM. However, in this group, the development of dyslipidemia was associated with endothelial dysfunction and enhanced processes of oxidative stress, which manifested itself from the early stages of pregnancy [7].

In our study, a relationship was established between dyslipidemia in pregnant women and the development of some perinatal complications. A weak positive correlation was revealed between TG level and macrosomia, as well as the AI value with the development of severe PE. However, a number of studies indicated the absence of significant relationships between lipid profile indicators and development of unfavorable outcomes in pregnant women with DM [20, 22, 24, 25].

The peak accumulation of fetal adipose mass occurs at late stages of prenatal development, which coincides with maternal hyperlipidemia. If a woman has DM, not only the plasma lipid concentration changes, but also the placental transfer of fatty acids to the fetus increases, which is explained by the increased activity of placental LPL [26]. A sharp gradient of TG concentrations also contributes to their enhanced transport. Fetal hyperinsulinemia is assumed to have an inhibitory effect on its ANGPTL4, and as a result, the high LPL activity of the fetal adipose tissue leads to excessive fat accumulation and the birth of a large fetus [6]. According to another hypothesis, fatty acids activate transcription factors in the fetus and initiate the transformation of mesenchymal stem cells into adipocytes [26]. Some studies demonstrated no relationship between newborn weight and lipid levels in women in the third trimester of pregnancies with and without DM [22, 24, 25]. Among the lipids determined in late pregnancy, the leading place in relationship with macrosomia is attributed to TG [4, 10, 13, 19, 23, 27, 28]. Our results do not contradict these studies. X. Wang et al. (2018) established that an increase in the TG level by every 1 mmol/l corresponds to an increase in the risk of macrosomia by 27% in women without DM [10]. In pregnant women with GDM, a positive correlation was found between the levels of TG, free fatty acids with macrosomia, and fetal adipose mass, regardless of glycemic control, pregnant woman BMI, and weight gain [4, 13, 19, 27]. Data from these studies demonstrated that concentration of lipids circulating in the mother's bloodstream determines the fetal size in late pregnancy, with well-controlled GDM. G. Son et al. (2010) determined the threshold value of TG (≥3.33 mmol/L) in female patients with GDM in the third trimester of pregnancy to predict the birth of a large fetus [13]. Effective correction of hypertriglyceridemia with insulin significantly reduces the estimated weight of the newborn. Thus, the effect of lipids is not irreversible for fetal growth, and their correlation with the newborn's body weight is most significant in late pregnancy (35.7 ± 1.5 weeks) [23].

P. Olmos et al. (2014) revealed that plasma TG levels correlate significantly with newborn weight only in overweight or obese mothers (taking into account pregnancies complicated by GDM) [28]. According to the data of other researchers, not only hypertriglyceridemia is a predictor of the development of macrosomia [29–31]. Thus, B. Krstevska et al. (2016), when studying pregnant women with GDM and type 2 DM, revealed a direct correlation between the level of LDL and TC in the third trimester and the weight of the newborn [29]. Few studies showed a significant inverse relationship between HDL levels in pregnant women with DM and the risk of macrosomia [30, 31]. In a study by J. Zhou et al. (2012), low HDL values (<2.2 mmol/L) at a term of 20 weeks of gestation predicted the development of fetal macrosomia with a sensitivity of 65% and a specificity of 48% [31]. Works presented ultimately have very different results, which often contradict with each other; therefore, making an unambiguous conclusion about the advisability of determining the lipid level in women with DM to predict the risk of macrosomia is impossible.

In a study by A. Basu et al. (2012) conducted on women with type 1 DM, no correlation was revealed between lipid levels and development of PE. Authors studied these biomarkers throughout pregnancy [20]. However, results of our study demonstrated a relationship between AI and severe PE. In addition, indicators such as TG, VLDL, and AI can be used as predictors of severe PE. In their recent work, C. Smith et al. (2018) demonstrated that dyslipidemia in women in late pregnancy is associated with a 1.5-fold increase in the risk of any type of preterm delivery [32]. In our study, we did not reveal such a relationship in pregnant women with DM.

Thus, the study of lipid metabolism in women with various types of DM in late pregnancy revealed deviations from the indicators of the control group. In this category of patients, the plasma levels of TG and VLDL is increased, AI is increased, and the levels of antiatherogenic HDL are decreased. These changes could potentially explain the high incidence of perinatal complications in women with DM. Correlation analysis revealed a connection between lipid profile disorders and some adverse perinatal outcomes. These results differ from a number of studies conducted earlier, the data of which are also largely contradictory. Possible causes for inconsistencies are heterogeneity of populations, frequency of obesity in different regions, and gestational age at which measurements were taken. Further research on this issue is required.

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ОБ АВТОРАХ

***Роман Викторович Капустин**, канд. мед. наук;
адрес: Россия, 199034, Санкт-Петербург,
Менделеевская линия, д. 3;
ORCID: https://orcid.org/0000-0002-2783-3032;
ResearcherID: G-3759-2015; eLibrary SPIN: 7300-6260;
e-mail: kapustin.roman@gmail.com

Елизавета Михайловна Цыбук;
ORCID: https://orcid.org/0000-0001-5803-1668;
ResearcherID: ABB-6930-2020;
eLibrary SPIN: 3466-7910;
e-mail: elizavetatcybuk@gmail.com

Елена Николаевна Алексеенкова;
ORCID: https://orcid.org/0000-0003-1409-5680;
ResearcherID: W-3735-2017;
eLibrary SPIN: 3976-2540;
e-mail: ealekseva@gmail.com

Екатерина Вадимовна Коптеева;
ORCID: https://orcid.org/0000-0002-9328-8909;
eLibrary SPIN: 9421-6407;
e-mail: ekaterina_kopteeva@bk.ru

AUTHORS INFO

***Roman V. Kapustin**, MD, PhD;
address: 3, Mendeleevskaya line,
Saint Petersburg, 199034, Russia;
ORCID: https://orcid.org/0000-0002-2783-3032;
ResearcherID: G-3759-2015; eLibrary SPIN: 7300-6260;
e-mail: kapustin.roman@gmail.com

Elizaveta M. Tsybuk;
ORCID: https://orcid.org/0000-0001-5803-1668;
ResearcherID: ABB-6930-2020;
eLibrary SPIN: 3466-7910;
e-mail: elizavetatcybuk@gmail.com

Elena N. Alexeyenkova;
ORCID: https://orcid.org/0000-0003-1409-5680;
ResearcherID: W-3735-2017;
eLibrary SPIN: 3976-2540;
e-mail: ealekseva@gmail.com

Ekaterina V. Kopteyeva;
ORCID: https://orcid.org/0000-0002-9328-8909;
eLibrary SPIN: 9421-6407;
e-mail: ekaterina_kopteeva@bk.ru

ОБ АВТОРАХ

Ольга Николаевна Аржанова, д-р мед. наук, профессор, засл. врач РФ;
ORCID: https://orcid.org/0000-0003-3059-9811;
ResearcherID: G-6895-2015;
eLibrary SPIN: 7910-6039;
e-mail: olga_arjanova@mail.ru

Татьяна Ивановна Опарина, канд. биол. наук;
ORCID: https://orcid.org/0000-0001-5133-2396;
eLibrary SPIN: 2719-5432;
e-mail: oparinat@mail.ru

Жанна Николаевна Тумасова;
e-mail: iagmail@ott.ru

AUTHORS INFO

Olga N. Arzhanova, MD, PhD, DSci (Medicine), Professor, Honoured Doctor of the Russian Federation;
ORCID: https://orcid.org/0000-0003-3059-9811;
ResearcherID: G-6895-2015;
eLibrary SPIN: 7910-6039;
e-mail: olga_arjanova@mail.ru

Tatyana I. Oparina, PhD, Biologist;
ORCID: https://orcid.org/0000-0001-5133-2396;
eLibrary SPIN: 2719-5432;
e-mail: oparinat@mail.ru

Zhanna N. Tumasova;
e-mail: iagmail@ott.ru