DOI: https://doi.org/10.17816/JOWD64108

Evaluation of sFlt-1 and PlGF for predicting preeclampsia in pregnant women with diabetes mellitus

© Roman V. Kapustin[1, 2], Elizaveta M. Tsybuk[2], Sergey V. Chepanov[1], Elena N. Alexeyenkova[1], Ekaterina V. Kopteyeva[2], Olga N. Arzhanova[1, 2]

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

AIM: The aim of this study was to evaluate soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) levels in the blood of women with various types of diabetes mellitus, depending on the correction method applied, and to determine the prognostic significance of the sFlt-1 / PlGF ratio for predicting the development of preeclampsia in this patient population.

MATERIALS AND METHODS: We examined 140 pregnant women who were included in six main study groups: type 1 diabetes mellitus (with or without pregravid preparation), type 2 diabetes mellitus (diet therapy or insulin therapy), and gestational diabetes mellitus (diet therapy or insulin therapy). The comparison groups consisted of pregnant women with preeclampsia and patients without complications of pregnancy. Using electrochemiluminescence analysis, PlGF and sFlt-1 levels in the blood serum were determined twice, at 11^{+0}–13^{+6} and 30^{+0}–33^{+6} weeks of gestation. Statistical data processing was performed using the IBM SPSS Statistics version 23 and GraphPad Prism version 8.0 software packages.

RESULTS: In the blood serum of pregnant women with diabetes mellitus in the first and third trimesters of pregnancy, we found an increase in sFlt-1 level and a decrease in PlGF level, as well as an increase in the sFlt-1 / PlGF ratio. These changes were most pronounced in individuals with type 1 diabetes mellitus without pregravid preparation and with type 2 diabetes mellitus on insulin therapy. In patients with pregestational types of diabetes mellitus, the sFlt-1 / PlGF ratio was a predictor of preeclampsia already in the early stages of pregnancy. Analysis of the ROC curve showed that the threshold sFlt-1 / PlGF ratio for predicting preeclampsia in pregnant women with diabetes mellitus in the first trimester was 32.5 (sensitivity 92.9%, specificity 50.0%) and in the third trimester 71.8 (sensitivity 85.7%, specificity 82.3%) with AUC 0.78 (95% CI 0.68–0.88) and 0.89 (95% CI 0.83–0.95), respectively. In the first trimester, the positive and negative predictive values of the sFlt-1 / PlGF ratio as a predictor of preeclampsia in pregnant women with diabetes mellitus were 63.3% and 97.6%, respectively; in the third trimester, 38.9% and 93.6%, respectively.

CONCLUSIONS: Blood level alterations of PlGF and sFlt-1 are characteristic of patients with diabetes mellitus in the first and third trimesters of pregnancy. An increase in the sFlt-1 / PlGF ratio is associated with a higher incidence of unfavorable perinatal outcomes in women with impaired carbohydrate metabolism. Determination of the sFlt-1 / PlGF ratio is a valid method for predicting the development or absence of preeclampsia in women with diabetes mellitus.

Keywords: preeclampsia; diabetes mellitus; placental growth factor; soluble fms-like tyrosine kinase-1; sFlt-1 / PlGF.

To cite this article:
Kapustin RV, Tsybuk EM, Chepanov SV, Alexeyenkova EN, Kopteyeva EV, Arzhanova ON. Evaluation of sFlt-1 and PlGF for predicting preeclampsia in pregnant women with diabetes mellitus. *Journal of Obstetrics and Women's Diseases.* 2021;70(4):43–56. DOI: https://doi.org/10.17816/JOWD64108

Received: 24.03.2021 **Accepted:** 30.06.2021 **Published:** 31.08.2021

УДК 616.379-008.64:618.3-06:616-009.24-036.3
DOI: https://doi.org/10.17816/JOWD64108

Оценка уровня растворимой fms-подобной тирозинкиназы-1 и плацентарного фактора роста для предикции развития преэклампсии у беременных с сахарным диабетом

© Р.В. Капустин[1, 2], Е.М. Цыбук[2], С.В. Чепанов[1], Е.Н. Алексеенкова[1], Е.В. Коптеева[2], О.Н. Аржанова[1, 2]

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

Цель — оценить содержание растворимой fms-подобной тирозинкиназы-1 (sFlt-1) и плацентарного фактора роста (PlGF) в крови у женщин с различными типами сахарного диабета с учетом метода его коррекции, а также определить прогностическую значимость соотношения sFlt-1/PlGF для предикции развития преэклампсии у данных пациенток.

Материалы и методы. В исследование включены 140 беременных, которые составили шесть основных групп: с сахарным диабетом 1-го типа (с наличием и отсутствием прегравидарной подготовки) и сахарным диабетом 2-го типа и гестационный сахарным диабетом (диетотерапия, инсулинотерапия). В группы сравнения вошли беременные с преэклампсией и пациентки без осложнений. Концентрацию плацентарного фактора роста (PlGF) и мембранного рецептора fms-подобной тирозинкиназы-1 (sFlt-1) в сыворотке крови определяли при помощи электрохемилюминесцентного анализа дважды — в 11^{+0}–13^{+6} и в 30^{+0}–33^{+6} нед. Статистическую обработку данных проводили при помощи пакетов программ IBM SPSS Statistics version 23 и GraphPad Prism version 8.0.

Результаты. У беременных с сахарным диабетом выявлено увеличение содержания sFlt-1 и снижение содержания PlGF, а также увеличение соотношения sFlt-1/PlGF в сыворотке крови в I и III триместрах беременности. В наибольшей степени эти изменения были выражены у женщин с сахарным диабетом 1-го типа без прегравидарной подготовки и с сахарным диабетом 2-го типа на инсулинотерапии. У пациенток с прегестационными типами сахарного диабета соотношение sFlt-1/PlGF являлось предиктором преэклампсии уже на ранних сроках. Анализ ROC-кривой показал, что пороговое соотношение sFlt-1/PlGF для предикции преэклампсии у беременных с сахарным диабетом в I триместре составило 32,5 (чувствительность — 92,9 %, специфичность — 50,0 %), а в III — 71,8 (чувствительность — 85,7 %, специфичность — 82,3 %) при показателях AUC 0,78 (95 % ДИ 0,68–0,88) и 0,89 (95 % ДИ 0,83–0,95) соответственно. В I триместре положительная прогностическая ценность соотношения sFlt-1/PlGF как предиктора преэклампсии у беременных с сахарным диабетом составила 63,3 %, отрицательная — 97,6 %; в III триместре — 38,9 и 93,6 % соответственно.

Заключение. Изменения концентраций PlGF и sFlt-1 характерны для пациенток с сахарным диабетом в I и III триместрах. Увеличение соотношения sFlt-1/PlGF ассоциировано с более высокой частотой неблагоприятных перинатальных исходов у женщин с нарушениями углеводного обмена. Определение соотношения sFlt-1/PlGF является валидным методом предикции развития или отсутствия преэклампсии у женщин с сахарным диабетом.

Ключевые слова: преэклампсия; сахарный диабет; плацентарный фактор роста; растворимая fms-подобная тирозинкиназа-1; sFlt-1/PlGF.

Как цитировать:
Капустин Р.В., Цыбук Е.М., Чепанов С.В., Алексеенкова Е.Н., Коптеева Е.В., Аржанова О.Н. Оценка уровня растворимой fms-подобной тирозинкиназы-1 и плацентарного фактора роста для предикции развития преэклампсии у беременных с сахарным диабетом // Журнал акушерства и женских болезней. 2021. Т. 70. № 4. С. 43–56. DOI: https://doi.org/10.17816/JOWD64108

Рукопись получена: 24.03.2021 **Рукопись одобрена:** 30.06.2021 **Опубликована:** 31.08.2021

BACKGROUND

Preeclampsia (PE) occurs in 2%–8% of pregnant women and is one of the leading causes of adverse maternal and perinatal outcomes worldwide [1, 2]. Although the exact pathogenetic mechanisms of its occurrence are still unknown, we know that the placenta plays a key role in the pathogenesis of this gestational complication [3]. Its ischemic damage due to insufficient cytotrophoblast invasion into the coiled uterine arteries results in an impairment of the synthesis of angiogenic factors. As a result, vascular factors are released into the maternal bloodstream in excess amount leading to systemic endothelial dysfunction and subsequently cause the entire range of clinical manifestations of PE [1, 3, 4].

Angiogenic factors contribute to the development and maturation of placental vessels. The main angiogenic factor is placental growth factor (PlGF) which belongs to the family of vascular endothelial growth factor and enhances its angiogenic activity. The action of these proteins is mediated through the fms-like tyrosine kinase-1 (sFlt-1) membrane receptor [5]. However, under unfavorable conditions, the production of this protein in its soluble form is excessively increased and it interacts with angiogenic factors circulating in the bloodstream. This leads to a significant decrease in the levels of free PlGF, thereby preventing its binding to membrane receptors [4, 5]. A decrease in the plasma level of PlGF and an increase in sFlt-1 are characteristic of women who will develop PE from early pregnancy [4, 6–8].

There is currently a steady increase in the incidence of diabetes mellitus (DM) among pregnant women. Recent studies reveal that hyperglycemia accompanies every sixth pregnancy, with gestational diabetes mellitus (GDM) accounting for the majority (84%) [9]. This condition is associated with a high incidence of adverse perinatal outcomes. Thus, the risk of PE increases by 2–4 times in the presence of maternal DM [10]. With insufficient compensation of carbohydrate metabolism in in patients with DM, the number of immature villi in the placenta increases, and peripheral villi become ischemic. Enhanced angiogenesis under hypoxic conditions leads to pathological changes in the placenta similar to processes occurring in PE [11, 12]. Thus, the pathogenesis of both PE and DM is based on similar pathological reactions: endothelial dysfunction, oxidative stress, angiogenic imbalance, and systemic inflammatory response [2, 12, 13]. This is associated with changes in the levels of angiogenic factors in patients with DM in the early stages of pregnancy, regardless of the further development of PE. In some studies, it is noted that the concentration of free PlGF in women with pregestational types of DM is significantly lower even in comparison with pregnant women from high-risk groups for PE [14], as opposed to the level of sFlt-1 [15]. In patients with DM, the sFlt-1/PlGF ratio takes on higher values relative to patients without carbohydrate metabolism disorders throughout pregnancy [16]. This greatly complicates the diagnosis of PE and the possibility of predicting its development in patients with DM. Paucity of information is available on this subject and findings are often contradictory. However, early identification of pregnant women with a high risk of this hypertensive complication is necessary for more careful monitoring and for a timely start of prevention of its occurrence [17, 18].

We therefore aimed at assessing the blood levels of sFlt-1 and PlGF in women with different types of DM at 11^{+0}–13^{+6} and 30^{+0}–33^{+6} weeks of pregnancy, considering the method of DM correction and the presence of pregravid preparation, as well as determining the prognostic significance of the sFlt-1/PlGF ratio for predicting the development of PE in these patients.

MATERIALS AND METHODS

Study design

A prospective cohort single-center study was performed in the D.O. Ott Scientific Research Institute of Obstetrics, Gynecology, and Reproduction. We analyzed the clinical and laboratory parameters of pregnant women registered at the dispensary and received inpatient treatment within the period from 2017 to 2019. The type of DM and diagnosis of PE was established based on relevant national clinical guidelines [19, 20]. We included those with singleton pregnancy, the presence of DM (type 1, type 2, GDM), and have consented to participate in the study. Exclusion criteria included multifetal pregnancy, cancer, severe somatic pathology, diabetes insipidus, and refusal to participate in the study.

The study included 140 pregnant women who divided into six main groups depending on the type of DM, the method of its correction (diet/insulin), and pregravid preparation. The comparison group included women with PE without DM, and the control group included conditionally healthy patients:

- type 1 DM — unplanned pregnancy, the level of glycated hemoglobin (HbA1c) > 6.5% (n = 20);
- type 1 DM — planned pregnancy, HbA1c level < 6.5% (n = 20);
- type 2 DM (insulin therapy) — n = 20;
- type 2 DM (diet therapy) — n = 15;
- GDM (insulin therapy) — n = 20;
- GDM (diet therapy) — n = 20;
- comparison group, PE — n = 10;
- control group — n = 15.

The levels of sFlt-1 and PlGF were determined in patients with pregestational types of DM and in the control group twice, at 11^{+0}–13^{+6} and 30^{+0}–33^{+6} weeks of gestation. In patients with developed GDM and PE, measurements were performed at 30 30^{+0}–33^{+6} weeks.

Electrochemiluminescence assay

After obtaining peripheral venous blood and serum, the samples were stored at –70°C until analysis. The levels of sFlt-1 and PlGF in peripheral blood serum was determined by electrochemiluminescence assay using commercial test systems; Elecsys sFlt-1 and Elecsys PIGF made by Roche Diagnostics GmbH (Germany) on an automatic immunochemical analyzer Cobas e411 (Japan). The study results were evaluated quantitatively (pg/mL).

Statistical analysis

Data was analyzed using SPSS V. 23.0 (USA) and Prism 8-GraphPad (USA). The distribution parameters of the sample were assessed using the Kolmogorov–Smirnov test. Statistical significance of the differences between the quantitative parameters of the normally-distributed variables was determined, and one-way analysis of variance was performed with the calculation of a 95% confidence interval (CI). For nonparametric distribution of varaibles, the Kruskal–Wallis test of multiple group comparisons was used with interquartile ranges (IQR). Dunn's post hoc test was used in calculations. The Mann–Whitney *U* test was used to compare two independent groups. Statistical processing of qualitative attributes was performed using the Pearson χ^2 test. To assess the predictive value of biomarker concentrations, a ROC analysis was performed and the areas under the curves (AUC), positive (PPV) and negative (NPV) predictive values obtained were calculated with the determination of 95% CI. The hypothesis of equality of mean values in the studied groups was rejected at a significance level of $p < 0.05$.

RESULTS

Clinical characteristics of the study groups

The characteristics of the studied groups are presented in the Table 1. Female patients with type 2 DM and GDM were older and had a higher pregestational body mass index compared to patients in other groups ($p < 0.05$). The average level of HbA1c was consistently higher throughout pregnancy with type 1 DM without pregravid preparation relative to the values of the other groups (Table 1).

The highest body weight at birth was in children from mothers with type 1 DM and GDM (Table 1). Women with type 1 DM and those without disorders of carbohydrate metabolism were more primiparas, while those with type 2 DM and GDM were more multiparous. Four women who were in the GDM groups on insulin therapy and with PE, conceived through assisted reproductive technologies.

Most pregnant women with type 1 DM (70%) had diabetic microangiopathies. In groups with type 2 DM, microvascular complications occurred in only 30% of women who received insulin. Every third patient with type 1 DM without pregravid preparation had diabetic nephropathy (35%) (Table 1).

Hypertensive complications of pregnancy were significantly more frequent in patients with various types of DM. In most cases, PE developed late, and severe forms of this disease were typical for pregnant women with more pronounced metabolic disorders (on insulin therapy). However, PE most often occurred in women with type 1 DM without planning pregnancy (40%) and with type 2 DM who received insulin (50%). The average time of the PE manifestation onset did not differ significantly between the groups, but in women with type 1 DM without pregravid preparation and type 2 DM on insulin therapy, this disease was diagnosed a little earlier than in pregnant women in other groups, on average, at week 34. In patients with DM, childbirth occurred earlier than full-term and ended in a low-birth-weight fetus compared with women in the control group. The highest prevalence of preterm birth (40%) and low birth weight (30%) were recorded among pregnant women from the comparison group (PE). Cases of fetal macrosomia were most common in patients with type 1 DM and GDM (27.5%) (Table 1).

Assessment of sFlt-1 and PlGF levels

During the study of the levels of sFlt-1 and PlGF during pregnancy, differences were found in the serum concentration of these biomarkers in women with disorders of carbohydrate metabolism and PE as compared with patients in the control group (Table 2, Fig. 1).

In the trimester I of pregnancy, the highest average sFlt-1 values were recorded in patients with type 1 DM without pregravid preparation and in those with type 2 DM on insulin therapy, which were more than 2 times higher than the level of PlGF in pregnant women in the control group ($p < 0.001$). The PlGF concentration was lower in women with pregestational types of DM, regardless of the type of correction and pregnancy planning, compared with values in healthy patients ($p < 0.01$). The opposite tendency was noted for the sFlt-1/PlGF ratio: significantly higher in pregnant women with DM, and the highest value was registered in women with type 1 DM without pregravid preparation ($p < 0.001$) (Table 2, Fig. 1).

In trimester III of pregnancy, the levels of these biomarkers differed between the groups in a similar way. However, in patients with PE, the differences in sFlt-1 and PlGF concentrations from those in the control group were most pronounced. Among pregnant women with DM, the highest concentrations of sFlt-1 were revealed in patients with type 1 DM without pregravid preparation and with type 2 DM on insulin therapy. Patients with GDM were also characterized by an increase in sFlt-1 level, but to a lesser extent than women with pregestational types of DM. This indicator was strongly influenced by the type of DM correction. Thus, in pregnant women on insulin therapy, the sFlt-1 concentration was almost twice higher than in patients with GDM on a diet. The lowest PlGF values were found in

DOI: https://doi.org/10.17816/JOWD64108

Table 1. Clinical characteristics of the studied groups

Groups	Type 1 diabetes mellitus		Type 2 diabetes mellitus		Gestational diabetes mellitus		Preeclampsia *n* = 10	Control *n* = 15	*F*	*p*
	no planning *n* = 20	planning *n* = 20	diet *n* = 15	insulin *n* = 20	diet *n* = 20	insulin *n* = 20				
Characteristics of mother and child										
Age, years (95% CI)	29.7 (27.6–31.8)	28.7 (26.5–30.85)	33.4 (31.1–35.6)	33.9 (31.6–36.12)	30.9 (28.4–33.4)	34.45 (32.17–36.73)	31.5 (29–33.9)	28.93 (26.32–31.5)	4.84	0.01
BMI, kg/m^2 (95% CI)	24.3 (23–25.7)	23.2 (21.6–24.7)	28.8 (27–30)	29.6 (26.7–32.4)	26.3 (24.8–27.8)	28.8 (27–30)	25.7 (23–28.4)	22.2 (21.4–23.1)	8.82	0.001
HbA1c in the trimester I, % (95% CI)	7.8 (7.1–8.5)	6.5 (6.2–6.8)	6 (5.7–6.3)	6.8 (6.4–7.3)	–	–	–		8.2	0.0001
HbA1c in the trimester II, % (95% CI)	7.2 (6.7–7.8)	6.3 (6.1–6.6)	5.8 (5.1–6.4)	6.5 (6.0–7.1)	–	–	–	–	5.57	0.003
HbA1c in the trimester III, % (95% CI)	6.6 (6.1–7.1)	6.2 (5.8–6.6)	5.4 (5.2–5.7)	5.9 (5.2–6.5)	5.3 (5–5.7)	5.8 (5.3–6.3)	–	4.8 (4.3–5.1)	7.88	0.0001
Newborn weight, g (95% CI)	3800 (3570–4029)	3729 (3542–3915)	3437 (3130–3745)	3559 (3418-3700)	3600 (3397–3802)	3690 (3375–4020)	3238 (2576–3399)	3314 (3111–3517)	2.4	0.025
Length of a newborn, cm (95% CI)	52.5 (51.7–53.3)	52.4 (51.5–53.2)	51.4 (49.9–52.8)	52.3 (51.5–53.1)	51.8 (50.8–52.8)	52.5 (51.3–53.7)	50.2 (48.3–52)	51.7 (50.2–51.8)	1.9	0.073
Parity									χ^2	
Primiparas, *n*, %	13 (65)	13 (65)	6 (40)	8 (40)	8 (40)	7 (35)	7 (70)	9(60)	7.46	0.38
Pregnancy										
Spontaneous conception, *n*, %	20 (100)	20 (100)	15 (100)	20 (100)	20 (100)	18 (90)	8 (80)	15 (100)	11.1	0.095
ART, *n*, %	0	0	0	0	0	2 (10)	2 (20)	0	13.6	0.05
Diabetic complications										
Diabetic vasculopathy, *n*, %	15 (75)	13 (65)	0	6 (30)	–	–	–	–	95.4	0.0001
Diabetic nephropathy, *n*, %	7 (35)	5 (25)	0	0	–	–	–	–	21.3	0.001
Gestational complications										
Gestational AH, *n*, %	3 (15)	4 (20)	2 (13.3)	5 (25)	3 (15)	7 (35)	–	0	10.9	0.046
Moderate PE, *n*, %	5 (25)	6 (30)	3 (20)	6 (30)	2 (10)	4 (20)	6 (60)	0	15.7	0.03
Severe PE, *n*, %	3 (15)	0	1 (6.7)	4 (20)	0	2 (10)	4 (40)	0	19.04	0.008
Early PE, *n*, %	1 (5)	0	0	2 (10)	0	0	3 (30)	0	21.7	0.003
Late PE, *n*, %	7 (35)	6 (30)	4 (26.7)	8 (40)	2 (10)	6 (30)	7 (70)	0	19.5	0.007
Term of manifestation of PE. weeks (25%–75%)	34 (31–35)	36 (33–38)	37 (34–38)	34 (31–36)	37 (35–39)	36 (33–38)	34 (31–37)	–	3.8	0.15
Preterm labor, *n*, %	2 (10)	1 (5)	0	3 (15)	0	2 (10)	4 (40)	0	15.4	0.002
Fetal growth retardation, *n*, %	0 (0)	0	0	0	0	1 (5)	1 (10)	0	12.3	0.04
Low-birth-weight fetus, *n*, %	1 (5)	0	0	2 (10)	1 (5)	4 (20)	3 (30)	0	10.6	0.05
Macrosomia, *n*, %	6 (30)	5 (25)	1 (6.7)	2 (10)	4 (20)	7 (35)	–	0	12.3	0.043

Note. CI — confidence interval; BMI — body mass index; HbA1c — glycated hemoglobin; ART — assisted reproductive technologies; AH — arterial hypertension; PE — preeclampsia. Quantitative variables are presented as mean; 95% CI. *$p < 0.05$ relative to the control group.

Table 2. Levels of sFlt-1 and PlGF in trimesters I and III of pregnancy

Group	*n*	sFlt-1, pg/mL	PlGF, pg/mL	sFlt-1/PlGF
		11^{+0}–13^{+6} weeks		
T1DM (no planning)	20	2555.46* (1583.75–3628.75)	42.46* (32.66–50.51)	65.17* (34.7–81.08)
T1DM (planning)	20	1790.3* (1559.25–2006.38)	43.45* (25.75–54.6)	48.99* (30.06–65.34)
T2DM (insulin)	20	2268.15* (1305.75–2863.75)	43.43* (35.25–51.51)	58.92* (29.01–69.94)
T2DM (diet)	15	1793.5* (1346–2187)	43.76* (31–51.07)	44.09* (35.42–49.82)
Control	15	927.01 (665.3–1113)	69.94 (48.7–78.4)	15.05 (9.42–20.16)
χ^2		34.5	15.31	36.37
p		**<0.001**	**<0.01**	**<0.001**
		30^{+0}–33^{+6} weeks		
T1DM (no planning)	20	7473.1* (5086.5–9009.75)	70.85* (37.43–83.21)	189.07* (83.76–294.39)
T1DM (planning)	19	5204.42* (3876–6620)	89.81* (67.8–112)	66.77* (34.47–94.47)
T2DM (insulin)	20	6689.12* (4601.5–8813.85)	102.32* (39.98–133.83)	140.57* (32.97–187.77)
T2DM (diet)	14	4743.96* (4213.88–5096.88)	104.92* (66.76–135.71)	48.79* (32.5–69.88)
GDM (insulin)	20	4911.9* (3613–6127.5)	117.69 *(62.87–170.28)	72.42* (29.16–115.68)
GDM (diet)	20	2495.95 (1545.5–3211.5)	214.23* (163.26–289.65)	19.56 (6.62–32.5)
Control	15	1828.47 (1506–2194)	320.54 (250.8–379.32)	7.08 (4.24–8.29)
Preeclampsia	10	8568.1* (6277.75–10499)	54.8* (36.68–76.33)	171.09* (122.95–190.84)
χ^2		81.79	62.49	65.73
p		**<0.001**	**<0.001**	**<0.001**

Note. T1DM — type 1 diabetes mellitus; T2DM — type 2 diabetes mellitus; GDM — gestational diabetes mellitus. Data are presented as median (IQR). *$p < 0.05$ relative to the control group.

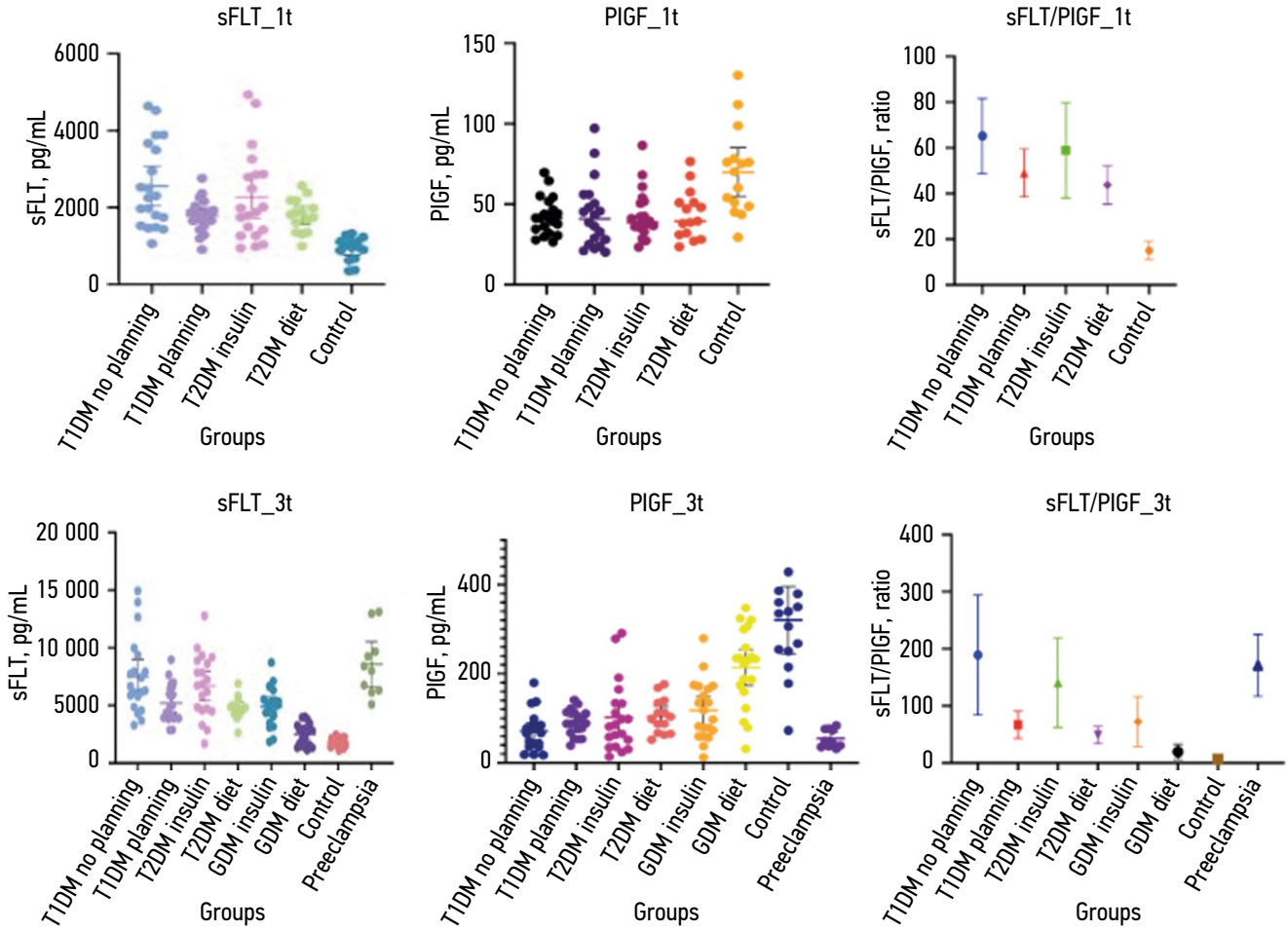

Fig. 1. Levels of sFlt-1 and PlGF in trimesters I and III of pregnancy: T1DM — type 1 diabetes mellitus; T2DM — type 2 diabetes mellitus; GDM — gestational diabetes mellitus

patients with PE, as they were six times lower than those in the control group. Among patients with DM, the lowest PlGF values were revealed in patients with type 1 DM. The sFlt-1/PlGF ratio was highest in pregnant women with type 1 DM without pregravid preparation. In other types of DM, the value of this indicator was significantly influenced by the method of glycemic correction. With insulin therapy, the sFlt-1/PlGF ratio was higher (Table 2, Fig. 1)

Changes in the concentrations of angiogenic and antiangiogenic factors in women with disorders of carbohydrate metabolism were assessed, depending on the subsequent development of PE (Table 3).

In patients with type 1 DM without pregravid preparation (n = 20), already in the trimester I, a high level of sFlt-1 was associated with the development of PE in late pregnancy (n = 8) ($p < 0.05$). The sFlt-1/PlGF ratio, which was

Table 3. Levels of sFlt-1 and PlGF in patients with diabetes mellitus depending on the development of preeclampsia

Indicator	*n*	T1DM (no planning)	*U*	*p*	*n*	T1DM (planning)	*U*	*p*
	11^{+0}–13^{+6} weeks							
sFlt-1, pg/mL	No PE —12 PE — 8	2097.83 (1493.75–2448.5) 3241.9 (2215.9–3888.25)	22	0.045*	No PE — 14 PE — 6	1863.35 (1626.5–2183.5) 1619.83 (1263.75–1876.8)	27	0.216
PlGF, pg/mL	No PE — 12 PE — 8	44.78 (35.01–53.09) 38.98 (28.53–49.23)	33	0.25	No PE — 14 PE — 6	46.12 (27.62–59.12) 37.23 (24–50.08)	34.5	0.536
sFlt-1/PlGF	No PE — 12 PE — 8	52.34 (30.2–60.73) 84.4 (70.88–99.71)	13	0.007*	No PE — 14 PE — 6	48.38 (29.7–64.69) 50.4 (30.61–72.67)	39	0.81
	30^{+0}–33^{+6} weeks							
sFlt-1, pg/mL	No PE —12 PE — 8	6543.58 (4338–7801.25) 8867.38 (6147.25–11991.5)	26	0.09	No PE — 14 PE — 6	4385.54 (3845.5–4928.5) 6978.67 (5874.5–7984.5)	6	0.004*
PlGF, pg/mL	No PE —12 PE — 8	82.18 (42.28–125.18) 53.85 (18.55–79.58)	34	0.28	No PE — 14 PE — 6	100.32 (88.05–117.5) 67.04 (50.49–80.03)	10.5	0.012*
sFlt-1/PlGF	No PE —12 PE — 8	110.11 (93.39–121.74) 307.52 (81.52–646.75)	30	0.165	No PE — 14 PE — 6	45.64 (31.28–53.68) 116.07 (73.58–148.83)	6	0.003*
Indicator	***n***	**T2DM (insulin)**	***U***	***p***	***n***	**T2DM (diet)**	***U***	***p***
	11^{+0}–13^{+6} weeks							
sFlt-1, pg/mL	No PE —10 PE — 10	1657.2 (1022.75–2058.5) 2879.1(1959.25–3906.25)	16	0.01	No PE — 11 PE — 4	1816.59 (1605–2187) 1730 (1321.75–2256.25)	19	0.695
PlGF, pg/mL	No PE —10 PE — 10	43.12 (31.9–47.17) 43.75 (35.75–52.36)	42.5	0.57	No PE — 11 PE — 4	43.07 (32–50.92) 45.67 (27.25–70.22)	22	0.99
sFlt-1/PlGF	No PE —10 PE — 10	45.15 (20.39–69.91) 72.69 (36.54–108.85)	23	0.07	No PE — 11 PE — 4	43.7 (35.42–46.9) 45.18 (24.53–62.78)	17	0.514
	30^{+0}–33^{+6} weeks							
sFlt-1, pg/mL	No PE —10 PE — 10	5337.74 (3188.5–7202.85) 8040.5 (6339.16–9491.68)	20	0.023*	No PE — 11 PE — 4	4647.07 (4059.5–5096.88) 4986.2 (4567.9–5601.25)	15	0.48
PlGF, pg/mL	No PE —10 PE — 10	152.41 (89.7–213) 52.23 (28.94–82.7)	8.5	0.002*	No PE — 11 PE — 4	120.13 (95.85–147.01) 66.9 (54.75–81.95)	1.5	0.009*
sFlt-1/PlGF	No PE —10 PE — 10	51.77 (20.08–77.54) 229.37 (89.65–282.12)	8	0.001*	No PE — 11 PE — 4	38.16 (28.16–48.46) 78.01 (59.93–102.15)	2	0.009*
Indicator	***n***	**GDM (insulin)**	***U***	***p***	***n***	**GDM (diet)**	***U***	***p***
	30^{+0}–33^{+6} weeks							
sFlt-1, pg/mL	No PE —14 PE — 6	4516.64 (3146–5352) 5834.17 (4973.5–6800)	19	0.058	No PE — 18 PE — 2	2359.06 (1506.5–2982.75) 3728 (55.91–7400.09)	2	0.044*
PlGF, pg/mL	No PE —14 PE — 6	144.81 (92.74–173.1) 54.4 (31.08–79.58)	6	0.003*	No PE — 18 PE — 2	228.57 (183.96–301.73) 85.17 (7.28–163.06)	2	0.044*
sFlt-1/PlGF	No PE —14 PE — 6	35.8 (22.04–48.18) 157.85 (71.46–241.1)	1	0.001*	No PE — 18 PE — 2	16.82 (3.02–30.61) 44.26 (39.48–128)	26	0.119

Note. СД1 — type 1 diabetes mellitus; СД2 — type 2 diabetes mellitus; GDM — gestational diabetes mellitus; PE — preeclampsia. Data are presented as median (IQR). *$p < 0.05$.

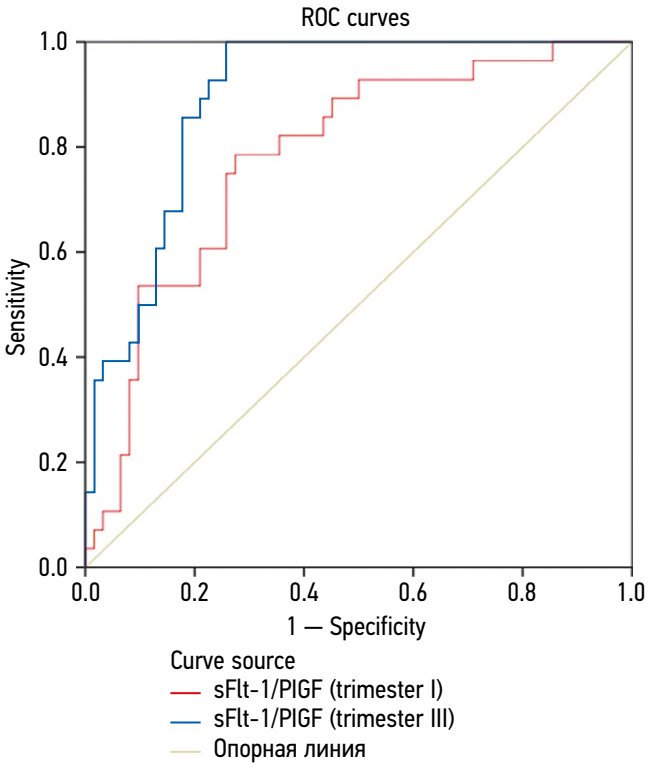

Fig. 2. Assessment of the predictive ability of the sFlt-1/PlGF index in relation to the development of preeclampsia in women with diabetes mellitus at 11^{+0}–13^{+6} and 30^{+0}–33^{+6} weeks of gestation

significantly higher in patients with PE , turned out to be informative from the point of view of early prediction of PE. For patients with type 1 DM who underwent pregravid preparation, in trimester III, higher sFlt-1 concentrations, increase in the sFlt-1/PlGF ratio, and decrease in the PlGF level with the development of PE were characteristic. However, none of these indicators in the trimester I of pregnancy differed significantly in patients who were subsequently diagnosed with PE. Nevertheless, the indicators in the trimester I of pregnancy in the groups of type 1 DM did not differ significantly.

The development of PE in the early stages in women with type 2 DM, who received insulin, can be assumed by determining the plasma level of sFlt-1. In trimester III of pregnancy, these patients had higher levels of sFlt-1, low levels of PlGF, and an increase in the sFlt-1/PlGF ratio ($p < 0.05$). In the case of correction of type 2 DM by diet, no differences in the levels of angiogenic and antiangiogenic factors were revealed in trimester I of pregnancy. However, in late gestation, patients with PE showed a decrease in the plasma PlGF level and an increase in the sFlt-1/PlGF ratio by almost 2 times ($p < 0.01$).

In pregnant women diagnosed with GDM, on insulin therapy, a low PlGF level and an increased sFlt-1/PlGF ratio in trimester III was associated with the development of PE ($p < 0.05$). A decrease in the PlGF level was also associated to the development of PE for patients on diet therapy, but the sFlt-1 level increased more ($p < 0.05$) (Table 3).

The ROC analysis revealed that sFlt-1/PlGF ratios higher than 32.5 (sensitivity 92.9%, specificity 50%) in trimester I and higher than 71.8 (sensitivity 85.7%, specificity 82.3%) in trimester III of pregnancy could predict the risk of PE in pregnant women with various types of DM. AUC for these indicators was 0.78 (95% CI 0.68–0.88) and 0.89 (95% CI 0.83–0.95) in trimesters I and III of pregnancy, respectively ($p < 0.001$) (Fig. 2). For sFlt-1/PlGF indicators in trimester I, the positive predictive value (PPV) was 63.3%, the negative predictive value (NPV) was 97.63%; and for the sFlt-1/PlGF ratio at 30–34 weeks of gestation, PPV was 38.9% and NPV was 93.6%.

DISCUSSION

This study confirms that pregnancy patients with DM are associated with a significant increase in the incidence of PE and other adverse perinatal outcomes.

When studying the concentrations of angiogenic and antiangiogenic factors in women with disorders of carbohydrate metabolism, an increase in the serum level of sFlt-1 and a decrease in PlGF (increase in the sFlt-1/PlGF ratio) were observed in trimester I of pregnancy.

Similar results have been obtained in a few previous studies. Thus, when determining the level of angiogenic biomarkers in pregnant women with a high risk of PE, it was revealed that in women with pregestational DM, the concentration of PlGF was lowest compared to that in other patient groups [14]. Cohen et al. (2013) noted that in pregnant women with type 1 and type 2 DM without subsequent hypertensive complications, the sFlt-1/PlGF ratio were higher at the early stages of gestation relative to patients without DM. At later stages, this value exceeded the indicators in the control group by a factor of 3 [16]. When studying the degree of placenta insufficiency in pregnant patients with DM (pregestational and gestational types), immunoexpression of sFlt-1 was significantly pronounced in them [15]. There was also a significant increase in the concentration of sFlt-1 in the blood of these women compared to that of healthy patients. A similar tendency was also noted in relation to PlGF, of which an increased synthesis in the placenta was accompanied by an increase in its blood serum level [15]. In another study by Ong et al. (2004), it was revealed that in pregnant women with disorders of carbohydrate metabolism in trimester I of pregnancy, the PlGF values were significantly higher than those in women with uncomplicated pregnancy [21]. The patients with diagnosed GDM were also characterized by an increase in the concentration of serum PlGF at the end of trimester II of pregnancy. This increase is compensatory for the enhancement of angiogenesis under conditions of hyperglycemia-induced placental hypoxia [22]. The difference in results was probably due to the method

for determining the concentration of PlGF. In studies that reported an increase in the concentration of this biomarker, enzyme immunoassay was used to measure its general form (bound and unbound) [21, 22]. In studies where a decrease in the factor was found, only free PlGF was determined [14].

In our study, the levels of these biomarkers were analyzed in various types of DM (T1DM, T2DM, GDM) as well as methods of correcting hyperglycemia. The most pronounced changes were established in women with type 1 DM without planning pregnancy and in those with type 2 DM on insulin therapy. With the development of GDM, these parameters changed in a similar way in the third trimester of pregnancy, but to a lesser extent than in the case of pregestational types of DM. In DM with insulin correction, the differences in the concentration of vasotropic factors were more pronounced than in patients with DM with diet therapy. However, maximum changes in the levels of these biomarkers in trimester III of pregnancy was characteristic of PE patients without diabetes mellitus.

On assessing the levels of sFlt-1 and PlGF in pregnant patients with DM we found that they could be considered as predictors of the development of PE. In some groups of patients with severe disorders of carbohydrate metabolism (with type 1 DM without pregravid preparation and with type 2 DM on insulin therapy), the predictive use of these biomarkers was already possible from trimester I. Earlier studies mainly examined pregnant women with pregestational types of DM without differentiation into types 1 and 2; they also did not consider the method of correction of metabolic disorders, and their results often contradicted with each other. In one of the first works on this subject, Cohen et al. (2007) assessed the level of biomarkers in ten pregnant women with pregestational DM at full term. Patients with PE were characterized by similar changes, but the difference in indicators was more pronounced, as the PlGF level was 3 times lower, the average sFlt-1 value was 5 times higher, and the sFlt-1/PlGF ratio increased significantly [23]. Similar results were demonstrated by Yu et al. (2009) in patients with 32 weeks of gestation. They studied the concentration of angiogenic factors throughout pregnancy in patients with type 1 DM, while women with microalbuminuria, diabetic nephropathy, and other concomitant systemic diseases were excluded from the study. In the early stages, the levels of these biomarkers did not change significantly with respect to the outcome of pregnancy, thereby rendering their predictive use irrelevant [24]. The same conclusions were made by Cohen et al. (2013) when studying the concentrations of sFlt-1 and PlGF at different stages of pregnancy in women with type 1 and type 2 DM [16].

The largest study to date on the role of angiogenic and antiangiogenic factors in predicting PE in pregnant women with type 1 DM involved 540 patients, and 94 (17%) of them had PE [25]. The levels of biomarkers at week 26 differed significantly in patients with PE compared with those who did not develop it. They were characterized by a decrease in the PlGF level and an increase in the sFlt-1 level. At the same time, the sFlt-1/PlGF coefficient was most predictive for assessing the risk of PE. Thus, the addition of this ratio to a logistic model containing only risk factors for PE in patients with DM will improve significantly its quality (AUC 0.846). Holmes et al. (2013) explored different indicators of patients with various diabetic complications. Due to this, it was possible to obtain results in the majority of pregnant women with type 1 DM [25].

Some studies indicate the absence of significant differences in the concentrations of angiogenic and antiangiogenic factors in patients with DM, depending on the development of PE [24, 26]. Powers et al. (2010), in a study of high-risk pregnant women with PE, did not reveal significant changes in the levels of sFlt-1 and PlGF in patients with pregestational DM on insulin therapy in the event of PE. Nevertheless, the chances of developing PE were reduced by a factor of two for each two-fold increase in the level of PlGF in the maternal bloodstream when pregnant women were included in the study [14].

There is paucity of data on the role of angiogenic and antiangiogenic factors in predicting PE in pregnant women with GDM. Vieira et al. (2018) investigated the PlGF levels in obese patients at the early trimester II of pregnancy and their relationship with the development of PE. It was established that in pregnant women with GDM, in contrast to women without any disorder of carbohydrate metabolism, the PlGF concentration did not change during the development of PE [26]. The results of Nuzzo et al. (2021) were equally comparable to ours. In trimester III of pregnancy in patients with GDM with the development of PE, the PlGF level was significantly lower, and the sFlt-1/PlGF ratio was higher than in women without PE [27].

We revealed that the determination of the sFlt-1/PlGF ratio is a valid method for predicting PE in patients with DM in trimesters I and III of pregnancy. However, a recent study demonstrated that the level of PlGF is optimal for predicting PE. Zen et al. (2020) studied the concentration of biomarkers throughout pregnancy in patients with pregestational types of DM [28]. In women with the development of PE from early pregnancy, the PlGF level was significantly lower than in pregnant women without PE. The sFlt-1 level increased only in trimester III. PlGF was the only marker that was significantly lower throughout pregnancy in women with poor perinatal outcomes associated with placental insufficiency. According to the authors, the increase in the sFlt-1 level corresponded only to an increased risk of diseases of the cardiovascular system [28].

In our study, threshold values for the sFlt-1/PlGF ratio were determined at over 32.5 in trimester I and 71.8 in trimester III of pregnancy, and were considered valid predictors of the development of PE in patients with pregestational types of DM. These results can be compared with those obtained in a study in which the sFlt-1/PlGF ratio was determined at 24^{+0}–36^{+6} weeks of pregnancy with a presumptive diagnosis of PE using similar testing systems [29]. The authors obtained the threshold of the sFlt-1/PlGF ratio as 38, and this enabled the implementation of the clinical management of pregnant women with suspected PE. At values below this threshold, the occurrence of PE in the next week was practically unexpected (NPV 99.3%), and at higher values, the risk of PE development within the next four weeks was highly probable (PPV 36.7%) [29]. The value we obtained in trimester III of pregnancy turned out to be high. This may probably be due to the presence of initial endothelial dysfunction in patients with DM, which has a strong effect on placentation processes [13]. Biomarkers associated with angiogenesis reflect information about the functioning of the placenta; therefore, any pathological changes in it can cause an increase in the sFlt-1/PlGF index, which further contributes to an increase in the threshold value for predicting the occurrence of PE [30]. Verlohren et al. (2013) determined the threshold values of the sFlt-1/PlGF ratio for establishing the diagnosis of PE, depending on the gestational age. At a 20^{+0}–33^{+6} weeks of gestation, sFlt-1/PlGF values higher than 85, and at 34^{+0} weeks and further, its value higher than 110 showed high specificity for effective prediction of PE [31]. When studying the threshold ratio of sFlt-1/PlGF at 85 in patients with GDM before week 34 of gestation, its diagnostic significance was established only for patients with severe PE [32].

CONCLUSION

In patients with DM, the level of fms-like tyrosine kinase-1 and PlGF changes in comparison with these indicators in pregnant women without disorders of carbohydrate metabolism from trimester I. This could result to a higher incidence and risk of adverse obstetric and perinatal outcomes in patients with DM. At the same time, the imbalance of these factors is noted earlier and is more pronounced in the presence of more significant metabolic disorders, in which it was necessary to prescribe insulin therapy, and in the absence of pregravid preparation.

Determination of the sFlt-1/PlGF ratio is a valid method for predicting the risk of PE in women with various types of DM; it can also be used ascertain differential diagnoses of hypertensive disorders in these patients. This will in turn optimize the management of women with carbohydrate metabolism disorders and improve perinatal outcomes.

ADDITIONAL INFORMATION

Conflict of interest. The authors declare no conflict of interest.
Funding. The work was performed within the state assignment of the Ministry of Education and Science of Russia on applied research with the state registration number of the subject AAAA-A20-120041390024-2.

Author contributions. *R.V. Kapustin* created the study concept, collected and analyzed the data, wrote and edited the article, reviewed the critical content, approved the manuscript for publication. *E.M. Tsybuk* performed analysis and interpretation of the data, reviewed the publications on the subject of the article, and wrote the text of the manuscript. *S.V. Chepanov* performed the laboratory stage, analyzed and interpreted the data. *E.N. Alekseyenkova, E.V. Kopteyeva* analyzed and interpreted the data, wrote the text of the manuscript. *O.N. Arzhanova* created the study design, reviewed the critical content, and approved the manuscript for publication.

REFERENCES

1. Poon LC, Shennan A, Hyett JA, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. *Int J Gynaecol Obstet*. 2019;145(Suppl 1):1–33. DOI: 10.1002/ijgo.12802

2. Mol BWJ, Roberts CT, Thangaratinam S, et al. Pre-eclampsia. *Lancet*. 2016;387(10022):999–1011. DOI: 10.1016/S0140-6736(15)00070-7

3. Ma'ayeh M, Rood KM, Kniss D, Costantine MM. Novel Interventions for the prevention of preeclampsia. *Curr Hypertens Rep*. 2020;22(2):17. DOI: 10.1007/s11906-020-1026-8

4. Wang A, Rana S, Karumanchi SA. Preeclampsia: the role of angiogenic factors in its pathogenesis. *Physiology (Bethesda)*. 2009;24:147–158. DOI: 10.1152/physiol.00043.2008

5. Chau K, Hennessy A, Makris A. Placental growth factor and pre-eclampsia. *J Hum Hypertens*. 2017;31(12):782–786. DOI: 10.1038/jhh.2017.61

6. Yusuf AM, Kahane A, Ray JG. First and second trimester serum sFlt-1/PlGF ratio and subsequent preeclampsia: A systematic review. *J Obstet Gynaecol Can*. 2018;40(5):618–626. DOI: 10.1016/j.jogc.2017.07.014

7. Kholin AM, Ivanets TYu, Khodzhaeva ZS, Gus AI. Screening of early preeclampsia in the first trimester of pregnancy on the basis of combined estimate of maternal serum placental growth factor and uterine artery doppler. *Obstetrics and Gynecology*. 2015;(5):42–48. (In Russ.)

8. Ivanets TYu, Kan NE, Tyutyunnik VL, et al. The role of the soluble fms-like tyrosin kinase-1 / the placental growth factor ratio in the diagnostics of preeclampsia in physiological pregnancy and pregnancy after IVF. *Obstetrics and Gynecology*. 2018;(3):37–43. (In Russ.). DOI: 10.18565/aig.2018.3.37-42

9. International Diabetes Federation. *IDF Diabetes Atlas*. 9th edn. Brussels, Belgium; 2019.

10. Weissgerber TL, Mudd LM. Preeclampsia and diabetes. *Curr Diab Rep*. 2015;15(3):9. DOI: 10.1007/s11892-015-0579-4

11. Huynh J, Dawson D, Roberts D, Bentley-Lewis R. A systematic review of placental pathology in maternal diabetes mellitus. *Placenta.* 2015;36(2):101–114. DOI: 10.1016/j.placenta.2014.11.021
12. Mitsui T, Tani K, Maki J, et al. Upregulation of angiogenic factors via protein kinase C and hypoxia-induced factor-1α pathways under high-glucose conditions in the placenta. *Acta Med Okayama*. 2018;72(4):359–367. DOI: 10.18926/AMO/56171
13. Ottanelli S, Napoli A, Clemenza S, et al. *Hypertension and preeclampsia in pregnancy complicated by diabetes*. In: Lapolla A, Metzger BE, editors. Gestational Diabetes. A Decade after the HAPO Study. Vol. 28. Basel: Karger; 2020:171–182. DOI: 10.1159/000480173
14. Powers RW, Jeyabalan A, Clifton RG, et al. Soluble fms-Like tyrosine kinase 1 (sFlt1), endoglin and placental growth factor (PlGF) in preeclampsia among high risk pregnancies. *PLoS One*. 2010;5(10):e13263. DOI: 10.1371/journal.pone.0013263
15. El-Tarhouny SA, Almasry SM, Elfayomy AK, et al. Placental growth factor and soluble Fms-like tyrosine kinase 1 in diabetic pregnancy: A possible relation to distal villous immaturity. *Histol Histopathol*. 2014;29(2):259–272. DOI: 10.14670/HH-29.259
16. Cohen AL, Wenger JB, James-Todd T, et al. The association of circulating angiogenic factors and HbA1c with the risk of preeclampsia in women with preexisting diabetes. *Hypertens Pregnancy*. 2014;33(1):81–92. DOI: 10.3109/10641955.2013.837175
17. Vestgaard M, Sommer MC, Ringholm L, et al. Prediction of preeclampsia in type 1 diabetes in early pregnancy by clinical predictors: a systematic review. *J Matern Fetal Neonatal Med*. 2018;31(14):1933–1939. DOI: 10.1080/14767058.2017.1331429
18. Bartsch E, Medcalf KE, Park AL, Ray JG, High risk of Preeclampsia Identification Group. Clinical risk factors for preeclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ*. 2016;353:i1753. DOI: 10.1136/bmj.i1753
19. *Gestacionnyj saharnyj diabet: diagnostika, lechenie, poslerodovoe nabljudenie. Klinicheskie rekomendacii (protokol lechenija).* Ministerstvo Zdravoohranenija Rossijskoj Federacii. Pis'mo ot 17 dekabrja 2013. No. 15-4/10/2-9478. (In Russ.). [cited 2021 July 1]. Available from: http://zdrav.spb.ru/media/komzdrav/documents/document/file/gestantsionni_sax_diabet_.pdf
20. *Gipertenzivnye rasstrojstva vo vremja beremennosti, v rodah i poslerodovom periode. Prejeklampsija. Jeklampsija. Klinicheskie rekomendacii (protokol lechenija)*. Pis'mo Ministerstva zdravoohranenija RF ot 7 ijunja 2016. No. 15-4/10/2-3483. (In Russ.). [cited 2021 July 1]. Available from: https://rd1.medgis.ru/uploads/userfiles/shared/StandartMed/Protokol-acusher/2.pdf
21. Ong CY, Lao TT, Spencer K, Nicolaides KH. Maternal serum level of placental growth factor in diabetic pregnancies. *J Reprod Med.* 2004;49(6):477–480.
22. Gorkem U, Togrul C, Arslan E. Relationship between elevated serum level of placental growth factor and status of gestational diabetes mellitus. *J Matern Fetal Neonatal Med.* 2020;33(24):4159–4163. DOI: 10.1080/14767058.2019.1598361
23. Cohen A, Lim KH, Lee Y, et al. Circulating levels of the antiangiogenic marker soluble FMS-like tyrosine kinase 1 are elevated in women with pregestational diabetes and preeclampsia: angiogenic markers in preeclampsia and preexisting diabetes. *Diabetes Care*. 2007;30(2):375–377. DOI: 10.2337/dc06-1514
24. Yu Y, Jenkins AJ, Nankervis AJ, et al. Anti-angiogenic factors and pre-eclampsia in type 1 diabetic women. *Diabetologia*. 2009;52(1):160–168. DOI: 10.1007/s00125-008-1182-x
25. Holmes VA, Young IS, Patterson CC, et al. The role of angiogenic and antiangiogenic factors in the second trimester in the prediction of preeclampsia in pregnant women with type 1 diabetes. *Diabetes Care*. 2013;36(11):3671–3677. DOI: 10.2337/dc13-0944
26. Vieira MC, Begum S, Seed PT, et al. Gestational diabetes modifies the association between PlGF in early pregnancy and preeclampsia in women with obesity. *Pregnancy Hypertens*. 2018;13:267–272. DOI: 10.1016/j.preghy.2018.07.003
27. Nuzzo AM, Giuffrida D, Moretti L, et al. Placental and maternal sFlt1/PlGF expression in gestational diabetes mellitus. *Sci Rep*. 2021;11(1):2312. DOI: 10.1038/s41598-021-81785-5
28. Zen M, Padmanabhan S, Zhang K, et al. Urinary and serum angiogenic markers in women with preexisting diabetes during pregnancy and their role in preeclampsia prediction. *Diabetes Care*. 2020;43(1):67–73. DOI: 10.2337/dc19-0967
29. Zeisler H, Llurba E, Chantraine F, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. *N Engl J Med*. 2016;374(1):13–22. DOI: 10.1056/NEJMoa1414838
30. Herraiz I, Llurba E, Verlohren S, Galindo A; Spanish Group for the Study of Angiogenic Markers in Preeclampsia. Update on the diagnosis and prognosis of preeclampsia with the aid of the sFlt-1/PlGF ratio in singleton pregnancies. *Fetal Diagn Ther*. 2018;43(2):81–89. DOI: 10.1159/000477903
31. Verlohren S, Herraiz I, Lapaire O, et al. New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for preeclampsia. *Hypertension*. 2014;63(2):346–352. DOI: 10.1161/HYPERTENSIONAHA.113.01787
32. Bettiher OA. *Osobennosti patogeneza i klinicheskih projavlenij prejeklampsii u beremennyh s gestacionnym saharnym diabetom*. [dissertation abstract]. St. Petersburg; 2020. [cited 2021 Jul 1]. Available from: https://www.dissercat.com/content/osobennosti-patogeneza-i-klinicheskikh-proyavlenii-preeklampsii-u-beremennykh-s-gestatsionny

СПИСОК ЛИТЕРАТУРЫ

1. Poon L.C., Shennan A., Hyett J.A. et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on preeclampsia: A pragmatic guide for first-trimester screening and prevention // Int. J. Gynaecol. Obstet. 2019. Vol. 145. Suppl. 1. P. 1–33. DOI: 10.1002/ijgo.12802
2. Mol B.W.J., Roberts C.T., Thangaratinam S. et al. Preeclampsia // Lancet. 2016. Vol. 387. No. 10022. P. 999–1011. DOI: 10.1016/S0140-6736(15)00070-7
3. Ma'ayeh M., Rood K.M., Kniss D., Costantine M.M. Novel interventions for the prevention of preeclampsia // Curr. Hypertens. Rep. 2020. Vol. 22. No. 2. P. 17. DOI: 10.1007/s11906-020-1026-8
4. Wang A., Rana S., Karumanchi S.A. Preeclampsia: the role of angiogenic factors in its pathogenesis // Physiology (Bethesda). 2009. Vol. 24. P. 147–158. DOI: 10.1152/physiol.00043.2008

5. Chau K., Hennessy A., Makris A. Placental growth factor and pre-eclampsia // J. Hum. Hypertens. 2017. Vol. 31. No. 12. P. 782–786. DOI: 10.1038/jhh.2017.61

6. Yusuf A.M., Kahane A., Ray J.G. First and second trimester serum sFlt-1/PlGF ratio and subsequent preeclampsia: A systematic review // J. Obstet. Gynaecol. Can. 2018. Vol. 40. No. 5. P. 618–626. DOI: 10.1016/j.jogc.2017.07.014

7. Холин А.М., Иванец Т.Ю., Ходжаева З.С., Гус А.И. Скрининг ранней преэклампсии в I триместре беременности на основе комбинированной оценки материнского сывороточного плацентарного фактора роста и допплерометрии маточных артерий // Акушерство и гинекология. 2015. № 5. С. 42–48.

8. Иванец Т.Ю., Кан Н.Е., Тютюнник В.Л. и др. Роль соотношения растворимой fms-подобной тирозинкиназы-1 и плацентарного фактора роста в диагностике преэклампсии при физиологической беременности и беременности после вспомогательных репродуктивных технологий // Акушерство и гинекология. 2018. № 3. С. 37–43. DOI: 10.18565/aig.2018.3.37-42

9. International Diabetes Federation. IDF Diabetes Atlas. 9th ed. Brussels, 2019.

10. Weissgerber T.L., Mudd L.M. Preeclampsia and diabetes // Curr. Diab. Rep. 2015. Vol. 15. No. 3. P. 9. DOI: 10.1007/s11892-015-0579-4

11. Huynh J., Dawson D., Roberts D., Bentley-Lewis R. A systematic review of placental pathology in maternal diabetes mellitus // Placenta. 2015. Vol. 36. No. 2. P. 101–114. DOI: 10.1016/j.placenta.2014.11.021

12. Mitsui T., Tani K., Maki J. et al. Upregulation of angiogenic factors via protein kinase C and hypoxia-induced factor-1α pathways under high-glucose conditions in the placenta // Acta Med. Okayama. 2018. Vol. 72. No. 4. P. 359–367. DOI: 10.18926/AMO/56171

13. Ottanelli S., Napoli A., Clemenza S. et al. Hypertension and preeclampsia in pregnancy complicated by diabetes // Gestational Diabetes. A Decade after the HAPO Study. Ed. by A. Lapolla, B.E. Metzger. Vol. 28. Basel: Karger, 2020. P. 171–182. DOI: 10.1159/000480173

14. Powers R.W., Jeyabalan A., Clifton R.G. et al. Soluble fms-Like tyrosine kinase 1 (sFlt1), endoglin and placental growth factor (PlGF) in preeclampsia among high risk pregnancies // PLoS One. 2010;5(10):e13263. DOI: 10.1371/journal.pone.0013263

15. El-Tarhouny S.A., Almasry S.M., Elfayomy A.K. et al. Placental growth factor and soluble Fms-like tyrosine kinase 1 in diabetic pregnancy: A possible relation to distal villous immaturity // Histol. Histopathol. 2014. Vol. 29. No. 2. P. 259–272. DOI: 10.14670/HH-29.259

16. Cohen A.L., Wenger J.B., James-Todd T. et al. The association of circulating angiogenic factors and HbA1c with the risk of preeclampsia in women with preexisting diabetes // Hypertens. Pregnancy. 2014. Vol. 33. No. 1. P. 81–92. DOI: 10.3109/10641955.2013.837175

17. Vestgaard M., Sommer M.C., Ringholm L. et al. Prediction of preeclampsia in type 1 diabetes in early pregnancy by clinical predictors: a systematic review // J. Matern. Fetal. Neonatal. Med. 2018. Vol. 31. No. 14. P. 1933–1939. DOI: 10.1080/14767058.2017.1331429

18. Bartsch E., Medcalf K.E., Park A.L., Ray J.G. High risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies // BMJ. 2016. Vol. 353. P. i1753. DOI: 10.1136/bmj.i1753

19. Гестационный сахарный диабет: диагностика, лечение, послеродовое наблюдение. Клинические рекомендации (протокол лечения). Министерство здравоохранения Российской Федерации. Письмо от 17 декабря 2013 г. № 15-4/10/2-9478. [дата обращения 1.07.2021]. Доступ по ссылке: http://zdrav.spb.ru/media/komzdrav/documents/document/file/gestantsionni_sax_diabet_.pdf

20. Гипертензивные расстройства во время беременности, в родах и послеродовом периоде. Преэклампсия. Эклампсия. Клинические рекомендации (Протокол лечения). Письмо Министерства здравоохранения РФ от 7 июня 2016 г. № 15-4/10/2-3483. [дата обращения 1.07.2021]. Доступ по ссылке: https://rd1.medgis.ru/uploads/userfiles/shared/StandartMed/Protokol-acusher/2.pdf

21. Ong C.Y., Lao T.T., Spencer K., Nicolaides KH. Maternal serum level of placental growth factor in diabetic pregnancies // J. Reprod. Med. 2004. Vol. 49. No. 6. P. 477–480.

22. Gorkem U., Togrul C., Arslan E. Relationship between elevated serum level of placental growth factor and status of gestational diabetes mellitus // J. Matern. Fetal. Neonatal. Med. 2020. Vol. 33. No. 24. P. 4159–4163. DOI: 10.1080/14767058.2019.1598361

23. Cohen A., Lim K.H., Lee Y. et al. Circulating levels of the antiangiogenic marker soluble FMS-like tyrosine kinase 1 are elevated in women with pregestational diabetes and preeclampsia: angiogenic markers in preeclampsia and preexisting diabetes // Diabetes Care. 2007. Vol. 30. No. 2. P. 375–377. DOI: 10.2337/dc06-1514

24. Yu Y., Jenkins A.J., Nankervis A.J. et al. Anti-angiogenic factors and pre-eclampsia in type 1 diabetic women // Diabetologia. 2009. Vol. 52. No. 1. P. 160–168. DOI: 10.1007/s00125-008-1182-x

25. Holmes V.A., Young I.S., Patterson C.C. et al. The role of angiogenic and antiangiogenic factors in the second trimester in the prediction of preeclampsia in pregnant women with type 1 diabetes // Diabetes Care. 2013. Vol. 36. No. 11. P. 3671–3677. DOI: 10.2337/dc13-0944

26. Vieira M.C., Begum S., Seed P.T. et al. Gestational diabetes modifies the association between PlGF in early pregnancy and preeclampsia in women with obesity // Pregnancy Hypertens. 2018. Vol. 13. P. 267–272. DOI: 10.1016/j.preghy.2018.07.003

27. Nuzzo A.M., Giuffrida D., Moretti L. et al. Placental and maternal sFlt1/PlGF expression in gestational diabetes mellitus // Sci. Rep. 2021. Vol. 11. No. 1. P. 2312. DOI: 10.1038/s41598-021-81785-5

28. Zen M., Padmanabhan S., Zhang K. et al. Urinary and serum angiogenic markers in women with preexisting diabetes during pregnancy and their role in preeclampsia prediction // Diabetes Care. 2020. Vol. 43. No. 1. P. 67–73. DOI: 10.2337/dc19-0967

29. Zeisler H., Llurba E., Chantraine F. et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia // N. Engl. J. Med. 2016. Vol. 374. No. 1. P. 13–22. DOI: 10.1056/NEJMoa1414838

30. Herraiz I., Llurba E., Verlohren S., Galindo A.; Spanish Group for the Study of Angiogenic Markers in Preeclampsia. Update on the diagnosis and prognosis of preeclampsia with the aid of the sFlt-1/PlGF ratio in singleton pregnancies // Fetal. Diagn. Ther. 2018. Vol. 43. No. 2. P. 81–89. DOI: 10.1159/000477903

31. Verlohren S., Herraiz I., Lapaire O. et al. New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for

preeclampsia // Hypertension. 2014. Vol. 63. No. 2. P. 346–352. DOI: 10.1161/HYPERTENSIONAHA.113.01787

32. Беттихер О.А. Особенности патогенеза и клинических проявлений преэклампсии у беременных с гестационным сахарным диабетом: автореф. дис. ... канд. мед. наук. Санкт-Петербург, 2020. [дата обращения 1.07.2021]. Доступ по ссылке: https://www.dissercat.com/content/osobennosti-patogeneza-i-klinicheskikh-proyavlenii-preeklampsii-u-beremennykh-s-gestatsionny

AUTHORS INFO

***Roman V. Kapustin**, MD, Cand. Sci. (Med.);
address: 3 Mendeleevskaya Line,
Saint Petersburg, 199034, Russia;
ORCID: https://orcid.org/0000-0002-2783-3032;
eLibrary SPIN: 7300-6260;
e-mail: kapustin.roman@gmail.com

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

Sergey V. Chepanov, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0001-6087-7152;
eLibrary SPIN: 6642-6837;
e-mail: chepanovsv@gmail.com

Elena N. Alexeyenkova;
ORCID: https://orcid.org/0000-0002-0642-7924;
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

Olga N. Arzhanova, MD, Dr. Sci. (Med), Professor;
ORCID: https://orcid.org/0000-0003-3059-9811;
eLibrary SPIN: 7910-6039;
e-mail: arjanova_olga@mail.ru

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;
eLibrary SPIN: 7300-6260;
e-mail: kapustin.roman@gmail.com

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

Сергей Владимирович Чепанов, канд. мед. наук;
ORCID: https://orcid.org/0000-0001-6087-7152;
eLibrary SPIN: 6642-6837;
e-mail: chepanovsv@gmail.com

Елена Николаевна Алексеенкова;
ORCID: https://orcid.org/0000-0002-0642-7924;
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

Ольга Николаевна Аржанова, д-р мед. наук, профессор;
ORCID: https://orcid.org/0000-0003-3059-9811;
eLibrary SPIN: 7910-6039;
e-mail: arjanova_olga@mail.ru