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RISK FACTORS OF PATHOLOGICAL GLYCEMIC VARIABILITY IN PREGNANT WOMEN WITH TYPE 1 DIABETES MELLITUS

© A.V. Tiselko

The Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott,
Saint Petersburg, Russia

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▪ ***Hypothesis/aims of study.*** Academician Vasily G. Baranov's statement that achieving normal glycemia is the main condition for successful pregnancy outcomes in women with diabetes mellitus has already been proven. Unfortunately, these tight glycemic targets are hard to be achieved especially in metabolic changes during pregnancy. Glycemic variability is a new glycemic parameter available due to continuous glucose monitoring (CGM). Pathological glycemic variability can be an important risk factor for oxidative stress along with chronic hyperglycemia in patients with type 1 diabetes mellitus (T1D). However, there is no enough literature confirming the effect of pathological glycemic variability on pregnancy course and outcomes in T1D women. The aim of the study is to analyze different modes of insulin therapy for glycemic targets achievement and glycemic variability reduction in T1D pregnant women.

Study design, materials, and methods. 100 women treated with continuous subcutaneous insulin infusion (CSII) and another 100 women treated with multiple daily injections (MDI) of insulin were examined. Indices of glycemic variability were estimated.

Results. Glycemic variability was significantly lower in CSII patients compared to the MDI group. The influence of glycemic variability on endothelial dysfunction was confirmed for T1D pregnant women. CSII proved advantages in achieving glycemic targets without increasing glycemic variability and hypoglycemia.

Conclusion. CSII combined with CGM is the most optimal insulin therapy for glycemic targets achievement without an increased risk for glycemic variability and hypoglycemia.

▪ **Keywords:** diabetes mellitus type 1; pregnancy; glycemic variability; continuous subcutaneous insulin infusion; continuous glucose monitoring.

ФАКТОРЫ РИСКА РАЗВИТИЯ ПАТОЛОГИЧЕСКОЙ ВАРИАБЕЛЬНОСТИ ГЛЮКОЗЫ У БЕРЕМЕННЫХ С САХАРНЫМ ДИАБЕТОМ 1-ГО ТИПА

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ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии им. Д.О. Отта»,
Санкт-Петербург

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▪ ***Актуальность.*** Общепризнанным стал тезис академика Василия Гавриловича Баранова о необходимости достижения физиологических значений гликемии как основного условия благополучного течения и исходов беременности у женщин с сахарным диабетом (СД). Однако достичь таких целевых уровней трудно, так как во время беременности происходят изменения метаболизма в организме матери, связанные с обеспечением роста и развития плода. Одним из новых параметров гликемического профиля, полученного с помощью непрерывного мониторирования глюкозы, является вариабельность концентрации глюкозы. Патологическая вариабельность глюкозы может быть значимым фактором в развитии оксидативного стресса наряду с хронической гипергликемией у пациентов с СД 1-го типа. Данные литературы, подтверждающие влияние па-

тологической вариабельности глюкозы на течение и исходы беременности у женщин с СД 1-го типа, малочисленны.

Цель — проанализировать эффективность различных режимов инсулинотерапии в достижении целевых значений гликемии, уменьшении вариабельности глюкозы у беременных с СД 1-го типа.

Материалы и методы исследования. Проведен анализ показателей вариабельности глюкозы с помощью непрерывного мониторирования глюкозы у 100 женщин, использовавших постоянную подкожную инфузию инсулина, и у 100 женщин, использовавших режим множественных инъекций инсулина.

Результаты исследования. Вариабельность глюкозы была значительно ниже в группе пациенток с СД 1-го типа, применявших постоянную подкожную инфузию инсулина, по сравнению с пациентками, использовавшими режим множественных инъекций инсулина. Подтверждена роль вариабельности глюкозы в развитии эндотелиального повреждения у беременных с СД 1-го типа. Доказано преимущество режима постоянной подкожной инфузии инсулина в достижении целевых значений гликемии без увеличения степени вариабельности глюкозы и частоты гипогликемических состояний.

Заключение. Постоянная подкожная инфузия инсулина в сочетании с непрерывным мониторированием глюкозы является оптимальным режимом инсулинотерапии в достижении целевых значений гликемии без увеличения частоты гипогликемических состояний и вариабельности глюкозы.

▪ **Ключевые слова:** сахарный диабет 1-го типа; беременность; вариабельность глюкозы; постоянная подкожная инфузия инсулина; непрерывное мониторирование глюкозы.

Introduction

The possibility of childbearing in female patients with type 1 diabetes mellitus (DM1) depends on the degree of compensation of diabetes-related carbohydrate metabolism disorders. Metabolic changes in pregnancy are due to the increasing production of placental hormones during late pregnancy, reaching maximum values in trimester III. The insulin resistance that develops during pregnancy leads to increased use of lipid metabolism products, while glucose, which is the main energy substrate, is saved for the nutrition of the fetus. Glucose passes through the placental barrier by accelerated diffusion depending on the concentration gradient and is utilized by the fetus two to three times faster than an adult [1]. In early terms of physiological pregnancy, glucose utilization is increased because of the high rate of glucose transplacental transition to the fetus and the accumulation of adipose tissue in the maternal body. Fasting glycemia in the mother decreases by 0.5–1.0 mmol/L and amounts to 3.8–4.2 mmol/L. During embryogenesis from week 8 to week 13 of pregnancy, the need for insulin decreases by 5 %–20 % [2, 3]. The average daily glycemia during physiological pregnancy is lower during the day, and the level of glycemia in the fetus is 10 %–20 % lower than in the mother [4]. This increases the risk of hypoglycemic conditions and requires the adjustment of insulin therapy (both bolus doses and basal doses of insulin).

Metabolic changes in the pregnant woman's body with DM1 can affect significantly the state of carbohydrate metabolism, lead to the progression of DM vascular complications, and require adequate glycemic control and optimization of the insulin therapy mode. The primary condition for the prevention of acute vascular complications of DM1 and progression of chronic ones during pregnancy is the compensation of metabolic disorders typical for DM, both at the planning stage and throughout the pregnancy period.

Insulin therapy in DM1 patients is mainly aimed at the compensation of insulin deficiency and the maximum reproduction of physiological fluctuations in its blood level. When choosing a mode of insulin therapy, the specialists are guided by the task of achieving the target levels of glycemia in DM1 female patients during pregnancy. However, achieving physiological targets for blood glucose during pregnancy can increase the risk of occurrence of hypoglycemic conditions and pathological glucose variability and lead to complications both in the mother and in her unborn child [5–7].

Achievement of physiological values of glucose during pregnancy in DM1 female patients is the main condition for a successful course and outcome of pregnancy [8]. At present, target glycemia values (in the absence of severe vascular complications of DM) should be within the following limits: fasting glucose should be < 5.1 mmol/L, that 1 h after meal should be < 7.0 mmol/L in blood plasma, and glycated hemoglobin level (HbA1c) must be < 6.0 % [9]. The target glycemic values after meals in a pregnant woman with DM1 can be achieved with a correct estimate of the consumed amount of not only carbohydrates but also proteins and fats, which affect significantly the nature of the glycemic profile after meals. It should be known and taken

into account that the amount of protein and fat equivalent to 100 kcal (418.4 kJ) corresponds to 1 XE and leads to an increase in blood glucose levels after meals by 3–4 h. Calculation of a bolus (prandial) dose of insulin is difficult for patients, and often, postprandial hyperglycemia is associated with an incorrect dose of insulin before meals.

Because of the introduction in the clinical practice of a new method of round-the-clock monitoring of glucose, it was possible to obtain information on fluctuations in glucose levels during the day in DM patients [10, 11, 13]. Various indices are currently used to assess glucose variability. The mean amplitude of glucose excursion (MAGE) index was originally designed to estimate the degree of glucose level fluctuations using the interval between the data. The mean of daily differences (MODD) index shows the circadian periodicity of glycemic changes and thereby specifies the duration of glucose variability. The continuous overall net glycemic action (CONGA) index reflects changes in the rate of glucose fluctuations to a greater extent, and the standard deviation shows the difference in the maximum values of glucose level. A decrease in glucose variability reduces the likelihood that glucose readings become within the range of hypoglycemia of <3.5 mmol/L [14].

At present, only a few works are presented in the literature, which demonstrates the influence of pathological glucose variability on pregnancy and the growth and development of the fetus [15, 16].

For more than 30 years, the mode of continuous subcutaneous insulin infusion (CSII) using an insulin pump has been used to optimize glycemic control. Over the past decades, the technical capabilities of the insulin pump have been improved significantly. A bolus calculator has been introduced into insulin dispensers, which optimize the dose of bolus insulin depending on the meal or the necessary correction of hyperglycemia. The insulin dispenser simulates the fast and slow phases of the secretion of insulin taken with food, which enables it to obtain glycemic postprandial glucose profile close to a physiological one [17]. One of the important functions of an insulin pump is the possibility of reducing the speed or stopping the administration of insulin, which is the main mechanism that simulates a decrease in insulin secretion while lowering the level of glucose in the blood of a healthy person. A number of authors emphasize a decrease in the incidence of hypoglycemic conditions when using CSII during pregnancy. Hypoglycemia is a predictor of pathological glucose variability. Both hypoglycemia and glucose variability are factors in the development of oxidative stress and can initiate macrovascular and microvascular DM complications [18, 19].

This study aimed to analyze the efficacy of various modes of an insulin pump to reduce glucose variability and achieve target glycemia values in pregnant female patients with DM1.

Materials and Methods

Continuous glucose monitoring (CGM) was conducted to 100 pregnant female patients with DM1 who used CSII and to 100 women who used multiple insulin injections (MII) to evaluate the efficacy of these insulin therapy modes in achieving glycemic target values. For this purpose, the 24-h (continuous) Paradigm real-time glucose monitoring system, the Guardian system, and the Paradigm® VeoTM system (Medtronic) were used. The total monitoring duration for each woman ranged from 288 to 432 h. Over the entire monitoring period, between 85,000 and 99,000 glucose samples in the intercellular fluid were taken from each patient. The transfer to CSII was conducted at the Center for High-Tech Methods for Treatment of Diabetes Mellitus in the Reproductive Endocrinology Department of the D.O. Ott Scientific Research Institute of Obstetrics, Gynecology and Reproduction based on recommendations for the provision of specialized care for DM patients in the Russian Federation "Algorithms for specialized care for DM patients," as well as local practice conditions [9].

The age of women ranged from 18 to 38 years. The average ages in the groups of women who used CSII and MII were 26.5 ± 5.6 and 25.2 ± 6.1 years, respectively. The duration of DM in the CSII group was 11.0 (5.0–17.9) years and in the MII group was 11.0 (5.0–15.0) years. The frequency of DM1 complications significant for pregnancy was comparable in both groups, and their median for diabetic proliferative retinopathy was 11.5 % (8.0 %–12.8 %) and for diabetic nephropathy, chronic kidney disease C2, A2– A3 stages was 13.0 % (7.5 %–16.8 %). To analyze the nature of the glycemic profile in all pregnant women enrolled in the study, the amplitude of glucose excursions was evaluated, and the glucose variability indices MAGE, MODD, and CONGA were calculated.

To compare the studied parameters with different methods of insulin administration, the nonparametric Mann–Whitney *U*-test or *t*-test for independent samples was used. When conducting

multiple comparisons, either single-factor analysis of variance and the posthoc Tukey or the Kruskal–Wallis *H*-test was used. Correlation analysis was performed using the Spearman rank correlation assessment. When comparing the indicators measured in the nominal or ordinal scale, the chi-squared test ($\chi 2$) was used, and for small samples, this criterion was calculated with Yates' correction. Statistical processing was performed using the Statistica 10.0 program.

Results

To choose the optimal bolus for controlling postprandial glycemia in pregnant female patients with DM1, a comparative analysis of bolus effectiveness was performed using MII, a standard bolus, and a multi-wave bolus using CSII. The diet of a pregnant woman with DM1 involves a rational ratio of proteins, fats, carbohydrates, and fiber, which requires fast and slow action of insulin. The ratio of fast and slow parts of the bolus in the CSII mode was distributed as follows: for breakfast, the fast part was 58.8 % ± 4.5 %, and the slow part was 41.2 % ± 4.0 %. For lunch and dinner, the percentage distributions of fast and slow parts of the bolus were 68.5 % ± 5.5 % and 31.5 % ± 5.5 %, respectively (Fig. 1). The frequency of application of a multi-wave bolus during the day was 75.55 % ± 8.80 %. Under MII mode, the entire bolus dose of fast-acting insulin was administered as a single stage, which could cause hypoglycemic conditions after 2.5–3 h.

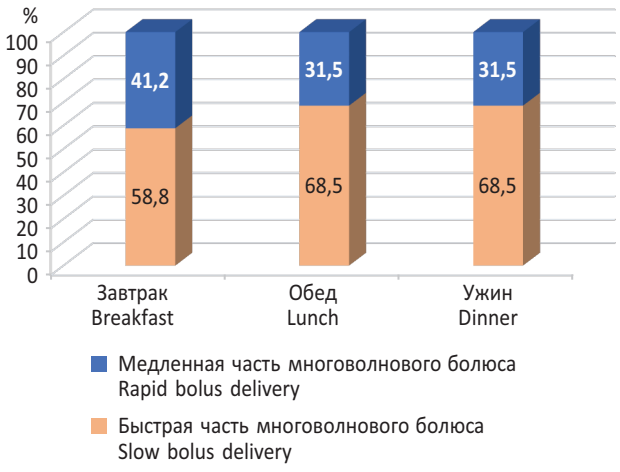

Fig. 1. Percentage distribution of rapid and slow bolus delivery in type 1 diabetes mellitus pregnant women treated with continuous subcutaneous insulin infusion

Рис. 1. Процентное распределение быстрой и медленной частей многоволнового болюса у беременных с сахарным диабетом 1-го типа, использовавших режим постоянной подкожной инфузии инсулина

The ratio of the bolus and basal daily doses of insulin during pregnancy did not significantly differ in the CSII and MII groups (Fig. 2).

In the group of pregnant women who used the double (multi-wave) bolus mode using an insulin pump, the levels of postprandial glycemia reached the target values after breakfast, lunch, and dinner ($p < 0.05$) and were lower than in pregnant women who used a simple bolus in the CSII and MII modes (Fig. 3).

It is noteworthy that glucose variability after meals in terms of standard deviation in the group of pregnant women who had injections of a multi-wave bolus using an insulin pump was lower at 1.8 ± 0.6 compared with the data of pregnant female patients with DM1 who used only a simple bolus both in the MII (2.5 ± 0.8) and FII (2.1 ± 0.6) modes ($p < 0.01$).

One of the important characteristics of efficacy and safety of various modes of insulin therapy is the frequency of hypoglycemic episodes in DM1 patients. The frequency of hypoglycemic episodes per week with self-monitoring of glycemia (measurement frequency of 8–10 times a day) in the CSII group was significantly lower in trimesters I, II, and III of pregnancy compared with the MII group (Fig. 4).

The duration of the hypoglycemic state according to the CGM results in the group of women using CSII was less and amounted to 8.0 (0–12.6) min per 24 h, and in the group of women treated in the MII mode, it was 20.0 (2.5–63.3) min per 24 h ($Z = 4.56$; $p < 0.001$).

In the course of the work, the average glucose level, the minimum and maximum values of the glucose level in the extracellular fluid for the entire examination period were analyzed in both the CSII (Fig. 5a) and MII (Fig. 5b) groups.

As can be seen from the data presented, the amplitude of fluctuations in glucose levels was significantly lower in women who used the CSII mode (Fig. 5a).

The analysis of changes in glucose variability in the dynamics in trimesters I, II, and III of pregnancy with various modes of insulin therapy was performed. The glucose variability indices (the MAGE, MODD, and CONGA indices) improved, as already from trimester II of pregnancy in pregnant female patients with DM1 who used the CSII mode, which was not registered in women treated in the MII mode (Fig. 6).

Glucose variability was significantly lower in the group of DM1 patients who used CSII compared with pregnant DM1 female patients who used the MII mode.

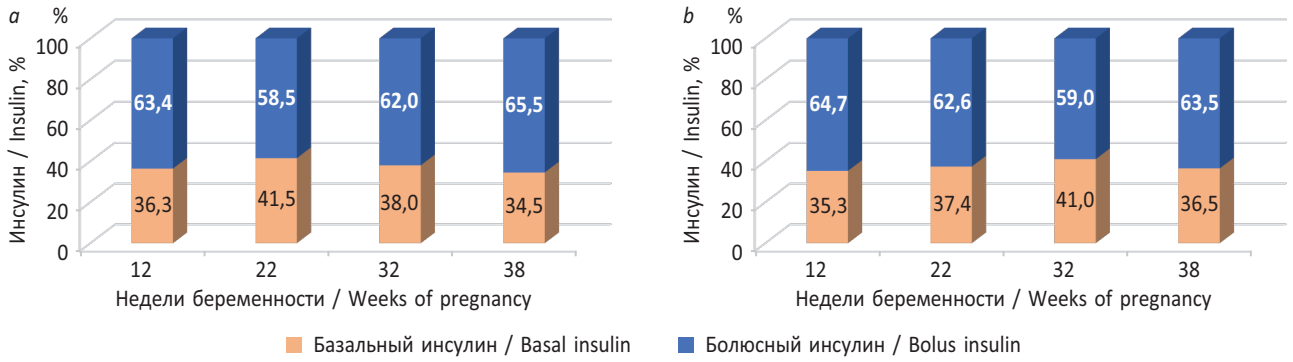

Fig. 2. Daily dose ratio of basal to bolus insulin in type 1 diabetes mellitus pregnant women treated with continuous subcutaneous insulin infusion (*a*) and multiple daily injections of insulin (*b*)

Рис. 2. Соотношение суточных доз базального и болюсного инсулина у беременных с сахарным диабетом 1-го типа, использовавших режим постоянной подкожной инфузии инсулина (*a*) и режим множественных инъекций инсулина (*b*)

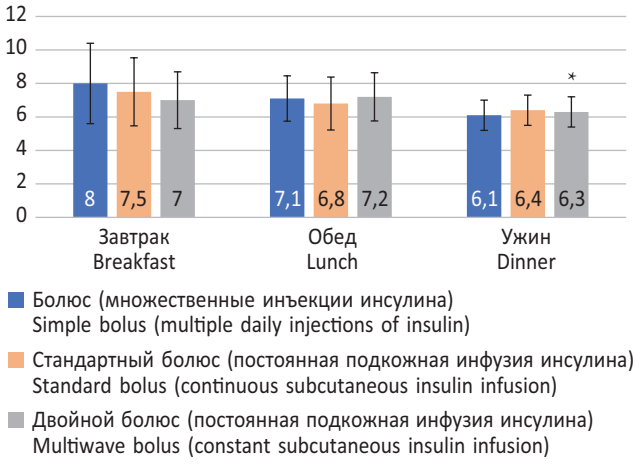

Fig. 3. Levels of postprandial glycemia in type 1 diabetes mellitus pregnant women who used a simple bolus via multiple daily injections of insulin, a standard bolus via continuous subcutaneous insulin infusion, and a multiwave bolus via constant subcutaneous insulin infusion (* $p < 0.05$, when compared to the "bolus via multiple daily injections of insulin" group)

Рис. 3. Уровень постпрандиальной гликемии у беременных с сахарным диабетом 1-го типа, использовавших простой болюс в режиме множественных инъекций инсулина, стандартный болюс в режиме постоянной подкожной инфузии инсулина и многоволновой болюс в режиме постоянной подкожной инфузии инсулина (* $p < 0{,}05$ — отличие между группами «болюс в режиме множественных инъекций инсулина» и «многоволновой болюс в режиме постоянной подкожной инфузии инсулина»)

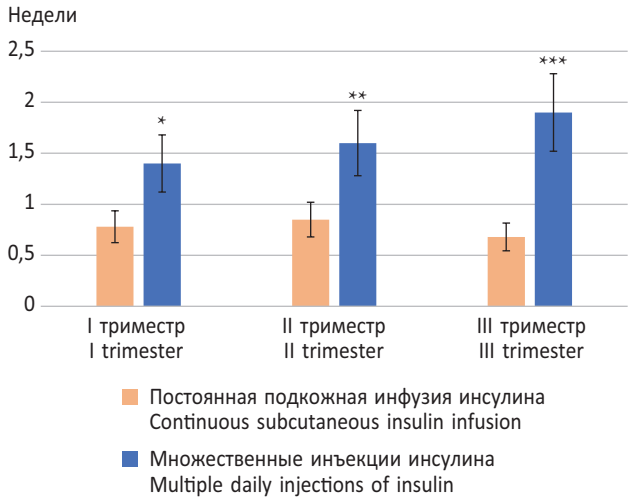

Fig. 4. Frequency of hypoglycemic episodes (per week) in type 1 diabetes mellitus pregnant women treated with continuous subcutaneous insulin infusion and multiple daily injections of insulin (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, when compared to the constant subcutaneous insulin infusion regimen in the relevant trimesters of pregnancy)

Рис. 4. Частота гипогликемических эпизодов (в неделю) у беременных с сахарным диабетом 1-го типа, использовавших режим постоянной подкожной инфузии инсулина и режим множественных инъекций инсулина (* $p < 0{,}05$, ** $p < 0{,}01$, *** $p < 0{,}001$ — отличия между группами «режим множественных инъекций инсулина» и «режим постоянной подкожной инфузии инсулина» в соответствующих триместрах беременности)

A positive correlation was revealed between the duration of DM and glucose variability, namely, the indices MAGE ($r = 0.47$; $p < 0.001$), MODD ($r = 0.39$; $p < 0.001$), and CONGA ($r = 0.23$; $p < 0.05$) for the entire period of CGM in pregnant women who used CSII. The data obtained can be applied when choosing an insulin therapy mode for women with a long duration of the disease. The data are important, which are the evidence of a positive correlation between the duration of

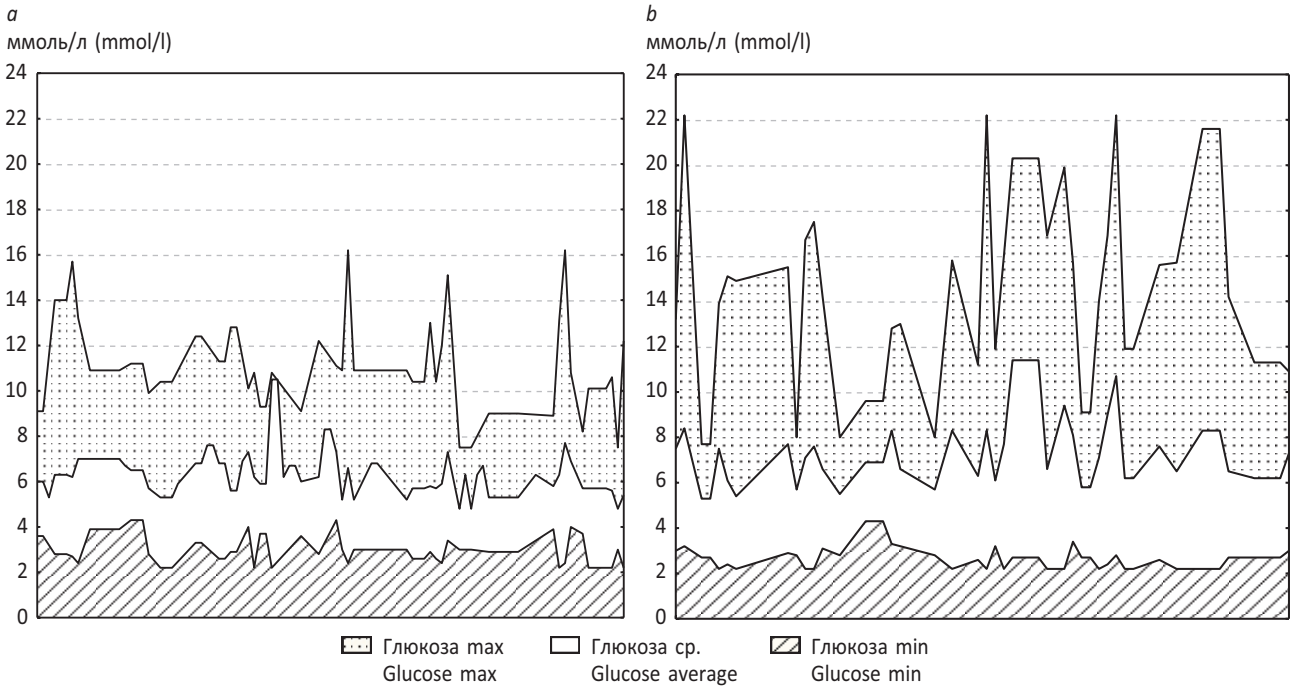

Fig. 5. The average, minimum and maximum values of glucose in the intercellular fluid during the period of continuous monitoring in pregnant women with type 1 diabetes mellitus, using the mode of continuous subcutaneous insulin infusion (*a*) and the mode of multiple insulin injections (*b*)

Рис. 5. Средние, минимальные и максимальные значения уровня глюкозы в межклеточной жидкости за период проведения непрерывного мониторирования у беременных с сахарным диабетом 1-го типа, использовавших режим постоянной подкожной инфузии инсулина (*a*) и режим множественных инъекций инсулина (*b*)

the hypoglycemic state in the group of pregnant DM1 female patients and the von Willebrand factor indices in the study group ($r = 0.23$, $p < 0.001$) and the group of women who used CSII ($r = 0.25$, $p < 0.01$).

The dependence of glucose concentration variability indices and the endothelial damage index of the von Willebrand factor was studied. The dependence of the CONGA glucose variability index (determination of glucose level changes over time) on the von Willebrand factor ($r = 0.17$; $p < 0.05$) was revealed. In the group of pregnant female patients with DM1, who used MII, the correlation coefficient of the MAGE index and von Willebrand factor was 0.54 ($p < 0.05$) and of the MODD index and von Willebrand factor was 0.52 ($p < 0.05$).

The proportions of DM1 patients who reached an HbA1c level of < 6 % were 40 % in the CSII group and 21.5 % in the MII group in trimester 1, 70% in the CSII group and 50 % in the MII group in trimester II, and 56 % in the CSII group and 35 % in the MII group in trimester III. The target level of HbA1c (≤ 6.0 %) was achieved in a large percentage of cases without an increase in glucose variability and the frequency of hypoglycemic conditions in women who used CSII for the entire period of CGM, which, in our opinion, is associated with the functions of the insulin pump.

Discussion

According to Tay [20], postprandial glycemia determines 46 % of the total HbA1c and 80% of the average daily glycemia level. It is also the main factor in endothelial damage as well as causes somatomegaly in newborns from DM1 mothers. In our work, the frequencies of insulin administration in DM1 female patients using the CSII and MII modes were 8.20 ± 0.55 and 3.90 ± 0.65 times a day, respectively ($p < 0.01$), which enabled to achieve the target values of postprandial glycemia in the CSII group for most time of the day.

One of the priorities of our study was to assess glucose variability in DM1 female patients at different terms of pregnancy and its role in the development of endothelial dysfunction. In recent decades, data have been presented, which demonstrate the significant role of pathological glucose variability in the occurrence of endothelial damage, which is one of the causes of vascular complications of DM [18, 21–24].

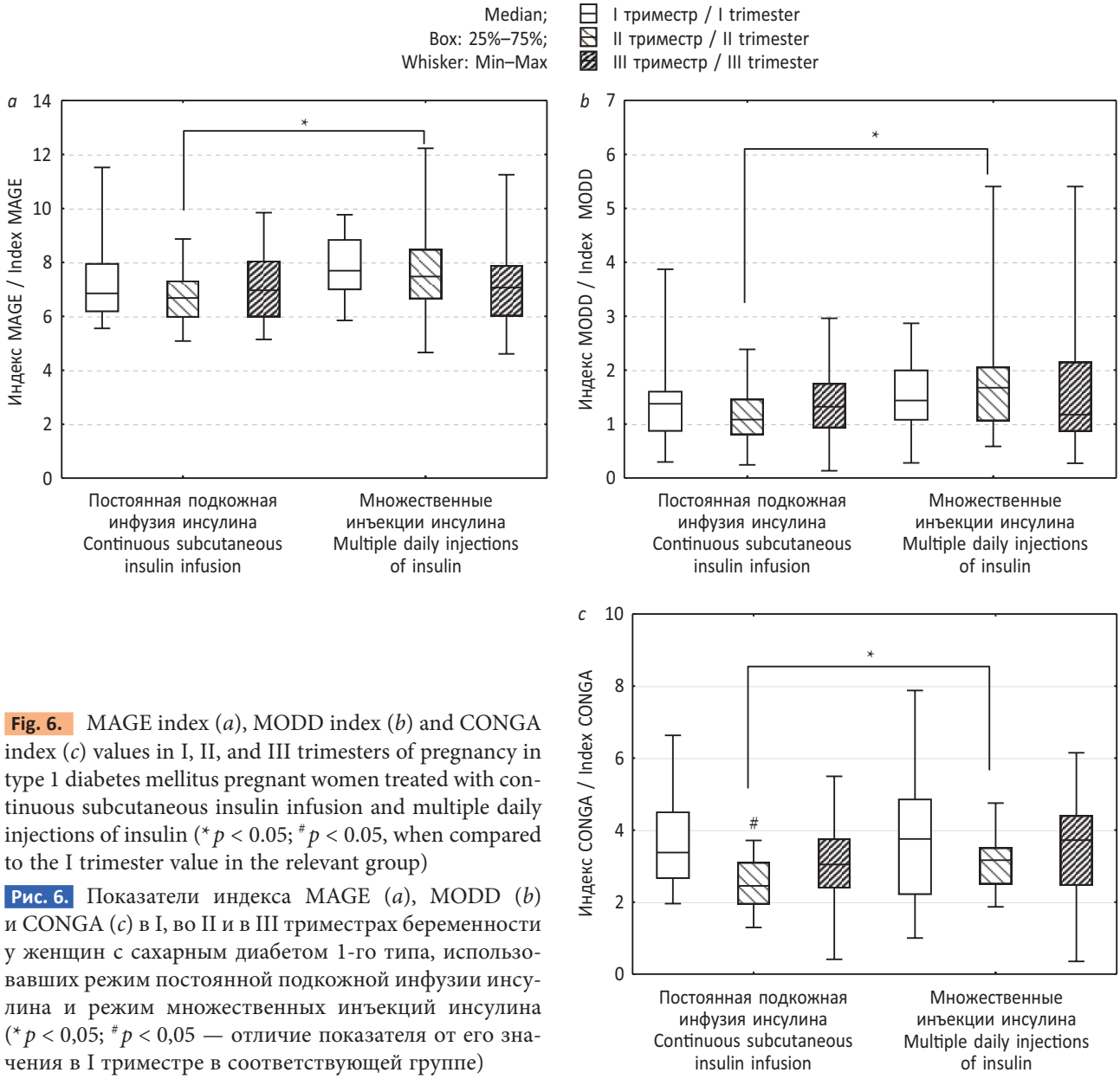

Fig. 6. MAGE index (*a*), MODD index (*b*) and CONGA index (*c*) values in I, II, and III trimesters of pregnancy in type 1 diabetes mellitus pregnant women treated with continuous subcutaneous insulin infusion and multiple daily injections of insulin ($^{*}p < 0.05$; $^{\#}p < 0.05$, when compared to the I trimester value in the relevant group)

Рис. 6. Показатели индекса MAGE (*a*), MODD (*b*) и CONGA (*c*) в I, во II и в III триместрах беременности у женщин с сахарным диабетом 1-го типа, использовавших режим постоянной подкожной инфузии инсулина и режим множественных инъекций инсулина ($^{*}p < 0{,}05$; $^{\#}p < 0{,}05$ — отличие показателя от его значения в I триместре в соответствующей группе)

Morrow [25] found that oxidative stress markers 8-iso-prostaglandin F2/creatinine correlate with both high levels of postprandial glycemia and the glucose concentration variability index MAGE ($r = 0.676$ and $r = 0.457$, respectively). The correlation of oxidative stress markers was more powerful with glucose variability indices ($r = 0.69$, $p < 0.001$) than with HbA1c levels ($r = 0.33$, $p < 0.001$). The authors suggested that "acute" glucose fluctuation may be a significant factor in the development of oxidative stress along with chronic hyperglycemia in DM1 patients, which is consistent with the data on correlation dependence of glucose variability in pregnant female patients with DM1 on the von Willebrand factor.

Some researchers suggest that the fluctuation of glucose can reduce the expression of genes regulating the decomposition of free radicals [26].

One of the common causes of pathological glucose variability is the hypoglycemic state. In response to hypoglycemia, a series of compensatory reactions are initiated in the body, aimed at maintaining blood glucose levels within physiological values. The level of catecholamines, acetylcholine, and cortisol in the blood increases, which in turn leads to responsive hyperglycemia. Changing the concentration of glucose levels causes hypercalcemia and hypomagnesemia, increases the strength of heart contractions, cardiac output, and peripheral systolic pressure, and activates the processes of coagulation. This leads to a change in hemodynamics, an increase in blood pressure,

and an exacerbation of disorders in the hemostatic system in pregnant female patients with DM1 [27–29]. The duration of the hypoglycemic state in the group of women using CSII in our study was 8.0 (0–12.6) min per 24 h and was less than that of women who applied the MII mode (20.0 [2.5–63.3] min per 24 h; $Z = 4.56$; $p < 0.001$).

Analysis of the study results revealed a positive relationship between the DM duration and hypoglycemia duration during the period of CGM ($r = –0.19$; $p < 0.05$). These data can be used to determine the strategy of insulin therapy to reduce the risk of hypoglycemic conditions in women with a long duration of DM.

Conclusions

The data obtained confirm the effectiveness of the use of CSII and CGM in DM1 female patients during pregnancy to achieve the target values of glycemia, decrease the frequency and severity of hypoglycemic conditions, and reduce glucose variability. A decrease in the degree of glucose variability in DM1 female patients during pregnancy can be a condition to prevent the development of endothelial dysfunction, which underlies obstetric and perinatal complications in this category of patients..

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■ **Information about the author** *(Информация об авторах)*

Alyona V. Tiselko — MD, PhD, Senior Researcher. The Department of Endocrinology of Reproduction, The Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia. https://orcid.org/0000-0002-2512-833X. SPIN-code: 5644-9891. **E-mail:** alenadoc@mail.ru.

Алена Викторовна Тиселько — канд. мед. наук, старший научный сотрудник отдела эндокринологии репродукции. ФГБНУ «НИИ АГиР им. Д.О. Отта», Санкт-Петербург. https://orcid.org/0000-0002-2512-833X. SPIN-код: 5644-9891. **E-mail:** alenadoc@mail.ru.