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Predictive calculator of the risk of perinatal complications in women with pregestational diabetes mellitus

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ABSTRACT

Background. The prevalence of impaired carbohydrate metabolism among women of reproductive age is increasing worldwide. Despite tremendous progress in the treatment and management of blood glucose levels, pregnancy in women with pregestational diabetes still carries risks for the fetus.

This study aims to develop a calculator for predicting perinatal complications in women with pregestational diabetes mellitus by mathematical modeling.

Materials and Methods. This observational analytical study with a case-control design was conducted at the Altai Regional Clinical Perinatal Center "DAR" (Barnaul). The study included 147 women, with the main group comprising 95 pregnant women, including 47 with type 1 diabetes mellitus (group 1A) and 48 with type 2 diabetes mellitus (group 1B). No carbohydrate metabolism disorders were detected in 52 patients of the control group. All patients in the main group received insulin therapy. Medical documentation was analyzed, and statistical processing of the data was performed using mathematical modeling methods with appropriate software.

Results. In order to predict the combined indicator of perinatal complications, logistic regression analysis was used to calculate coefficients (b) for each of the indicators that have the most significant influence on the formation of complications.

The calculated values of regression coefficients can be utilized to predict the risk of perinatal complications in women with type 1 diabetes mellitus. For more practical use, a calculator for assessing the risk of perinatal complications in type 1 and type 2 diabetes mellitus was created using a computer program.

Diagnostic evaluation of the prognostic scale (calculator) for assessing perinatal complications risk assessment in type 2 diabetes mellitus demonstrated a sensitivity of 97.6%, specificity of 87.5%, and a prognostic value of positive risk assessment of 97.5%. Therefore, the calculator enables the prediction of the risk of perinatal complications in 97.5% of cases. At the same time, the prognostic scale of perinatal complications risk and the Perinatal Complications Risk Calculator for type 1 diabetes mellitus created on its basis showed 100% sensitivity and specificity.

Conclusion. The frequency of perinatal complications remains high, so the creation of a sufficiently effective prognostic model will make it possible to predict perinatal complications and influence the tactics of management of pregnant women and their newborns.

Keywords: pregestational diabetes mellitus; hyperglycemia; diabetic fetopathy.

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Прогностический калькулятор риска перинатальных осложнений у женщин с прегестационным сахарным диабетом

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АННОТАЦИЯ

Введение. Во всём мире растёт число женщин репродуктивного возраста с нарушением углеводного обмена. Несмотря на огромный прогресс в лечении и регулировании уровня глюкозы в крови, беременность у женщин с прегестационным диабетом по-прежнему сопряжена с рисками для плода.

Цель исследования — путём математического моделирования разработать калькулятор прогноза перинатальных осложнений у женщин с прегестационным сахарным диабетом.

Материалы и методы. В обсервационное аналитическое исследование с дизайном «случай — контроль», проводимое на базе Алтайского краевого клинического перинатального центра «ДАР» (Барнаул), вошли 147 женщин.

Основную группу составили 95 беременных, из них 47 — с сахарным диабетом 1-го типа (группа 1А) и 48 — с сахарным диабетом 2-го типа (группа 1В). У 52 пациенток контрольной группы нарушений углеводного обмена не выявлено. Все пациентки основной группы получали инсулинотерапию.

Для проведения анализа использовали медицинскую документацию. С помощью программного обеспечения проведена необходимая статистическая обработка данных с применением методов математического моделирования.

Результаты. С целью прогнозирования объединённого показателя — перинатальных осложнений, путём логистического регрессионного анализа провели расчёт коэффициентов (b) для каждого из показателей, имеющих наиболее значимое влияние на формирование осложнений.

С помощью рассчитанных значений регрессионных коэффициентов можно прогнозировать риск перинатальных осложнений у женщин с сахарным диабетом 1-го типа. Для более практичного использования с помощью компьютерной программы создан «Калькулятор риска перинатальных осложнений при сахарном диабете 1-го и 2-го типа».

Диагностическая оценка прогностической шкалы (калькулятора) оценки риска перинатальных осложнений при сахарном диабете 2-го типа показала её чувствительность 97,6%, специфичность 87,5%, при этом прогностическая ценность положительной оценки риска составила 97,5%, то есть калькулятор позволяет прогнозировать риск перинатальных осложнений в 97,5% случаев. При этом прогностическая шкала риска перинатальных осложнений и созданный на её базе «Калькулятор риска перинатальных осложнений при сахарном диабете 1-го типа» показали 100% чувствительность и специфичность.

Заключение. Частота перинатальных осложнений остаётся высокой, поэтому создание достаточно эффективной прогностической модели позволит прогнозировать перинатальные осложнения, влиять на тактику ведения беременных и их новорождённых.

Ключевые слова: прегестационный сахарный диабет; гипергликемия; диабетическая фетопатия.

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BACKGROUND

The prevalence of impaired carbohydrate metabolism among women of reproductive age is increasing worldwide. Pregestational diabetes mellitus (DM) affects 1–14% of pregnant women worldwide, depending on the region and nationality [1]. Despite enormous progress in the treatment and regulation of blood glucose levels, pregnancy in women with pregestational DM still poses risks to the fetus [2, 3].

Despite delivering a newborn with normal weight at birth and without signs of diabetic fetopathy, the child may be overweight in the future because of maternal hyperglycemia, which is certainly associated with impaired placenta formation from early gestation [2, 4, 5].

Assessing risk factors for complicated pregnancy and adverse perinatal outcomes is essential for understanding the prognosis of pregnancy and possible ways for the prevention and early diagnosis of complications and determining the method and timing of delivery [6–8]. A major study covering data over the past 40 years in Japan revealed that maternal glycemic control has reduced maternal complications in recent years but has not improved perinatal outcomes despite modern technology [9, 10]. Modern obstetrics throughout the world and in Russia is largely aimed at improving perinatal outcomes; currently, our very important task is to confer the possibility of women having healthy children, despite the presence of serious extragenital pathologies such as pregestational DM.

This study aimed to develop a calculator for predicting perinatal complications in female patients with pregestational DM using mathematical modeling.

MATERIALS AND METHODS

An observational analytical study with a case–control design, conducted at the Altai Regional Clinical Perinatal Center “DAR” (Barnaul), included 147 female patients.

The main group consisted of 95 pregnant women, 47 of whom had type 1 DM (T1DM, group 1A) and 48 patients had type 2 DM (T2DM, group 1B). Among 52 patients in the control group, no carbohydrate metabolism disorders were identified. The main group received insulin therapy.

The main group included women with singleton pregnancy and diagnosis of T1DM (group 1A) or T2DM (group 1B). The control group included women without carbohydrate metabolism disorders, had a singleton pregnancy, and consented to participate in the study.

Exclusion criteria from the compared groups were the presence of extragenital pathology in the stage of decompensation, severe preeclampsia and its complications, congenital anomalies of fetal development incompatible with life, and refusal to participate in the study.

In the analysis, medical documentation was used (delivery and notification records, medical card of the pregnant and postpartum woman, birth history, and history of the newborn), based on which clinical data and results of laboratory

and instrumental research methods were analyzed. All patients underwent laboratory and instrumental examinations indicated for female patients with DM. Ultrasound (US) examination included the measurement of geometric parameters according to standard US protocols. By calculating the ratios of the biparietal head/abdominal circumference or the femur length/abdominal circumference, the symmetry of fetal development was calculated. Placental blood flow disorders were registered by assessing the velocity characteristics in the uterine arteries in different trimesters using a Voluson E10 ultrasonography apparatus.

The study was performed in accordance with the Declaration of Helsinki of the World Medical Association “Ethical principles for medical research involving human subjects” and was approved at a meeting of the local ethics committee at the Altai State Medical University (protocol dated December 24, 2021, No. 11).

Using the software, the authors performed the necessary statistical processing of the data by employing mathematical modeling methods. The proportion of values for qualitative characteristics was calculated using the following equation:

$$\bar{p} = \frac{m}{n},$$

where n is the total number of patients studied and m was the characteristic being studied. The significance of differences between indicators in the two samples was assessed using a contingency table based on the χ^2 test for frequency values <5 (Fisher’s exact test).

The analysis of variance (ANOVA) was performed to select significant risk factors based on the analysis of indicators in the main and control groups. By comparing the observed and critical values of the Fisher–Snedecor F -statistic, significant indicators were selected for inclusion in the prognosis model [11].

Then, the relationship between the values of risk factors and the possible risk of complications was established using the logistic regression method. Since the indicators have different scales of change, they were first scaled, and their values were brought to the interval (0, 1) by subtracting the minimum value and dividing the result by the range of the indicator, i.e. normalization.

The numerical values of regression coefficients can be considered a relative assessment of how much the risk of complications will change in the presence of relevant risk factors compared with their absence.

The calculations performed enable the assessment of the risk of perinatal complications using a predictor calculated using the following equation:

$$f(X_1, \dots, X_p) = \frac{1}{1 + \exp \left\{ -a_0 - \sum_{i=1}^p b_i X_i \right\}}.$$

where a_0 is a constant, p is the number of indicators involved in prediction, $b_1, \dots, b_p$ are regression coefficients, and $X_1, \dots,$

X_p are values of specific indicators. The values of the indicators must be substituted into this equation without preliminary scaling, which is already considered when determining the coefficients. As shown in the equation, the discriminant function always takes values from 0 to 1, where 1 as an output value can be interpreted as a high probability of complications, and a high perinatal risk can be suggested. All predictor values are between 0 and 1 and can be interpreted as the probability of complications. If the result is 0, a low risk can be predicted; if the result is 1, a high risk of complications can be predicted. To evaluate the resulting prognostic model based on the discriminant function, indicators of its sensitivity and specificity were calculated.

Statistical analysis of the data was performed using the statistical computing package IBM SPSS Statistics version 23.

RESULTS

An assessment of the clinical and anamnestic data of pregnant women showed that the groups were comparable in parity, where multigravidas accounted for 77.0% and 67.0%, respectively, and that in the control group was 73.1% ($p > 0.05$). The disease duration differed between female patients with T1DM and T2DM, which were 12.1 and 4.6 years, respectively ($p < 0.05$).

Pregavid preparation was performed in only 10 women, i.e., in 6 (4.1%) patients with T1DM and 4 (2.7%) with T2DM ($p > 0.05$).

Analysis of glycemic indicators revealed that at the first visit, glycated hemoglobin and fasting glucose levels were significantly higher in female patients with T1DM than in those with T2DM ($p = 0.016$) (Table 1).

Obstetric complications (preeclampsia and preterm abortion of a normally located placenta) occurred in female patients of the two groups with nearly the same incidence rates, which were 14.9% in group 1A and 6.25% in group 1B ($p > 0.05$).

To predict the combined indicator, namely, perinatal complications, which included fetal distress, diabetic fetopathy, and cerebral ischemia of newborns, using logistic regression

analysis, coefficients (b) were calculated for each of the indicators that have the most significant effect on the development of complications. The initial model included >25 risk factors, among which the most significant indicators for each type of DM were determined using one-way ANOVA. Thus, for T1DM, significant predictors of perinatal complications, which formed the basis of the prognostic model, were a history of preterm delivery and a family history of DM, as well as US criteria such as hepatomegaly, fetal head and abdominal circumference, and laboratory indicators, namely, pregnancy-associated plasma protein A (PAPP-A) and newborn glucose on day 1 after birth (Table 2).

When calculating the risk, the values of indicators such as PAPP-A (mIU/mL), newborn glucose on day 1 after birth (mmol/L), and fetal head and abdominal circumference values are entered into the prognostic model as specific indicator values. The calculated values of regression coefficients can be used to predict the risk of perinatal complications in female patients with T1DM using the above predictor equation. For a more practical application, the authors used Microsoft Excel and created a "Risk Calculator for Perinatal Complications in Type 1 Diabetes Mellitus" (Table 3).

When analyzing predictors of perinatal complications in female patients with T2DM, the most significant indicators influencing the risk of perinatal complications were a family history of DM, DM duration (years), and chronic arterial hypertension. Laboratory criteria included fasting venous plasma glucose and glycated hemoglobin at the first visit and PAPP-A protein level. US criteria included blood flow indicators (resistance index in the uterine arteries at screening 1 and 2), hepatomegaly, placental thickness, fetal head circumference, and polyhydramnios (Table 4).

When calculating the risk using the proposed equation and the obtained regression coefficients in the model for calculating the risk of perinatal complications in female patients with T2DM, obtaining risk 1 can be regarded as a high risk of perinatal complications in these patients. For use in practical healthcare, a "Risk Calculator for Perinatal Complications in

Table 1. Characteristics of glycemic indices in the examined women

Parameter	Main group (n = 95)		Control group (n=52) (3)	p ₁₋₂ (between T1DM and T2DM)	p ₂₋₃ (between the control group and T2DM)	p ₁₋₃ (between the control group and T1DM)
	1A (1)	1B (2)				
HbA1c, %:						
trimester I	7.3	5.7	4.5	0.005	0.000	0.000
trimester II	6.8	5.4	4.8	0.000	0.000	0.000
trimester III	6.7	5.3	4.2	0.000	0.000	0.000
Fasting venous plasma glucose, mmol/L (IU)	6.7	5.7	4.6	0.001	0.000	0.000

Note. HbA1c — glycated hemoglobin; p_{1-2} — statistical significance of differences between subgroups of the main group; p_{1-3} — statistical significance of differences between subgroup A of the main group (1A) and the control group; p_{2-3} — statistical significance of differences between subgroup B of the main group (1B) and the control group.

Table 2. Regression coefficients in the prognostic model for calculating the risk of perinatal complications in women with type 1 diabetes mellitus

Predictor	Coefficient in predictor (b)	Standard error	p
History of preterm delivery	-51.938	3761.805	0.000
Glucose levels of a newborn on day 1 after birth	-355.877	4350.711	0.007
Family history of diabetes mellitus	79.786	1779.442	0.002
Hepatomegaly	171.569	6222.751	0.001
Fetal head circumference (HC)	-14.209	176.374	0.006
Fetal abdominal circumference (AC)	12.275	120.537	0.010
PAPP-A	-29.744	953.766	0.001
Constant	1737.232	29267.223	0.004

Table 3. Prognostic calculator of the risk of perinatal complications in women with type 1 diabetes mellitus

Full name of the patient	History of preterm delivery (0, – no; 1, – yes)	Glucose level of the newborn on day 1 after birth, mmol/L	Family history of diabetes mellitus (0, no; 1, yes)	Hepato-megaly (0, no; 1, yes)	PAPP-A, mIU/mL	Head circumference (HC), mm, 34–38.5 weeks	Fetal abdominal circumference (AC), mm, 34–38.5 weeks
	0	3.1	1	0	2.05	322	339

Note. Prognosis: risk 1 is high, risk 0 is low.

Table 4. Regression coefficients in the model for calculating the risk of perinatal complications in women with type 2 diabetes

Predictor	Coefficient in the predictor	Standard error	p
Family history of diabetes mellitus	48.921	8799.088	0.000
DM duration, years	5.423	2327.327	0.000
Chronic arterial hypertension	-9.513	11647.654	0.000
Venous plasma glucose levels at the first visit	4.125	11326.992	0.000
Glycated hemoglobin at the first visit	4.509	11677.303	0.000
PAPP-A	2.090	1694.037	0.000
UA RI on the right, 11–13.6 weeks	173.406	37589.626	0.000
UA RI on the left, 11–13.6 weeks	-129.922	34147.658	0.000
Uterine artery RI on the right, 19–21.6 weeks	159.356	42144.245	0.000
Uterine artery RI on the left, 19–21.6 weeks	69.289	39879.166	0.000
Fetal head circumference (HC)	-0.175	249.739	0.000
Hepatomegaly	0.840	851.934	0.000
Placental thickness	-22.811	6504.444	0.000
Polyhydramnios	-2.372	12431.193	0.000
Constant	-171.486	86800.781	0.000

Note. UA RI is the index of resistance of the uterine artery.

Type 2 Diabetes Mellitus” was created using Microsoft Excel (Table 5).

Then, the authors conducted a diagnostic assessment of the developed program “Risk Calculator for Perinatal Complications in Type 1 and Type 2 Diabetes Mellitus.”

The predictive value of the “Calculators” was determined using the available data from female patients in the main group ($n=147$). A diagnostic assessment of the prognostic scale (calculator) for assessing the risk of perinatal complications in T2DM showed a sensitivity of 97.6% and specificity

Table 5. Prognostic calculator of the risk of perinatal complications in women with type 2 diabetes mellitus

Full name of the patient	Family history of DM	Duration of DM, years	Chronic arterial hypertension	Venous plasma glucose level at the first visit (mmol/L)	Glycated hemoglobin at the first visit, %	PAPP-A, mIU/mL	UA RI on the right, 11–13.6 weeks	UA RI on the left, 11–13.6 weeks	UA RI on the right, 19–21.6 weeks	UA RI on the left, 19–21.6 weeks	Fetal head circumference (HC), mm	Placental thickness (mm)	Hepato-megaly	Polyhydramnios
	0	6	0	5.8	6.1	9.15	0.65	0.47	0.62	0.72	328	32	1	1

Note. Prognosis: risk 1 is high, risk 0 is low.

of 87.5%, whereas the predictive value of a positive risk assessment was 97.5%; that is, the calculator can be used to predict the risk of perinatal complications in 97.5% of cases. Moreover, the prognostic risk scale for perinatal complications and the “Risk Calculator for Perinatal Complications in Type 1 Diabetes Mellitus,” created based on it, showed 100% sensitivity and specificity.

DISCUSSION

Pregestational DM increases the risk of obstetric and perinatal complications. Although obstetric complications have significantly reduced in recent years through dynamic examinations of female patients and monitoring and self-monitoring of glycemia, perinatal complications remain a pressing problem that requires additional management mechanisms [9]. One of the possible ways is the prediction of these complications, timely detection, and delivery.

Using mathematical modeling based on the analysis of possible predictors that had a greater influence on perinatal complications, automated “Risk Calculators of Perinatal Complications” for female patients with T1DM and T2DM were created using a computer program. The calculation result enables us to obtain the categories “high risk” or “low risk”.

Predictors of perinatal risk differ in T1DM and T2DM, showing that considerably more factors are significantly influencing T2DM, and there is a degree of compensation for T2DM in pregnancy (a “significant” predictor is fasting venous plasma glucose and glycated hemoglobin in the first trimester of pregnancy), the comorbidity of this pathology with chronic arterial hypertension, and the role of vascular disorders in the uteroplacental circulation (significant predictors are indicators of the resistance index in the uterine arteries, such as at the first and second screening).

Considering the significance of these predictors and their combination, for each type of DM, the authors developed a prognostic risk scale, based on which a “Risk Calculator for Perinatal Complications” was created for female patients with T1DM and T2DM, which can predict perinatal complications with high sensitivity and specificity.

CONCLUSION

Despite significant achievements in the issues of examination, follow-up, and correction of glycemia in female patients with pregestational DM, the incidence of perinatal complications remains high. Therefore, an effective prognostic model will enable the prediction of perinatal complications and influence the management of pregnant women and their newborns.

ADDITIONAL INFO

Authors’ contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work: Dudareva Yu.A. — organization of research, advisory assistance; Seroshtanova D.N. — data collection and analysis of results, writing an article; Dronov S.V. — statistical processing of the data obtained; Antoshkina L.V. — data collection and analysis of results, writing an article.

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Competing interests. The authors declares that there are no obvious and potential conflicts of interest associated with the publication of this article.

Ethics approval. The research work was carried out in accordance with the Helsinki Declaration of the World Medical Association “Ethical principles of conducting scientific medical research with human participation” and approved at a meeting of the local ethics committee at the Altai State Medical University (Protocol No. 11 of December 24, 2021).

Consent for publication. All the patients who participated in the study signed the necessary documents on voluntary informed consent to participate in the study and the publication of their medical data.

ДОПОЛНИТЕЛЬНО

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией: Дударева Ю.А. — организация исследования, консультативная помощь; Сероштанова Д.Н. — сбор данных и анализ результатов, написание статьи; Дронов С.В. — статистическая обработка

полученных данных; Антошкина Л.В. — сбор данных и анализ результатов, написание статьи.

Финансирование. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Этическое утверждение. Научно-исследовательская работа проведена в соответствии с Хельсинкской декларацией

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