

POSSIBILITIES FOR PREDICTING PREECLAMPSIA DEVELOPMENT IN PREGNANT WOMEN WITH BRONCHIAL ASTHMA

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■ **Hypothesis/aims of study.** Currently, preeclampsia is one of the most pressing problems of obstetrics due to the complexity of pathogenesis and to the lack of early and reliable diagnostic criteria. The preeclampsia rate in patients with bronchial asthma is proved higher than in asthma free pregnant women. This study aimed to establish the prediction algorithm of preeclampsia development in pregnant women suffering from bronchial asthma of varying severity and different level of control.

■ **Study design, materials and methods.** Asthma duration was studied in 110 pregnant women using the SPSS Discriminant Function Analysis method. Basic therapy and level of asthma control were studied together with respiratory tests, obstetrician medical history, and complications of the first and second trimesters of pregnancy. In addition, serum interleukin panel was assessed and placental Doppler measurement was carried out.

■ **Results.** Clinical and statistical analysis made it possible out of 87 significant risk factors for the development of hypertensive disorders and preeclampsia to form a highly informative set of signs for a linear discriminant model for predicting preeclampsia: 1) asthma exacerbation in the first trimester of pregnancy; 2) asthma duration severity; 3) average dose of inhaled glucocorticosteroid drugs administered to the exact patient during pregnancy; 4) serum levels of tumor necrosis factor, interferon gamma, and interleukins-4, 6, and 8.

■ **Conclusion.** The inclusion method of step-by-step discriminant analysis allowed establishing a highly informative four-component complex of clinical predictors for preeclampsia development in pregnant women with asthma. The results of the model testing showed its extremely high reliability (up to 100% within study selection as well as within control selection). Thus, the study results can be recommended for clinical use.

■ **Keywords:** bronchial asthma; preeclampsia; prediction.

ВОЗМОЖНОСТИ ПРОГНОЗИРОВАНИЯ РАЗВИТИЯ ПРЕЭКЛАМПСИИ У БЕРЕМЕННЫХ, СТРАДАЮЩИХ БРОНХИАЛЬНОЙ АСТМОЙ

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■ **Актуальность.** В настоящее время преэклампсия является одной из самых актуальных проблем акушерства из-за сложности патогенеза, отсутствия ранних и достоверных диагностических критериев. Доказано, что у больных бронхиальной астмой преэклампсия развивается чаще, чем у беременных, не страдающих этим заболеванием.

Цель — разработать модель для прогнозирования развития преэклампсии у беременных, страдающих бронхиальной астмой различной тяжести и с различной контролируемостью течения.

Материал и методы исследования. У 110 больных бронхиальной астмой с применением методики дискриминантного анализа (SPSS Discriminant Function Analysis) было проанализировано течение этого заболевания в период беременности, степень его контролируемости, характер терапии, функциональные показатели системы внешнего дыхания, особенности акушерско-гинекологического анамнеза, наличие осложнений I и II триместров беременности, данные доплерометрии плацентарного комплекса, уровни интерлейкинов сыворотки крови.

Результаты исследования. С помощью клинико-статистического анализа из 87 значимых факторов риска развития гипертензивных расстройств и преэклампсии был сформирован высокоинформативный набор признаков для линейной дискриминантной модели прогнозирования преэклампсии: 1) наличие обострения бронхиальной астмы в I триместре беременности; 2) тяжесть течения бронхиальной астмы; 3) средняя доза ингаляционных глюкокортикостероидных препаратов, назначавшихся пациентке в период беременности; 4) содержание в крови фактора некроза опухоли, интерферона гамма, интерлейкинов-4, -6, -8.

Выводы. На основе высокоинформативного набора, включавшего четыре признака, была построена линейная дискриминантная модель, позволяющая прогнозировать появление преэклампсии у беременных до развития клинической картины. Результаты проверки работоспособности модели подтвердили ее исключительно высокую надежность (100 % прогнозирование и по обучающей выборке, и при контрольной оценке), на основании чего ее можно рекомендовать для применения в клинической практике.

■ **Ключевые слова:** бронхиальная астма; преэклампсия; прогнозирование.

Introduction

One of the most common and serious respiratory diseases is bronchial asthma, which can also complicate the course of pregnancy [1, 2]. Numerous studies have shown that female patients with bronchial asthma have a higher risk of developing a number of complications during pregnancy and childbirth. These complications include preeclampsia, premature birth, intrauterine growth retardation of the fetus, and weight loss in newborns [3, 4]. Pregnant women with a severe course of this disease are most prone to developing these complications [5]. One of the most common and serious complications of late pregnancy is preeclampsia. The pathogenesis of preeclampsia involves severe endothelial dysfunction, the activation of platelet-vascular unit of the hemostatic system, circulatory disorders, and vasoconstriction. In preeclampsia, the incomplete invasion of the cytotrophoblast causes an incorrect reconstruction of the spiral arteries, which ultimately leads to inferiority of the vasculature of the mother-placenta-fetus system and the associated clinical manifestations [6].

Currently, preeclampsia is one of the most urgent problems of obstetrics due to the complexity of its pathogenesis, the lack of early and reliable diagnostic criteria, limited effective preventive and treatment measures, a high maternal and perinatal morbidity and mortality rate, and high financial costs of intensive care [7]. Preeclampsia complicates pregnancy, and since many years it ranks as the 2nd or 3rd leading cause of maternal and perinatal mortality, as well as in terms of the

incidence [8]. The number of severe cases, low-symptom forms, and those with an atypical course, which often cause maternal and perinatal morbidity and mortality, are increasing [9]. According to recent data, a genetic predisposition that affects the development of preeclampsia accounts for up to 50% of all risk factors, and pathology can be inherited both by the female and male lines. It has been noted that the likelihood of preeclampsia occurring in the family is significantly higher if both spouses were born as a result of a pregnancy complicated by this pathology [10]. For women who suffered from preeclampsia during their first pregnancy, the risk of recurrence increases by 12 times, and in patients who had increased blood pressure during their first pregnancy, the probability of preeclampsia is 2–4 times higher in a subsequent pregnancy [10].

Our study aimed to develop a model for predicting preeclampsia in pregnant women suffering from bronchial asthma of varying severity and disease controllability.

Materials and methods

To develop a linear discriminative model for predicting the development of preeclampsia, we used the step-by-step discriminative analysis method (SPSS Discriminative Analysis application package). We analyzed the data obtained by pulmonologists and obstetrician-gynecologists who monitored 110 pregnant women suffering from bronchial asthma of varying severity and disease controllability from the first trimester of pregnancy.

Results

To identify the main prognostic criteria, 87 signs were selected by experts, including the age of the pregnant women, the severity of bronchial asthma before and during pregnancy, the degree of the disease controllability, the nature of therapy, the functional parameters of the external respiration system, the aspects of obstetric and gynecological anamnesis, the presence of complications in the first and second trimesters, data from placental complex dopplerometry, and serum interleukin (IL) levels. At the analysis

stage, only the cases that did not contain system and user missing values in predictor variables were used.

Clinical and statistical analysis enabled the identification of 87 significant risk factors for the development of hypertensive disorders and preeclampsia. Four of these signs (described below) were selected using the step-by-step discriminative analysis method to predict the occurrence of preeclampsia in pregnant women using a linear discriminative model, before the development of the clinical presentation.

Table 1 / Таблица 1

Risk factors for preeclampsia

Факторы риска развития преэклампсии

Risk factors	Designation
No exacerbation	0
Mild exacerbation	1
Severe exacerbation	2
Severity of bronchial asthma	
Mild intermittent course [Mild BA(i)]	1
Mild persistent controlled course [Mild BA(c)]	2
Mild persistent uncontrolled course [Mild BA(u/c)]	3
Moderate controlled course [Moderate BA(c)]	4
Moderate uncontrolled course [Moderate BA (u/c)]	5
Duration of iGCS intake	
None	0
First trimester	1
Second trimester	2
Third trimester	3
iGCS dose	
None	0
Low	1
Medium	2
High	3
Hypertensive disorders and preeclampsia	
None	0
Hypertension	1
Moderate preeclampsia	2
Severe preeclampsia	3

Note. iGCS: inhalant glucocorticosteroids

Table 2 / Таблица 2

Order of inclusion of the signs in the model of the appearance of preeclampsia

Порядок включения признаков в модель появления преэклампсии

Stage	Introduced	Wilks' lambda							
		Statistics	Degree of freedom 1	Degree of freedom 2	Degree of freedom 3	Precise value F			
						Statistics	Degree of freedom 1	Degree of freedom 2	Value
1	Deterioration in first trimester	0.275	1	1	68.000	179.444	1	68.000	0.000
2	Interleukin 6	0.209	2	1	68.000	126.550	2	67.000	0.000
3	iGCS dose	0.173	3	1	68.000	105.129	3	66.000	0.000
4	BA severity	0.157	4	1	68.000	87.207	4	65.000	0.000

Note. iGCS: inhalant glucocorticosteroids; BA: bronchial asthma.

Table 3 / Таблица 3

Coefficients of the classifying function

Коэффициенты классифицирующей функции

Function	Groups 0 + 1 and 2 + 3	
	0 + 1	2 + 3
Deterioration in the first trimester	6.011	16.796
BA severity	3.002	4.676
iGCS dose	-1.142	-4.610
Interleukin-6	0.271	0.616
Constant	-8.774	-32.431

Note. iGCS: inhalant glucocorticosteroids; BA: bronchial asthma.

1. The exacerbation of bronchial asthma in the first trimester of pregnancy

2. The severity of bronchial asthma course

3. The average dose of inhalant glucocorticosteroid drugs prescribed to the patient during pregnancy

4. The blood levels of tumor necrosis factor, interferon-gamma, and IL-4, -6, and -8.

Table 1 presents the risk factors for preeclampsia.

Table 2 presents the order of inclusion of the risk factors in the linear discriminative model.

At each step of selecting a risk factor, a variable was included in the model that minimized the Wilks' lambda indicator.

For the selected four signs, the coefficients and constants of linear discriminative functions of the hypertensive disorder prediction model were calculated. The decision to assign the patient to the group 0 + 1 or the group 2 + 3 was made when comparing the values of the Fisher linear discriminant function (LDF). The patient belonged to the group in accordance with the LDF value and the forecast model (Table 3).

Fisher LDFs

$$\begin{aligned} \text{LDF1} &= (\text{deterioration}) \cdot 6.011 + \\ &+ (\text{BA severity}) \cdot 3.002 + (\text{dose}) \times \\ &\times (-1.142) + (\text{IL-6}) \cdot 0.271 - 8.774; \\ \text{LDF2} &= (\text{deterioration}) \cdot 16.796 + \\ &+ (\text{BA severity}) \cdot 4.676 + (\text{dose}) \times \\ &\times (-1.142) + (\text{IL-6}) \cdot 0.616 - 32.431 \end{aligned}$$

The results of verifying the accuracy of prognosis using the developed model in the training sample (initial data) and during the verification using a special procedure of unbiased estimation (cross-verification) are presented in Table 4. The results of testing the model's performance showed it exhibits high reliability (100% prognosis both in the training sample and in the control evaluation); therefore, it is recommended for application in clinical practice.

Conclusions

The principal risk factors that increase the likelihood of preeclampsia development in pregnant women suffering from bronchial asthma include the severity of the disease, the deterioration of the course (exacerbation) in the first trimester

Table 4 / Таблица 4

Checking the accuracy of preeclampsia prediction

Результаты проверки правильности прогнозирования преэклампсии

Classification results ^{a, b}					
Groups 0 + 1 and 2 + 3			Predicted belonging to a group		Total
			0 + 1	2 + 3	
Initial	Frequency	0 + 1	87	0	87
		2 + 3	0	23	23
	%	0 + 1	100.0	0.0	100.0
		2 + 3	0.0	100.0	100.0
Cross-verified ^b	Frequency	0 + 1	87	0	87
		2 + 3	0	23	23
	%	0 + 1	100.0	0.0	100.0
		2 + 3	0.0	100.0	100.0

NOTE a) 100.0% of the initial grouped cases were classified correctly; b) cross-verification was conducted only for cases in the analysis. In the cross-verification, each case was classified by functions derived from all cases, with the exception of itself; c) 100.0% of cross-verified grouped cases were classified correctly.

of pregnancy, and an increase in IL-6, which can be detected before the clinical presentation of preeclampsia. Furthermore, the likelihood of preeclampsia development is reduced by a comprehensive therapy, which involves an adequate dose of inhalant glucocorticosteroid drugs. A comprehensive assessment with the use of the listed signs and a discriminative analysis model enables the reliable prediction of the development of preeclampsia.

Additional information

The authors declare no obvious or potential conflicts of interest related to the publication of this article.

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