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PROGNOSIS OF ABNORMAL UTERINE BLEEDING IN WOMEN OF REPRODUCTIVE AGE WITH EXTRAGENITAL DISORDERS

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*The **purpose** of the study was to elaborate on a prognostic model for predicting the development of abnormal uterine bleeding in women of reproductive age with accompanying extragenital disorders based on mathematical methods.*

***Materials and methods.** The study, which was in 2019-2022, involved 100 women of reproductive age with AUB and accompanying extragenital disorders under observation, who made up the main group. The control group comprised 50 women of reproductive age undergoing medical checkups. On the basis of 23 diagnostic indicators, the most informative ones were mathematically selected for the prognosis of AUB in women with extragenital abnormalities.*

***Results and their discussion**. The prognosis of the risk of developing AUB in women of reproductive age with extragenital disorders was carried out on a double scale (0 – low probability, 1 – high probability). The search for diagnostically informative factors involved a set of 23 working indicators that were investigated in the examined patients using four levels of the risk scale. In order to solve this issue, the factors that have the greatest importance in the formation of the prognosis were selected using discriminant analysis methods, and a corresponding mathematical model was created. The classification functions made it possible to enter the practical plane and form rules for assessing the presence/absence of the risk of developing AUB in patients of reproductive age with extragenital disorders. The corresponding expressions are the following equations:*

*NP=BAS ART*75.57+FSH*2.96+prolac*0.02+estrad*0.02–40.78*

*PP=BAS ART*105.35+FSH*0.79+prolac*0.1+estrad*0.0-8114.49,*

where NP is a negative prognosis, PP is a positive prognosis.

If NP>PP, then the most likely prognosis is the absence of AUB in the patient; otherwise, if PP > NP – there is an increased risk of AUB.

***Conclusion.** Pulsation index in the basal arteries of the uterus, FSH, prolactin and estrogens are prognostically significant indicators for predicting the risk of abnormal uterine bleeding in patients of reproductive age with extragenital disorders. The above formula, obtained from the conducted discriminant analysis, makes it possible to predict bleeding in a specific patient*

***Keywords**: abnormal uterine bleeding, discriminant analysis, risk prediction, mathematical model, classification functions*

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1. Introduction

Abnormal uterine bleeding (AUB) is uterine bleeding with an abnormal frequency, duration, and volume of bleeding compared to a normal menstrual period [1]. AUB is a very common symptom of disease/diseases and refers to all bleeding that differs from normal menstrual bleeding [2, 3]. Women face the problem of AUB in puberty (10 %), reproductive period (25–30 %), late reproductive age (35–55 %), and menopause (up to 55–60 %) [4, 5]. Due to the significant prevalence of AUB, it creates medical, social and economic problems for women, their families and medicine in general [6]. However, despite the extremely negative impact of AUB on women's health, progress in understanding the pathophysiology of AUB and the development of new effective treatment methods is slow due to the lack of reliable diagnostic models.

Recently, a prognostic method has been intensively developed in clinical medicine. A medical, medicinal, or clinical prognosis predicts the likely development and outcome of a disease based on knowledge of the patterns of pathological processes and the course of the disease. The prognosis makes it possible to determine the predictors of the onset of the disease, the effectiveness of the treatment and the risk of relapse using specially developed systems with statistical methods [7]. Under such conditions, information on history, symptoms, laboratory and instrumental study data are taken into account [8–

10]. The importance of prognosis in clinical practice is determined by the main tasks of modern medicine: prevention of diseases and treatment of patients. In view of this, there are two types of medical prognosis: a prognosis of the possibility of the occurrence of the disease and a prognosis of the development of the disease, that is, an assessment of the probability of complications. Therefore, the goal of prognosis is to improve clinical decision-making, which ultimately affects patient outcomes [11, 12].

Available evidence suggests low satisfaction with standard treatment options, often resulting in major surgery such as a hysterectomy. Therefore, each patient requires an individual approach for the diagnosis of AUB. R. Chodankar and H. Critchley [13] pay attention to biomarkers, highlighting the scarcity of research on this issue. The prospect of such an approach may improve the understanding of AUB and create the opportunity to use modern treatment methods and adapt research and treatment strategies to ensure the best results according to personalised medicine principles.

The purpose of the study. Based on mathematical methods, to develop a prognostic model for predicting the development of abnormal uterine bleeding in women of reproductive age with accompanying extragenital disorders.

2. Materials and methods

The study was conducted at the clinical base of the Department of Obstetrics, Gynecology, and Pediatric Gynecology of the KhNMU (Communal non-profit enterprise "Kharkiv Maternity Hospital No. 1" of Kharkiv City Council) in 2019–2022. 100 women of reproductive age with accompanying extragenital disorders, who sought help for AUB, were under observation and made up the main group. The control group comprised 50 women of reproductive age who visited the clinic for a checkup.

On the basis of 23 diagnostic indicators, the most informative for the prognosis of AUB in women with extragenital disorders were mathematically selected.

The materials of the article were reviewed and approved at the meeting of the Committee on Bioethics of Kharkiv National Medical University (Protocol No. 2, 17.09.2019).

To create a prognostic model for predicting the development of abnormal uterine bleeding in women of reproductive age with accompanying extragenital abnormalities, the method of multivariate statistics, discriminant analysis (DA), was used. DA methods are used to decide which variables differentiate (discriminate) the studied populations (women with a risk of bleeding and women without a clear threat of bleeding) from each other. For this purpose, the DA procedure receives as input a set of indicators that, according to the researcher, differ in the studied populations (groups). The immediate task of the DA is to select such a part of these indicators that will allow predicting the belonging to one or another group of a new case (patient). The forecast is performed by constructing new variables (linear combinations of a selected part of the primary indicators) and evaluating their numerical values. As a result, on the basis of 23 analyzed diagnostic indicators, the most informative ones for the prediction of AUB in women with extragenital abnormalities were mathematically selected.

3. Results and discussion

The prognosis of the risk of developing AUB in women of reproductive age with extragenital disorders was carried out on a two-point scale (0 – low probability, 1 – high probability). The search for diagnostically informative factors was carried out on a set of 23 working indicators that were assessed in the examined patients using four levels of the risk scale. To solve this issue, by using the methods of discriminant analysis, the factors that have the greatest importance in the formation of prognosis were selected, and the corresponding mathematical model was built (hereinafter referred to as the Model 1-2-3-4). These were the indicators shown in Fig. 1 of the calculation protocol in the statistical environment STATISTICA 6.0, namely: the pulsation index (PI), obtained during the dopplerometric study of blood flow in the basal arteries of the uterus (BAS ART) and the levels of such hormones as FSH, prolactin, estradiol in blood serum.

	Discriminant Function Analysis Summary (tab_bleeding_full) Step 35, N of vars in model: 4; Grouping: group (2 grps) Wilks' Lambda: .04805 approx. F (4.144)=713.17 p<0.0000					
N=150	Wilks' Lambda	Partial Lambda	F-remove (1,144)	p-level	Toler.	1-Toler. (R-Sqr.)
BAS ART	0.052085	0.922596	12.0813	0.000673	0.958066	0.041934
FSH	0.054030	0.889379	17.9107	0.000041	0.955754	0.044246
Prolactin	0.139828	0.343658	275.0213	0.000000	0.972893	0.027107
estradiol	0.055294	0.869043	21.6996	0.000007	0.942779	0.057221

Fig. 1. Summary table of the results of the discriminant analysis conducted in the statistical environment STATISTICA 6.0 (Model 1-2-3-4) (fragment of the original protocol)

The informative part of the table reports that the results are statistically significant ($p<0.0001$) and are characterized by satisfactory discrimination, as evidenced by the so-called Wilks' lambda statistic (λ). The values of this statistic belong to the interval [0.1], and the closer its value is to zero, the better the discrimination. The first column of the table shows the values of Wilks's lambda for each variable, which should be interpreted opposite to the previous, general Wilks's lambda: the greater λ, the more desirable the indicator is in the discrimination procedure.

The third and fourth columns of the table (Fig. 1) contain the values of "F-remove" and "p-value", and the larger the "F-remove" and the smaller the "p-level", the

more desirable is the presence of the indicator in the discrimination procedure. Therefore, in view of this sign, indicators such as prolactin and estradiol have the greatest influence on the prognosis of the risk of developing AUB.

The classification matrix shown in Fig. 2 indicates the quality of the classification and contains information about the number and percentage of correctly classified observations in each group.

Classification Matrix (tab_bleeding_full)
Rows: Observed classifications
Columns: Predicted classifications

Group	Percent Correct	G_1:0 p=.32886	G_2:1 p=.67114
G_1:0	100.0000	50	0
G_2:1	100.0000	0	100
Total	100.0000	50	100

Fig. 2. Classification table of the discriminant analysis protocol for predicting the risk of AUB in women of reproductive age with extragenital disorders, conducted in the statistical environment STATISTICA 6.0 (fragment of the original protocol)

It is clear that the proposed model works with 100 per cent sensitivity and specificity.

The factor structure of canonical variables (integral indicators) consisting of selected parameters is shown in Fig. 3:

Factor Structure Matrix (tab_bleeding_full)
Correlations Variables - Canonical Roots
(Pooled-within-groups correlations)

Variable	Root 1
BAS ART	0.345969
FSH	-0.251679
Prolactin	0.763498
estradiol	0.441672

Fig. 3. Matrix of the factor structure of the discriminant analysis protocol for predicting the risk of AUB in women of reproductive age with extragenital disorders, conducted in the statistical environment STATISTICA 6.0. (fragment of the original protocol)

The factor structure of three new variables (roots), which characterize the contribution of each of the primary indicators to the formation of these variables, indicates the informational significance of each of the indicators. Thus, in the formation of the first variable, the indicators of PI in the basal arteries, the level of prolactin and estradiol in the blood serum of patients with AUB and accompanying extragenital disorders are the most important.

The basis of the model-building protocol is Fig. 4, which directly demonstrates the classification rules:

Classification Functions; grouping: group (tab_bleeding_full)

Variable	G_1:0 p=.32886	G_2:1 p=.67114
BAS ART	75.5714	105.345
FSH	2.9550	0.792
Prolactin	0.0192	0.098
estradiol	0.0186	0.083
Constant	-40.7834	-114.492

Fig. 4. Classification functions of the discriminant analysis protocol for predicting the risk of AUB in women of reproductive age with extragenital disorders, conducted in the statistical environment STATISTICA 6.0. (fragment of the original protocol)

The algorithm for predicting the risk of AUB in women of reproductive age with extragenital disorders (0 – low probability, 1 – high probability) consists of adding constants (the last line of the table of classification functions, Fig. 4) to the results of multiplying the input values of the selected factors (PI values in the basal arteries according to the data of a dopplerometric study, the level of FSH, prolactin and estradiol in blood serum) to the classification coefficients of each of the possible predictions (the intersection of lines 1–4 of the table of classification functions and column 1 for the prognosis "0" and column 2 for the prediction "1") and determining the most likely prediction based on the larger of the two values obtained. Thus, the classification functions shown in Fig. 4 made it possible to enter the practical plane and form rules for assessing the presence/absence of the risk of AUB in reproductive-age patients with extragenital disorders.

The use of the rules involved adding constants with the results of multiplying the initial values of the selected factors by the classification coefficients, obtaining two linear expressions for calculations, and determining the most probable prognosis based on the larger of these values regarding the presence/absence of the risk of AUB in reproductive age patients with extragenital disorders.

The corresponding expressions are the following equations:

NP=BAS ART*75.57+FSH*2.96+prolac*0.02+estrad*0.02–40.78;

PP=BAS ART*105.35+FSH*0.79+prolac*0.1+estrad*0.08–114.49,

where NP is a negative prognosis, PP is a positive prognosis.

If NP>PP, then the most likely prognosis is the absence of AUB in the patient; otherwise, if PP > NP, there is an increased risk of AUB.

For example, patient M. (case history No. 187) had the following baseline values:

BAS ART=0.9; FSH=1.8; Prolactin=850; Estradiol=200.3

When substituting these values into the equation of NP and PP, we get:
NP=0.9*75.57+1.8*2.96+850*0.02+200.3*0.02–40.78=53.567,
PP=0.9*105.35+1.8*0.79+850*0.1+200.3*0.08–114.49=82.771, i.e. 82.771>53.567.

Since PP>NP, the predicted result is a positive prognosis, the possibility of the development of AUB in this patient.

The above algorithm can easily be implemented in an expert system using any of the electronic spreadsheets, in particular, Microsoft Excel.

The resulting model can be easily implemented based on any electronic spreadsheet both on a personal computer and on a mobile device and will allow, without additional funds, equipment and training of a doctor, to single out patients with a risk of bleeding for more thorough monitoring.

The study did not include women with pregnancy, as a possible cause of metrorrhagia, with accompanying somatic and gynaecological oncology, and on the background of hormonal treatment at the time of examination**.**

Prospects of the study. The use of mathematical models for predicting abnormal uterine bleeding in women of reproductive age with extragenital abnormalities will make it possible to prevent the occurrence of this condition, improve the quality of life of women, and reduce state costs for their treatment.

6. Conclusion

To predict the risk of abnormal uterine bleeding in patients of reproductive age with extragenital disorders, the pulsation index in the basal arteries of the uterus, FSH, prolactin and estrogens are prognostically significant indicators. The given formula, which was obtained as a result of the conducted discriminant analysis, makes it possible to predict bleeding in a specific patient.

Conflict of interest

The authors declare that there is no conflict of interest in relation to this paper, as well as the published research results, including the financial aspects of conducting the research, obtaining and using its results, as well as any non-financial personal relationships.

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Data availability

Data will be made available on reasonable request.

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