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Mathematical modeling of the risk of antenatal fetal death based on retrospective analysis

N. M. Hychka[1], S. V. Beniuk[1], T. V. Kovaliuk[1], S. Ya. Solskyy[1], V. M. Komar[1], D. O. Kovaliuk[2], A. S. Chebotarova[1]
[1]Bogomolets National Medical University, Kyiv
[2]National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute"

Current issue in obstetrics is the early prediction of perinatal pathology arises by determining the degree of risk, especially when it comes to reproductive losses.
The objective: **to develop a mathematical model for predicting antenatal fetal death (AFD) based on retrospective analysis.**
Materials and methods**. Logistic regression model was constructed by analyzing medical cards for pregnancy monitoring of 46 women with AFD and 50 women with live births who were 18–40 years old and had singleton pregnancy. Variables that demonstrated statistical significance in the univariate logistic model were included in a multivariate stepwise model.**
Results**. Analysis of extragenital pathology allowed us to isolate a number of clinical factors associated with an increased risk of AFD. Thyroid diseases tended to increase the risk of AFD by 2.25 times; cardiovascular pathology – by 2.37 times. The predictive value of sexually transmitted infections was 2.38. According to the results of LASSO regression (Least Absolute Shrinkage and Selection Operator), the most informative predictors were identified: age > 35 years, body mass index ≥ 30 kg/m², thyroid pathology, vaginal microbiocenosis disorders, spontaneous abortions in history, placental dysfunction, D-dimer.**
Conclusions**. The identification of the main prognostic markers and the mathematical analysis of the prediction of perinatal pathology in AFD allowed us to assess the predictive power of some anamnestic indicators, which contributed to the creation of a seven-factor prognostic model of AFD.**
Keywords: *antenatal fetal death, perinatal complications, placental dysfunction, mathematical modeling, logistic regression, risk prediction.*

Математичне моделювання ризику антенатальної загибелі плода на основі ретроспективного аналізу

Н. М. Гичка, С. В. Бенюк, Т. В. Ковалюк, С. Я. Сольський, В. М. Комар, Д. О. Ковалюк, А. С. Чеботарьова

Актуальним питанням в акушерстві постає раннє прогнозування перинатальної патології з визначенням ступеня ризику, особливо якщо це стосується репродуктивних втрат.
Мета дослідження: на основі ретроспективного аналізу розробити математичну модель прогнозування антенатальної загибелі плода (АЗП).
Матеріали та методи. Побудову моделі логістичної регресії проводили на підставі аналізу медичної документації 46 жінок з АЗП та 50 жінок із живонародженням віком 18–40 років з одноплідною вагітністю. Змінні, що продемонстрували статистичну значущість при побудові однофакторної логістичної моделі, включали до багатофакторної моделі з покроковим відбором.
Результати. Аналіз екстрагенітальної патології дав змогу відокремити низку клінічних чинників, асоційованих із підвищеним ризиком АЗП. Захворювання щитоподібної залози асоціювалися з підвищенням ризику АЗП у 2,25 раза; патологія серцево-судинної системи – у 2,37 раза. Прогностична цінність інфекцій, що передаються статевим шляхом, становила 2,38. За результатами LASSO-регресії (Least Absolute Shrinkage and Selection Operator) ідентифіковано найбільш інформативні предиктори: вік > 35 років, індекс маси тіла ≥ 30 кг/м², патологія щитоподібної залози, порушення мікробіоценозу піхви, самовільні викидні в анамнезі, плацентарна дисфункція, D-димер.
Висновки. Визначення основних прогностичних маркерів та проведення математичного аналізу прогнозування перинатальної патології при АЗП дало змогу оцінити предикторну потужність деяких анамнестичних показників, що сприяло створенню семифакторної прогностичної моделі АЗП.
Ключові слова: *антенатальна загибель плода, перинатальні ускладнення, плацентарна дисфункція, математичне моделювання, логістична регресія, прогнозування ризику.*

In recent decades, significant negative changes in demographic indicators have been noted not only in Ukraine, but also throughout the world. However, against the background of a decrease in natural growth, maternal, perinatal and infant mortality rates have been observed [3, 6, 23, 24]. The main reason for these changes is the development of civilization and scientific and technological progress. The routine uses of modern engineering, pharmacological and medical-biological components is becoming more accessible to all segments of the population [1, 13].

The perinatal mortality rate in some countries has decreased due to early diagnosis and the use of prognosis for some pathologies. This applies to antenatal fetal death (AFD), which has decreased by up to 1.5 times over

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the past 10 years [2, 9]. But as the perinatal mortality rate decreases, the level of neonatal disability increases [11, 23]. Thus, in Western European countries, when early signs of fetal distress are detected, an emergency cesarean section is performed, regardless of the relative risk of postnatal complications [14, 18, 25]. Therefore, scientists were faced with the question of how to reduce the frequency of perinatal pathology and thereby not increase the frequency of complications in the postnatal period.

On the other hand, in practical obstetrics, in order to accelerate the preliminary period and childbirth, obstetric aggression techniques are widely used, which leave an imprint on the health of newborns [9, 16, 19, 23].

Doctors resort to using tactics and methods of pregnancy and childbirth that are not always scientifically based, where the essence of the natural process of birth is lost. In addition, the routine use of obstetric aggression techniques serves to increase the frequency of lawsuits against medical personnel and fear of implementing future reproductive plans [2, 16]. On the other hand, in some situations, doctors are afraid to provide emergency medical care without the patient's written consent, which also leads to an increase in perinatal complications [5, 7, 21].

Therefore, the most promising and effective way to reduce maternal and perinatal trauma remains early prediction of perinatal pathology, especially in high-risk women, starting at the antenatal consultation stage [4, 15, 17]. But in the scientific circles of obstetrics there is no single scale for predicting perinatal pathology, which is confirmed by the European Association of Perinatal Medicine [12, 20].

Prediction of perinatal pathology should be based on determining factors that include hereditary history, social and living conditions, the presence of extragenital pathology, and the severity of obstetric and gynecological history, namely the presence of stillbirth and miscarriage, the course of the previous pregnancy, and the condition of the newborn [12, 22].

It is worth noting that among the scientific community, predicting perinatal pathology from early pregnancy remains a debatable issue. Depending on the gestational age and high-risk factors, only 10–30% of pregnant women classified as high-risk experience negative consequences for perinatal pathology [8, 10, 15].

The main goal of determining the degree of perinatal risk is early medical examination, which will allow for appropriate monitoring of the course of pregnancy, as well as differentiation of tactics for managing labor and the postpartum period.

The objective: based on retrospective analysis, develop a mathematical model for predicting AFD.

MATERIALS AND METHODS

According to the objective, we analyzed 96 medical cards for pregnancy monitoring (form No. 113/o) and pregnancy and childbirth histories (form No. 096/o) of women who were observed and gave birth in Kyiv City Maternity Hospital No. 3 in the period from 2020 to 2024. The main group (MG) consisted of women with AFD (n = 46) and the control group (CG) consisted of women with a live birth (n = 50).

Inclusion criteria: age of women from 18 to 40 years; singleton pregnancy; gestational age ≥ 22 weeks; presence of AFD (for the MG); absence of AFD and other perinatal losses in the anamnesis (for the CG); presence of a full range of clinical and obstetric documentation necessary for mathematical modeling.

Exclusion criteria: multiple pregnancy; congenital malformations and chromosomal abnormalities in the fetus; severe somatic diseases in the decompensation stage; incomplete or missing medical data necessary for statistical analysis.

The main indicators in the primary medical documentation were data on socioeconomic status, somatic (pathology of the cardiovascular system, thyroid gland, urinary tract, sexually transmitted infections (STIs), obesity) and obstetric and gynecological history (menstrual cycle disorders (MCDs), uterine leiomyoma, history of AFD, habitual miscarriage), pregnancy characteristics (preeclampsia, fetal growth retardation (FGR), placental dysfunction), and laboratory test results (D-dimer).

The construction of a logistic regression model was carried out based on retrospective analysis data with stepwise inclusion and exclusion of variables, which made it possible to identify the most informative predictors of the impact on the development of AFD and determine the appropriate regression coefficients for assessing individual risk in the early stages of gestation.

The developed model calculates an individual probability of AFD ranging from 0 to 1. For clinical interpretation, a cut-off value of 0.69 was applied. A predicted probability ≥ 0.69 was classified as a high-risk category, whereas values < 0.69 were classified as low risk. Intermediate risk categories were not defined in order to ensure clear clinical decision-making.

To assess the strength of associations between potential risk factors and AFD, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. In the case of a small number of observations or a rare event, logistic regression with Firth penalty was used, which allowed to reduce the bias of parameter estimates.

The analysis of risk factors for AFD was performed using logistic regression models. In the first stage, a univariate analysis was performed for each potential predictor. Variables that demonstrated statistical significance were included in a multivariate model with stepwise selection, using the inclusion criteria of $p < 0.05$ and exclusion criteria of $p > 0.15$.

To select a set of factorial features associated with the risk of developing AFD, the LASSO (Least Absolute Shrinkage and Selection Operator) regularization method was used. This approach allowed us to objectively determine the factors with the greatest prognostic value and reduce the impact of multicollinearity between variables. The regression coefficients were estimated using the Wald test with the determination of p-values and 95% CI. To establish the optimal threshold value of the prediction probability, the Youden index was used, which ensured maximum diagnostic efficiency of the model. Model adequacy was assessed using the likelihood ratio chi-square test.

For the purpose of practical implementation, the developed predictive model was primarily developed and statistically validated using the EZR v.1.54 software package, then was adapted as an interactive tool based on Microsoft Excel, which provided automated calculation of individual risk of AFD.

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RESULTS AND DISCUSSION

When conducting a retrospective analysis of medical records, it was found that the average age of women in the MG was 31.2 ± 2.3 years; in the CG – 30.4 ± 1.9 years ($p < 0.05$).

Socio-demographic analysis showed that women in the CG were significantly more likely to be in a registered marriage compared to the MG (41 (82.0%) vs 24 (52.2%) women; $p < 0.05$), while in the MG, civil marriages and single mother status were more common (7 (15.2%) women). Most of the respondents lived in urban areas, had higher education and permanent employment without intergroup differences ($p > 0.05$), however, women in the CG were more likely to work in the civil service, while in the MG, physical labor prevailed.

It was found that the absence of legal marital relations was associated with a significant increase in the probability of AFD – by 5.5 times ($p < 0.001$), which indicated a significant role of socio-psychological determinants in the formation of an unfavorable course of pregnancy (Table 1).

Among extragenital pathologies in women of the MG, thyroid diseases significantly prevailed (16 (34.8%) vs 9 (18.0%) women; $p < 0.05$); cardiovascular system diseases (13 (28.3%) vs 6 (12.0%) women; $p > 0.05$); urinary system pathology (14 (30.4%) vs 5 (10.0%) women; $p < 0.05$); varicose veins of the lower extremities (12 (26.1%) vs 7 (14.0%) women; $p < 0.05$) and metabolic syndrome (11 (23.9%) vs 3 (6.0%) women; $p < 0.05$).

Univariate analysis of extragenital pathology allowed us to isolate a number of clinical factors associated with an increased risk of AFD. Thus, the presence of thyroid diseases was accompanied by a tendency to increase the risk of AFD by 2.25 times ($p = 0.052$). Cardiovascular pathology was significantly associated with an increase in the risk of AFD by 2.37 times ($p = 0.039$). At the same time, the presence of urinary tract diseases significantly increased the probability of AFD by 3.17 times ($p = 0.004$).

Obesity (body mass index (BMI) ≥ 30 kg/m^2) was an independent risk factor for AFD, increasing its probability by 3.48 times ($p = 0.031$). In addition, obesity was often combined with gestational complications, such as preeclampsia (4 (8.7%) women) and gestational diabetes mellitus (3 (6.5%) women), which could potentiate the development of placental dysfunction and perinatal loss.

Among gynecological pathologies in women of the MG, a high percentage of inflammatory diseases of the genital tract was noteworthy. In particular, nonspecific inflammatory diseases of the vagina and cervix were found 2.1 times more often compared to the CG (MG – 27 (58.7%), CG – 14 (28.0%) women; $p < 0.05$). In particular, STIs were found in every 5th woman of the MG (9 (19.6%) vs 3 (6.0%) women; $p < 0.05$). Uterine leiomyoma occurred in a fourth of women of the MG, which is 2.4 times more often compared to the CG (MG – 11 (23.9%), CG – 5 (10.0%) women; $p < 0.05$).

Every 5th woman in the MG reported MCDs (9 (19.6%) vs 4 (8.0%) women; $p < 0.05$). The main clinical manifestations were: dysmenorrhea (6 (13.0%) women), anovulatory menstrual cycle (3 (6.5%) women), intermenstrual uterine bleeding (2 (4.3%) women).

The prognostic value of STIs was manifested in a statistically significant increase in the risk of AFD (OR = 2.38; $p = 0.017$). At the same time, the degree of this risk was significantly lower compared to nonspecific disorders of the vaginal microbiocenosis (OR = 4.95), which probably had differences in the pathogenetic mechanisms of influence.

Statistical analysis of factors such as uterine leiomyoma and MCDs showed a tendency towards an increased risk of AFD (OR = 2.63 and 2.55, respectively), however, the results obtained did not reach a statistically significant level ($p = 0.103$ and 0.082, respectively).

Evaluating the obstetric history, the following results were obtained: spontaneous miscarriages were recorded in the history of every 6th case of the MG (8 (17.4%) women),

Table 1

Results of logistic regression analysis of risk factors for AFD

Indicators	Model coefficient value, b ± m	p-value	OR indicator (95% CI)	AUC
Age < 35 years	–0.75 ± 0.70	0.284	0.47 (0.12–1.86)	0.773 (0.503–1.000)
Age > 35 years	0.01 ± 0.05	0.908	1.01 (0.91–1.11)	0.514 (0.403–0.624)
Marital status (single)	1.71 ± 0.44	< 0.001	5.50 (2.31–13.10)	0.676 (0.602–0.75)
History of spontaneous miscarriages	0.82 ± 0.36	0.025	2.27 (1.11–4.63)	0.601 (0.515–0.687)
Obesity (BMI ≥ 30 kg/m^2)	1.25 ± 0.58	0.031	3.48 (1.12–10.90)	0.576 (0.517–0.635)
Thyroid pathology	0.81 ± 0.42	0.052	2.25 (0.99–5.12)	0.58 (0.504–0.656)
Pathology of the cardiovascular system	0.86 ± 0.42	0.039	2.37 (1.04–5.38)	0.586 (0.51–0.662)
Urinary tract pathology	1.15 ± 0.40	0.004	3.17 (1.46–6.87)	0.63 (0.55–0.71)
STIs + non-specific	0.87 ± 0.36	0.017	2.38 (1.16–4.85)	0.606 (0.52–0.692)
MCD	0.97 ± 0.59	0.103	2.63 (0.83–8.36)	0.553 (0.497–0.609)
Uterine leiomyoma	0.94 ± 0.54	0.082	2.55 (0.89–7.33)	0.56 (0.5–0.621)
Disorders of the vaginal microbiocenosis	1.60 ± 0.39	< 0.001	4.95 (2.33–10.50)	0.684 (0.602–0.766)
Preeclampsia	1.43 ± 0.58	0.013	4.20 (1.36–13.00)	0.594 (0.533–0.654)
FGR / placental dysfunction	2.05 ± 0.76	0.007	7.75 (1.73–34.7)	0.602 (0.549–0.655)

Notes: AFD – antenatal fetal death; BMI – body mass index; STIs – sexually transmitted infections; MCD – menstrual cycle disorder; FGR – fetal growth retardation; b – logistic regression coefficient; m – standard error; OR – odds ratio; CI – confidence interval; AUC – area under the curve.

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Table 2

Coefficients of the logistic regression model for predicting the risk of AFD

Factorial features	Model coefficient value, b ± m	p-value	OR indicator (95% CI)
Age > 35 years	1.06 ± 1.09	0.333	2.87 (0.39–31.59)
Obesity (BMI ≥ 30 kg/m²)	–0.77 ± 0.81	0.341	0.46 (0.09–2.33)
Thyroid disorders	0.04 ± 0.65	0.949	1.04 (0.28–3.7)
Disorders of the vaginal microbiocenosis (vaginal dysbiosis)	1.75 ± 0.59	0.003	5.74 (1.87–19.84)
History of spontaneous miscarriages	0.90 ± 0.58	0.12	2.47 (0.8–8.05)
FGR / placental dysfunction	1.51 ± 0.93	0.105	4.55 (0.85–37.6)
D-dimer	0.33 ± 0.06	< 0.001	1.4 (1.25–1.6)

Notes: AFD – antenatal fetal death; BMI – body mass index; FGR – fetal growth retardation; b – logistic regression coefficient; m – standard error; OR – odds ratio; CI – confidence interval.

in particular, repeated cases of stillbirth were indicated in 2 patients (2 (4.3%) women); artificial abortions were experienced by every 4th woman in the MG (11 (23.9%) vs 6 (12.0%) women, respectively).

The course of this pregnancy in women of the MG was characterized by the occurrence of certain complications that could affect placental perfusion disorders. Among the frequent complications, the following were distinguished: threatened miscarriage (18 (39.1%) vs 5 (10.0%) women, respectively); hypertensive disorders during pregnancy (10 (21.7%) vs 3 (6.0%) women, respectively); placental dysfunction (11 (23.9%) vs 2 (4.0%) women, respectively); anemia of pregnancy (12 (26.1%) vs 8 (16.0%) women, respectively).

Based on univariate analysis, it was found that hypertensive disorders during pregnancy had high prognostic significance among pregnancy complications, which were associated with an increase in the probability of the risk of AFD by 4.20 times ($p = 0.013$), FGR and signs of placental dysfunction – by 7.75 times ($p = 0.007$).

Based on the results of LASSO regression, the most informative predictors were identified, which ensured increased stability and predictive accuracy of the model (Table 2).

The constructed multivariate logistic regression model is statistically adequate ($\chi^2 = 94.218$; df (degrees of freedom) = 7; $p < 0.001$) and includes seven independent predictors. The greatest contribution to the formation of the risk of AFD was made by disorders of the vaginal microbiocenosis and the presence of placental dysfunction, while obesity demonstrated an inverse relationship with the obtained result. The following logistic regression equation was derived, where $\text{logit}(P_{AFD})$ represents the natural logarithm of the odds of adverse fetal outcome:

$$\text{logit}(P_{AFD}) = -5.795 + 1.056 \times X_1 - 0.775 \times X_2 + 0.042 \times X_3 + 1.747 \times X_4 + 0.905 \times X_5 + 1.515 \times X_6 + 0.334 \times X_7,$$

where:

X_1 – age > 35 years;
X_2 – BMI ≥ 30 kg/m²;
X_3 – pathology of the thyroid gland;
X_4 – disorders of vaginal microbiocenosis;
X_5 – history of spontaneous miscarriages;
X_6 – FGR / placental dysfunction;
X_7 – the level of D-dimer;
P_{AFD} – probability of AFD.

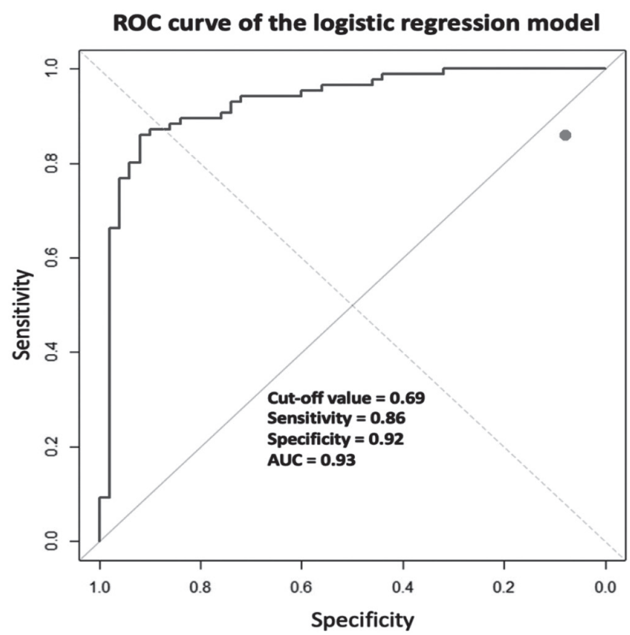

Fig. 1. ROC curve of a multifactorial model for predicting the risk of AFD with determination of the optimal boundary

Notes: ROC – Receiver Operating Characteristic; AFD – antenatal fetal death; AUC – the area under the ROC curve.

The constructed model was characterized by high discriminatory power: the area under the ROC (receiver operating characteristic) curve (AUC) was 0.93 (95% CI: 0.88–0.978), which confirms its high accuracy in predicting the development of AFD. The ROC curve of the model is shown in Fig. 1.

When using a cutoff value of 0.69, the seven-factor logistic model for predicting AFD was characterized by high sensitivity – 92.0% (95% CI: 80.8–97.8%) and specificity – 86.0% (95% CI: 76.9–92.6%). The positive and negative predictive values of the model were 79.3% (95% CI: 66.6–88.8%) and 94.9% (95% CI: 87.4–98.6%), respectively.

For the purpose of convenience for practical use, a logistic model for estimating the AFD was developed and adapted for implementation using Microsoft Excel software (Fig. 2, 3).

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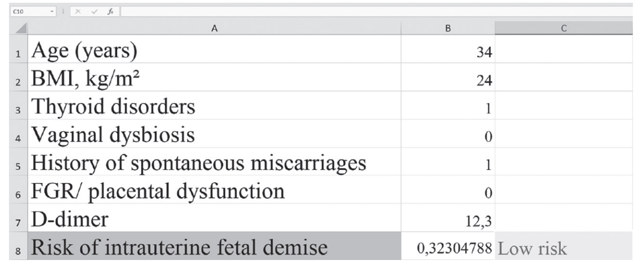
	A	B	C
1	Age (years)	34	
2	BMI, kg/m²	24	
3	Thyroid disorders	1	
4	Vaginal dysbiosis	0	
5	History of spontaneous miscarriages	1	
6	FGR/ placental dysfunction	0	
7	D-dimer	17,8	
8	Risk of intrauterine fetal demise	0,749735102	High risk

Fig. 2. Interface of the AFD forecasting system in Microsoft Excel software. High risk calculation

Notes: AFD – antenatal fetal death; BMI – body mass index; FGR – fetal growth retardation.



	A	B	C
1	Age (years)	34	
2	BMI, kg/m²	24	
3	Thyroid disorders	1	
4	Vaginal dysbiosis	0	
5	History of spontaneous miscarriages	1	
6	FGR/ placental dysfunction	0	
7	D-dimer	12,3	
8	Risk of intrauterine fetal demise	0,32304788	Low risk

Fig. 3. Interface of the AFD forecasting system in Microsoft Excel software. Low risk calculation

Notes: AFD – antenatal fetal death; BMI – body mass index; FGR – fetal growth retardation.

This model for predicting the risk of AFD can be adapted for use by practicing physicians in antenatal clinics, based on anamnestic and clinical data, and provide opportunities for the introduction of preventive measures in the early stages of pregnancy.

Thus, the use of a mathematical model for predicting perinatal pathology is a promising tool for modern obstetrics, ensuring a transition to a personalized approach to risk assessment [10, 22]. The use of a multivariate logistic model with high discriminant ability (AUC = 0.93) allows identifying women with an increased probability of developing perinatal complications, in particular AFD, even at the pre-pregnancy stage [4, 15]. Integration of clinical, anamnestic and laboratory indicators into a single prognostic system contributes to the objectification of perinatal risk stratification and forms the basis for the timely implementation of individualized preventive and therapeutic measures. Practical implementation of the model in the form of an automated prediction tool expands the possibilities of clinical decision-making and increases the efficiency of managing women with a history of AFD [17, 22].

CONCLUSIONS

The conducted univariate logistic regression analysis of risk factors for AFD allowed us to determine and assess the predictive power of some anamnestic indicators, namely: thyroid diseases increased the risk of AFD by 2.25 times ($p = 0.052$), cardiovascular system pathology – 2.37 times ($p = 0.039$), urinary tract diseases – 3.17 times ($p = 0.004$), obesity – 3.48 times ($p = 0.031$).

The prognostic value of gynecological pathology indicated an increased risk of AFD, namely: STIs (OR = 2.38; $p = 0.017$), nonspecific inflammatory diseases of the vagina and cervix (OR = 4.95; $p < 0.001$), MCDs (OR = 2.63; $p = 0.103$), and uterine leiomyoma (OR = 2.55; $p = 0.082$).

Reproductive losses in history confirmed the prognostic significance in this pregnancy, and it was found that spontaneous miscarriages in history are a statistically significant risk factor associated with an increase in the odds of developing the event by 2.27 times (OR = 2.27; $p = 0.025$), but are characterized by moderate discriminatory ability as an individual predictor (AUC = 0.601). Among the gestational complications during this pregnancy, conditions with high prognostic value were identified, which include hypertensive disorders during pregnancy (OR = 4.20; $p = 0.013$) and placental dysfunction (OR = 7.75; $p = 0.007$).

The use of LASSO regression allowed us to form a stable seven-factor predictive model of AFD with high sensitivity (95% CI: 80.8–97.8%), specificity (95% CI: 76.9–92.6%), and predictive value, which confirms its clinical effectiveness. Adaptation of the model for practical application in the Microsoft Excel environment makes it a convenient tool for individual assessment of AFD risk in everyday clinical practice.

Conflict of interest. The authors declare no conflicts of interest.

Information about the authors

Hychka Nazarii M. – Bogomolets National Medical University, Kyiv. *E-mail: ag3nmu@gmail.com*
ORCID: 0000-0001-9863-6207
Beniuk Svitlana V. – Bogomolets National Medical University, Kyiv; tel.: (067) 900-67-67. *E-mail: sbenyuk@ukr.net*
ORCID: 0000-0003-4273-3934
Kovaliuk Tetiana V. – Bogomolets National Medical University, Kyiv; tel.: (066) 422-47-21. *E-mail: likargyn@gmail.com*
ORCID: 0000-0001-9339-881X
Solskyy Sergiy Ya. – Bogomolets National Medical University, Kyiv; tel.: (050) 310-08-65. *E-mail: solskyys@gmail.com*
ORCID: 0009-0002-9977-6505
Komar Viktoria M. – Bogomolets National Medical University, Kyiv; tel.: (066) 032-41-70. *E-mail: vickimd12@gmail.com*
ORCID: 0009-0008-7193-1984
Kovaliuk Dmytro O. – National Technical University of Ukraine “Igor Sikorsky Kyiv Polytechnic Institute”; tel.: (067) 938-09-80. *E-mail: dmytro.kovalyuk@gmail.com*
ORCID: 0000-0002-9729-1443
Chebotarova Antonina S. – Bogomolets National Medical University, Kyiv; tel.: (093) 833-09-55. *E-mail: doctortonya@ukr.net*
ORCID: 0000-0003-4365-2685

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Відомості про авторів

Гичка Назарій Михайлович – Національний медичний університет імені О. О. Богомольця, м. Київ. *E-mail: ag3nmu@gmail.com*

ORCID: 0000-0001-9863-6207

Бенюк Світлана Василівна – Національний медичний університет імені О. О. Богомольця, м. Київ; тел.: (067) 900-67-67. *E-mail: sbenyuk@ukr.net*

ORCID: 0000-0003-4273-3934

Ковалюк Тетяна Володимирівна – Національний медичний університет імені О. О. Богомольця, м. Київ; тел.: (066) 422-47-21. *E-mail: likargyn@gmail.com*

ORCID: 0000-0001-9339-881X

Сольський Сергій Якович – Національний медичний університет імені О. О. Богомольця, м. Київ; тел.: (050) 310-08-65. *E-mail: solskyys@gmail.com*

ORCID: 0009-0002-9977-6505

Комар Вікторія Миколаївна – Національний медичний університет імені О. О. Богомольця, м. Київ; тел.: (066) 032-41-70. *E-mail: vickimd12@gmail.com*

ORCID: 0009-0008-7193-1984

Ковалюк Дмитро Олександрович – Національний технічний університет України «Київський політехнічний інститут імені Ігоря Сікорського»; тел.: (067) 938-09-80. *E-mail: dmytro.kovalyuk@gmail.com*

ORCID: 0000-0002-9729-1443

Чеботарьова Антоніна Сергіївна – Національний медичний університет імені О. О. Богомольця, м. Київ; тел.: (093) 833-09-55. *E-mail: doctortonya@ukr.net*

ORCID: 0000-0003-4365-2685

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