"Karaganda Medical University" NC JSC

ABSTRACT

Dissertation for the degree of Doctor of Philosophy (PhD)
Specialty: 8D10100 – Medicine

Title: "Multifactorial prediction of the risk of reproductive loss in women"

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Relevance

Currently, the program of the national strategy for the protection of reproductive health of women in Kazakhstan is being implemented in accordance with current regulations, including the Law "On Protection of Health of Citizens in the Republic of Kazakhstan" and "Message of the President to the People of Kazakhstan". One of the main goals of this program is to improve the reproductive health of women in the country.

Miscarriage is a major problem in obstetrics and gynecology that has a significant impact on women's reproductive health in modern times. This condition occurs in approximately 10% to 25% of pregnancies [1]. According to the European Society for Reproductive Medicine and Embryology, repeated pregnancy loss is defined as two or more unsuccessful pregnancy outcomes within the first 12 weeks of gestation [2]. Globally, approximately 10% to 12% of women experience early miscarriages and 1% to 4% suffer from recurrent miscarriage during their childbearing years [3]. Disruption of the balance between fibrin formation and breakdown leads to a hypercoagulable state and thrombophilia, resulting in microthrombosis at the implantation site, which can lead to implantation failure and recurrent miscarriage [4].

The prerequisites for this study are the frequent cases of reproductive loss in the Karaganda region. A study conducted in 2019 found that, on average, more than 30% of pregnant women's visits to medical institutions in the region in the first trimester were associated with an unviable pregnancy, and there has been an annual increase of 6.7% in this trend. Systemic and local inflammatory processes play a crucial role in the successful implantation of the embryo and the establishment of a healthy gestation. The maintenance of homeostatic equilibrium between procoagulant markers, such as plasminogen activator inhibitor-1 (PAI-1) and thrombomodulin (TM), and anti-inflammatory mediators like interleukin-6 (IL-6) is essential for the progression of a normal pregnancy.

Pregnancy with its characteristic hypercoagulation, even under physiological conditions, is accompanied by an increase in coagulation markers. This should be taken into account when evaluating markers of thrombophilia in pregnant women. However, an increase in the levels of molecular markers in uncomplicated pregnancy is noted no earlier than the second trimester of pregnancy. A violation of the balance of procoagulant, anticoagulant, and pro-inflammatory activity at the stage of trophoblast invasion and implantation may cause incomplete implantation of the fetal egg into the endometrium and predestine the subsequent development of gestational complications [6]. Coagulation and fibrinolytic potential undergo certain changes during pregnancy, which requires a detailed assessment of their role in predicting unfavorable reproductive outcomes in early pregnancy [7]. It has been proven that a normal pregnancy leads to a shift in maternal plasma towards a state of hypercoagulation in preparation for hemostasis after childbirth [8]. The balance between coagulation and fibrinolysis is an important part of early pregnancy, and it is assumed that thrombophilia contributes to the pathophysiology of premature birth [9]. Insufficient trophoblast invasion plays an important role in the pathogenesis of repeated pregnancy loss due to the increased presence of

microthrombi in the vessels of the decidual tissue [10]. Women of reproductive age with a history of premature birth are at increased risk of complications during subsequent pregnancies compared to the general population [11].

Research Objective

To evaluate the integrative significance of the influence of laboratory and socio-clinical factors on the risk of reproductive losses in early pregnancy.

Research Tasks

1. Analyze the prognostic significance of indicators of coagulation potential disorders, including parameters of coagulogram and platelet hemostasis, in assessing the risk of reproductive losses.

2. Investigate the relationship between prognostic laboratory blood markers — thrombomodulin, interleukin-6 and plasminogen activator inhibitor-1 — and histopathological changes in reproductive losses in early pregnancy.

3. Assess the influence of socio-clinical factors on the risk of reproductive losses in early gestation.

4. Develop a predictive model based on the logistic regression equation to assess the risk of gestational loss in the presence of endothelial dysfunction of the endometrium in women of reproductive age at the stage of pre-pregnancy training.

5. Develop and implement a screening algorithm for screening women of reproductive age at the pre-pregnancy stage in order to identify risk factors for adverse reproductive outcomes early.

Scientific Novelty

1. For the first time, an analysis of the relationship between biochemical, histopathological and social factors in a vulnerable group of women of reproductive age was carried out with the development of screening forecasting the risk of reproductive losses at the pre-pregnancy stage.

2. For the first time, the association of biochemical markers thrombomodulin and interleukin - 6 with histological pregnancy outcomes (hemorrhagic and inflammatory changes, respectively).

3. For the first time, the reference values of the biochemical predictors thrombomodulin and interleukin-6 were identified with the determination of their clinical, diagnostic and practical significance in predicting reproductive losses.

4. For the first time, a logistic regression model for predicting the risks of reproductive losses was developed based on laboratory predictors (interleukin-6 and thrombomodulin) with high sensitivity (Se-90%), specificity (Sp-93%) and correctness of case classification (92%).

Key Findings for Defense

1. Thrombomodulin is the main prognostic predictor in the diagnosis of hemorrhagic/ischemic changes and/or impaired vasculogenesis, such as early vascular karyorexis, interstitial hemorrhage, hemorrhagic gestational endometrium, parabasal infarcts and hemorrhages in the basal lamina with parabasal necrosis, severe hypoplasia of chorionic villi and avascular villi. As a result of the listed endometrial vasculopathies, an increase in thrombomodulline was noted by 64.5% (Me = 8,360 [Q1: 7,120–Q3:9,030], p = 0.001) in comparison with the other study groups. Statistically significant changes in thrombomodulin parameters were

revealed at the site of coagulopathic defect of the uterine endothelium due to hemorrhagic and ischemic disorders of vasculogenesis.

2. The presence of endothelial dysfunction of inflammatory origin in the form of acute and chronic villitis, acute intervillositis, massive perivillous fibrin deposition, chronic histiocytic intervillositis, lymphoplasmocytic deciduitis, decidual vasculitis in women with increased interleukin-6 levels was established (Me = 7,090 [Q1: 5,730–Q3: 8,715], p = 0.001) by 66.5 % compared to the rest of the study groups. This fact confirms the hypothesis of the development of inflammatory disorders of the endometrial endothelium - villitis, vasculitis with mobilization of the immune response in the vascular bed (increased production of interleukin-6).

3. Association of laboratory markers - thrombomodulin (AUC = 0.836, p < 0.001, 95% CI:0.742- 0.9072) and interleukin-6 (AUC = 0.830, p < 0.001, 95% CI:0.735-0.902) with socio-clinical factors: the number of pregnancies (OR - 2.0255, 95% CI; 0.9149 - 4.4839; p level - 0.081) and body mass index (OR - 1.1606, 95% CI; 0.8985 - 1.4997; p level - 0.025) are predictors of early detection of the risk of reproductive losses at the pre-pregnancy stage. The developed logistic regression model had high classification accuracy (92.05%), and diagnostic accuracy along the ROC curve (AUC 0.964, 95% CI 0.901-0.992; p < 0.0001) indicated reliability as a tool for predicting reproductive losses.

4. The developed screening algorithm for the examination of women of reproductive age allows predicting the risk of reproductive loss with high accuracy (correctly classified cases - 87.05%), has a high "sensitivity" (Se - 87.3%) and "specificity" (Sp - 86.8%).

Practical Significance

The clinical, diagnostic and prognostic significance of determining the levels of interleukin-6 and thrombomodulin in combination with the results of histological examination in women with a history of reproductive losses has been demonstrated. A comprehensive assessment of these indicators makes it possible to identify groups of women with an increased risk of gestational loss and can be used for early prediction of adverse pregnancy outcomes. The results of the dissertation research were implemented at the outpatient stage of the examination of patients at the Karaganda Railway Hospital LLP, KGP Multidisciplinary Hospital No. 1.

Based on the results of the study, a screening algorithm for predicting the risk of reproductive losses at the pre-pregnancy stage of women's examination was developed and implemented at the outpatient level of KGP "Multidisciplinary Hospital No. 1" in Karaganda and LLP "Karaganda Railway Hospital". The implementation of this algorithm has made it possible to increase the effectiveness of detecting women with signs of endothelial dysfunction, considered as one of the pathogenetic mechanisms of gestational loss, which is confirmed by the results of ultrasound examination methods.

The introduction of a predictive model for stratification of the risk of developing reproductive losses contributes to early prediction of the risk of developing an unfavorable pregnancy outcome in women of reproductive age.

Contribution of the author of the thesis

All the data used in the work were obtained with the participation of the author, who personally conducted a questionnaire survey of women with early reproductive losses, collected and processed primary materials, as well as analyzed and summarized the results. Based on the conducted review of the scientific literature on the research topic, hypotheses, goals and objectives of the conducted research have been developed. The conducted laboratory and histopathological studies were conducted with the direct participation of the dissertator. Based on the data obtained, the author analyzed the results and statistically processed the data, the results of which are presented in the conclusions and practical recommendations. The main directions of improving the early prognosis of reproductive losses in women at the pre-pregnancy stage are scientifically substantiated.

The approval of the thesis

The key points of the dissertation were introduced, presented, and debated at the following events:

- 33rd Annual Scientific and Practical Conference of the European Society for Gynecological Endoscopy (ESGE), Marseille, France, October 27–30, 2024;
- Extensive meeting of the departments of internal medicine, obstetrics, gynecology, and perinatology (Minutes No. 5, December 26, 2024).

Publications

In accordance with the materials provided for the dissertation research, a single publication has been published in a journal indexed in the Scopus database (29th percentile impact factor) and the Web of Science Core Collection (Q3 ranking). Additionally, four publications have been published in journals endorsed by the Committee for Supervision in the field of science and higher education under the jurisdiction of the Ministry of Education and Science of the Republic of Kazakhstan. Furthermore, two abstracts have been presented at an international conference, and three certificates of registration of intellectual property rights have been obtained.

Certificates of Copyright

1. Certificate No. 53075, issued on December 27th, 2024: Mathematical Model of Logistic Regression for Predicting the Risk of Reproductive Losses during the Pre-Pregnancy Stage.
2. Certificate No. 53690, issued on January 21st, 2025: Screening for Predicting Reproductive Loss Risk.
3. Certificate No. 55077 issued February 24th, 2025. It pertains to the reference values of thrombomodulin and interleukin-6, which serve as predictive indicators of the risk of reproductive failure in women at the preconception stage.

Materials and research methods

A retrospective and prospective case-control study [7] was conducted in accordance with ethical principles. Informed consent was obtained from all participants in the study. The research protocol was approved by the Bioethics Committee Protocol No. 18 dated 04/14/2021.

The study was conducted at the clinical bases of KGP "Regional Clinical Hospital", KGP "Multidisciplinary Hospital No. 1, LLP "Karaganda Railway Hospital" in Karaganda, Republic of Kazakhstan, from 2020 to 2023. The study was conducted in accordance with the Helsinki Declaration (2013) of the World Medical Association. The study was approved by the Ethics Committee of the Medical School of the NAO "Karaganda Medical University, Protocol No. 23).

Stages of the study

To achieve the set goals and objectives, a research strategy has been defined, which includes 2 interrelated stages. At the first stage, a retrospective analysis of medical documentation was performed, including a study of the inpatient's medical record and the exchange card of the pregnant and maternity patient. The second stage of the study was prospective and included the formation of a sample of patients followed by statistical analysis of socio-clinical, laboratory and histological data.

The first stage was to analyze the prognostic significance of the violation of coagulation potential markers, a one-stage retrospective study was performed.

The study included 215 women of fertile age, divided into two groups.

Group 1 (observations) consisted of 127 patients of fertile age who sought medical help at the gynecological department of the Karaganda Regional Clinical Hospital in the period from 2020 to 2022. The reason for the appeal was reproductive losses during pregnancy up to 12 weeks in the presence of a history of two or more adverse pregnancy outcomes.

Group 2 (comparison) included 88 women of fertile age without a burdened obstetric history who were under dispensary supervision for pregnancy for up to 12 weeks at the KGP "Multidisciplinary Hospital No. 1" for the same time period. This group was formed as a comparison group.

All women underwent a retrospective assessment of the results of laboratory tests, reflected in the medical record of the inpatient (group 1) and the exchange card of the pregnant woman and the maternity ward (group 2). Additionally, an analysis of the course and outcome of pregnancy in group 2 patients was performed. The criterion for a favorable outcome was timely physiological delivery during full-term pregnancy without clinical signs of gestosis (data were also obtained from the exchange card of the pregnant woman and the maternity hospital). The laboratory research data obtained as a result of a retrospective analysis has been subjected to statistical processing in order to determine their prognostic significance.

The second stage: A prospective case-control study.

The first step.

The study included 271 women of reproductive age. To participate in the study, patients with clinical diagnoses were included: "undeveloped pregnancy", "spontaneous abortion that has begun", "abortion in progress", as well as patients who applied for voluntary termination of pregnancy with a gestation period of up to 12 weeks. The average age of the examined persons was 28 ± 6 years. Verification of the clinical diagnosis was carried out on the basis of data from a clinical examination and the conclusion of a routine ultrasound examination of

pregnant women in the first trimester, performed at the hospital admission department level.

To achieve the goal of analyzing the impact of socio–clinical factors on the development of RP, upon admission, a thorough analysis of EPR and medical documentation was carried out in order to determine compliance with the inclusion criteria of this study. During the registration of the inpatient's medical record, a standardized survey of the patient was carried out. Obtaining informed consent was a prerequisite for the inclusion of patients in the study. The data obtained for structuring information were entered into a table, which was divided into blocks: block 1 – "passport part" – included full name and age; block 2 – "medical history and objective data" – included information about height, weight, smoking, pregnancy parity; block 3 – "social part" – characterized working conditions the interviewees. Based on height and weight data, BMI was calculated using standardized protocols. Based on the data of the medical history, the medical record of the inpatient patient and the EPZ, socio-clinical information was collected for subsequent statistical analysis of the influence of the studied factors on the outcome of pregnancy.

After completing the initial examination and obtaining informed consent, venous blood was taken on an empty stomach for laboratory tests. Taking into account the clinical verification of the condition (the presence of an unfavorable pregnancy outcome, or voluntary termination of pregnancy at up to 12 weeks), blood sampling was performed simultaneously to perform routine laboratory tests. The list includes: a general blood test (assessment of the level of leukocytes and platelets) and a coagulological examination (PV, APTT, fibrinogen level, PTI). The concentration of the studied markers was quantified by enzyme immunoassay using standard commercial kits: ELISA Kit for Thrombomodulin (TM) 96T, ELISA Kit for Interleukin-6 (IL-6) 96T and ELISA Kit for Plasminogen Activator Inhibitor-1 (PAI-1) 96T (Cloud&Clone Corp., China). All studies were performed in accordance with the manufacturer's instructions on the basis of the laboratory of collective use of the NAO "Karaganda Medical University" with the direct participation of the author of the study.

Ultrasound examination.

The study was performed once upon admission of the patient to the hospital and was a mandatory component. The examination was performed using transvaginal and transabdominal sensors, which provided a comprehensive assessment of the embryo and extra-embryonic structures in the uterine cavity. The key diagnostic criterion was the assessment of the cardiac activity of the embryo. The absence of cardiac activity during confirmed imaging of the embryo was regarded as a sign of fetal death and served as the basis for verifying the diagnosis of an undeveloped pregnancy. One of the mandatory conditions for inclusion in the control group of the study was the presence of a uterine pregnancy, confirmed by ultrasound examination for up to 12 weeks of gestation. To this end, before the artificial termination of pregnancy at the request of the woman, a control ultrasound examination was performed to verify the compliance of the fetus with

the gestational age, the absence of delayed internal development, as well as the absence of genetic abnormalities in fetal development.

Histological examination of tissues

The biological material obtained by the author as a result of medical termination of pregnancy, vacuum aspiration or curettage of the uterine cavity was sent to the pathology unit of the Regional Clinical Hospital. The processing of the material was carried out in accordance with the applicable national standards. After completing a routine histological examination and forming a pathoanatomical conclusion, the paraffin blocks and micro-preparations were removed by the author for a second expert assessment. The Regional Clinical Hospital is the clinical base of the NAO Karaganda Medical University, which provided the opportunity for further analysis of the material on the basis of the University's pathology unit. The re—examination of the seized histological preparations was carried out in full on the basis of the pathology unit of the NAO "Karaganda Medical University" clinic under the supervision of the head of the department, a pathologist of the highest category, PhD, associate Professor E.K. Kamyshansky. According to the results of the histological examination, all participants were divided into subgroups.

The second step.

After the distribution of the study participants into subgroups based on the results of the histomorphological features of the studied material, an in-depth comparative analysis was conducted.

Subgroup 1 (n = 106) — "Chorionic villi branching disorders and chorionic dysmorphic villi" — and subgroup 3 (n = 39) — "Other changes: reactive cellular infiltration in decidual tissue, chorionic villi edema" — were characterized by the following morphological features: pronounced violations of the architecture of the villous tree with extremely uneven shapes and villous contours, the presence of at least one focus of trophoblastic invasion and/or multiple invaginations; reactive cellular infiltration of decidual tissue; chorionic villous edema with phenomena of myxoid stromal degeneration; sclerosis and fibrosis of the villi; diffuse hydropic enlargement of the villi with trophoblast hyperplasia; in some cases, neoplastic changes. Given the lack of a convincing direct pathogenetic relationship between these morphological phenomena and the probable causes of RP, as well as the high level of morphological heterogeneity of these groups, their further inclusion in the analytical model was considered methodologically inappropriate due to the risk of obtaining statistically and clinically incorrect conclusions.

For the next stage of the study, patients from subgroup 2 (n = 33) — "Inflammatory changes: acute and chronic villitis, acute intervillositis, lymphoplasmocytic deciduitis, decidual vasculitis" — and subgroup 3 (n = 25) — "Hemorrhagic/ischemic changes and/or disorders of vasculogenesis" were selected. These subgroups were combined into the main study group due to clearly differentiable histomorphological changes of an inflammatory and hemorrhagic-ischemic nature, which have a pathogenetically justified association with the development of adverse pregnancy outcomes. At the initial stage, subgroup 5 (n = 68), the "Normal decidual reaction", was considered as the control group, which included women with voluntary termination of pregnancy without signs of

pathological morphological changes. The calculation of the required sample size for the second stage of the study was performed using the Epi Info 7.0 software (Centers for Disease Control and Prevention, USA). With a given statistical power of 80%, a confidence interval of 95%, and a significance level of $\alpha = 0.05$, the estimated minimum sample size was 88 patients.

Taking into account the calculation results, the **main** group (n = 58) was formed by women with a history of two or more cases of RP, including:

• 33 patients with histologically confirmed inflammatory changes (subgroup 2 of the primary distribution);

• 25 patients with signs of vasculogenesis disorders and hemorrhagic-ischemic changes (subgroup 3 of the primary distribution).

The number of the **control** group was optimized in accordance with the calculated parameters of the study capacity and amounted to 30 women. The control group included patients with no history of adverse pregnancy outcomes who applied for voluntary termination of pregnancy at a gestation period of up to 12 weeks.

At the final stage of the second stage of the study, a comparative statistical analysis of laboratory and histological parameters of the main and control groups was performed in order to identify statistically significant patterns characterizing the mechanisms of formation of adverse pregnancy outcomes. The analysis of the influence of socio-clinical factors on the risk of developing RP has been carried out. Based on the data obtained, a statistical model of logistic regression has been developed, which makes it possible to predict the risk of developing RP. The result of the study was the formation and implementation of a screening algorithm for the examination of women of reproductive age, aimed at early identification of high-risk patients and personalization of preventive and therapeutic measures

Statistical analysis

The statistical analysis was performed using the Statistica statistical software package (Trial version https://statistica.software.informer.com/12.6 /) and IBM SPSS Statistics (Trial version 26, IBM, Armonk, NY, USA https://www.ibm.com/products/spss-statistics). All quantitative variables were analyzed to verify the distribution (Shapiro-Wilk test). The data were presented using descriptive statistics methods: for quantitative data with a different distribution from normal using Median, upper and lower quartiles (Q1 and Q3), and Range for categorical data in the form of absolute numbers and a percentage of the entire group. A comparative analysis of quantitative variables in unpaired (independent) groups with a distribution different from the normal distribution was performed using the nonparametric Mann-Whitney U-test. All p-values were adjusted for multiple pairwise comparisons of the number of tests using the Bonferroni correction ($p=0.005$). A nonparametric method of calculating the chi-square criterion was used to compare groups by categorical variables For Pearson, with the number of degrees of freedom = 1, the correction for continuity (Yates) was applied, with a small number of observations (less than 5), the exact Fisher criterion was used. ROC analysis (MedCalc https://www.medcalc.org /), was used to determine the sensitivity and specificity of biochemical predictors. Logistic

regression is a mathematical model for determining the value of a variable based on the relationship of predictors. Odds Ratio (OR) was analyzed for each statistically significant predictor. The quality of the model was assessed by the area under the curve (AUC) and using the Hosmer–Lemeshov test.

A 5-fold cross-validation (k-fold cross-validation, k=5) was used to evaluate the generalizing ability of the logistic regression model. Logistic regression was implemented using the scikit-learn library (Python, version 1.0.2), and the features (IL-6, thrombomodullin) were pre-scaled using the Standard Scaler

Research Findings

1. Platelet and fibrinogen values were statistically significantly different (p=0.01, p=0.04, respectively, at p<0.05) in pregnant women in the main and control groups. However, only the fibrinogen level had minimal prognostic value. The percentage of correct predictions based on this predictor was 63.26%, with $\chi 2$=7.283; p=0.007.

2. Thrombomodulin levels in the main group with hemorrhagic/ischemic changes and/or vasculogenesis disorders (Me = 8,360 (Q1: 7,120–Q3:9,030) were 64.5% higher than in the control group (Me = 5,390 (Q1: 5,214 – Q3: 6,300, at p = 0.001) and indicated the presence of endothelial dysfunction. There was a statistically significant difference in the level of thrombomodulin between the other compared groups: group 1 - Me = 5.496 (Q1: 5.051 –Q3: 6.219), group 2 - Me = 5.850 (Q1: 5.430 –Q3: 6.463), group 4 - Me = 5.320 (Q1:5.241–Q3: 6.667), at p = 0.001, (p<0.005).

The level of interleukin-6 in the main group with inflammatory histological changes (Me = 7,090 (Q1: 5,730–Q3: 8,715) was 66.5% higher than in the control group (Me = 4.331 (Q1: 3.362 –Q3: 6.133, p = 0.001) and indicated the presence of inflammatory disorders of the endometrial endothelium with the production of a pro-inflammatory marker. The value of interleukin-6 also significantly differed between the other groups: Group 1 - (Me = 4.044 (Q1: 3.220 –Q3: 6.119), Group 3 - (Me = 4.480 (Q1: 3.540 –Q3: 6.910), Group 4 - (Me = 4.760 (Q1:3.110–Q3: 6.234), at p = 0.001, (p<0.005).

3. Socio-clinical factors increase the risk of reproductive losses: with a history of 5 or more pregnancies (Me = 5. Q1:4–Q3: 6) 2.5 times higher than in the control group (Me = 2 (Q1:1–Q3:3), p = 0.0001); "heavy physical labor" (df=3, x2= 15.40, p = 0.03, at p<0.05) increases by 35%; "smoking" (df=1, x2= 4.73, p = 0.02 at p<0.05) increases by 21%; in women with pre–obesity (BMI 25.0 and above) (Me = 24.60. Q1:22.15-Q3: 29.31), the risk of reproductive problems is higher than in the control group (Me = 21.99 (Q1:21.3–Q3: 232), p = 0.0004); older women (over 31 years old) were more susceptible to reproductive losses (Me = 31.5 (Q1:24–Q3: 37) than in the control group (Me = 25.0 (Q1: 21–Q3:28), p = 0.0003);

4. The developed model (logistic regression equation) accurately predicts the risk of reproductive losses in the presence of endothelial dysfunction of the endometrium in women of reproductive age at the pre-pregnancy stage. The model correctly classified 92.05% of cases and the area under the logistic regression curve was AUC 0.964 (95% CI 0.901-0.992; p < 0.0001), which confirms the high

predictive ability of the model. The correct identification of persons with a history of reproductive losses was 93.1%, and of persons without a burdened history - 90.0%. The Hosmer-Lemeshev test for the developed model was $\chi 2 = 3.1611$, $p = 0.8702$, which indicates a good match to the logistic regression model.

5. A screening algorithm for the examination of women of reproductive age at the pre-pregnancy stage has been developed, which has the following statistically significant characteristics: "sensitivity" - Se - 87.3%, "specificity" - Sp - 86.8% and the percentage of correctly classified cases - 87.05%.

Practical recommendations

1. In women with a history of adverse pregnancy outcomes, the assessment of interleukin 6 and thrombomodullin levels in combination with the results of histological studies and anamnestic socio-clinical factors will reduce the risk of reproductive losses in early pregnancy.

2. Association of laboratory markers thrombomodulin - (AUC = 0.836, $p < 0.001$, 95% CI: 0.742- 0.9072) and interleukin-6 (AUC = 0.830, $p < 0.001$, 95% CI: 0.735-0.902) with socio-clinical factors: number of pregnancies (OR -2.0255, 95% CI; 0.9149 - 4.4839; p level - 0.081) and body mass index (OR -1.1606, CI 95%; 0.8985 - 1.4997; p level - 0.025) are recommended as predictors of early detection of the risk of reproductive losses at the pre-pregnancy stage.

3. The prognostic model of risk stratification of reproductive losses is recommended for predicting the risk of developing an unfavorable pregnancy outcome in women of reproductive age.

4. For outpatient practice of specialists who observe women at the pre-pregnancy stage and patients with a history of reproductive losses, a developed screening algorithm is proposed that allows detecting endometrial endothelial dysfunction in the examined patients.

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