

TOPICAL ISSUE

B.M. Gasanova, M.L. Polina, N.I. Douglas

IMPROVEMENT OF PERINATAL RESERVES
IN WOMEN WITH EXTRAGENITAL
DISEASES

DOI 10.25789/YMJ.2022.77.19

УДК 61.618.2

Risk factors were determined and a prognostic model of adverse perinatal outcomes was constructed in a sample of pregnant women with extragenital diseases (EGD) (anemia, chronic pyelonephritis, chronic arterial hypertension) by logistic regression. The search for prognostic criteria is optimal in the comprehensive examination of pregnant women with EGD (assessment of microbiome, immune status, utero-fetal-placental blood flow and placental pathomorphology).

The morphology of the placenta reflects the fullness of embryo- and fetogenesis of women with EGD, mediated by the resources of the mother's body, optimal in the dogestational recovery and prevention of placental insufficiency in the early gestation. Prediction of the risks of perinatal outcomes and morbidity in pregnant women with EGD – anemia, CP and CAG is realizable using logistic regression model resources.

Keywords: extragenital diseases, risk factors, adverse perinatal outcomes.

Improving the reserves of perinatal outcomes in women with extragenital diseases (EGD), such as chronic pyelonephritis (CP), anemia, chronic arterial hypertension (CAH), presents great difficulties due to the high frequency of pregnancy complications in women with EGD and violations of maternal-fetal-placental interaction [1].

The analysis of the completeness of the examination of pregnant women with EGD seems to be manageable from the standpoint of identifying and monitoring high-risk groups of gestational complications [7,14]. It is known that a vicious circle of pathological changes is created in the "mother-placenta-fetus" system of pregnant women with EGD, however, the nature and degree of compensatory-adaptive reactions are poorly understood [3]. The inconsistency of data on the state of the fetoplacental complex is associated with EGD duration, as well as medical tactics before and during pregnancy. The focus of scientific attention is the analysis of perinatal risks based on expanding the diagnostic capabilities of the features of uterine-fetal-placental blood flow, homeostasis, microbiota and immune status of pregnant women with EGD [6,8].

The lack of study of the morphofunctional viability of the fetoplacental complex (FPC) in pregnant women with EGD

and high infectious potential confirms the prospect for identifying predictors of placental dysfunction under conditions of endogenous intoxication and immune dysregulation. The search for highly informative clinical, instrumental and laboratory markers that allow to predict sub-optimal pregnancy outcomes antenatally will contribute to the pathogenetic therapy and the choice of an adequate method of delivery for women with EGD.

The aim of the study was to determine risk factors and prognostic criteria for adverse perinatal outcomes in pregnant women with extragenital diseases (EGD) (anemia, chronic pyelonephritis, chronic arterial hypertension).

Material and methods. The study population – 576 pregnant women with EGD (anemia (n = 62), CP (n = 135) and CAG (n = 376)) were retrospectively divided into groups depending on the results of the placental pathomorphological study.

Inclusion criteria: singleton progressive pregnancy; the woman's informed consent for the use of biological material for scientific purposes, extragenital diseases found before pregnancy and confirmed by specialists (CP, anemia).

Groups: I – pregnant women with high infectious risk (graduation was carried out on the basis of data from history, a complex of laboratory and instrumental studies) (n = 182) and PI (116 – with subcompensation, 64 – compensation); II – with compensation PI (n = 126); III – subcompensation of PI (n = 143); IV – without PI (n = 122).

Placental insufficiency was morphologically verified in 451 out of 576 examined.

Determinants of pregnancy complications and adverse perinatal outcomes were determined depending on the presence of PI.

Methods of research: assessment: lower genital microbiota (smear microscopy for the degree of purity (Gram stain), bacteriological inoculation of cervical discharge for flora and sensitivity to antibiotics, polymerase chain reaction (PCR study), molecular genetic research (Femoflor), microscopy and culture examination of urine for flora and sensitivity to antibiotics, cellular link of immunity (CD3+, CD20+, CD4+, CD16+, CD8+, CD95+, HLA-DR+)).

Immunoreactivity was studied based on the results of ELISA-detected Probably of pathology, an enzyme-linked immunosorbent assay of the number and affinity of individual embryotropic auto-antibodies interacting with embryogenesis regulatory proteins (Biopharm – test LLC).

During the screening period and according to the indications, sonography and blood flow in the mother-placenta-fetus system, cardiotocography (CTG) of the fetus were carried out. Pathomorphological examination of the placenta was carried out according to a standard scheme.

The degree of reliability and approbation of the results of the work. The statistical analysis was carried out using the IBM SPSS Statistics 23 program, parametric analysis methods in accordance with the results of checking the compared masses for the normality of distribution, descriptive statistics (arithmetic mean (M), mean error of the mean (m), Student's t-test, odds ratio (OR), confidence interval (CI, 95%).

The analysis of intergroup differences in qualitative characteristics was carried out using the criterion χ^2 , less than five – the exact two-sided Fischer test. The significance level (p) when testing statistical hypotheses was taken to be $p \leq 0.05$.

The construction of a predictive model for calculating the risk was performed us-

GASANOVA Bakhtykey Musalavovna – Candidate of Medical Sciences, Doctoral student, Medical Institute of the Peoples' Friendship University of Russia, gsbhms69@gmail.com, <https://orcid.org/0000-0001-6871-7102>; **POLINA Miroslava Leonidovna** – PhD, Medical Center for Women's Health, Moscow, <https://orcid.org/0000-0003-3883-3967>; **DOUGLAS Natalia Ivanovna** – MD, Head of the Department, Medical Institute of the M.K. Ammosov Northeastern Federal University

ing the binary logistic regression method according to the formula:

$$P = \frac{1}{1+e^{-z}}, z = a_0 + a_1x_1 + a_2x_2 + a_3x_3 + \dots + a_nx_n,$$

where p is the probability of the outcome, $x_1 \dots x_n$ are the values of the predictors in a nominal, ordinal or quantitative scale, $a_1 \dots a_n$ are the regression coefficients, using Wald statistics. The effectiveness (the proportion of correctly predicted cases of the presence and absence of the studied pathology), sensitivity (the presence of pathology), specificity (the absence of pathology), the prognostic value of a negative result (PVNR) and a positive one (PVPR) were determined, ROC analysis (receiver operating characteristic) of the error curve was done. The Area Under Curve (AUC) under the ROC curve was calculated.

Results and discussion. The condition of newborns from mothers with extragenital diseases (EGD) turned out to be worse than that of healthy women ($p < 0.05$). The need to transfer newborns to the intensive care unit (ICU) was 16.6%; at the second stage of nursing – 15.8% vs 5.9% with physiological pregnancy ($p > 0.05$); at home discharge – one and a half times less often (66.8% vs 94.1%, $p < 0.05$).

The morbidity of newborns in the sample of women with a high infectious risk was higher than with subcompensation of placental insufficiency (PI): hypotrophy and morphofunctional immaturity – twice (35.7%, $p < 0.05$) and 4.5 times (7.9%) – with PI compensation; cerebral ischemia – one and a half times (46.2%, $p < 0.05$), prematurity – twice (22.5%, $p < 0.05$), infectious and inflammatory diseases (omphalitis, conjunctivitis, vesiculosis) – three times (12.6%, $p < 0.05$).

In order to identify risk factors and predict unfavorable perinatal outcomes, the method of logistic regression was used. The calculation results are shown in Table.

The effectiveness of the prognostic model for identifying the contingent of pregnant women with EGD when calculating the risks of unfavorable perinatal outcomes is reflected by the following data: regression coefficient $B - 1.11$; Wald statistics $\chi^2 - 1.0$; Exp $B - 3.0$, Nagelkerke index – 0.79.

The calculation was carried out according to the formula:

$$P = \frac{1}{1+e^{-z}}, z = a_0 + a_1x_1 + a_2x_2 + a_3x_3 + \dots + a_nx_n,$$

Risk factors for adverse perinatal outcomes on the EGD background

Factors	Regression coefficient B	Wald statistics, χ^2	Value p	Exp B
Chronic pyelonephritis exacerbation	2.377	6.433	0.011	10.770
Bacterial vaginosis (BV) relapses + contamination of the cervical canal loci, urine	3.012	10.367	0.001	20.337
Hyporeactivity according to ELI-P test	2.405	7.522	0.006	11.078
Absence of pregravid phase / PI prevention or delayed therapy	2.015	3.822	0.047	7.500
Index "CD 4 + / CD 8+" > 1.0	1.625	4.529	0.033	5.078
Violation of hemodynamics 1B, 2nd degree	4.057	7.800	0.005	57.781
Untypical cardiotocography (CTG) type	1.608	5.084	0.024	4.992
Thinning of the placenta by sonography in the first half of pregnancy	-3.463	6.098	0.014	0.031
Weak compensatory changes in the placenta	-4.795	14.171	0.000	0.008
Inflammatory changes in the placenta	-2.563	5.928	0.015	0.077
>60% non-functional zones	2.371	5.968	0.015	10.708
Dystrophic changes in the placenta	2.871	13.267	0.000	17.661
Constant	1.112	1.047	0.03	3.039

where p is the probability of the outcome, $x_1 \dots x_n$ are the predictor values measured on a nominal, ordinal or quantitative scale, $a_1 \dots a_n$ are the regression coefficients (Figure).

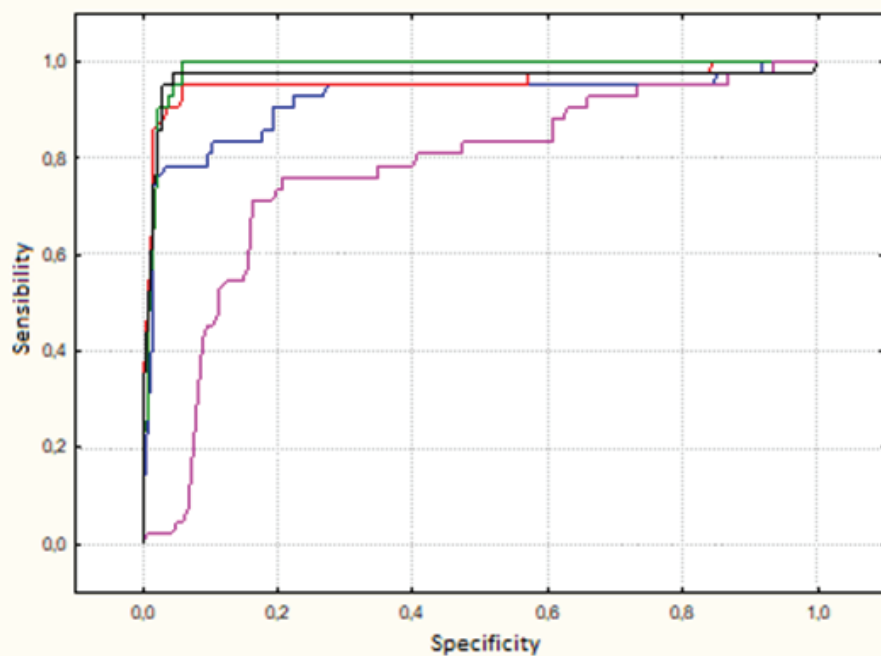
The area under the AUC curve 0.97 allows us to regard it as reliable.

The cut-off criterion ("cut-off" – 0.6) is a sign of high prognostic effectiveness of the model, which is realized when the index is more than 0.6. The high predictive value of the model with identified risk

factors is proved by the following criteria: sensitivity – 96.5%, specificity – 82.0%, diagnostic efficiency – 93.2%, positive predictive value (PPV) – 96.5%, negative predictive value (NPV) – 82.0%.

A negative effect on perinatal outcomes was found in the absence of pregravid recovery and / or placental insufficiency (PI) prevention (or delayed therapy, after the completion of the second wave of placentation) ($\chi^2 = 3.8$; $p = 0.04$).

Recovery at the pregravid stage



ROC analysis of the prognostic model (the area under the AUC curve is 0.97) for predicting unfavorable perinatal outcomes on the EGD background

among women with EGD was least often carried out in the group with a high infectious risk (17.6%): in comparison with the stage of PI subcompensation (28.7%) – 1.6 times ($p = 0.02$), compensation (78.6%) – 4.5 times ($p = 0.005$). PI prevention in early pregnancy took place among 81.0% women with EGD, twice less often – with subcompensation of placental dysfunction (40.6%) ($p = 0.0005$), a high infectious risk – 3.5 times (24.2%) ($p = 0.0005$).

Exacerbation of chronic pyelonephritis (CP) ($\chi^2 = 6.4$; $p = 0.01$) with a temperature reaction in inflammatory urine sediment negatively affected the fetal-placental interaction only in the absence of regular urine monitoring and treatment of asymptomatic bacteriuria (AB). Exacerbation of CP with bacteriuria occurred in 35.4% of pregnant women with a high infectious risk, 5.3% with PI compensation ($p = 0.001$) and 19.3% with subcompensation.

The probability of developing unfavorable obstetric outcomes with the lack of rational management tactics for pregnant women with CP was confirmed by other authors. The expediency of treating urinary tract infections [16], the prevalence of which in pregnant women reaches 10%, is explained by the risk of CP exacerbation [11].

AB requires treatment to avoid the risk of developing acute pyelonephritis in 25-30% [10]. The formation of a focus of inflammation in persistent infection is determined by the ability of uropathogenic strains to synthesize virulence factors and damage kidney tissues [15]. Bacterial contamination (pathogenic and / or conditionally pathogenic flora in a titer $> 10^4$) of several loci simultaneously (in the cervical canal, vagina, urine sediment) was detected in a third of pregnant women with a high infectious risk (32.4%), three times less often – with PI compensation ($p = 0.02$). During PCR testing, pregnant women with a high infectious risk were distinguished by infection of the cervix with herpes simplex virus (HSV2) (17.6% vs 7.3% with PI, $p = 0.05$), *Gardnerella* (26.4% vs 12.4% on average, $p = 0.0008$) and *genitalium mycoplasma* (20.3% vs 15.4% with PI subcompensation, $p = 0.002$). When calculating the factors affecting perinatal outcomes, the cumulative infection of the cervical canal, urine, and recurrence of bacterial vaginosis (BV) were identified ($\chi^2 = 10.4$, $p = 0.001$).

The role of monitoring the immunological homeostasis of pregnant women with EGD in predicting gestational complications – PI, prematurity as a consequence

of a maladaptive state uncorrected at the pregravid stage – turns out to be important [12]. Violation of the immune response in pregnant women with a high infectious risk was determined by a high level of embryotropic autoantibodies production (81.9% vs 55.3% with PI subcompensation, 47.9% with its compensation). Hyporeactivity (54.9% vs 45.5%, $p = 0.0005$) in pregnant women with PI subcompensation was detected more often than a hyperreactive response (36.8% vs 9.8%, $p < 0.05$). This fact proved the prognostic significance of hyporeactivity in fetal outcomes ($\chi^2 = 7.5$, $p = 0.006$), as well as the immunoregulatory index "CD4 + / CD8 +" at a value above 1.0 ($\chi^2 = 4.5$, $p = 0.033$).

Obviously, a decrease in immunoresistance in pregnant women with a high infectious risk is the pathogenetic basis for disorders of the uterine-fetal-placental interaction [2]. Various researches prove the prospect of a comprehensive study of the systems providing the activity of the fetoplacental complex (FPC) and the degree of maladaptation of the homeostasis mechanisms in pregnant women with EGD.

Among sonographic stigmas, placental thinning has prognostic potential in women with EGD in the first half of pregnancy ($\chi^2 = 6.1$, $p = 0.01$).

Low activity of the uteroplacental complex (UPC) in groups with a high infectious risk and PI subcompensation [5,13] contributed to the identification of predictors of unfavorable perinatal outcomes in pregnant women with EGD: hemodynamic disorder 1B, 2nd degree ($\chi^2 = 7.8$, $p = 0.005$) and an atypical CTG type ($\chi^2 = 5.1$, $p = 0.02$).

Hemodynamic disorders correlated with the discrepancy between the plastic resources of the placenta and the needs of the growing fetus, most pronounced with PI subcompensation. The disruption of protein synthesis that contributes to the transformation of spiral arteries into tortuous sinusoidal vessels, progressing in the second half of pregnancy, reflects a different degree of adaptive and homeostatic resources in women with EGD.

A comprehensive assessment of the metabolic resources of the FPC (Doppler and CTG) allows us to predict the morphostructure of the placenta: the violation of the biophysical profile of the fetus corresponded to "functionally inactive zones" – thrombosis, placental infarctions and pathology of the villous tree.

The features of the placenta of pregnant women with a high infectious risk were determined in comparison with PI subcompensation: dystrophic changes in

villi – 100.0% ($\chi^2 = 13.267$, $p = 0.000$); dissociation of their development (87.4%) – almost twice as often ($p = 0.0005$); calcifications (77.5%) – 1.3 times ($p = 0.0005$); pseudoinfarctions (37.9% vs 17.5%, $p = 0.0007$) and dyscirculatory disorders (49.5% vs 25.9% $p = 0.0005$) – twice. Inflammatory changes in the placenta (basal deciduitis, membranitis, interillitis) ($\chi^2 = 5.9$, $p = 0.01$) were identified as predictors of a low neonatal health index, 6.6 times more often in the group with a high infectious risk than with subcompensation (87.4%, $p < 0.05$); weak compensatory reactions ($\chi^2 = 14.2$; $p = 0.000$); the presence of "> 60% of non-functional zones" ($\chi^2 = 5.9$, $p = 0.01$).

Weak compensatory reactions in a high infectious risk and PI subcompensation corresponded to the peculiarity of metabolism under stressful conditions, with a decrease in placental mass [4,9]. The discrepancy between the characteristics of the placenta and the trophic needs of the fetus was confirmed by low weight, purulent-septic diseases of newborns and unfavorable perinatal outcomes [17,18,19].

Conclusion. Thus, the morphology of the placenta reflects the usefulness of embryo and fetogenesis in women with EGD, mediated by the resources of the mother's body, optimal in the dogestational recovery and prevention of placental insufficiency in the early gestation. Prediction of the risks of perinatal outcomes and morbidity in pregnant women with EGD – anemia, CP and CAG is realizable using logistic regression model resources.

Reference

1. Apresyan SV. Beremennost' i rody pri ekstragenital'nyh zabolevaniyakh [Pregnancy and childbirth in extragenital diseases]. Ed. VE. Radzinsky. 2nd ed., revised. and additional M.: GEOTAR-Media, 2015; 536 (In Russ.).
2. Bondarenko KR, Mavzyutov AR, Ozoliny LA. Vedushchaya rol' infekcii v formirovani platentarnoj nedostatochnosti [The leading role of infection in the formation of placental insufficiency]. Zhurnal mikrobiologii, epidemiologii i immunobiologii [Journal of microbiology, epidemiology and immunobiology]. 2013; 4:3-9 (In Russ.).
3. Bushtyreva IO, Kuznetsova NB, Levchenko MV. Matochno-placentalnyj krovotok v period pervoj volny invazii citotrofoblasta pri patologicheskom techenii beremennosti [Uteroplacental blood flow during the first wave of cytotrophoblast invasion in pathological pregnancy]. Voprosy ginekologii, akusherstva i perinatologii [Issues of gynecology, obstetrics and perinatology]. 2012; 11(6): 30-33 (In Russ.).
4. Voevodin SM, Shemanaeva TV, Dubova EA. Ul'trazvukovaya i kliniko-morfologicheskaya ocenka placentalnoj disfunkcii pri kriticheskikh sostoyaniyakh u ploda [Ultrasound and clinical and morphological assessment of placental dys-

function in critical conditions in the fetus]. *Ginekologiya* [Gynecology]. 2013;15(5):65–69 (In Russ.).

5. Kuznetsov RA, Peretyatko LP, Rachkova OV. Morfologicheskie kriterii pervichnoj placentalnoj nedostatochnosti [Morphological criteria for primary placental insufficiency]. *Vestnik RUDN. Seriya «Medicina. Akusherstvo i ginekologiya* [Bulletin of RUDN University. Series "Medicine. Obstetrics and gynecology"]. 2011; 5:34–39 (In Russ.).

6. Kryukova NI, Kulavsky VA, Kryukov AA, Frolov AL. Prognozirovaniye i rannyya diagnostika fetoplacentalnoj nedostatochnosti u zhenshchin pozdnego reproduktivnogo vozrasta [Prediction and early diagnosis of placental insufficiency in women of late reproductive age]. *Rossiyskij vestnik akushera-ginekologa* [Russian Bulletin of an obstetrician-gynecologist]. 2013; 4:45–49.

7. Radzinsky VE, Orazmuradov AA. Beremennost' rannih srokov. Ot pregravidarnoy podgotovki k zdorovoy gestacii [Early pregnancy. From preconception preparation to healthy gestation]. 3rd ed., rev. and additional M., Status Praesens. 2018; 800 (In Russ.).

8. Tirskeya Yul, Rudakova EB, Shakina IA. et al. Sovremennye predstavleniya ob etiologii i patogeneze sindroma poteri ploda [Contemporary

characteristics of etiology and pathogenesis of fetal loss syndrome]. *Ural'skij medicinskij zhurnal* [Ural Medical Journal]. 2010;1(66):100–106. (In Russ.).

9. Tayupova IM, Sakhautdinova IV, Almukhametova LD. Rol' defitsita zheleza v vozniknovenii infekcionnyh oslozhnenij vo vremya beremennosti [The role of iron deficiency in the occurrence of infectious complications during pregnancy]. *Vestnik RUDN, seriya Medicina. Akusherstvo i ginekologiya* [Bulletin of RUDN University, Medicine series. Obstetrics and gynecology]. 2012; 5:54–59 (In Russ.).

10. Lai YJ, Hsu TY, Lan KC [et al]. Asymptomatic pyuria in pregnant women during the first trimester is associated with an increased risk of adverse obstetrical outcomes. *Taiwan J Obstet Gynecol*. 2017;56(2):192–195.

11. Cheesbrough M. District Laboratory Practice in Tropical Countries. Part 2. United States of America by Cambridge University Press. New York: Cambridge university press; 2006. Examination of urine; 105–15.

12. Hypertension in response to placental ischemia during pregnancy: role of B lymphocytes. LaMarca B, Wallace K, Herse F, et al. *Hypertension*. 2011; 57(4):865–71.

13. Amarante-Paffaro AM, Hoshida MS, Yokota S, et al. Localization of cathepsins D and B at

the maternalfetal interface and the invasiveness of the trophoblast during the postimplantation period in the mouse. *Cells Tissues Organs*. 2011. 193 (6). 417–25.

14. Barbosa IR, Silva WB, Cerqueira GS, et al. Maternal and fetal outcome in women with hypertensive disorders of pregnancy: the impact of prenatal care. *Ther Adv Cardiovasc Dis*. 2015;9(4):140–6.

15. Matuszkiewicz-Rowińska J, Małyszko J, Wieliczko M. Urinary tract infections in pregnancy: old and new unresolved diagnostic and therapeutic problems. *Arch Med Sci*. 2015;11(1):67–77.

16. Moreno Santillan AA, Briones Garduño JC, Diaz de Leon Ponce MA. Uric Acid in Pregnancy: New Concepts / *Contrib Nephrol*. 2018;192:110–115.

17. Naresh A, Simhan HN. Association of polymicrobial growth from urine culture with adverse pregnancy outcomes. *Am J Perinatol*. 2011;28(7):537–42.

18. Nahar L, Nahar K, Hossain MI, et al. Placental changes in pregnancy induced hypertension. *Mymensingh Med J*. 2013;22(4):684–93.

19. Cardenas I, Means RE, Aldo P, et al. Viral infection of the placenta leads to fetal inflammation and sensitization to bacterial products predisposing to preterm labor. *J Immunol*. 2010; 185:1248–1257.

