

Prognostic Model of Postpartum Endometritis Development

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Received: December 25, 2019; **Published:** January 11, 2020

Abstract

Introduction: High frequency of postpartum purulent-inflammatory diseases has generated a need for development of modern means of diagnosis and prognosis of such complications and their involvement.

Aim: We aimed to build a prognostic model to forecast development of postpartum endometritis based on the use of standard diagnostic algorithm. Additionally, we implied the use of fluorescent spectroscopy, logistic regression and ROC-analysis.

Materials and Methods: The main cohort consisted of 75 women with postpartum endometritis and control group consisted of 40 women with uncomplicated course of the postpartum period.

Methodology: Clinical, laboratory, biochemical and instrumental techniques, including a number of statistical analysis techniques such as logistic regression and ROC-analysis, as well as the use of fluorescent spectroscopy.

Results: As a part of this study we have analysed the course of pregnancy, labour and postpartum period of both main and control cohorts. Moreover, we carried out an extended analysis of the clinical and laboratory data, including information obtained during instrumental examination of the patients. Furthermore, we determined 5 factors whose cumulative effect has the biggest impact on occurrence of postpartum endometritis among the main cohort of patients. Logistic regression enabled identification of these factors as such: extragenital pathology, TORCH-infections, colpitis, fluorescence intensity ≤ 0.845 , a number of bed days.

Conclusion: A proposed prognostic model to forecast development of postpartum endometritis is correct with a probability of 99% ($p < 0,001$; $\chi^2 = 118,63$; $df = 5$).

Keywords: Endometritis; Prognostic Model; The Method of Logistic Regression; ROC-Analysis

Introduction

Despite the fact that the problem of postpartum purulent-inflammatory diseases has been highlighted before, unfortunately it still remains unsolved. It has been showed that this pathology has a high frequency among low income countries. However, it should be highlighted that currently developed countries are also experiencing a growing frequency of this postpartum complication, mostly caused by an increase in frequency of patients who opt for caesarean section. For instance, in 2014, 32% of new mothers in the USA have opted

for caesarean section [1] and it was stated by a number of other publications that the frequency of postoperative complications varies between 3% and 20%.

For high-risk patients struggling from obesity and related complication the risks and frequency of this complication to occur can rise up to 30%. This therefore determines a need for development of highly effective methods for diagnosis and prognosis of purulent-inflammatory diseases [2].

Recently, the use of numerous laboratory methods in diagnosis of purulent-inflammatory diseases, sepsis and postpartum endometritis has seen a considerable increase. It was established that clinical signs of systemic inflammatory reaction such as tachycardia, leucocytosis or fever and its markers (endotoxin, cytokine and procalcitonin concentration) are not reliable indicators for diagnosis of postpartum endometritis (PPE) and inflammatory diseases.

Diagnosis of postpartum inflammatory diseases is primarily based on a clinical picture and the data obtained via laboratory and instrumental techniques. A reliable diagnosis of postpartum infection remains a highly complex issue due to the uniqueness of the physiology of the patients after labour.

Therefore, building a prognostic model aimed to track the development of postpartum endometritis (PPE) as well as enabling individual risk evaluation for each patient becomes critical. Such an approach corresponds to the idea of personalised medicine by demonstrating tailored means of diagnosis and treatment.

The research carried out by American scientists [1] has proposed a prognostic model of postpartum endometritis (PPE) development following a caesarean section, implying the method of logistic regression. BMI increase, frequency of caesarean sections, wound closure using stainless steel staples, chorioamnionitis, maternal asthma and small for gestation age (SGA) were determined risk factors leading to PPE development. The reasoning behind this investigation was a dramatic increase in expenditure on healthcare due to hospitalisation of such patients.

During our investigation, apart from conventional means of diagnostics, we implied fluorescent spectroscopy in sepsis diagnosis (the patent of Ukraine №76953) [3] as well as in postpartum purulent-inflammatory diseases (patent of Ukraine №133472). Blood serum (BS) stimulation was done under wavelength of 280 nm. The choice of this particular wavelength can be supported by the fact, that it detects albumin molecules, which undergo conformational changes during purulent-inflammatory diseases as a result of endogenous intoxication.

This is related to an interaction between albumins and the biproducts of bacterial metabolism by endotoxins. Pathologically altered albumin leads to reduced fluorescence of blood serum, which is proportional to the severity of the disease. In patients with severe cases we were able to observe a dislocation of the maximum values of blood serum fluorescent spectrum towards long wavelength region, considered as a negative prognostic indicator. The aforementioned method allows detection of pathological changes 24 - 48 hours before clinical symptoms of the disease appear. As a result, we suggest this method to be used for early sepsis diagnosis [3] and for control of the treatment efficacy.

Aim of the Study

We aimed to build a prognostic model to forecast development of postpartum endometritis based on the use of standard diagnostic algorithm. Additionally, we implied the use of fluorescent spectroscopy, logistic regression and ROC-analysis.

Methodology

The clinical research centre for this particular investigation was the Department of Gynecology №2 of Vinnytsia Council Clinical Hospital №2. The luminescent laboratory of the Department of Experimental Physics, Ivan Franko Lviv National University was an experimental

research centre. The research study took place between 2014 and 2018 inclusively.

The main cohort of patients consisted of 75 new mothers with PPE. The inclusion criteria for this study were as follows: histologically verified diagnosis of PPE following a single pregnancy, availability and informed consent of women to participate in the study. Control group consisted of 40 new mothers, who experienced a normal course of postpartum period. The research methods used in diagnosis of postpartum endometritis included clinical, laboratory, biochemical, instrumental and statistical techniques (logistic regression), as well as the use of fluorescent spectroscopy.

Results

As a part of our investigation we thoroughly analysed 40 factors which characterised the unique features of the course of pregnancy, postpartum period and the clinical data obtained from both main and control cohorts of patients. We carried out a detailed analysis of the lab examinations (general blood and urine tests, biochemical blood tests, immunofixation analysis for TORCH-infections, bacterioscopy of vaginal and cervical samples), results of instrumental examination (ultrasonography of lesser pelvis, histological analysis of metroaspirate, fluorescent spectroscopy) and statistical methods (logistic regression). We built a prognostic model of PPE development based on the standard diagnostic algorithm of this disease, implying the use of fluorescent spectroscopy and logistic regression.

Clinical description

In this study, we performed and implemented a stepwise logistic regression (with forward selection) aimed to separate the factors, who cumulative effect would have a significant effect on PPE. R-Studio (Version 1.1.442) was used in order to perform statistical analysis, followed by the export and processing of the data using Microsoft Excel.

The following indicators were analysed as well [5]:

- Sensitivity (true positive rate, TPR) - percentage of correctly forecasted positive cases
- Specificity (true negative rate, TNR) - percentage of correctly forecasted negative cases
- Positive prognostic value (PPV) - ratio of correctly forecasted positive cases to overall quantity of positively forecasted cases
- Negative prognostic value (NPV) - ratio of correctly forecasted negative cases to overall quantity of negatively forecasted cases
- Ratio of the validity of positive results (LR+) - ratio of sensitivity (TPR) to percentage of incorrectly forecasted cases (FPR), or $\frac{\text{Sensitivity}}{(1 - \text{Specificity})}$
- Ratio of validity of negative result (LR-) - ratio of mistakenly prognosed negative results (FNR) to specificity (TNR), or $\frac{(1 - \text{Sensitivity})}{\text{Specificity}}$

Aforementioned indications enable evaluation of socio-economic consequences of late- or misdiagnosis, the use of this model for early diagnosis and its verification and enable prompt patient screening.

Logistic regression enabled identification of 5 core factors whose cumulative effect has the biggest impact on occurrence of postpartum endometritis among the main cohort of patients. Logistic regression enabled identification of these factors as such: extragenital pathology, TORCH-infections, colpitis, fluorescence intensity ≤ 0.845 , a number of bed days. In terms of cohort formation, women were divided into 4 groups: under 18 years old (Group 0), 18 - 24 years old (Group 1), 25 - 34 years old (Group 2) and older than 35 years old (Group 3). The results of this analysis are presented in table 1.

A probability of PPE taking place (Q), depending on the selected factors was calculated using the following formula:

$$Q = \frac{1}{1 + e^{-R}} * 100\% \quad (1.1)$$

Factor	Coefficient β	Exp (β)	Annotations	Z	p
Constant	-9,0604			-3,26	0,001
Extragenital pathology	2,8766	17,75	V1	2,19	0,028
TORCH	3,9922	54,17	V2	2,24	0,025
Colpitis	5,2389	188,46	V3	3,51	0,000
Fluorescence intensity $\leq 0,845$ r.u.	2,9127	18,41	V4	2,87	0,004
Bed days	0,6711	1,96	V5	1,77	0,077

Table 1: The results of regression coefficients related to the occurrence of postpartum endometritis (n = 75) using logistic regression.

where $e = 2,72...$ - is the base of a natural logarithm

R - is the quantity calculated according to the formula 1.2, mentioned below:

$$R = K + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_n x_n \tag{1.2}$$

where K - is a constant

n - the number of factors which are included in prognostic model

β_i - coefficients that correspond to a number of calculated factors

x_i - corresponding numerical values of the factors

Theoretically, Q can hold a value ranging from 0% (an impossible event) to 100% (a constantly occurring event). The meaning of β_i coefficients are calculated by the software and are represented by the natural log of the correlation of probabilities of corresponding variables. Increasing the value of the independent variable by a unit of measurement would increase the chances of developing complications in EXP (β) times.

The equation was evaluated according to Akaike information criterion (AIC) [6], verification using χ^2 for the likelihood ratio test and by Nagelkerke's R^2 (Pseudo R-squared) [7,8].

The resulting model is correct with a probability of 99% ($p < 0.001, \chi^2 = 116.26, df = 10$).

By substituting derived coefficient β into the equation 1.2 we can determine the R (3) and hence predict the probability of PPE and haematometra occurrence in main cohort.

$$R = - 9,0604 + 2,8766*V1 + 3,9922*V2 + 5,2389*V3 + 2,9127*V4 + 0,6711*V5 \tag{2}$$

Nagelkerke coefficient of determination of this model equals 0.8872 (i.e. the set of variables in this model explains almost 89% of dispersion of the dependent variable). The area under curve (AUC) = 0.99.

Furthermore, ROC-analysis was used in order to determine a mathematical credibility of the model and calculate an optimal threshold of decision making (cut-off point).

As a result, a ROC-curve was implied in order to demonstrate correlation between specificity and sensitivity. The area under the curve (AUC) was calculated to characterise the model's quality, where the scale varied between 0.5 (method is unacceptable) to 1 - 100% which is an indication of the congruence in prognosis based on the model. The results of this investigation are demonstrated on figure 1.

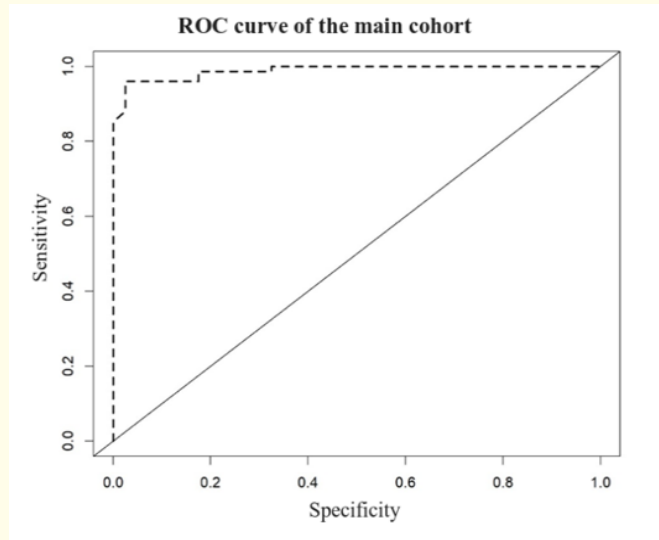


Figure 1: ROC curve of the mathematical model for the main cohort of patients with postpartum endometritis.

Optimal threshold of decision making (cut-off point) which allows a maximum balance between sensitivity and specificity for this model was 0.53. Therefore, when the risk of PPE occurrence is ≤ 0.53 , we can conclude that the patient has a high risk of developing PPE. Consequently, if the ≥ 0.53 , we can confirm the absence of risk of PPE development. Results of this investigation are demonstrated on figure 2.

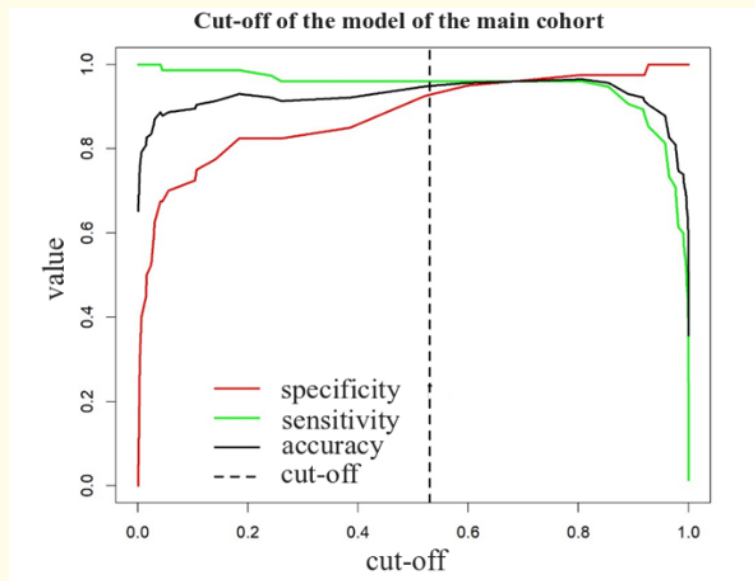


Figure 2: Threshold of decision making (cut-off point) in relation to specificity, sensitivity and accuracy of the mathematical model for the patients with postpartum endometritis.

Discussion

Consequently, the core aim behind this investigation was to derive a prognostic model of the development of PPE using a standardised diagnostic algorithm and implying fluorescent spectroscopy, logistic regression and ROC-analysis.

When the threshold of decision making (cut-off point) is 0.53, the values for the core parameters are as follows: sensitivity is 96.0%, specificity is 95.0%, the likelihood ratio of the of the positive result (LR+) is 19.20, the likelihood ratio of the negative result (LR-) is 0.04, positive prognostic value (PPV) is 97.30%, negative prognostic value (NPV) is 92.68%. The data used in the aforementioned prognosis using threshold of decision making of 0.53 are outlined in table 2.

	Uncomplicated course of postpartum period (n = 40)	Diagnosed postpartum endometritis without any following pathologies (n = 75)	Total
Calculated value < 0,53	38 (95,0%)	3 (4,0%)	41
Calculated value ≥ 0,53	2 (5,0%)	72 (96,0%)	74
Total	40	75	115

Table 2: Diagnostic value of the mathematical model implied in prognosis of postpartum endometritis among new mothers with uncomplicated endometritis.

Table 3 and 4 demonstrate the results of spectrofluorescent characteristics of blood serum (I_f and λ_{max}) and probability of developing postpartum endometritis among the main and control patient cohorts.

Nº	I_f	λ_{max}	Probability
1.	0,87	330,6	0,000482652
2.	0,89	335,1	0,362823042
3.	0,93	333,2	0,002656288
4.	0,99	332,9	0,004867508
5.	1	331,1	0,023146758
6.	0,91	330,1	0,000777064
7.	0,87	330,1	0,096466759
8.	0,99	333,1	0,00248786
9.	0,96	334,5	0,047484295
10.	0,95	335,1	0,004130458

Table 3: Probability of PPE in control group.

Nº	I_f	λ_{max}	Probability
1.	0,67	333,2	0,9997
2.	0,55	334,1	0,95762
3.	0,58	336,1	0,99989
4.	0,63	338,1	0,99982
5.	0,75	334,1	0,99995
6.	0,56	340,1	0,99873
7.	0,35	343,1	0,99515
8.	0,77	332,8	0,85514
9.	0,57	343	0,92031
10.	0,79	336,1	0,95762

Table 4: Probability of PPE development in the main cohort.

Conclusion

A proposed multifactorial model which involved logistic regression and ROC-analysis can be implied in prognosis of the risk of postpartum endometritis among new mothers has a substantial diagnostic value.

The core factors which cumulatively have a major impact on development of postpartum endometritis were determined as follows: extragenital pathology, TORCH-infections, colpitis, fluorescence intensity of blood serum $\leq 0,845$, and a number of bed days. This model is correct with a probability of 99% ($p < 0,001$; $\chi^2 = 118,63$; $df = 5$) and allows to establish risk groups for development of postpartum endometritis.

Conflict of Interest

None.

Funding

No competing actual or potential financial interests exist in this pages.

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Volume 9 Issue 2 February 2020

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