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LABORATORY MARKERS FOR PREDICTING CRITICAL OBSTETRIC CONDITIONS

M.M. Padrul¹, N.V. Isaeva¹, S.N. Berseneva^{2*}, E.V. Cherkasova³, A.A. Gorokhova⁴

¹*Ye.A. Vagner Perm State Medical University,*

²*Perm Regional Clinical Hospital,*

³*Medical Information Analytical Center, Perm,*

⁴*Women's Health Clinic, Perm, Russian Federation*

ЛАБОРАТОРНЫЕ МАРКЕРЫ ПРОГНОЗИРОВАНИЯ КРИТИЧЕСКИХ АКУШЕРСКИХ СОСТОЯНИЙ

М.М. Падруль¹, Н.В. Исаева¹, С.Н. Берсенева^{2*}, Е.В. Черкасова³, А.А. Горохова⁴

¹*Пермский государственный медицинский университет имени академика Е.А. Вагнера,*

²*Пермская краевая клиническая больница,*

³*Медицинский информационный аналитический центр, г. Пермь,*

⁴*Клиника женского здоровья, г. Пермь, Российская Федерация*

Objective. To identify early laboratory markers of the risk for developing critical obstetric conditions (COC).
Materials and methods. As a retrospective analysis, the medical and birth histories of both favorable and adverse obstetric outcomes that occurred in medical organizations of all levels in Perm and the Perm Region in 2007–2018 were used. The comparative analysis included clinical and laboratory characteristics of the examination results and the course of pregnancy, delivery and the postpartum period. The risk of COC was assessed using the Kruskal – Wallis test. The relationship between quantitative variables was determined using

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e-mail: bers.s2014@yandex.ru

[Padrul M.M. – DSc (Medicine), Professor, Head of the Department of Obstetrics and Gynecology, ORCID: 0000-0002-6111-5093; Isaeva N.V. – DSc (Medicine), Professor, Vice-Rector for Continuous Professional Development, Head of the Department of Public Health and Healthcare with a Course in Law, ORCID: 0009-0007-0626-7979; Berseneva S.N. (*contact person) – PhD (Medicine), Obstetrician-gynecologist, ORCID: 0009-0003-1668-6748; Cherkasova E.V. – DSc (Medicine), Methodologist, ORCID: 0009-0001-4696-3545; Gorokhova A.A. – Obstetrician-gynecologist, ORCID: 0009-0006-6062-8854].

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e-mail: bers.s2014@yandex.ru

[Падруль М.М. – доктор медицинских наук, профессор, заведующий кафедрой акушерства и гинекологии, ORCID: 0000-0002-6111-5093; Исаева Н.В. – доктор медицинских наук, профессор, проректор по непрерывному профессиональному развитию, заведующая кафедрой общественного здоровья и здравоохранения с курсом права, ORCID: 0009-0007-0626-7979; Берсенева С.Н. (*контактное лицо) – кандидат медицинских наук, акушер-гинеколог, ORCID: 0009-0003-1668-6748; Черкасова Е.В. – доктор медицинских наук, врач-методист, ORCID: 0009-0001-4696-3545; Горохова А.А. – акушер-гинеколог, ORCID: 0009-0006-6062-8854].

the linear correlation coefficient (r). The data were analyzed in the Excel® 2016 spreadsheet processor using the author's Stat2015 package. The LII was assessed (in conventional units – c. u.), according to the Ya.Ya. Kalf-Kalif formula at different stages of pregnancy and in the postpartum period, which allowed us to determine the dynamics of changes depending on the risk group and gestation period.

Results. Early laboratory markers of COC were established (iron deficiency anemia, high levels of LII, elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), urea and creatinine, decreased fibrinogen, prothrombin index (PI) and prolonged thrombin time (TT)).

Conclusions. Reliably significant laboratory markers of the risk for developing COC have been identified.

Keywords. Laboratory markers, critical obstetric conditions, maternal mortality, maternal near-miss, leukocyte intoxication index.

Цель. Определить ранние лабораторные маркеры риска развития критических акушерских состояний (КАС).

Материалы и методы. В качестве ретроспективного анализа использованы истории болезней и родов – благополучных и неблагополучных акушерских исходов, произошедших в медицинских организациях всех уровней г. Перми и Пермского края в 2007–2018 гг. Сравнительный анализ включал клинико-лабораторную характеристику результатов обследования и течения беременности, родов и послеродового периода. Оценку степени риска КАС проводили с помощью статистического критерия Краскела – Уоллиса. Зависимость между количественными признаками определялась с помощью коэффициента линейной корреляции (r). Анализ данных проводился в табличном процессоре Excel® 2016 с использованием авторского пакета Stat2015. Для оценки ЛИИ применялась формула Я.Я. Кальф-Калифа на разных стадиях беременности и в послеродовом периоде, что позволило выявить динамику изменений в зависимости от группы риска и срока гестации.

Результаты. Установлены ранние лабораторные маркеры КАС (железодефицитная анемия, высокий уровень ЛИИ, повышенные показатели аланинаминотрансферазы (АЛТ) и аспаратаминотрансферазы (АСТ), мочевины и креатинина, сниженный уровень фибриногена, протромбинового индекса (ПТИ) и удлинение тромбинового времени (ТВ)).

Выводы. Определены достоверно значимые лабораторные маркеры риска развития КАС.

Ключевые слова. Лабораторные маркеры, критические акушерские состояния, материнская смертность, несостоявшаяся материнская смертность, лейкоцитарный индекс интоксикации.

INTRODUCTION

Critical obstetric conditions (COC) are syndromes, symptoms, and complications that require timely, highly specialized care and intensive measures for women during pregnancy, childbirth, and the 42 days following delivery [1–3]. Severe maternal outcomes are divided into near-miss maternal mortality (NMM) and obstetric death, the main causes of which are extragenital diseases, hemorrhage, preeclampsia and eclampsia, amniotic fluid embolism, clinically narrow pelvis, and

unsafe abortion [4]. Near-miss maternal mortality is a critical obstetric condition (COC) close to death experienced by a pregnant woman or woman who has recently given birth, who survived as a result of timely and high-quality highly specialized medical care [3]. The incidence of NMM worldwide reaches 1.4 % of all pregnancies and varies by region.

Systematic analysis of causes and monitoring of COC in Russia can reduce maternal mortality (MM) [5]. Consequently, the priority area for reducing MM in the population is the prediction and timely identification of risk

factors and laboratory markers for the development of COC. The relevance of early pre-clinical prediction of COC is currently high.

The currently accepted methods for assessing the prognosis of obstetric pathology, regulated by Order No. 572n of the Ministry of Health of the Russian Federation dated November 12, 2012, based on the analysis of obstetric-gynecological and somatic medical histories and previous obstetric complications, are imperfect, as their prognostic value remains limited. For example, chronic diseases are recorded in 80 % of pregnant women, infectious and inflammatory processes in 74.6 %, and placental dysfunction and fetal hypoxia in 25–77 % of cases [6–9], while truly life-threatening conditions are detected in only 1.3–2.7 % of births [10].

A complete blood count is part of the standard set of tests during pregnancy, and an increase in white blood cells and changes in the white blood cell count do not always predict obstetric complications. This has sparked interest in the leukocyte intoxication index (LII), calculated using the formula developed by Y.Y. Kalf-Kalifa, which reflects the severity of the systemic inflammatory response and can therefore be used as an early marker of COC, since exceeding the LII level in the first (especially), second, and third trimesters can be considered a risk for the development of COC. A comparative analysis between the groups showed that the LII level for women in the control group in the first trimester was 0.84 ± 0.40 conventional units (95 % CI 0.70–0.99), in the second trimester it was 1.64 ± 1.40 conventional units (95 % CI 1.07–2.21), and in the third trimester it was 1.59 ± 0.96 conventional units (95 % CI 1.15–2.03) [12], while in complicated pregnancies it significantly exceeded 1.5, 2.21, and

2.03 conventional units in the first, second, and third trimesters, respectively [12].

The COC prediction method, based on risk factors (socio-behavioral, general somatic, and obstetric-gynecological) and increased LII in the first and second trimesters of pregnancy [13; 14], allows for the identification of high-risk groups for obstetric complications*. To date, there is no laboratory prediction of adverse maternal outcomes, therefore early laboratory markers of COC are proposed based on complete blood count, biochemical results, and coagulogram.

The aim of the study is to identify early laboratory markers of risk for the development of critical obstetric conditions.

MATERIALS AND METHODS

The comparative analysis includes medical records and birth histories with favorable and unfavorable outcomes from medical institutions of all levels of care in Perm and the Perm Territory between 2007 and 2018. Depending on the outcome of the pregnancy and the severity of complications, all observations were classified into four groups:

Control group (Group I) – women with a favorable pregnancy course and outcome in childbirth ($n = 52$).

Group II – patients with complications requiring hospitalization or drug therapy, but

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who completed their pregnancy without severe maternal and perinatal complications ($n = 50$).

Group III – women who have experienced severe obstetric complications and survived thanks to emergency and highly skilled medical care ($n = 54$).

Group IV – cases of death during pregnancy, childbirth, or within 42 days after their completion, accompanied by fetal or infant loss ($n = 30$).

A retrospective analysis was conducted of clinical and laboratory characteristics, including examination results: the course of pregnancy, childbirth, and the postpartum period in groups with favorable and unfavorable outcomes. The Kruskal–Wallis statistical test was used to assess the significance of differences between groups.

Correlations between quantitative variables were analyzed using Pearson's linear correlation coefficient (r). Statistical data processing was performed in Excel® 2016 using the proprietary software package Stat2015.

To assess LII (in conventional units – conv. units) using the formula developed by Y.Y. Kalf-Kalifa, indicators were determined at various stages of gestation and in the postpartum period, which made it possible to track the dynamics of changes depending on the risk of developing COC and the outcome of pregnancy.

RESULTS AND DISCUSSION

The analysis showed that almost all patients in the compared groups were diagnosed with anemia, which increases the risk of maternal and perinatal complications: in group I – in 37 women (71.2%); in group II – 38 (76.0%); in group III – 26 (48.1%); and in group IV – 21 (70.0%), which is statistically significant ($H = 13,341; p < 0,05$) (Fig. 1).

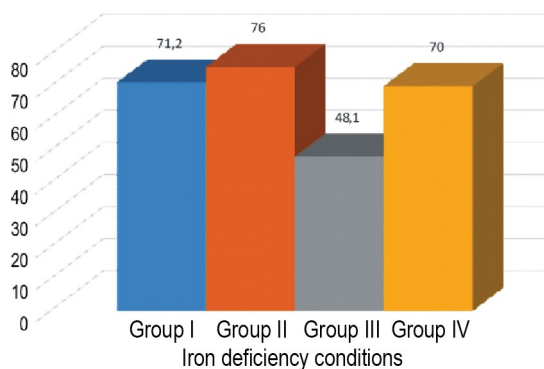


Fig. 1. Iron deficiency conditions in comparison groups, %

Most women in the control group were diagnosed with grade I anemia. In group II, 66.0 % had grade I anemia, 6.0 % had grade II anemia, and 4.0 % had grade III anemia. In group III, 44.0 % of patients were diagnosed with grade I anemia, and 3.7 % had severe anemia. The highest rate of severe anemia was recorded in group IV – 23.3 % (Fig. 2). Pairwise comparisons revealed significant differences between groups III and II ($U = 950.0; p = 0.05$), III and IV ($U = 444.0; p = 0.05$), as well as between the control and I groups ($U = 548.0; p = 0.05$).

The leukocyte intoxication index (LII) remained within normal limits in women with favorable pregnancy outcomes (in the first trimester ≤ 1.5 conventional units; in the second trimester ≤ 2.21 ; in the third trimester ≤ 2.03). In the group of women with maternal losses, the LII was significantly higher from the first trimester onwards and remained high until delivery and in the postpartum period. In the first trimester, the LII in group IV was 27.05 ± 50.9 , in the second trimester – 26.6 ± 44.2 , and in the third trimester and postpartum period, significant differences were found between the compared groups ($H = 31,942; p < 0,001$).

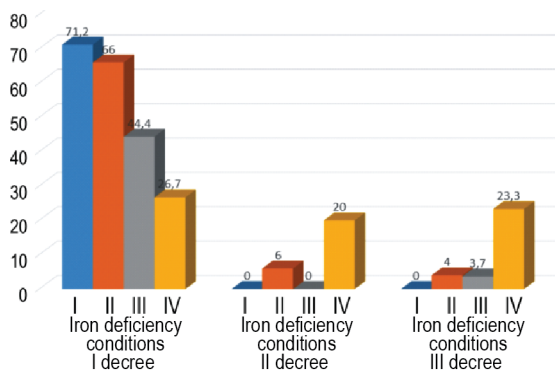


Fig. 2. Iron deficiency conditions by severity in comparison groups, %

In the third trimester, the average LII level in deceased women was 6.7 ± 2.9 versus 1.7 ± 0.5 in the control group ($t = 3.333$; $p < 0.005$). On days 1–2 after delivery, the LII in deceased women reached 45.6 ± 47.4 compared to 3.9 ± 1.2 in the control group ($U = 93.00$; $p < 0.012$), and on days 3–4, it was 154.7 ± 270.5 versus 2.6 ± 0.8 , respectively ($H = 42.099$; $p = 0.001$; $U = 55.00$; $p < 0.001$). On days 5–6, the LII in group III was 6.6 ± 3.0 , and in group IV, it was 8.4 ± 2.6 ($t = 4.371$; $p < 0.001$), which also confirms the persistence of inflammatory activity (Table 1).

Biochemical blood analysis showed no significant differences between the groups in terms of sugar and bilirubin levels. On the contrary, total protein levels in groups II and IV (66.3 ± 2.0 and 64.2 ± 3.4 , respectively) differed significantly from those in the control group (69.0 ± 2.1), differences are significant (groups II and I – $U = 953.0$; $p = 0.029$; groups IV and I – $U = 204.0$; $p = 0.003$). The AST level was significantly higher in group IV (46.7 ± 27.5) compared to the control group (14.5 ± 2.1 ; $U = 204.0$; $p = 0.003$) and group III (21.2 ± 8.0 ; $U = 191.5$; $p = 0.034$). In group II, the AST level (19.9 ± 4.9) was significantly lower compared to the data for group IV ($U = 204.0$; $p = 0.003$).

Renal function indicators (urea and creatinine) were significantly higher in deceased women: for urea ($H = 20.209$; $p < 0.001$) and creatinine ($H = 10.711$; $p = 0.013$), significant differences were recorded with groups II and III ($U = 113.0$ and $U = 75.0$; both $p < 0.001$). Creatinine was also higher in group II compared to group I ($U = 678.0$; $p = 0.002$) (Table 2).

Table 1

Level of LII (leukocyte intoxication index) at different stages of pregnancy, childbirth, and the postpartum period in the compared groups, conditional units

Leukocyte intoxication index	Group I, $n = 52$	Group II, $n = 50$	Group III, $n = 54$	Group IV, $n = 30$	H- criterion	p-value
First trimester	1.3 ± 0.3	$1.7 \pm 0.3^*$	1.4 ± 0.3	27.5 ± 50.9	5.921	0.116
Second trimester	2.0 ± 0.5	2.0 ± 0.4	$1.6 \pm 0.4^{****}$	26.6 ± 44.2	2.782	0.426
Third trimester	1.7 ± 0.5	$1.7 \pm 0.4^{****}$	$3.0 \pm 1.2^{****}$	$6.7 \pm 2.9^*$	31.942	0.001
Before delivery	$2.2 \pm 1.0^{***}$	2.8 ± 0.7	4.5 ± 1.7	–	34.5	0.298
1–2 days after delivery	3.9 ± 1.2	4.7 ± 2.4	6.1 ± 1.2	$45.6 \pm 47.4^*$	7.411	0.060
3–4 days after delivery	$2.6 \pm 0.8^{***}$	$2.60 \pm 0.8^{****}$	$3.9 \pm 1.8^{****}$	$154.7 \pm 270.5^*$	42.099	0.001
5–6 days after delivery	2.4 ± 0.6	–	$6.6 \pm 3.0^{****}$	$8.4 \pm 2.6^*$	–	–

Note: here and further in the tables: * – reliable difference in data with group I; ** – with group II; *** – with group III; **** – with group IV; p/p – postpartum period. Normal range: first trimester – 1.51 conventional units; second trimester – 2.21 conventional units; third trimester of pregnancy – 2.03 conventional units.

Table 2

Biochemical blood parameters during pregnancy in different study, $M \pm 2m$

Indicator	Group I, <i>n</i> = 52	Group II, <i>n</i> = 50	Group III, <i>n</i> = 54	Group IV, <i>n</i> = 30	<i>H</i> - criterion	<i>p</i> -value
Blood sugar, mmol/L (normal range: 3–6.1)	4.3 ± 0.2	4.3 ± 0.2	5.4 ± 2.1	4.4 ± 0.7	0.361	0.948
Total protein, g/L (normal range: 60–85 g/L)	69.0 ± 2.1	66.3 ± 2.0*	67.2 ± 2.2	64.2 ± 3.4*	6.932	0.074
Bilirubin, μmol/L (normal range: 0–20.5)	11.0 ± 1.1	9.8 ± 0.9	9.6 ± 1.0	14.5 ± 5.6	4.835	0.184
AST, U/l (normal: 0–32)	14.5 ± 2.1	19.9 ± 4.9****	21.2 ± 8.0****	46.7 ± 27.5*	10.206	0.017
ALT, U/L (норма: 0–31)	16.6 ± 4.3	22.4 ± 11.4	21.5 ± 7.5	50.7 ± 36.6	2.855	0.414
Creatinine, μmol/L (normal range: 44–97)	36.2 ± 9.5	57.8 ± 6.8*	42.1 ± 11.0	68.6 ± 40.2	10.714	0.013
Urea, mmol/L (normal range: 1.7–8.3)	3.2 ± 0.4	2.9 ± 0.3****	2.9 ± 0.3****	5.7 ± 1.5*	20.209	< 0.001

The fibrinogen level in the comparison groups has reliable values ($H = 9.178$; $p = 0.028$). Fibrinogen in group II is significantly higher than in the control group ($U = 817.0$; $p = 0.042$) and the group of deceased women ($U = 226.0$; $p = 0.023$).

In the group of survivors, the fibrinogen level is significantly lower than in group II ($U = 568.0$; $p = 0.015$).

A decrease in the international normalized ratio (INR) was also noted in the comparison groups ($H = 9.735$; $p = 0.021$), with the indicator in group II significantly lower than in group IV ($t = 2.721$; $p = 0.010$) and the control group ($U = 217.5$; $p = 0.008$).

The prothrombin index (PTI) in the compared groups showed a significant difference ($H = 42.041$; $p < 0.001$). A decrease in PTI was recorded in the group of deceased women, especially in comparison with the control group ($t = 9.240$; $p < 0.001$), and reduced values in the group of deceased women compared to the values in group II ($t = 7.767$; $p < 0.001$). Signifi-

cance was determined between groups II and IV ($U = 20.0$; $p < 0.001$) and between the control group and group III ($t = 11.312$; $p < 0.001$).

In the group of women with maternal losses, thrombin time (TT) was prolonged (21.0 ± 13.4) compared to data from groups II ($U = 54.0$; $p = 0.007$) and IV ($t = 3.510$; $p = 0.002$). In group II, thrombin time was shorter compared to the control group ($t = 3.573$; $p = 0.001$) (Table 3).

The study results showed a high level of moderate anemia among patients from socially vulnerable groups (SVG), which can be explained by social and behavioral factors.

The data obtained confirm the important role of LII as a predictor of complications: already in the first trimester, it exceeded the norm in women with unfavorable outcomes, and after childbirth, it increased tenfold. This reflects the development of a toxic-inflammatory process, indicating decompensation of homeostasis systems.

Table 3

**Hemostasis system indicators in women
from different study groups, $M \pm 2m$**

Indicator	Group I, <i>n</i> = 52	Group II, <i>n</i> = 50	Group III, <i>n</i> = 54	Group IV, <i>n</i> = 30	<i>H</i> - criterion	<i>p</i> -value
Fibrinogen, g/L (normal range: 2–4)	4.7 ± 1.3	4.8 ± 0.4* ****	4.0 ± 0.4**	3.9 ± 0.4	9.178	0.028
INR (international normalized ratio)	2.1 ± 2.1	1.0 ± 0.0 *****	1.0 ± 0.0	1.1 ± 0.2	9.735	0.021
PTT, with (norm: 24,3–35)	27.5 ± 1.2	28.7 ± 1.6	29.3 ± 1.6	26.6 ± 5.9	2.500	0.475
PTI (norm: 80–110)	1.0 ± 0.0***	11.7 ± 11.8 ****	88.6 ± 15.2 **	88.0 ± 18.4 *	42.041	< 0.001
PTT, with (norm is up to 11 per minute)	13.8 ± 1.1	14.1 ± 0.6	14.1 ± 0.6	17.2 ± 3.9	3.667	0.300
TT, with (norm 11–17.8 s)	14.9 ± 1.3	11.9 ± 1.2 *****	21.0 ± 13.4**	15.9 ± 1.3	15.900	< 0.001
Fibrin monomers soluble complex, unit (norm 0–3.5)	6.2 ± 2.0	5.8 ± 0.9	4.6 ± 1.3	–	4.140	0.247
D-dimer, ng/mL (norm 0– 1680)	521.0 ± 357.9* **	587.4 ± 78.0	4530.5 ± 5355.8**	–	9.099	0.028

CONCLUSIONS

Signs of multiple organ failure have been identified in women with severe outcomes: increased AST, ALT, urea, and creatinine, which may serve as early biochemical markers of adverse pregnancy outcomes. Hemostasis disorders (decreased fibrinogen and PTI, prolonged TT) can be regarded as early manifestations of DIC syndrome before the development of clinically significant critical obstetric conditions.

1. Early laboratory markers associated with the risk of developing critical obstetric conditions (COC) include: iron deficiency anemia, especially severe anemia, common among women from high social risk groups; an increase in the leukocyte intoxication index (LII) as early as the first trimester of pregnancy, with an increase during pregnancy and in the postpartum period, reflecting a systemic inflammatory response and decom-

pensation of adaptive mechanisms; biochemical signs of incipient multiple organ failure – increased levels of AST, ALT, urea, and creatinine with a decrease in total protein; hemostasis system disorders: decreased fibrinogen, prothrombin index (PTI), prolonged thrombin time (TT), which can be regarded as initial manifestations of developing DIC syndrome.

2. The laboratory profile of a pregnant woman at high risk of COC can be established long before the clinical manifestation of se-

vere complications, which emphasizes the diagnostic significance of a comprehensive assessment of standard indicators of general, biochemical, and coagulation analyses.

3. Timely interpretation of laboratory data in dynamics can significantly improve the accuracy of early prediction of adverse pregnancy outcomes and justify the need for: interdisciplinary consultation; hospitalization in a specialized hospital (level III); early initiation of therapy aimed at correcting pathological processes.

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Author contributions:

Padrul M.M. – defining the concept of the publication and editing the scientific material.

Isaeva N.V. – developing the research design and writing the text.

Berseneva S.N. – collecting and processing the material and writing the text.

Cherkasova E.V. – writing the text, compiling the list of references.

Gorokhova A.A. – statistical processing of data.

All authors approved the final version of the article and are responsible for the integrity of all parts of the article.

Study limitations. The study complies with the standards of the Declaration of Helsinki and has been approved by the Ethics Committee of the Ye.A. Vagner State Medical University, protocol No. 3 dated April 30, 2025.

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