



## PREDICTING THE RISK OF PRETERM BIRTH IN CASES OF GENITOURINARY SYSTEM INFECTION

A.G. Bozorov, G.A. Ikhtiyarova

Bukhara State Medical Institute, Uzbekistan

### ✓ Resume

*Preterm birth are associated with a high incidence of neonatal and perinatal morbidity and mortality, and therefore are among the most pressing problems of obstetrics. Taking into account the urgency of the problem, we conducted a study of biochemical markers: metalloproteinase-12 and cystatin C in pregnant women at risk of preterm labor and the presence of an infection of the genitourinary system.*

*The aim of the study is to predict the threat of preterm labor against the background of urogenital tract infection, taking into account the study of biochemical markers.*

*Material and methods. To solve the tasks set in the work, 128 women (Group I-65 women with IMS and at risk preterm birth and II 63 women with preterm birth (group without infections) and 25 women in the control group are conditionally healthy pregnant women who will undergo an enzyme-linked immunosorbent assay (ELISA). The level of metalloproteinase 12, cystatin C in the blood serum.*

*Research results. There was an association of high plasma levels of matrix metalloproteinase-12 (ADAM-12) in pregnant women with BMI (9.1-11 ng/ml in 49.2% of women) compared to pregnant women with risk of miscarriage without BMI (7.1-9.0 ng/ml in 7.9% of women) and the control group (3.1-5.0,0 ng/ml in 16% of women). The level of cystatin C in the blood serum is inversely proportional to the glomerular filtration rate. The worse the kidneys filter (renal failure), the higher the concentration of cystatin C. The assay is used to evaluate renal function as an alternative to creatinine testing.*

*Key words: preterm labor, urogenital system infection, metalloproteinase-12, cystatin C*

## ПРОГНОЗИРОВАНИЕ РИСКА РАЗВИТИЯ ПРЕЖДЕВРЕМЕННЫХ РОДОВ ПРИ ИНФЕКЦИИ МОЧЕПОЛОВОЙ СИСТЕМЫ

А.Г.Бозоров, Г.А.Ихтиярова

Бухарский государственный медицинский институт, Узбекистан

### ✓ Резюме

*Преждевременные роды (ПР) ассоциированы с высокой частотой неонатальной и перинатальной заболеваемости и смертности, в связи с чем относятся к числу наиболее актуальных проблем акушерства. Учитывая актуальность проблемы нами проведено исследование биохимических маркеров: металлопротеиназы-12 и цистатина С у беременных с риском преждевременных родов и наличие инфекции мочеполовой системы.*

*Цель исследования – прогнозирование угрозы преждевременных родов на фоне инфекции мочеполового тракта с учетом изучения биохимических маркеров.*

*Материал и методы. Для решения поставленных в работе задач 128 женщинам (I группа 65 женщин с инфекцией мочевыделительной системы (ИМС) и угрозой ПР и II 63 женщины с ПР группа без инфекций и 25 женщин контрольная группа условно здоровые беременные, которым будет проведен иммуноферментный анализ (ИФА). Уровень металлопротеиназы 12, цистатина С в сыворотке крови.*

*Результаты исследования. Выявлена ассоциация высокого уровня матриксной металлопротеиназы-12 (ММП-12) в плазме крови у беременных женщин с наличием ИМТ (9,1-11 ng/ml у 49,2% женщин) чем сравнение беременных с угрозой выкидыша без ИМТ (7,1-*

9,0 ng/ml у 7,9% жєнєцин) и контрольную группу (3,1-5,0 ng/ml у 16% жєнєцин). Уровєнь цистатина С в сыворотке крови обратно пропорционален скорости клубочковой фильтрации. Чем хуже фильтруют почки (почечная недостаточность), тем выше концентрация цистатина С. Анализ используется для оценки функции почек как альтернативы исследованиям креатинина.

**Ключевые слова:** преждевременные роды, инфекция мочеполовой системы, металлопротеиназа-12, цистатин С

## SIYDIK CHIQRISH TIZIMI INFEKSIYASIDA MUDDATIDAN OLDIN TUG'ILISHNING RIVOJLANISH XAVFINI BASHORATLASH

A.G.Bozorov, G.A.Ixtiyorova

Buxoro davlat tibbiyot instituti, O'zbekiston

### ✓ *Rezyume*

*Erta tug'ilish neonatal va perinatal kasalliklar va o'limning yuqori darajasi bilan bog'liq va shuning uchun akusherlikda eng dolzarb muammolaridan biridir. Muammoning dolzarbligini hisobga olgan holda, biz erta tug'ilish xavfi va siydik yo'llari infeksiyasining mavjud homilador ayollarda metalloproteinaz-12 va sistatin C kabi biokimyoviy markerlarni o'rgandik.*

*Tadqiqotning maqsadi biokimyoviy belgilarni o'rganishni hisobga olgan holda siydik yo'llari infeksiyasi fonida erta tug'ilish xavfini taxmin qilish.*

*Materiallar va tekshirish usullar. Ishda qo'yilgan vazifalarni hal qilish uchun 128 nafar ayol (I-65 nafar I-guruh va ET xavfi bo'lgan ayollar va II-63 nafar infeksiyasiz ET guruhi) va nazorat guruhidagi 25 nafar ayol shartli sog'lom homilador bo'lib, ferment immunoassay tekshiruvidan o'tkaziladi. (ELISA). Qon zardobida metalloproteinaza 12, sistatin C darajasi.*

*Tadqiqot natijalari. BMI bo'lmagan homilador ayollarda (ayollarning 49,2 foizida 9,1-11 ng/ml) BMI bo'lmagan (7,1 -9,0) homilador ayollar bilan solishtirganda metalloproteinaza-12 (MMP-12) matritsasining yuqori plazma darajasi bilan bog'liqligi bor edi. ng/ml ayollarning 7,9 foizida) va nazorat guruhi (16 foiz ayollarda 3,1-5,0 ng/ml). Sarumdagi sistatin C darajasi glomerulyar filtratsiya tezligiga teskari proporsionaldir. Buyraklar filtri (buyrak etishmovchiligi) qanchalik yomon bo'lsa, sistatin C konsentratsiyasi shunchalik yuqori bo'ladi. Sinov kreatinin tadqiqotlariga muqobil ravishda buyrak funksiyasini baholash uchun ishlatiladi.*

*Kalit so'zlar: erta tug'ilish, siydik ajratish tizimi infeksiyasi, metalloproteinaza-12, sistatin C*

### Relevance

**D**uring the last years in Uzbekistan, the rate of preterm birth remains in the range of 9-11, 5%, in Europe-5-9%, and in the United States it even increased to 9-11, 2%. Perinatal mortality in premature infants is observed more than 33 times more often than in full-term newborns. In addition, about 70% of early neonatal deaths are associated with prematurity. To date, the solution to this problem consists in timely diagnosis and subsequent prevention of the threat of PR. Despite the presence of a large number of clinical and laboratory methods for the diagnosis of threatening preterm pregnancies, the issue of predicting the outcome of pregnancy and methods of treatment for the mother and fetus cannot be considered definitively resolved [1,2,3].

Pyelonephritis is one of the most common extragenital diseases during pregnancy, occurring in 8-12% of pregnant women. Its aggravation during gestation is facilitated by a complex of hormonal, water-electrolyte, immune and mechanical factors that are inextricably linked to pregnancy. Starting from the early stages of pregnancy, 80% of healthy women experience functional changes in the urinary tract, manifested by a decrease in the tone of the moustache and hypokinesia of the ureters. Against this background, vesicoureteral refluxes develop, внутрилоханочное intra-pulmonary pressure increases, and pelvic-renal refluxes occur, leading to the penetration of urine, microbes, and toxins into the kidney tissue, which predisposes to the development of acute or exacerbation of chronic pyelonephritis. Complicated course of pregnancy in this kidney pathology occurs in 82.3-89% of cases. It triggers an inflammatory response by releasing various inflammatory signaling molecules that

promote uterine contraction and cervical maturation, which triggers labor [4,5,6].

Among the risk factors for preterm birth, medical factors are distinguished, for example, preterm birth in the anamnesis, spontaneous miscarriages, abortions, inflammatory diseases of the genital organs and urinary tract infections, as well as socio-demographic factors, including young age, low social level, unsettled family life, etc. [7, 8, 9] A significant role in the occurrence of PR plays a complicated course of pregnancy, most often it is the threat of its termination. A special place is occupied by viral infections transferred during pregnancy, including acute respiratory viral infections. In this regard, it is worth noting the increase in the number of women at risk for preterm birth, such as patients with uterine scarring, severe extragenital diseases, etc. In addition, increasing the frequency of preterm birth is associated with the widespread introduction of assisted reproductive technologies, which has led to an increase in the number of multiple pregnancies, which are one of the risk factors for preterm birth. However, these factors, analyzed individually or collectively, do not allow predicting the outcome of preterm labor for the fetus [10,11,12].

As mentioned earlier, one of the leading links in pathogenesis preterm birth is an infectious factor, because when an infection occurs in 30% of cases, spontaneous PR is observed, and in half of cases - preterm birth, complicated by the phenomena of chorioamnionitis-inflammation of the fetal membranes against the background of amniotic fluid infection. However, the presence of infection is not obligatory for the induction of an inflammatory process in the fetus. According to R. Romero et al., who analyzed the outcomes of PR Even in the gestational period from 28 to 33 weeks, in 58% of cases, an inflammatory component is present in the amniotic fluid, while it is not possible to identify the pathogen. At the same time, when preterm birth for a period of 22 to 27 weeks, the inflammatory component is accompanied by the detection of pathogenic flora. Thus, in the case of development However, at a gestation period of less than 28 weeks, septic inflammation plays a leading role, and at a gestation period of more than 28 weeks, there is no inflammatory process. A number of researchers have recently confirmed and detailed these data regarding the possible mechanism of inflammation development in the absence of an infectious pathogen [13,14,15]. Retinol-binding protein (RBP4) is one of the peptides synthesized in adipose tissue, the only specific transport protein circulating in the bloodstream, whose function is to deliver vitamin A to target tissues. It plays a key role in the development of the insulin resistance described above, modulates glucose homeostasis, and reduces insulin sensitivity. A high level of RBP4 in the blood induces the expression of the liver gluconeogenesis enzyme phosphoenolpyruvate carboxykinase and impairs the insulin signal in muscle tissue. A decrease in the level of glucose transporter GLUT4 expression leads to an increase in the level of RBP4 synthesis in adipose tissue. The concentration of RBP4 in human blood plasma can be used as nephron marker of nephropathy and cardiovascular diseases [16,17,18].

The current literature does not cover enough indications for unloading the upper urinary tract in pregnant women with obstructive lesions with the choice of the optimal method of kidney drainage, especially against the background of gestational complications. There is no unity of views on the management of obstructive pyelonephritis in pregnant women, there is no common point of view on the duration of treatment, timing and different approaches to catheterization of the renal cavity system from the standpoint of not only correcting the condition of the kidneys and urination, but also reducing the severity of gestational complications, the risk of perinatal losses. In connection with the above, the problem of developing tactics for the complex treatment of pyelonephritis and retention-obstructive lesions of the upper urinary tract in pregnant women is relevant [19, 20].

**The aim of the study is to predict the threat of preterm labor against the background of urogenital tract infection, taking into account the presence of biochemical markers.**

#### **Maternal and metody**

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To solve the tasks set in the work, 128 women (Group I-65 women with IMS and at risk preterm birth and II 63 women with preterm birth (group without infections) and 25 women in the control group are conditionally healthy pregnant women who will undergo an enzyme-linked immunosorbent

assay (ELISA). The level of metalloproteinase 12, cystatin C, RBP4 in the blood serum. In venous blood, indicators of the hemostatic system will be studied. The microbiocenoses of the vagina and urine in women at risk of preterm birth will be studied.

The criteria for selecting patients were high-risk pregnant women with various obstetric and somatic pathologies, with a gestational age of 22-36 weeks.

26.3±3.2 years in the control group of women. A more detailed study of the age history showed that women (23.1%) were younger than 20 years of age in the main group (Fig. 3). The majority of women in the main and control groups were aged 21 to 26 years. And in the control group, the majority of women were aged after 35 years (12%).

When collecting anamnesis, we took into account the place of residence of patients, since the period of treatment of pregnant women to the doctor and the receipt of asymptomatic bacteriuria during treatment and early diagnosis could depend on this.

It turned out that among the patients there were more women living in urban areas, while among the women of the control group there were more women living in rural areas.

We also took into account the employment structure of patients. As can be seen from Figure 2, among the cohort of patients with physiologically occurring pregnancies, there were more women than working women (8/32%), and among the patients in the main group, there were more women who were housewives (60%/60.3%). Among patients with preterm birth in the group without infections, female employees also prevailed (6/9. 5%).

Among the surveyed women, there were also female students : with a physiologically occurring pregnancy of 2/8%, with preterm birth group with IMS – 5/7. 7% and with preterm birth group without BMI – 2/3, 2%. When analyzing professional affiliation, we took into account the possible reaction of pregnant women to the occurrence and development of IMS, etc. As can be seen from the presented data, the frequency of occurrence of IMS and other preterm birth did not depend on professional accessories.

Each examined pregnant woman had a separate follow-up card that answered the main questions on this problem: age, pregnancy parity, anamnesis, diagnosis (main, concomitant), clinical manifestation, course of labor (through natural routes and Cesarean section) and the postpartum period.

Table №1

### Somatic analysis of the examined women

Somatic diseases	Group I, (n=65)		Group II, (n=63)		control group (n=25)	
	abs.	%	abs.	%	abs.	%
Infectious and parasitic diseases	2	3,1	2	3,2	0	0,0
Covid-19	0	0,0	0	0,0	0	0,0
Metabolic syndrome (obesity)	12	18,5	8	12,7	3	12,0
Endocrine diseases (thyroid gland)	22	33,8	20	31,7	8	32,0
Diseases of blood, hematopoietic organs	17	26,2	14	22,2	0	0,0
Myopia section Sincetepeni	14	21,5	12	19,0	4	16,0
ENT diseases	2	3,1	2	3,2	0	0,0
CVD diseases	1	1,5	1	1,6	0	0,0
Gastrointestinal diseases	4	6,2	4	6,3	1	4,0
Respiratory diseases	9	13,8	10	15,9	2	8,0

All patients included in the study were in the same age group, the average age of which was 29.8±3.8 years in the group of women with IMS and at risk preterm birth, 28, 4±4.7 years in the group of women preterm birth group without infections and

When analyzing somatic pathology in the examined women, it was found that most of the patients have a history of certain diseases (tab. №1).

Iron deficiency anemia also occurred among all the women examined, but more often among women with IMS and at risk preterm birth (97.4%). The result of a metabolic disorder is obesity.

Among patients with IMS and the threat of IIP The overall incidence of obesity was 18.5% and the group of pregnant women at risk of miscarriage without a BMI was 12.7%. Some respiratory tract diseases occurred in 2 women of the control group, in 15.9% of women without BMI and at risk of preterm birth, and in 13.8% of women with BMI and at risk of preterm birth. The incidence of thyroid diseases among women with IMS and services preterm birth was 33.88%, in the group of women without BMI and at risk of preterm birth was (31.7%) and in 8 women in the control group (32%). Diseases of the gastrointestinal tract were equally common in patients with and without ICI and men preterm birth (6.2% and 6.3%, respectively). It was also recorded in 1 woman (4%) of the control group. The percentage of occurrence of blood loss and hematopoietic organs was higher in women with IMS and services IIP (26,2 It was lower among women without BMI and those with BMI (26.2%). Myopia of various degrees occurred in women with IMS and services PR 21.5% and without ICI and with preterm birth 19%.

Currently, the question of the potential possibility of using the level of biochemical agents as markers of the severity of the inflammatory response and predictors of prognosis in various pathologies in pregnant women is widely discussed. There was an association of high plasma levels of matrix metalloproteinase-12 (MMP-12) in pregnant women with BMI (9.1-11 ng/ml in 49.2% of women) compared to pregnant women with risk of miscarriage without BMI (7.1-9.0 ng/ml in 7.9% of women) and the control group (3.1-5.0,0 ng/ml in 16% of women) (Table 2).

**Table №2**

**determination of the level of the enzyme Metalloproteinase-12**

Blood Metalloproteinase-12 level, ng/ml	group I, (n=65)		group II, (n=63)		control group (n=25)	
	abs.	%	abs.	%	abs.	%
up to 1,0	0	0,0	0	0,0	2	8,0
1,1 - 3,0	0	0,0	22	34,9	19	76,0
3,1 - 5,0	0	0,0	23	36,5	4	16,0
5,1 - 7,0	2	3,1	13	20,6	0	0,0
7,1 - 9,0	8	12,3	5	7,9	0	0,0
9,1 - 11,0	32	49,2	0	0,0	0	0,0
11,1 -13,0	20	30,8	0	0,0	0	0,0
13,1 and above	3	4.6	0	0.0	0	0.0

Cystatin C refers to cysteine protease inhibitors - enzymes that break down protein molecules to amino acids. It is produced by all cells containing nuclei, enters the bloodstream at the same rate, and is released by the kidneys. It is metabolized in the renal tubules, and insignificant protein concentrations are detected in the urine. The level of cystatin C in the blood serum is inversely proportional to the glomerular filtration rate. The worse the kidneys filter (renal failure), the higher the concentration of cystatin C. The assay is used to evaluate renal function as an alternative to creatinine testing. The advantage of this test is its high sensitivity in the early stages of acute renal failure. Unlike creatinine, it affects the rate of cystatin synthesis (table 3).

Currently, there are quite a large number of recommendations for the treatment of this pathology, including empirical antimicrobial therapy of pyelonephritis during pregnancy. However, it should be borne in mind that even the most powerful drug therapy, including antibacterial therapy, may be ineffective if the violation of the passage of urine persists. Therefore, the defining moment in the treatment of obstructive forms of the disease is the restoration of adequate urodynamics using various methods of drainage of the renal pelvis.

## determination of the Cystatin C enzyme level

Blood Cystatin C level, ng/ml	Group I, (n=65)		group II, (n=63)		control group (n=25)	
	abs.	%	abs.	%	abs.	%
1,1 - 3,0	0	0,0	23	36,5	11	44,0
3,1 - 5,0	0	0,0	32	50,8	14	56,0
5,1 - 7,0	1	1,5	6	9,5	0	0,0
7,1 - 9,0	2	3,1	2	3,2	0	0,0
9,1 - 11,0	35	53,8	0	0,0	0	0,0
11,1 - 13,0	17	26,2	0	0,0	0	0,0
13,1 - 15,1	10	15,4	0	0,0	0	0,0

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Table №4

## Indicators of the total blood count of the examined women, (M±m)

Indicators	Control group, n=25	PB group without infections n=63	IMS and services PB n=65
Leu, x10 <sup>9</sup> kl/l	7.24,24±0.11	8,0±0,12*	9,2±0,4* **
Red blood cell, x10 <sup>12</sup> cells/l	3,1616±0,04	3,13±0,04	2,95,95±0,045* **
Hemoglobin, g / ml	107.5±0.34	95±1.38*	90,0±1.5* **
Hematocrit, %	35,3 ± 1,3	32,9 ± 1,2	29,6 ± 1,1* **
Platelet count, x10 <sup>9</sup> kl/l	202,7±2,66	196,4±2,0	193,4±1,4*
ESR, mm / h	18,4±0,4	21,1±0,5*	29,8,85±1,23* **

Note: \* The values are significant in relation to the control group, \*\* The values are significant in relation to the group PR group without infections (P<0.05-0.001)

Chiclennoct leykocitov ochohoй nepvoy gpсpе kotopse, bepemehnyx c PR group without infections in cpednem coctavil 8.0±0.12X10<sup>10</sup>/l I ochohoй o wopoy gpсpе kotopse bepemehnyx c indicators IMS and menace PB coctavil 9,2±0,44<sup>v</sup>X10<sup>9</sup>/l, togda kak v kontpoflaxoy gpсpе waso znachimo v 1 mkl coctavil 7,5±0,05·10<sup>9</sup>/ l. Pokazateli ckopocти oцedanie epitpocitov (CoE), ukazyvayushiy nactenen vocpaleniia i гeнepaaцию инфlysis of the inf ektion observed in ocnovyh tldx rpсpax: ocnobно hy o y nepboy rpсpе kotopse, bepemehnyx c PB group without infections in cpednem coctavили or 17.1±0.5<sup>v</sup> mm /nac, ochohoй wopoy gpсpе kotopse bepemehnyx c indicators IMS and menace of PB showed 28.8.85±1.23<sup>in</sup>mm/nac i, in kontpoflaxoy gpсpе waso doctovepno ne 12.4±0.4<sup>in</sup>mm/nac. Ob obshevocnaliteflaxx trendx taqle cтyпeelectvuet cdvig leykocitapnoy fopmules olevo.

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## Conclusions

1. From the number of examined pregnant women with PB only 32.8% had signs of BMI. Risk factors for developing BMI in pregnant women with PB came in: EGD with the presence of OHAA (6.3%), vaginal infections (87%).

2. For women with BMI and risk of miscarriage the level of metalloproteinase 12 is increased by 2.3 times relative to the control group. For women without BMI and the risk of miscarriage are characterized metalloproteinase-12 by an 8.2-fold increase in the level of metalloproteinase-12 and a more than 2-fold increase in the level of cystatin C. At the same time, the level of total protein is reduced, the level of creatinine, urea and fibrinogen is increased.

3. Based on the obtained data, an algorithm and a scale for predicting the development risk are developed PB in urogenital infections by clinical, laboratory and biochemical markers.

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