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SEARCH FOR NEW DIAGNOSTIC MARKERS OF RENAL FUNCTION IN PREGNANT WOMEN

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▪ Over the past few years, the prevalence of chronic kidney disease in pregnant women has been increasing rapidly, which is one of the most important problems of obstetrics, urology, and nephrology. The severity of the disease is assessed by a decrease in glomerular filtration rate (GFR). However, modern formulas of GFR give errors, therefore, it is necessary to search for new diagnostic markers of renal function in pregnant women. It is believed that elimination of cystatin C from the circulation by more than 99% is carried out by the kidneys. In an intact form, this molecule is not thought to undergo either tubular reabsorption or secretion. In this sense, cystatin C can be considered an almost ideal marker of GFR. This article discusses the possibilities of using cystatin C as a marker of renal function in pregnant women.

▪ **Keywords:** cystatin C; kidney; chronic kidney disease; pregnancy; pyelonephritis; urinary tract infections.

ПОИСК НОВЫХ МАРКЕРОВ ФУНКЦИОНАЛЬНОГО СОСТОЯНИЯ ПОЧЕК У БЕРЕМЕННЫХ

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▪ За последние несколько лет большими темпами увеличивается распространенность хронической болезни почек у беременных. Это является одной из важнейших проблем акушерства, урологии и нефрологии. Тяжесть заболевания оценивают по снижению скорости клубочковой фильтрации. Однако современные формулы скорости клубочковой фильтрации дают погрешности, поэтому необходим поиск новых маркеров функционального состояния почек у беременных. Принято считать, что элиминация цистатина С из циркуляции более чем на 99 % осуществляется почками. В интактном виде его молекула, как полагают, не подвергается ни канальцевой реабсорбции, ни секреции. В этом смысле цистатин С может считаться если не идеальным, то очень близким к нему маркером скорости клубочковой фильтрации. В данной статье рассмотрены возможности применения цистатина С в качестве маркера функционального состояния почек у беременных.

▪ **Ключевые слова:** цистатин С; почки; хроническая болезнь почек; беременность; пиелонефрит; инфекции мочевыводящих путей.

In recent years, researchers around the world are actively seeking simple and accurate biomarkers of the functional conditions of the kidneys in pregnant women. This endeavor can be attributed to the spread of nephrological diseases, which rank second in incidence in the range of extragenital pathology and are often asymptomatic and/or paucisymptomatic, first manifesting during pregnancy or contributing to the development of severe complications, such as preterm delivery, preeclampsia/eclampsia, delivery of small-for-date newborns, and so on. [1].

Pyelonephritis is one of the most commonly occurring kidney diseases in pregnant women. Pyelonephritis represents an inflammatory process in the kidneys with a predominant lesion of the interstitial tissue, caused by a specific bacterial infection, along with the involvement of the pelvis and calyces [2].

For the diagnostics of renal pathology, it is essential to determine the levels of total protein and protein fractions, cholesterol, electrolytes in the blood, acid–base balance, azotemia, etc. Additionally, ultrasound examination should also be performed for the same. A biochemical blood test reveals hypoproteinemia and dysproteinemia caused by the decrease in the level of albumin and an increase in the level of globulins. Furthermore, a short-term and moderate increase in the concentrations of urea and creatinine is also noted, which indicates impaired renal function [3].

The gold standard for determining the glomerular filtration rate (GFR СКФ) is the clearance method. However, in clinical practice, special formulas, which are particularly based on determining the concentration of blood serum creatinine, are used for determining GFR. This practice assists in avoiding the organizational difficulties and technical errors associated with the collection of daily urine outputs [4].

Errors in determining GFR by creatinine level can occur due to the non-standard body sizes, nutritional habits (high-protein diet, creatine-containing dietary supplements), pronounced body mass deficiency or obesity (body mass index lower than 15 kg/m^2 and more than 40 kg/m^2), changes in the muscle tissues, pregnancy, drug administration (trimethoprim, cimetidine, fenofibrate), and analytical errors due to the effects of ketones, bilirubin, and other molecules [5, 6]. In this regard, the search continues for new markers that can improve the accuracy of diagnostics of the functional condition of the kidneys in pregnant women.

Cystatin C has been proposed as an endogenous marker for determining GFR. Cystatin C is a basic peptide consisting of 122 amino acid residues with a molecular weight of about 13,260 Da. It is an important extracellular inhibitor of cysteine proteinases belonging to the second type of the cystatine superfamily. The structure of the cystatin C gene and its promoter determines the high stability of biosynthesis of this inhibitor of cysteine proteinases [7].

The constancy of production protects the body from the uncontrolled activation of proteolysis. Because of these circumstances, the production of cystatin C is considered to be slightly dependent on inflammation, tumor growth, age, gender, muscle mass, and the degree of the body hydration [8]. Cystatin C exerts a pronounced inhibitory effect on cysteine proteinases similar to that of papain or cathepsins B, H, and L.

Numerous studies have shown that cystatin C is synthesized at a constant rate by all the cells containing nuclei and, thus, enters the bloodstream. It is filtered completely (100%) in the glomeruli, and metabolized completely (100%) in the proximal tubules (although not secreted by them).

Thus, serum cystatin C levels can be attributed to the following reasons:

1) constant rate of its synthesis is practically independent of age, gender, and body weight;

2) constant rate of its elimination from the body, which depends:

a) mainly on renal functions;

b) the presence of renal pathology that impairs renal functions.

Additionally, unexpected when the pattern of neonatal mortality was analyzed with respect to the birth weight [9].

The severity of the renal pathology indicates the filtration (typically worse) of cystatin C in the kidneys and its level in the blood. A single measurement of the blood level of cystatin C enables the calculation of GFR values with the use of special formulas [10].

Many research works have demonstrated that cystatin C is a more sensitive marker of renal

function than creatinine, especially in the cases of a moderate decrease in GFR occurring in the so-called creatinine blind area in the range of 90–60 ml/min per 1.73 m^2. Within this range, there is no proportionality between creatinine and the true GFR values determined by an exogenous marker. A meta-analysis integrating the data of 46 articles and 8 reports containing the results of the cases of about 4,500 patients and individuals in the control groups showed that cystatin C provides a more accurate approximation to the real values of GFR than creatinine. Therefore, the correlation coefficient of cystatin C concentration with actually measured GFR values amounted 0.92 versus 0.74 for creatinine. The area under curve and receiver operating characteristic analysis values for cystatin C and creatinine were 0.93 and 0.84, respectively.

As a result, a single measurement of serum cystatin C enables the calculation of GFR according to the developed formulas, of which the Hoek formula is most frequently used:

$$\text{GFR (ml/min per 1.73 m}^2) = \\ = 80.35/\text{cystatin C (mg/l)} - 4.32.$$

The following two immunochemical methods can be used for determining the levels of cystatin C: turbidimetric (the analysis is performed using conventional clinical biochemical analyzers) and nephelometric (it is more accurate and requires special equipment) methods [11].

The reference levels of cystatin C (mg/l) are 0.50–0.96 for men; 0.57–0.96 for women; 1.37–1.89 for children under 1 month; 0.73–1.17 for children aged 1–12 months; and 0.51–0.95 for children older than 1 year [10].

In 2012, experts from Kidney Disease Improving Global Outcomes recommended the use of cystatin C levels as an indicator in addition to the creatinine levels for the more accurate determination of the GFR values and the assessment of renal filtration function [12].

Because the values of cystatin C are practically independent of body weight, gender, physical activity, and diet, its use as a marker of the functional state of the kidneys in pregnant women is highly desirable. The scientific literature has presented research works on the values of cystatin C in pregnant women, but their results are contradictory.

Various studies demonstrated that the values of cystatin C increased with an increase in gestational age. This tendency was repeated in each group of pregnant women with and without pyelonephritis. Statistically significant differences were found between trimesters I and II, as well as between trimesters I and III. Trimester III is accompanied by a statistically significant increase in cystatin C values regardless of the presence of urinary tract infections (UTIs).

Therefore, most researchers agree that higher cystatin C values are diagnosed in trimester III with a normally developing pregnancy. An increase in cystatin C values during physiological pregnancy is associated with hyperfiltration. Large studies of serum and urine cystatin C values in pregnant women with UTI, including those with a high degree of inflammatory response, are needed.

A study conducted in 2016 revealed that pregnant women are characterized by an increase in the level of cystatin C in urine in trimester I. A reference interval of cystatin C equal to 0.17–0.25 mg/l in urine for pregnant women has also been obtained. However, the hypothesis of an increase in the level of cystatin C in the urine of pregnant women with preeclampsia was not confirmed [11].

The need to study cystatin C levels in pyelonephritis is attributable to fact that the risk of developing pyelonephritis throughout pregnancy reaches 40% in the presence of lower UTIs, and the risk of adverse outcomes in the development of pyelonephritis for both the mother and the fetus is twice as higher than for other UTIs.

The purpose of this study is to investigate the possibility of using serum cystatin C as a biological marker of pyelonephritis in pregnant women.

Study materials

The study enrolled 87 pregnant women with UTI. The diagnosis of asymptomatic bacteriuria or acute cystitis (lower UTI) was established in 27 (31.01%) of these patients, whereas gestational pyelonephritis or chronic pyelonephritis in the acute stage (upper UTI) was diagnosed in 60 (68.97%) patients.

At the primary stage, the blood serum concentration of cystatin C was determined in all the pregnant women. The inclusion criteria were pregnant women, aged 18–40 years, in trimester III.

The exclusion criteria included the presence of diabetes mellitus, preeclampsia (including in the medical history), a complicated UTI requiring surgical intervention (severe hydronephrosis, purulent formations in the urinary tract), and autoimmune diseases of any localization.

After processing the data, the pregnant women were distributed into three groups (A, B, and C). Group A consisted of 27 pregnant women (gestational age of 30–37 weeks) with lower UTI, who received standard therapy with antibacterial drugs and herbal uroseptics. Group B included 30 pregnant women (gestational age of 29–37 weeks) with an upper UTI, who received combined treatment with antibacterial therapy, herbal uroseptics, and the immunomodulating drug Wobenzym®. Group C included 30 pregnant women (gestational age of 28–37 weeks) with an upper UTI, who received standard therapy with antibacterial drugs and herbal uroseptics without an immunomodulating drug. Along with the general clinical examination, the culture method of isolating microorganisms was used for considering the sensitivity to antibiotics. In all the patients, the number of days from the onset of symptoms, the absence or number of relapses over the last six months, and the presence of causative agents of UTI were assessed based on the results of urine culture. The blood serum concentration of cystatin C was assessed before and after therapy using a biochemical analyzer–UniCel D × C 600 Synchron Clinical System (Beckman Coulter) – and a diagnostic kit made by Audit Diagnostics. All the studies were conducted in the D.O. Ott Research Institute of Obstetrics, Gynecology, and Reproductive Medicine.

The compilation of special diagrams, electronic spreadsheets, and the design, as well as statistical processing of the material was performed on a computer using the Microsoft Office 2016 software package with the STASTICA 10.0 software. Values of $p < 0.05$ were considered statistically significant for this study.

The interaction of several factors in the analysis of changes in the parameters under study was assessed using a double analysis of variance. Continuous variables with normal distribution are presented as arithmetic mean (M) ± standard deviation (sd). Medians [25–75th percentiles] were used in the absence of normal distribution.

The Shapiro–Wilk test was used to assess the normal distribution. Nonparametric statistical methods were applied because of the abnormal distribution in most of the groups. The data were described using the median (Me) and quartiles: Me (Q_1–Q_3). The Wilcoxon test was used to assess the level of cystatin C before and after treatment, and the Kruskal–Wallis test was used to compare the levels of cystatin C among the groups after treatment.

The statistical significance of differences between the quantitative criteria was determined by using the Mann–Whitney U test.

Research results

We examined 87 pregnant women with UTI in this study. Pregnant women were comparable in terms of age and gestational age. The age of the patients ranged from 22 to 40 years (32.4 ± 4.1 years in group A, 31.6 ± 0.9 years in group B, and 30.6 ± 0.94 years in group C). The gestation period ranged from 28 to 37 weeks (33.2 ± 0.60 weeks in the patients of group A, 31.5 ± 0.68 weeks in the patients of group B, and 32.8 ± 0.43 weeks in in the patients of group C). The average number of days from the onset of symptoms to the start of therapy was 2.5 ± 0.64 days in group A, 3.7 ± 0.32 days in group B, and 3.1 ± 0.34 days in group C. Relapses in the last six months were noted in 17.1% of pregnant women in group A, in 30.2% of patients in group B, and in 23.3% of patients in group C.

In group A, according to the results of urine culture, the majority of pregnant women had *Escherichia coli* (67%), followed by *Klebsiella pneumoniae* (18.5%), *Enterobacter faecalis* (11.0%), *Candida spp.* (2.5%), and *Proteus mirabilis* (1%). In group B, *Enterococcus faecalis* was most commonly observed bacterium (40%). *Escherichia coli* (30%), *Klebsiella pneumoniae* (20%), and *Proteus mirabilis* (10%) were also revealed in group B. In group C, *Escherichia coli* was found in 40% of the cases, *Enterococcus faecalis* was found in 20%, and *Klebsiella pneumoniae* and *Streptococcus agalactiae* was detected in 16% of cases. *Proteus mirabilis* was identified in 8% of patients by urine culture.

Table 1 presents the levels of cystatin C by groups.

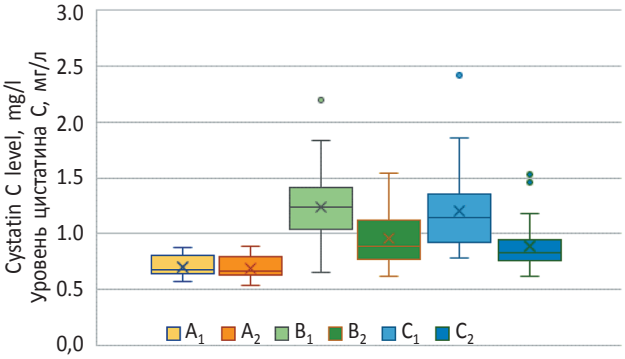
The analysis showed that the levels of cystatin C after treatment decreased statistically significantly in groups B and C ($p < 0.001$).

Serum cystatin C determination in the study groups
Определение уровня цистатина С в периферической крови у пациентов исследуемых групп

Groups	Comparison stages		*p*
	Before treatment	After treatment	
A	0,675 (Q_1–Q_3: 0,64–0,8)	0,660 (Q_1–Q_3: 0,63–0,78)	0,278
B	1,23 (Q_1–Q_3: 1,04–1,4)	0,885 (Q_1–Q_3: 0,78–1,1)	<0,001
C	1,14 (Q_1–Q_3: 0,93–1,33)	0,830 (Q_1–Q_3: 0,76–0,95)	<0,001
Comparison among the groups (after treatment)		χ^2 = 31,1; p < 0,001*; $p_{A–B}$ < 0,001*; $p_{A–C}$ < 0,001*; $p_{B–C}$ = 0,37	

N o t e. *changes in the indicators are statistically significant at p < 0.001.

There were statistically significant differences in cystatin C levels after treatment (p < 0.001). The comparison of the groups in pairs revealed that the level of cystatin C was significantly lower in group A as compared with groups B and C (p < 0.001). Additionally, statistically significant differences were not revealed between groups B and C. The results are presented in Fig. 1.



Serum cystatin C determination in the study groups: A_1 — patients with lower urinary tract infection before treatment; A_2 — patients with lower urinary tract infection after standard treatment; B_1 — patients with upper urinary tract infection before treatment; B_2 — patients after combination therapy with an immunomodulator; C_1 — patients with upper urinary tract infection before treatment; C_2 — patients after standart therapy

Определение цистатина С в периферической крови у пациентов исследуемых групп: A_1 — пациентки с инфекцией нижних мочевыводящих путей до лечения; A_2 — пациентки с инфекцией нижних мочевыводящих путей после стандартного лечения; B_1 — пациентки с инфекциями верхних мочевыводящих путей до лечения; B_2 — пациентки после проведения комбинированной терапии с иммуномодулятором; C_1 — пациентки с инфекциями верхних мочевыводящих путей до лечения; C_2 — пациентки после проведения стандартной терапии

Conclusion

UTIs belong to the category of the most common infectious diseases occurring during pregnancy and cause 10% of all hospitalizations during pregnancy. Pyelonephritis during pregnancy can lead to serious complications, such as anemia, arterial hypertension, sepsis, premature labor, and low birth weight of infants, in the mother and the fetus. That is why timely diagnostics and treatment determine the prognosis for both the mother and the fetus. The determination of cystatin C levels as a marker of the functional state of the kidneys in pregnant women is advisable because its values virtually do not depend on body weight, gender, physical activity, and diet. At the same time, the blood serum creatinine level, which was previously considered as an accurate marker of renal function, appeared to be significantly dependent on the external and internal factors. It is worth noting that with a lower UTI, the serum concentration of cystatin C did not differ from the norm. Therefore, it can be assumed that cystatin C is a diagnostic criterion and allows differential diagnostics between lower and upper UTIs. Both therapy regimens have shown their efficiency in relieving the acute manifestation of pyelonephritis. However, the susceptibility to recurrent pyelonephritis was not evaluated at this stage of the study. Such a non-invasive method will enable the obstetricians to start the treatment of pyelonephritis in a timely manner that is already at the stage of expecting the main test results.

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