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Published in the Russian Federation
European Journal of Medicine. Series B
Has been issued since 2014.
ISSN: 2409-6296
Vol. 2, Is. 1, pp. 12-17, 2015

DOI: 10.13187/ejm.s.b.2015.2.12
www.ejournal27.com



UDC 616.611 – 008.63: 618.3 – 06

Estimation of the Functional Renal Condition by Glomerular Filtration Rate in the Pregnant with Preeclampsy

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Abstract

Creatinine clearance (CC) by Reberg-Tareyev test has been analyzed with an essential condition to take urine analysis during 24 hours from pregnant women with various degree of preeclampsia. To characterize the renal excretory function in the regulation of nitrogen balance the indices of proteinemia and proteinuria have been used. Probable changes of the renal functional condition depending on the volume of 24-hour diuresis have been found. The necessity to analyze the indices using the standards for the pregnant according to the trimester of pregnancy is indicated.

Keywords: GFR (glomerular filtration rate); CC (creatinine clearance); proteinuria; preeclampsia of pregnancy.

Introduction

In clinical practice there are various formulae to calculate glomerular filtration rate (GFR) by the level of endo- or exogenous markers (Cockcroft-Gault, Bjornsson, Hull, Jelliffe-1, Mawer, Salasar-Corcoran) [1, 5, 7, 10].

The majority of experimentally reliable examinations is based in intravenous infusion of such exogenous markers as inulin, iotalamate, iohexol, markers with the use of isotopic mark (⁵¹Cr-EDTA), cystatin C protein and others [1, 5, 9].

However, the main method to estimate GFR used in clinical practice is detection of creatinine clearance (CC) considering its availability and low cost. Although, CC detection has some disadvantages, it remains rather adequate for everyday clinical work and quite available method of direct GFR measuring, and thus, it is more sensitive and specific method to find renal failure on early stages than usual evaluation of urea and creatinine contents in the blood as markers of nitrogen excretory function of the kidneys [2, 9, 11].

In fact, CC is the volume of blood plasma cleansed of creatinine per 1 minute while passing through the kidneys. The higher clearance is (to certain boundary value) the more effective

the kidneys function concerning clearance of blood from creatinine and its excretion with urine. Normal GFR is within the range 80-120 ml/min, in case age, sex and population peculiarities of patients are not taken into account [4, 7, 13].

So-called "physiological dilution of all the constants" is known to occur during pregnancy. This process is connected with increased volume of circulating plasma. In case pregnancy is physiological, GFR and circulation volume in the kidneys become 40-65 % and 50-85 % higher respectively, which characterizes the condition of physiological hyperfiltration with the increase of boundary values [6, 8, 12, 13].

Thereby, the norms peculiar for non-pregnant cannot be mechanically applied to pregnant patients. Usually pregnancy leads to increased GFR corresponding to 80-150 ml/min [5], and according to some other sources: 110-150 ml/min and it even reaches 160 ml/min in the third trimester [10]. There is another diametrically opposite opinion concerning maximal value of GFR in the first trimester of pregnancy (135 ml/min) and its gradual decrease to 110 ml/min in the last trimester of pregnancy. Before labour GFR can even be reduced to 90 ml/min [12].

Generally excepted formulae to evaluate GFR and renal excretory function are not valid for pregnant women.

One of the methods used today to estimate glomerular filtration during pregnancy is Reberg-Tareyev test on condition that urine is taken during 24 hours with CC evaluation.

Reberg-Tareyev test is examination of filtration on endogenous creatinine level. It enables to estimate filtration-reabsorption renal function on the basis of detection of minute diuresis and creatinine concentration in the blood plasma and urine. Endogenous creatinine is excreted through the kidneys by means of filtration, practically it is not reabsorbed back and not actively secreted in the tubules, and as a result its clearance reflects the volume of glomerular filtration ad maximum.

Disadvantages of this method are errors while taking urine for analysis and daily variations of GFR and creatinine excretion in time behavior. Contrary to urine creatinine its serum content is characterized by much higher stability. In addition, during pregnancy low reliability of this method might be connected with physiological stagnation of urine (up to 200-300 ml) in the dilated urinary tract and renal pelvis, due to a mechanical pressure caused by an enlarged uterus and modified hormonal background of renin-angiotensin-aldosterone system [3, 6, 13].

Materials and Methods

During the period from March 2013 to November 2014, 51 pregnant women with various degree of preeclampsia, who stayed at the Department of Anaesthesiology with beds for intensive care unit (ICU) of the Municipal Clinical Maternity Home № 1, the town of Chernivtsi were examined. To characterize the functional state of the patients' organisms certain clinical-biochemical examinations were conducted considering important prognostic constants of nitrogen balance estimation (general protein and blood albumins). General protein concentration was detected by means of the unified biuret method, albumins were detected by means of bromhexol green using the reagents of the Ukrainian producers "Filisit" and "Reagent" (Dnepropetrovsk) as well as the Polish firm "Cormay", all the reagents are certified on the territory of Ukraine.

To examine renal excretory function the concentrations of urea, creatinine, volume of daily proteinuria was detected, and CC monitoring was conducted (to estimate glomerular filtration rate and tubular reabsorption). Some patients underwent repeated CC detection to evaluate the dynamics of treatment. In general 61 examinations of GFR and CC estimation were performed.

To estimate CC urine was taken during 24 hours, for example, at 8 a.m. one day to 8 a.m. the following one. The material was taken into the container 3 liter in capacity with signs fixing urine volume with permissible variations ± 50 ml. The volume of daily urine was mixed and poured off into a dry clean tube in the amount of 5-7 ml and delivered to the laboratory for further examinations. The blood for CC was taken on empty stomach in the morning from the ulnar vein in the amount of 4-5 ml after urine had been taken. The procedures of taking blood and urine described above were conducted under supervision of senior and junior medical staff at the Department of Anaesthesiology with beds for ICU excluding errors while taking biomaterial for the examinations.

When clearance was performed physical exertion and water loading was limited for the patients, as well as meat containing food and the influence of diuretics and hormonal preparations was excluded.

Two tubes with biomaterial were delivered to the laboratory: blood and daily urine with the indicated volume of daily diuresis in milliliters.

The concentration of creatinine in urine and blood serum was detected by means of the kinetic method by Jaffe's reaction without deproteinization, which is based on measuring the rate of a coloured complex formation between creatinine and alkaline-picric acid using the set of reagents ПpAT «Reagent», Dnepropetrovsk, Ukraine. The advantage of the kinetic method application is the reduction of interfering impact of other substances. Enzymatic method (creatinase) is characterized by the highest measurement accuracy, but it is very expensive for public clinics.

The method of calculation of $GFR = (U_p \cdot V_n) / (C_p \cdot T)$,

where V_n – urine volume for 24 hours;

C_p – creatinine concentration in the serum;

U_p – creatinine concentration in the urine;

T – time of taking urine in minutes (1440 min per 24 hours).

Tubular reabsorption of the kidneys was equal the difference between glomerular filtration and minute diuresis, which was related to the volume of glomerular filtration and evaluated in percent.

Before examination urine was in 50 times diluted with water, the obtained creatinine concentration volume in urine was multiplied by the dilution coefficient.

Daily proteinuria was detected quantitatively by the turbidity reaction with sulfasalicylic acid using the set of the firm "Filisit". The principle of the method is to estimate turbidity degree of urine while adding sulfasalicylic acid, which is in direct proportion to the amount of protein and is detected by photoelectrocolorimetric method (KФK-2).

We divided the patients into four groups depending on the volume of diuresis (V_n):

I group – V_n up to 1000 ml (6 examinations);

II group – V_n from 1100 to 2000 ml (23 examinations);

III group – V_n from 2100 to 3000 ml (24 examinations);

IVgroup – V_n more than 3100 ml (8 examinations).

Considering the fact that the majority in the distribution of medical signs, especially in small samplings, is not normal, non-parametric methods of variation statistics were applied in statistical processing: Wilkison-Mann-Whitney and Craskell-Wallis criteria. The influence of factor on a sign was detected by Craskell-Wallis criterion. Independent sampling comparison was made by Wilkison-Mann-Whitney criterion. The results were considered reliable with $p < 0,05$.

Discussion

Preeclampsia of various severity was diagnosed in the patients who were examined concerning the characteristics of GFR level. The value of daily proteinuria ranged from 0,3 to 5,4 g, in three cases the test was negative. Hypoalbuminemia reflected pathological content of proteins in urine: an average content of albumin in the blood was 30,8 g/L, variations of its content was characterized by a wide range of values: from 20,8 g/L to 36,9 g/L.

In these groups average values of GFR, tubular reabsorption, minute diuresis, daily proteinuria, creatinine concentration in the blood serum and urine and their mean-quadratic variations were detected (Table 1).

Average values of daily proteinuria were the highest for two diametrically opposite groups by the volume of daily diuresis: in the group with high polyuria (more than 3100 ml) and in the group with diuresis lower than 1000 ml. In comparison of these groups by Craskell-Wallis criterion and relative to the control group (1100- 2000 ml) by Wilkison-Mann-Whitney criterion none differences were found. First of all, proteinuria is believed to be a sign of nitrogen balance disorder. After all, preeclampsia is characterized not only by the loss of low-molecular proteins during increased permeability of the renal glomeruli, in the base of which vascular disorders of an inflammatory character or structural disorganization of the basal membrane may occur; on the other hand, an intensified catabolism of tissues may occur with negative redistribution of nitrogen balance due to intoxication of the maternal body. Protein-synthesizing system becomes slower at the expense of manifestation of the adaptive-protective mechanisms. This is dangerous

for embryonic development of the fetus resulting in preterm labour or compulsory cesarean section due to indications. Protein excretion more than 3-4 g per day leads to severe hypotrophy of the fetus [13, 14].

Table 1: Estimation of Reberg-Tareyev test indices and daily proteinuria in pregnant with preeclampsia depending on the volume of diuresis

indices \ groups	I group (n=6) M ± m	II group (n=23) M ± m	III group (n=24) M ± m	IV group (n=9) M ± m
daily proteinuria (g/L)	2,19 ± 1,31	1,41± 0,46	1,37 ± 0,36	1,98 ± 0,57
minute diuresis (ml/min)	0,66 ± 0,02	1,01 ± 0,04	1,72 ± 0,04	2,55 ± 0,13
urine creatinine (mmol/L)	9,29 ± 1,25	7,12 ± 0,48	5,00 ± 0,21	3,75 ± 0,29
blood creatinine (mcmol/L)	86,57 ± 12,50	93,53 ± 4,42	85,48 ± 3,54	102,15±7,27
GFR (ml/min)	75,03 ±11,84	78,42 ± 5,89	106,92 ± 7,45	99,70±14,01
Tubular reabsorption (%)	99,00 ± 0,002	98,5± 0,001	98,2 ± 0,001	97,1 ± 0,004

Thereby, pronounced proteinuria (more than 2,0 g per day) is indicative of renal failure developed against the ground of preeclampsia of various degree. Two diametrically opposite by the volume of diuresis groups – I and IV ones – were in the risk group according to this sign.

Proteinuria in the amount of 4-5 g of protein per day is dangerous for vital activity of the embryo. Eight women out of all the number of the examined were characterized by the daily proteinuria higher than 4,2 g. If the probability of high proteinuria manifestation is expressed to the number of individuals in the group depending on the volume of diuresis the following picture is observed: in I group – **1:6**, in II group – **1:12**, in III group – **1:8**, in IV group – **1:4**. Dangerous manifestation of proteinuria is likely to be expected in case of severely pronounced enlargement (more than 3 100 ml) or in case of diuresis lower than 1000 ml.

Table 2: Comparison of all the groups by Craskell-Wallis criterion

daily proteinuria (g/L)	minute diuresis (ml/min)	urine creatinine (mmol/L)	blood creatinine (mcmol/L)	GFR (ml/min)	tubular reabsorption (%)
p>0,05	p<0,01*	p<0,01*	p>0,05	p<0,05*	p<0,01*

Note: * – the groups differ reliably.

Comparison by one-sided dispersive Craskell-Wallis analysis (Table 2) of all the groups did not find a reliable difference in the values of proteinuria and creatinemia which proves the hypothesis concerning individuality of these signs for every patient. The concentration of blood creatinine for the majority of the examined women was within the norm (44,0 – 97,0 mcmol/L), and only in 17 individuals it reached the value higher than 110,0 mcmol/L, but it was not higher than 141,4 mcmol/L. On the other hand, hypoprotein- and hypoalbuminemia are indicative of the necessity to reconsider the value of norms for the pregnant according to the trimester of pregnancy, especially when intensive growth of the maternal muscle tissue and increased fetal weight occur.

Considering our practical experience the norm of creatinine in the blood for physiological pregnancy is 40-60 mcmol/L. In case its value reaches more than 80 mcmol/L without apparent causes, it may serve as the sign of regression of nitrogen balance and changes of the renal filtration function.

The value of daily diuresis was taken as a criterion of distribution into the groups. It was II group with the optimal value of diuresis without the signs of poly- and initial oliguria which became the control one. The degree of preeclampsia and value of proteinuria being rather changeable were not taken as differentiation criterion. Besides, CC was conducted in case of satisfactory condition of the

patient in order to give maximal characteristic of the renal functional state without distortion of clinical manifestation under the influence of additional factors.

Non-parametric statistical Wilkison-Mann-Whitney criterion, applied to estimate the difference between both samplings by the level of any properly measured sign, enables to find differences in the meaning of the parameter between small samplings, as the groups with the smallest and largest volumes of diuresis were insignificant by the number of the patients examined (Table 3).

Tables 2 and 3 illustrate that the groups possess 100 % difference by the value of tubular reabsorption and minute diuresis which is indicative of a correct choice of diuresis sign as a criterion of intergroup comparison.

Table 3: Groups in comparison with the control# by Wilkison-Mann-Whitney criterion

group	daily proteinuria (g/L)	minute diuresis (ml/min.)	urine creatinine (mmol/L)	blood creatinine (mcmol/L)	GFR (ml/min)	tubular reabsorption (%)
I (n=6)	p>0,05	p<0,01*	p>0,05	p>0,05	p>0,05	p<0,05*
III(n=24)	p>0,05	p<0,01*	p<0,01*	p>0,05	p<0,01*	p<0,05*
IV (n=9)	p>0,05	p<0,01*	p<0,01*	p>0,05	p>0,05	p<0,01*

Note: # – Vn from 1100 to 2000 ml (n=23); * – the groups differ reliably

The values of tubular reabsorption norm constituting 98-99% should be revised, but it is the difference within the limits of one percent that might be prognostic and informative for the pregnant with preeclampsia of various degrees.

It should be noted that the indices of Na⁺ K⁺ excretion by the kidneys are an important condition of many-sided estimation of the renal functional state, GFR processes and tubular reabsorption. In the proximal tubular portions of the kidneys Na⁺ reabsorption occurs, by means of facultative reabsorption natriuretic renal function in the distal portions is regulated. During the period of pregnancy approximately 30-50 g of sodium is retained in the woman's organism, the amount of potassium becomes 30% higher (it promotes proliferation of tissues). At present the laboratory is not equipped with the analyzer to detect electrolytes.

The functional renal condition in pregnant women with preeclampsia is estimated with an essential condition to take urine analysis during 24 hours, which enables to make maximally accurate evaluation of creatinine and protein excretion with urine during 24 hours. The comparison of all the groups found a reliable difference in the indices of minute diuresis, urine creatinine, GFR and tubular reabsorption. The groups with moderate and pronounced polyuria differ reliably by these indices from the group with normal daily diuresis (from 1100 to 2000 ml). The values of proteinuria and concentration of blood creatinine are only individual characteristics for every patient.

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