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COMPARISON OF THREE FORMULAS TO EVALUATE ACUTE RENAL FAILURE IN PREECLAMPTIC PUERPERAL WOMEN

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Comparison of three formulas to evaluate acute renal failure in preeclamptic puerperal women

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Introduction: Acute renal failure in puerperal women who have suffered preeclampsia and HELLP syndrome has been scarcely studied. Aim: to compare the Cockroft-Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration equations with the 24 hour creatinine clearance formula in puerperal women. Materials & Methods: This was an observational study. The selected formulas were calculated at 1, 8, 16 and 24 hours after delivery. Pearson correlation and Bland-Altman tests were performed. Results: 38 patients (mean age 26.4 years) were included. The three highest correlation coefficients with the 24 h creatinine clearance were the Modification of Diet in Renal Disease at 8 hours (r^2 = 0.920), and the Chronic Kidney Disease Epidemiology Collaboration equation at 24 (r^2 = 0.847) and 16 hours (r^2 = 0.842) post-delivery. Conclusion: In puerperal women who have suffered preeclampsia and HELLP syndrome, the Chronic Kidney Disease Epidemiology Collaboration equation shows more consistent results the first 24 hours post-delivery.

Keywords: *CKD-EPI, creatinine clearance, HELLP syndrome, MDRD, preeclampsia.*

Босанғаннан кейінгі преэклампсиясы бар әйелдердің жіті бүйрек жетіспеушілігін бағалаудың үш формуласын салыстыру

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Преэклампсия және HELLP синдромымен ауырған жүкті әйелдердегі бүйрек жетіспеушілігін зерттеу – жоқтың қасы.

Мақсаты: босанғаннан кейінгі әйелдерде 24 сағат ішінде кератинин клиренсін анықтай отырып, Cockroft-Gault, MDRD, CKD-EPI формулалары бойынша шумақтық сүзілу жылдамдығының көрсеткіштерін салыстыру.

Материалдар мен әдістері: бақылау зерттеуі жүргізілді. Таңдалған формулалар босанғаннан кейін 1, 8, 16 және 24 сағат сайынға есептелді. Пирсон корреляциясы мен Бланда-Альтмана тесттері жүргізілді.

Нәтижелері: зерттеуге 38 пациент (орташа есеппен 26,4 жастағы) қатыстырылды. Клиренсті креатининнің корреляциясының үш ең жоғары коэффиценті босанғаннан кейін 24 сағат ішінде 8 сағаттан соң (r^2 = 0,920) MDRD, 24 сағаттан соң (r^2 = 0,877) және 16 сағаттан соң (r^2 = 0,842) CKD-EPI болды.

Тұжырым: преэклампсия және HELLP, CKD-EPI синдромымен ауырған пациенттерде босанғаннан кейін алғашқы 24 сағатта айтарлықтай кезекті нәтижелерді көрсетті.

Негізгі сөздер: *CKD-EPI, креатинин клиренсі, HELLP синдромы, MDRD, преэклампсия.*

Сравнение трех формул для оценки острой почечной недостаточности у женщин с преэкламсией после родов

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Острая почечная недостаточность у беременных женщин, перенесших преэклампсию и синдром HELLP, практически не изучалась.

Цель: сравнить показатели скорости клубочковой фильтрации по формулам Cockroft-Gault, MDRD, CKD-EPI с определением клиренса креатинина за 24 часа у женщин после родов.

Материалы и методы: проводилось наблюдательное исследование. Выбранные формулы были рассчитаны через 1, 8, 16 и 24 часа после родов. Были проведены корреляция Пирсона и тесты Бланда-Альтмана.

Результаты: в исследовании включены 38 пациентов (средний возраст 26,4 года). Три самых высоких коэффициента корреляции с клиренсом креатинина за 24 часа были по MDRD через 8 часов (r^2 = 0,920), по CKD-EPI через 24 (r^2 = 0,877) и 16 часов (r^2 = 0,842) после родов.

Вывод: у пациентов, перенесших преэклампсию и синдром HELLP, CKD-EPI показала более последовательные результаты в первые сутки после родов.

Ключевые слова: *CKD-EPI, клиренс креатинина, синдром HELLP, MDRD, преэклампсия.*

Introduction. During pregnancy, renal plasma flow and glomerular filtration rate (GFR) increase by 40–65 and 50–85%, respectively [1]. Of particular concern, preeclampsia, the most serious hypertensive complication during pregnancy, occurs in 3–5% of pregnancies and can be catastrophic if it goes undetected or untreated evolving to eclampsia [2]. Moreover, 95% of deaths worldwide attributed to preeclampsia occur in developing countries [3]. In cases of preeclampsia, effective renal plasma flow and GFR are decreased in relation to normal pregnancies.

Acute renal failure corresponds to 1-5% of the complications of preeclampsia [4], mostly associated with HELLP (Hemolysis, Elevated Liver enzymes Low Platelet count) syndrome (45-50%), abruptio placenta (30%) and other causes (20%). While in USA it is reported a case of acute renal failure per 15,000 pregnant women, in Mexico, the incidence of acute kidney injury (AKI) secondary to preeclampsia-eclampsia is reported in 11.8% [5,6].

It has been considered that the relationship between the serum creatinine and GFR is hyperbolic not linear, which results in a low diagnostic sensitivity for detection of acute renal failure. Furthermore, currently available evidence, agree that the evaluation of renal function should not rely solely on the results of the serum creatinine concentration [7].

Actual measurement of GFR with the 24 hour Creatinine Clearance (24 h CrCl) is recognized as the best method to evaluate kidney function. The values of references, related to age, sex and body surface are approximately 130 and 120 ml/min/1.73 m² in young men and non-pregnant women with a nadir in pregnancy up to 135 ml/min/1.73 m² [7,8].

Until now, there are over 40 formulas to calculate GFR, most of them for chronic renal failure, but the formula developed by Cockcroft and Gault has probably been the most used for ambulatory monitoring of renal function. This formula has a good correlation with the true GFR and is clinically useful in patients of 20-100 years; however, it is overestimated in situations of advanced renal insufficiency and especially in obese and edematous patients [9-11].

On the other hand, the Modification of Diet in Renal Disease (MDRD), combines nutrition and sociodemographic variables and is recommended by the National Kidney Disease Education Program (NKDEP) to measure GFR in the adult population [12,13].

Lastly, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed in an effort to create a formula more precise than the MDRD, especially when actual GFR is > 60 ml/min/1.73 m^2 [14].

Certainly, there are previous comparison with the above mentioned formulas [15,16] unfortunately, the information of comparing eGFR formulas for acute renal failure associated with pregnancy or postpartum preeclampsia syndrome is scarce [17,18]. The principal aim of this study was to compare the Cockroft-Gault, CDK-EPI and MDRD equations with the 24 h CrCl formula for estimating GFR in puerperal women with the diagnosis of AKI associated with preeclampsia and HELLP syndrome.

Material and Methods. In this prospective, descriptive, longitudinal, comparative, and non-randomized clinical study, all puerperal women with the diagnosis AKI associated with preeclampsia and HELLP syndrome attended at the Obstetric Intensive Care Unit (O-ICU), from September 2012 to September 2013 were analyzed. Each subject signed the acceptance of the study protocol. Preeclampsia was diagnosed if blood pressure was ≥140/90 mmHg and proteinuria ≥300 mg/day at anytime from week 20 of gestation. Women with mild or severe preeclampsia, who did not develop some degree of renal failure, were not included. Women requiring renal replacement therapy in acute or who developed AKI not associated with preeclampsia were discarded from the final analysis.

Medical history and anthropometry. Patients who took part in the investigation were subjected to a complete direct medical history. Every patient weight was determined with a calibrated scale (Brand HILL-ROOM®). Height was measured with a stadiometer. Body Mass Index (BMI) was calculated as weight (kg) divided by height (m) squared. Blood pressure was recorded at each visit using a standard sphygmomanometer (Riester Big Ben® Square, Germany) and appropriately sized cuff.

Laboratory analysis. All patients had a central venous access (subclavian, jugular or percutaneous), to facilitate blood samples that were obtained by aseptic and antiseptic techniques at 1, 8, 16 and 24 hours. All patients underwent standard care, including routine laboratory tests with a fasting period of eight hours: albumin (mg/dl), electrolytes (mg/dl), creatinine (mg/dl), urea (mg/dl)

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(Dimension® R Max, SIEMENS, Germany). To collect 24 hour urine, a urinary catheter was placed that was also used for the 1, 8 and 16 hours. All these tests were measured according to standardized procedures recommended by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).

Glomerular filtration rate. The GFR determination was made with the next aforementioned formulas through the electronic applications Clinic Calc® and Medical Pro® for iPod®:

24 h CrCl

$$CrCl = \frac{UCr \times Vm}{SCr}$$

where: UCr = concentration of creatinine in urine over 24 hours (mg/dl), Vm = Urinary volume (ml/min), SCr = serum creatinine (mg/dl).

Cockcroft and Gault

eGFR (ml/min) = [((140-age) x weight)/(72 x SCr)] x 0.85 if female

Age is expressed in years, weight is expressed in kilograms, and SCr is expressed in mg/dL.

MDRD

eGFR (ml/min/1.73 m²) = 186 x $SCr^{(-1,154)}$ x $Age^{(-0,203)}$ x 0.742 (woman) x 1.210 (if black)

Where SCr = serum creatinine (mg/dl).

CKD-EPI

eGFR = 141 X $\min(SCr/\kappa,1)^{\alpha}$ X $\max(SCr/\kappa,1)^{-1.209}$ X 0.993^{Age} X 1.018 [if female] X 1.159 [if black]

Where SCr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.

Acute Kidney Injury Network (AKIN)

The AKIN stage was classified with the calculation of renal failure index (RFI):

$$RFI = \frac{UNa}{UCr/SCr}$$

where UNa = urinary sodium (mg/dl), UCr = concentration of creatinine in urine over 24 hours (mg/dl), SCr = serum creatinine (mg/dl).

Bioethical implications. This protocol was approved by the Ethical and Research Committee (code: 217B500402013048). In accordance with the National Ministry of Health and the Declaration of Helsinki (Fortaleza, Brazil), this study was classified as zero risk to participants, since it did not involve added procedures to those strictly necessary to the high standard attention in the O-ICU.

Statistical analysis. The results were expressed as mean ± standard deviation (SD). Mann–Whitney U-test was used to compare the variables by AKIN classification. Lineal regression analysis for each of the formulas at 24 hours and age, BMI and SCr as predictors was also used. The association between two eGFR formulas was carried out using a linear regression analysis, and expressed as a result of the Pearson correlation coefficient (SPSS v.20, IBM, USA). The analysis of concordance between two tests was conducted with the Bland-Altman method (MedCal 15.2.2, MedCalc Software bvba, Ostend, Belgium). Worth the significant $p < 0.05$ was considered.

Results. The study was settled for a total of 38 patients aged between 17 and 36 years old with an average of 26.4 years of age. Anthropometric and laboratorial results were presented as mean ± standard deviation (SD). Table 1 shows the general characteristics of the patients.

In relation to the renal failure 10.52% (n = 4) had AKIN injury I, 73.68% (n = 28) were classified as AKIN II, and only 15.78% (n = 6) had AKIN III. Furthermore, 84.21% (n = 32) of the patients had RFI < 1 (hypovolemia, associated with prerenal renal failure), and only 15.78% (n = 6) presented a RFI > 1 (failure of renal origin related to acute tubular necrosis), there was not any case with failure of postrenal origin. By comparing AKIN I vs AKIN II there were differences in SNa (hour one) (P = 0.020), and as expected, in the four time measures of SCr (P = 0.002, 0.001, 0.001 and 0.002 for the hours 1, 8, 16 and 24). Between AKIN I and AKIN III the SNa was different at the eight hours of quantification (P = 0.019) and the four points of SCr measure showed the same significance (P = 0.010). The behavior between AKIN II and III was similar to the previous comparison (P = 0.001 for SNa at eight hours and $P \leq 0.001$ in the four points of SCr measure).

Taking into account age, BMI and the first SCr in lineal regression models for each of the formulas at 24 hours we got the data of Table 2, corroborating that changes in these three predictors are associated with changes in the estimation formulas of GFR.

When using the 24 h CrCl it was obtained an average of 44.4 ml/min/1.73 m² ± 29.05, range 11-149. The correlation coefficients for every formula with different time and the 24 h CrCl, showed the next values in decremental order, MDRD (8 hours) ($r^2 = 0.920$), CDK-EPI (24 hours) ($r^2 = 0.847$), CDK-EPI (16 hours) ($r^2 = 0.842$), MDRD (24 hours) ($r^2 = 0.827$) [Table 3]. The Bland-Altman plots for MDRD at 8 hours and CDK-EPI at 24 hours are shown in Figures 1 A and B.

In general, with the Crockoft-Gault the values were higher than with the 24 h CrCl. In contrast, the calculated values by MDRD were lower. As a whole group, the CDK-EPI formula shows better correlation (two times) than the MDRD within the first 24 hours.

Discussion. The mortality of pregnancy complicated acute renal injury remains unacceptably high. Being mandatory a more intensive and precise evaluation of this disease.[19] Despite the existence of plasma or urinary markers such as inulin, chromium-51 labeled ethylenediamine tetraacetic acid (Cr EDTA), diethylenetriaminepentaacetic acid (DTPA) or iohexol, to evaluate renal function, the clearance of these markers is complex in clinical practice [20]. Taking into account this information, the 24 h CrCl is still accepted as the best overall measure of kidney function [11].

In relation to the general characteristics of our patients, the age was in agreement with previous publication of

Table 1. Anthropometric and clinical characteristics of the population (mean ± 1 Standard Deviation [SD])

	Mean	SD	Range
Age (years and months)	26.4	6.8	17 – 39
BMI (kg/m^2)	30.4	4.6	21.4 - 38.7
BSA (m^2)	1.7	0.13	1.4 – 2
SCr^a	2.07	0.67	1.07 – 3.7
SCr^b	2.07	0.70	1.1 – 3.9
SCr^c	1.98	0.71	0.91 3.81
SCr^d	1.88	0.78	0.66 – 3.85
UCr^a	67.9	30.7	24 – 184
UCr^b	71.5	34.4	18.2 – 181
UCr^c	63.7	30.9	10 – 140
UCr^d	69.4	30.7	16.4 - 147

BMI: Body Mass Index; BSA: Body Surface Area, SCr: serum creatinine, UCr: urine creatinine. 1 hour, b: 8 hours, c: 16 hours, d: 24 hours

Table 2. Lineal regression for the final end points of each formula with age, BMI and SCr

	P	95% CI
Age	0.024^a 0.045^b 0.006^c 0.362^d	-1.55 – -0.11^a -1.05 – -0.01^b -2.37 – -0.42 -1.39 – 0.52
BMI	0.010^a 0.010^b ≤ 0.001^c 0.243^d	0.36 – 2.47^a 0.26 – 1.79^b 1.64 – 4.49 -0.58 – 2.22
SCr	≤ 0.001^a ≤ 0.001^b ≤ 0.001^c ≤ 0.001^d	-37.10 – -22.78^a -25.66 – -15.28^b -47.80 – -28.41 -42.32 – -23.20

BMI: Body Mass Index, SCr: serum creatinine.
a: CDK-EPI, b: MDRD, c: Crockoft-Gault, d: 24 h CrCl.

complicated obstetrical patients in Mexico.[21] Based on the study of Orozco et al. [5] who published that most of the patients with renal failure in pregnancy had HELLP syndrome 55.2% (n = 38), we only evaluated women with renal failure and this syndrome.

We believe it is extremely important to diagnose correctly cases of AKI in pregnancy and puerperium, due to the fact of the future prognosis related with the persistence of renal failure [22], although the main determinants to be correlated with the persistence of renal failure seems to be advanced age and higher BMI [23]. In this regard, the association of AKIN grade and RFI that we have found corroborates the descriptions of Tenorio, et al. who mentioned that prerenal failure patients are associated with hypovolaemia [24].

There have been several comparative studies of eGFR formulas against 24 h CrCl, however, most of them have been focused on chronic kidney injury. Despite the existence of huge information about the more precise GFR estimation with other formulas than the Cockcroft-Gault, this last is still been widely used [23]. In Mexico, Capellini et al. has made an approach, in non-pregnant woman, referring that the MDRD formula is as reliable as the 24 h CrCl [13]. Contrasting with other nations, when using the MDRD formula and despite the option of a mathematical constant for black people, we could not apply it as there was no any woman of this race; we believe this trend will change in the future with the low, but constant immigration into Mexico of foreign countries including Africa [25].

Since one of the main limitations of estimating GFR by MDRD is their low correlation with the true GFR values above 60 ml/min/1.73m^2 [26]. Levey et al. published that CKD-EPI should replace MDRD in routine clinical practice [27]. Furthermore, several international groups recommend

CDK-EPI over MDRD [28,29].

In the work of Alpert they found that neither Cockcroft-Gault nor MDRD formulas performed satisfactorily, with the Cockcroft-Gault formula routinely overestimating GFR and the MDRD formula significantly overestimating (majority of patients) and underestimating (minority of patients) GFR [30]. In this line, in our work, we also noted that trend. Another aspect deserve special attention, despite MDRD showed the best correlation at 8 hours post delivery, its behavior at 16 and 24 hours was disappointing, on the contrary CDK-EPI kept more consistent values.

Strictly speaking of puerperal women who suffered from preeclampsia, studies of GFR evaluation are not so extensive [Table 4] [31-35]. Specifically, Hladunewich et al. [33] concluded that the functional manifestations of the glomerular endothelial injury of preeclampsia largely resolve within the first postpartum month. Whereas Pechère-Bertschi et al. [34] used the the Cockroft-Gault formula reporting hyperfiltration, Lopes van Balen et al. [35] preferred the CDK-EPI. The same group of Alpert developed a new equation, the preeclampsia GFR (PGFR), based on ethnicity [36], but has not been tested in puerperal women.

A limitation of this study was that as 100% of patients were referred from other health institutions, it was not possible to register pre-pregnancy values of weight and

Table 3. Concordance analysis and correlation

Formula[J] and time	Mean	Range	r^2	Bland Atman		
				Mean	(-1.96 x SD)	(1.96 x SD)
CrCl[d]	44.4	11-149	1			
MDRD[b]	30.7	11-71	0.920	13.7	-20.6	48
CDK-EPI[d]	45.2	16-121	0.847	-0.8	-31.2	29.5
CDK-EPI[c]	40.8	16-97	0.842	3.5	-28.1	35.1
MDRD[d]	35.4	12-83	0.827	9	-25.3	43.2
CDK-EPI[a]	37.3	16-79	0.826	7	-28.1	42.1
CG[d]	62.9	23-157	0.820	-18.5	-57.9	20.8
MDRD[c]	31.7	11-73	0.819	12.6	-24.8	50.1
CDK-EPI[b]	37.7	14-79	0.810	6.6	-29.2	42.4
CG[b]	54.1	22-121	0.797	-9.7	-44.1	24.7
CG[a]	53.2	24-113	0.786	-8.9	-44.1	26.4
CG[c]	57.2	25-140	0.783	-12.8	-49.4	23.7
MDRD[a]	29.7	12-60	0.782	14.7	-26	55.4

CK: Crockoft-Gault, CDK-EPI: Chronic Renal Disease Epidemiology, MDRD: Modification of Diet in Renal Disease, CrCl: creatinine clearance. Media adjusted for weight, height and BMI, plus rank and Pearson correlation with estimated bias and correlation study by Bland Altman method. a: 1 hour, b: 8 hours, c: 16 hours, d: 24 hours. [J]: ml/min/1.73m^2

Table 4. Studies focused on puerperal renal function in women affected by preeclampsia

Author	Stage	Observation
Kaleta T. [31]	Pregnancy-puerperium	44 preeclamptic patients evaluated at time of delivery and at 6 months and 12 months postpartum.
Pahwa N. [32]	Puerperium	Description of causes of post-partum AKI, including 11 cases of preeclampsia.
Hladunewich MA. [33]	Puerperium	Evaluation of glomerular function over 4 wk postdelivery in 57 women with preeclampsia.
Pechère-Bertschi A. [34]	Puerperium	They studied 127 post-preeclamptic women at 6 weeks post-partum.
Lopes van Balen VA. [35]	Puerperium	775 primiparous women with a history of preeclampsia were included and evaluated at least one month post-delivery.
AKI: acute kidney injury, wk: weeks.		

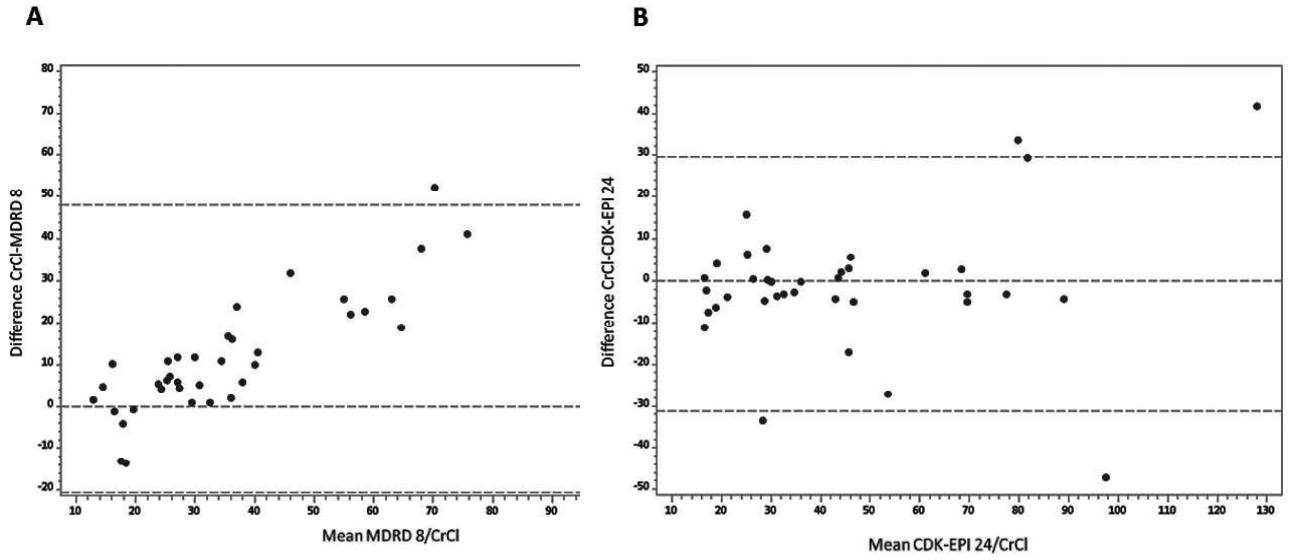

Figure legends

Figure 1. Bland-Altman plots of A) MDRD at 8 hours and 24 h CrCl and B) CDK-EPI at 24 hours and 24 h CrCl. MDRD: Modification of Diet in Renal Disease, CDK-EPI: Chronic Kidney Disease Epidemiology Collaboration.

creatinine to determine more accurately the degree renal injury. Notwithstanding, the major strength of this effort has been the evaluation at several time points of the three main eGFR formulas, giving support to the recommendation of preferring CDK-EPI for a close monitoring in puerperal women who have suffered from preeclampsia an HELLP syndrome.

We conclude that, in puerperal women who have suffered preeclampsia and HELLP syndrome, the MDRD formula offers the best option for an initial evaluation of renal function, while de CDK-EPI formula can be considered for close monitoring in the first 24 hours. In any case, it is without doubt the discontinuation of the Cockroft-Gault formula. Additionally, we think it is mandatory to establish a re-categorization of renal function one month after delivery aimed at those patients with diagnosis of AKIN II or III, due to the risk of developing chronic hypertension, renal failure or metabolic syndrome.

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