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Original Article

Biochemistry Section

Pre-Eclampsia: Epidemiology and Renal Biomarkers at Brazzaville University Hospital

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ABSTRACT

Introduction: Renal function exhibits physiological changes during the gestational period such as increased renal blood flow and glomerular filtration. These effect certain renal biomarkers whose normal and abnormal nature is necessary to be apprehended.

Aim: To analyse the epidemiological characteristics and renal biomarkers during Pre-Eclampsia (PE) at the Brazzaville University Hospital.

Materials and Methods: A case-control study was conducted at the Brazzaville University Hospital from 1 June to 30 November 2018, comparing PE and non-hypertensive gestates according to the ratio of one case for two controls. Assays for renal biomarkers were performed spectrophotometrically and potentiometrically. The variables studied were epidemiological, clinical, and renal biomarkers including creatinine, creatinine clearance, uraemia, serum uric acid, 24-hour creatinine, 24-hour proteinuria, sodium, chloride, and potassium. The tests of t-student and Mann Whitney were used respectively for the comparison of means and medians. The p-value of the probability was considered significant for a value less than 5%. A multivariate analysis was performed to eliminate confusion bias.

Results: PE were not different from controls with respect to median age {31.5 years (23-39.5) vs. 28 years (23.5-32), p>0.05}; parity {1.5 (1.5-2.5) vs. 1.5 (1.5-2), p>0.05} and the term of pregnancy (32.2±2.8SA vs. 32.1±2.7SA, p>0.05). Diuresis was lower in the cases (852.5 mL vs. 1365 mL, p<0.05). In bivariate analysis, renal markers associated with pre-eclampsia were serum creatinine (81.5 µmol/L vs. 56.5 µmol/L, p<0.05), creatinine clearance (91.8 mL/min vs. 140, 1 mL/min, p<0.05), serum uric acid (408 µmol/L vs. 250.5 µmol/L, p<0.05), and hypocreatinuria (p<0.05). The concentrations of azotaemia and electrolytes were not different from those of the controls. After logistic regression, the renal biomarkers retained were hypocreatinuria (p<0.05) and hyperuricaemia (p<0.05). Renal biomarkers were not influenced by age, parity, and the term of pregnancy (p<0.05).

Conclusion: Although having identical epidemiological characteristics, creatinuria and serum uraemia are significantly disturbed in pre-eclamptic patients. A subsequent multi-center study integrating multi-organ recall would clarify their prognostic value as well as the biological profile of PE in Brazzaville.

Keywords: High blood pressure, Kidney biochemistry, Pregnancy

INTRODUCTION

Physiological changes in renal function during pregnancy affect certain renal biomarkers, the normal and abnormal nature of which is necessary to understand [1]. The sudden or progressive disappearance of these renal physiological adaptations contributes to the pathophysiological processes observed during PE [2]. PE is a vasculo-renal syndrome that associates high blood pressure and significant proteinuria greater than 0.3 g/24 hours from 20 weeks of amenorrhea (SA). PE is observed in 4 to 6.6% [3,4] during pregnancy, in which body is already undergoing physiological changes among others renal changes, remains a concern for practitioners. It is a vascular event related to long-term renal and vascular complications [3].

At the Brazzaville University Hospital, studies have generally concerned hypertension during pregnancy and its complications without addressing renal biochemical markers [5,6]. The present study aimed to analyse the epidemiological characteristics and renal biomarkers during PE.

MATERIALS AND METHODS

It was a case-control study conducted from June 1st to September 30th, 2018, in the Departments of Gynaecology-Obstetrics and Biochemistry of the Brazzaville University Hospital Centre, comparing a ratio of one case for two witnesses, preeclamptic (case) pregnancies to non-hypertensive ones (controls).

PE was defined as systolic blood pressure greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg associated with proteinuria greater than 0.3 g/24 hours occurring after 20 weeks of amenorrhea [7]. Pregnant women whose serum was haemolysed after centrifugation were not included in the study. The variables studied were age, parity, term of pregnancy, blood pressure, blood renal biomarkers (creatinine and creatinine clearance, uraemia, serum uric acid, ionogram) and urine (24-hour proteinuria and creatinine).

We chose a ratio of one case to two witnesses. Thus, the minimum sample size for statistical analysis was 96, or 32 cases for 64 controls. Written consent was first obtained during an information session. The study carried in the Republic of Congo, obtained the approval of the ethics committee of Brazzaville University Faculty of Health Sciences N°085 of August 08, 2018.

For the blood test, four millilitres of whole blood were collected by venepuncture at the bend of the elbow and collected in a heparin tube in pregnant patients under fasting conditions. Blood samples were centrifuged at 3000 rpm for 5 minutes to obtain plasma. The collection of urine was done by urination in a 5-liter aseptic container for 24 hours. The serum creatinine, uraemia, serum uric, proteinuria, and creatinuria were measured spectrophotometrically using the CYAN Start semi-automated system. Proteinuria was preceded by a test strip impregnated with a chromogenic, bromophenol blue. Sodium, chloride and potassium were assayed by potentiometry using the 9180 AVL analyser.

The standards for renal biomarkers were as follows: - creatinine (50-100 µmol/L); Creatinine clearance (87-107 mL/min) - Uraemia (2.5-7.6 mmol/L); Uricaemia (180-300 µmol/L) - Natremia (133-143 mmol/L); Kaliemia (3.6-5 mmol/L); Chloremia (100-110 mmol/L) - Creatininuria 24 hours: 120-210 µmol/kg/24 h (i.e., 13-15 mg/kg/24 h) - Proteinuria 24 hours: <50 mg/L.

STATISTICAL ANALYSIS

The software Epi-info 7.2 was used for data analysis. Chi-square test of Pearson and Fisher were used for the comparison of percentages. The tests of t-student and Mann Whitney were used respectively for the comparison of means and medians. The Odds Ratio and its 95% confidence interval not including 1; allowed to appreciate the association between two variables. The p-value of the probability was considered significant for a value less than 5%. A multivariate analysis was performed to eliminate confusion bias.

RESULTS

Patients were similar in age, parity and term of pregnancy. Oliguria was significantly associated with PE [Table/Fig-1] with a median diuresis of 852.5 mL/24 h (755-982.5) vs. 1365 mL/24 h (1225-1605).

	Case N=32	Controls N=64	OR	IC (95%)	p-value
	n (%)	n (%)			
Age (years)					
Median (q1-q3)	31.5 (23-39.5)	28 (23.5-32)			0.07
Parity					
Median (q1-q3)	1.5 (1.5-2.5)	1.5 (1.5-2)			0.68
Term of pregnancy (AW)[1]					
Mean±SD	32.28±2.8	32.17±2.7			
Diuresis/24					
Oliguria	11 (34.4)	1 (1.6)	31.7	4.1-14.4	0.00001
SBP[2] (mmHg)					
(140-159)	1 (3.1)				
(160-220)	31 (96.9)				
DBP[3] (mmHg)					
(90-109)	31.9 (96.9)				
(110-120)	1 (3.1)				

[Table/Fig-1]: Epidemiological and clinical characteristics of pregnant women.
[1]Amenorrhea weeks
[2]Systolic blood pressure
[3]Diastolic blood pressure

Renal blood biomarkers are shown in [Table/Fig-2]. The proteinuria of 24H was significant in 68.7% of cases of PE (n=22) and massive in 31.3% (n=10). Compared with non-hypertensive pregnant, PE produced hypocreatinuria {56.3% vs. 3.1%, OR=39.8 (8.2-191.9), p<0.00004}. After logistic regression, the renal biomarkers associated with PE were hypocreatinuria {ORa=22.5 (4.1-12.3), p<0.05 and hyperuricaemia {ORa=26.7 (7.1-9.9), p<0.05}. Age, parity, and term of pregnancy were not associated with disruption of renal biomarkers in PE [Table/Fig-3].

	Case N=32	Controls N=64		OR	IC (95%)	p-value
	n (%)	n (%)				
Hypercreatininemia (µmol/L)[1]	9 (28.1)	3 (4.7)		7.7	1.7-4.5	0.002
Creatinine clearance (mL/min)[2]	8 (25)	-	-			0.00007
Hyperurea (mmol/L)[3]	1 (3.1)	-	-			0.33
Hyperuricaemia (µmol/L)[4]	23 (71.9)	4 (6.3)		35.9	9.5-17.5	0.00001
Natremia (mmol/L) Mean±SD	139.3±2.8	137.1±9.1				0.2
Kaliemia (mmol/L) Median (q1-q3)	3.8 (3.2-4.2)	3.8 (3.3-4)				0.4
Chloremia (mmol/L) Mean±SD	105.1±7.1	104.5±7.4				0.7

[Table/Fig-2]: Blood renal biomarkers.
[1]Median creatinine (µmol/L): 81.5 (68.5-95) vs. 56.5 (49.5-63.5)
[2]Median creatinine clearance (mL/min): 91.8 (77.7-112.7) vs. 140.1 (126.9-165.4)
[3]Median uraemia (mmol/L): 3.1 (2.2-4.7) vs. 2.3 (1.4-3.4)
[4]Median serum uricaemia (µmol/L): 408 (310-550) vs. 250.5 (89-572)

	Case n (%)	Controls n (%)	p-value
Age median (years) (q1-q3)	27 (23-38.5)	39 (26-40)	0.15
Parity median (q1-q3)	1 (0-2.5)	2 (1-3.5)	0.14
Term of pregnancy (AW)[1]			0.9
<34	11 (47.8)	5 (55.6)	
≥34	12 (42.2)	4 (44.4)	

[Table/Fig-3]: Influence of epidemiological and clinical characteristics on renal biomarkers.
[1]Amenorrhea weeks

DISCUSSION

In this series, hyperuricaemia, hypercreatininemia, and decreased urine creatinine were the renal biomarkers associated with PE, corroborating results of Khaliq OP et al., [8]. Indeed, compared to non-hypertensive gestants, preeclamps had a 27-fold increase in hyperuricaemia. Hyperuricaemia is an early marker of PE which can appear as early as 10 weeks of amenorrhea, well before the onset of signs of PE, and is linked to: renal dysfunction, tissue necrosis of the placenta, acidosis and an increase in the enzyme xanthine oxidase dehydrogenase [9]. It has historically been associated with reduced clearance, uric acid being filtered, reabsorbed, excreted by the kidney [5]. As a result, early hypovolemia in PE and reuptake of uric acid at the renal level may account for some of the elevated uric acid levels. The early onset of hyperuricaemia preceding arterial hypertension and proteinuria suggests uric acid involvement in the genesis of PE. In addition, uric acid is known to cause vascular wall remodelling or endothelial dysfunction, inhibition of nitric oxide production, impairment of inflammation cascades, and oxidative stress. Khaliq OP et al., reported the predictive role of uric acid in the genesis of PE [8].

The decrease in glomerular filtration rate, significant proteinuria, hypocreatinuria reflect the alteration of renal function seen in this series as well as in others [3,10]. However, Kasraeian M et al., noted a rise in serum creatinine proportionally to the severity of PE, making it a prognostic biomarker [11]. In addition, Moulin B et al., state that “the occurrence of Acute Renal Failure (ARF) is relatively rare. The ARI in PE appears most often in a context of obstetric complication: the retroplacental haematoma, HELLP (Haemolysis Elevated Enzyme Liver Low Platelets) syndrome and disorders of haemostasis” [2]. No association of urea and electrolytes was observed with PE, contrasting with the results of Oloruntoba A et al., and Rassavi A et al., who reported a significant association [7,12]. Indeed, hyperuremia found in these studies is justified by the existence of many cases of severe PE contrasting with predominance in the index series (almost all cases had moderate PE). Hyponatremia tends to appear more frequently in severe forms of PE. Also, the decrease in plasma volume could induce the secretion of non-osmotic antidiuretic hormone that would be involved in the onset of hyponatremia in pregnant women with PE.

Decreased glomerular filtration rate and renal plasma flow results in decreased sodium reabsorption at the distal nephron and decreased potassium secretion, thus inferring the possibility of inhibition of potassium excretion in the urines [13]. The increase in serum potassium may also be secondary to the effect of magnesium sulphate by reducing the activity of plasma renin and the angiotensin-converting enzyme resulting from low renin, angiotensin II and aldosterone [7]. Magnesium sulphate increases the excretion of sodium and chlorine but suppresses renal excretion

of potassium, which could justify the lack of association of these elements with PE in the index study.

Limitation(s)

Some of the preeclamps were on antihypertensive medications which could be a confounding bias. Indeed, it has been reported that some antihypertensives interfere with the metabolism of certain biomarkers such as alpha methyldopa which would increase the serum uric acid concentration [13]. Also, the existence of several levels of severity of PE could constitute a selection bias with greater impact on biomarkers in case of severe PE. Vascular lesions and glomerular endothelial lesions are responsible for a decrease in glomerular filtration rate, renal blood flow modifying several biochemical elements and their renal elimination, which includes creatinine, uric acid, sodium, potassium, chlorine, urea, and proteins.

CONCLUSION(S)

Hyperuricaemia and hypocreatininuria are significantly associated with PE. Their predictive and prognostic values remain to be clarified in subsequent multicenter studies that can integrate multivisceral repercussions in order to better define the biological profile of PE in Brazzaville and limit the carrying out of sometimes costly biological examinations.

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