

## Original Research Article

# Effect of pre-eclampsia on glomerular filtration rate in Sudanese women

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## ABSTRACT

**Background:** Creatinine clearance is safest method to measure glomerular filtration rate (GFR) in pregnancy. The objectives was to study a case-control study conducted in Omdurman Maternity Hospital aimed to assess GFR, using creatinine clearance and magnitude of changes of serum creatinine in pre-eclampsia.

**Methods:** Pre-eclamptic were 70, normal pregnant 96 and non-pregnant 63. Investigations were done at St Hellier's hospital London. Serum and urine creatinine were measured using Jaffé reaction and spectrophotometer. 24-hour urine output was measured and creatinine clearance calculated to find GFR. GFR was calculated in ml/min/mm<sup>2</sup> using John Hopkins' method.

**Results:** The mean serum creatinine in pre-eclamptic (68.6µmol/L) was less than non-pregnant (75.5µmol/L) (P=0.001) but was higher than normal pregnant (62.4µmol/L) (P=0.003). Mean GFR pre-eclamptic (68.6ml/min/1.73m<sup>2</sup>) was less than non-pregnant (87.0ml/min/1.73m<sup>2</sup>) (P=0.0001) and normal pregnant (89.0ml/min/1.73ml/min/1.73m<sup>2</sup>) (P =0.0001).

**Conclusions:** GFR decreased at term in normal pregnancy and even more in pre-eclampsia. Serum creatinine levels increased and did not correlate with GFR changes in pre-eclampsia.

**Keywords:** Creatinine, GFR, Pre-eclampsia

## INTRODUCTION

GFR is measured by the clearance of an endogenous substance such as serum creatinine or an exogenous substance such as inulin or radioactive material. The ideal marker is the endogenous substance which is freely filtered by the glomerulus and neither reabsorbed nor secreted.<sup>1</sup> The safest method to measure the GFR, in pregnancy, is the creatinine clearance. Changes in maternal physiology occur normally during pregnancy. The physiologic changes include plasma volume

expansion with increases in extracellular fluid and total body water leading to decreased plasma albumin concentration.<sup>2</sup> Marked "renal hemodynamic" changes are obvious by the end of the first trimester. Both GFR and effective renal plasma flow (ERPF) increase by fifty percent. ERPF in all probability increases more than GFR, hence, the filtration fraction is decreased during early to mid-pregnancy. This increase in glomerular plasma flow may explain the increase in GFR.<sup>3</sup> Conrad et al announced that the GFR and renal plasma flow (RPF) increased by 40-65% and 50-85% respectively during

normal pregnancy. They discovered that hyperfiltration in the kidney was due almost to the increase in RPF, which was attributed to the profound reductions in both the renal afferent and efferent arteriolar resistances.<sup>4</sup>

Pre-eclampsia, a multisystem disorder, is characterized by hypertension and proteinuria and occurs in the second half of pregnancy. It affects about 5% of pregnancies.<sup>5</sup> It is accompanied with increased rates of fetal and maternal morbidity and mortality.<sup>6,7</sup>

In pre-eclampsia, renal plasma flow (RPF) and GFR are decreased and the urine protein maybe in the nephritic range. GFR reduction is one of the early changes in renal involvement in pre-eclampsia and it reflects the progress of the disease.<sup>8</sup>

Hypofiltration is caused by the decreased RPF and deformed glomerular barrier integrity. As renal blood flow (RBF) and GFR decrease in pre-eclampsia; their absolute values may remain above the non-pregnant range. A decrease in the ultrafiltration coefficient ( $K_f$ ), in the order of 50% either alone or in combination with reduced RBF, is presented as the most likely mechanism for the decrease of GFR.<sup>9</sup>

Creatinine is a breakdown product of creatinine phosphate in muscle, and is usually produced at a fairly constant rate by the body (depending on muscle mass). Its molar mass is 113.12g/mol (molecular weight is 163.2). It is chiefly filtered out of the body by the kidneys (glomerular filtration and proximal tubular secretion). There is little-to-no tubular reabsorption of creatinine. Creatinine blood levels rise if the filtration of the kidney is poor.<sup>(10)</sup> The most commonly used endogenous filtration markers in clinical practice are serum creatinine value or it's reciprocal, alone or in conjunction with 24-hours urine collections for creatinine clearance.

Reports from the Sudanese Federal Ministry of Health showed that the number of patients with acute chronic renal failure in Sudan is increasing. The data indicated that there was an increase in the number of cases of renal failure between 2005 and 2010 by 11%.<sup>11</sup> The percentage mortality has also been increasing.<sup>12</sup> The number of Sudanese women who develop pre-eclampsia and subsequently eclampsia is high and a genuine concern.

The GFR is not frequently investigated in Sudan and no normal range value for GFR in Sudanese subjects was estimated. The GFR is usually measured in practice and teaching sessions using the creatinine clearance calculated values as the GFR values. In this study, we wanted to verify the difference between using the corrected creatinine clearance formula and the mere use of creatinine clearance as different formulas for calculating the GFR values, and to assess GFR, using creatinine clearance and magnitude of changes of serum creatinine in pre-eclampsia.

## METHODS

This was a cross-sectional, case-control and hospital-based study performed during a two year period from December 2008 to December 2010; in Omdurman Maternity Hospital. The study population included 3 female groups; pre-eclamptic cases, normal (second-half) pregnant subjects and non-pregnant subjects. The study pre-eclamptic participants (70) included newly discovered and/or already diagnosed and followed-up cases in their recent pregnancies. The control groups included non-pregnant women (63) and pregnant women (96) who were in their second half of pregnancy (20 weeks of pregnancy and onwards). Selected participants were informed about the study; and their written consent was taken. The investigations were performed at St Helier Hospital, London. The serum and urine creatinine were measured using the Jaffé reaction and quantitated spectrophotometrically at 500 – 530nm. 24-hour urine output was measured and creatinine clearance calculated to find GFR. Samples collection was done by trained nurses and laboratory technicians. GFR was calculated in ml/min/m<sup>2</sup> using John Hopkins' method.

The creatinine clearance method was used to find out the GFR.

The equations used were the following:

$$A. Ccr (ml/min) = \frac{(U_{cr} \times V)}{P_{cr}}$$

$$B. Ccr-corrected (ml/min/1.73m^2) = \frac{(Ccr \times 1.73)}{(BSA)}$$

Equation B did not yield the actual GFR values; thus we used the following equation (John Hopkins Equation):

$$GFR (ml/min/1.73m^2) = 0.81 \times Ccr-corrected (ml/min/1.73m^2) \text{ i.e.}$$

$$C. GFR (ml/min/1.73m^2) = \frac{0.81 \times Ccr \times 1.73^{(13)}}{BSA}$$

Where Ccr=creatinine clearance; U<sub>cr</sub>=urine creatinine concentration ;V =urine flow rate ; P<sub>cr</sub>=plasma creatinine concentration, BSA= Body Surface Area and 0.81 is a constant.

Generally, in physiology laboratory teaching in Sudan, the students are commonly taught that the GFR equals the creatinine clearance rate using the above equation (A).

Searching in-depth in literature, the first author of this study found that the accurate equation to calculate the GFR from creatinine clearance (Ccr) is to use equation (B) and then follow with equation (C) as shown above.

**Ethical consideration**

Ethical approval was given by the Research Committee (Faculty of Medicine, U of K). Permission was given from Omdurman Maternal Hospital to conduct the study for cases of pre-eclampsia and normal pregnant subjects. Selected participants were informed about the study; and their written consent was taken.

**Statistical analysis**

The data is presented as Means±S.E. of the means. The data was analyzed by SPSS software R 9.0 (SPSS, Inv., Chicago, IL, USA) program Version 20. Correlation between quantitative data was determined using Spearman’s test. P<0.05 was considered statistically significant.

**RESULTS**

**Serum creatinine (µmol/L) levels**

The mean serum creatinine of the pre-eclamptic (68.6µmol/L±1.8) was statistically significantly less than the non-pregnant (75.5µmol/L±0.8) (P =0.001) but was statistically significantly higher than the normal pregnant (62.4µmol/L±0.9) (P=0.003) (Tables 1 and 2).

**Glomerular filtration rate (GFR) ml/min/ 1.73 m<sup>2</sup>**

The mean GFR of the pre-eclamptic (68.6ml/min.1.73m<sup>2</sup>±3.3) was statistically significantly less than the non-pregnant (87.0ml/min/1.73m<sup>2</sup>±3.4) (P=0.0001) and the normal pregnant (89.0ml/min/1.73ml/min/1.73m<sup>2</sup>±2.8) (P=0.0001) Table 1 and 2).

**Table 1: Comparisons of means between the normal pregnant and pre-eclamptic cases.**

Category of participant		Mean±SE	P-value
a. Body mass index	Pregnant	25.6±0.5	0.000*
	Pre-eclampsia	29.5±1.0	
b. Urine creatinine (mmol/L)	Pregnant	6.8±0.3	0.074
	Pre-eclampsia	5.6±0.6	
c. Serum creatinine (µmol/L)	Pregnant	62.4±0.9	0.003*
	Pre-eclampsia	68.6±1.8	
d. GFR 1.73 (ml / min/ 1.73m <sup>2</sup> )	Pregnant	89.0±2.8	0.000*
	Pre-eclampsia	68.6±3.3	
e. Calculated creatinine clearance per body surface area (ml/min/1.73m <sup>2</sup> )	Pregnant	109.9±3.4	0.000*
	Pre-eclampsia	84.7±4.1	

\*P-value (<0.05) is significant.

**Table 2: Comparisons of means between the non- pregnant and pre- eclamptic cases.**

Category of participant		Mean ± SE	P-value
a. Body mass index	Non-pregnant	23.9±0.6	0.000*
	Pre-eclampsia	29.5±1.0	
g. Urine creatinine (mmol/L)	Non-pregnant	11.9±1.0	0.000*
	Pre-eclampsia	5.6±0.6	
o. Serum creatinine (µmol/L)	Non-pregnant	75.5±0.8	0.001*
	Pre-eclampsia	68.6±1.8	
q. GFR 1.73 (ml / min/ 1.73m <sup>2</sup> )	Non-pregnant	87.0±3.4	0.000*
	Pre-eclampsia	68.6±3.3	
r. Calculated creatinine clearance per body surface area (ml/min/1.73m <sup>2</sup> )	Non-pregnant	107.4±4.2	0.000*
	Pre-eclampsia	84.7±4.1	

\*P-value (<0.05) is significant.

**DISCUSSION**

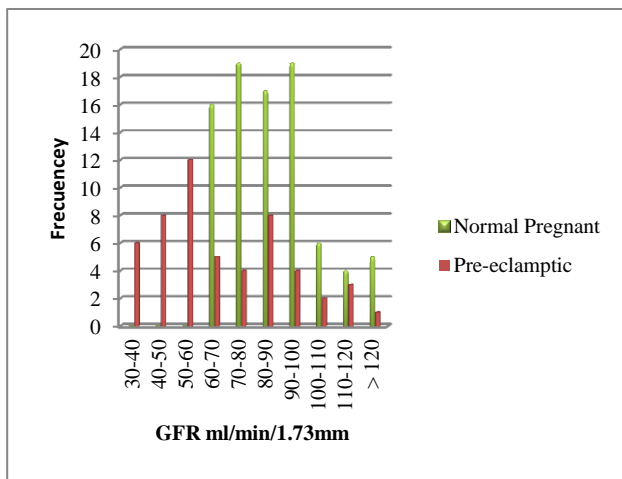
Normal pregnancy is associated with plasma volume expansion and an increase in the GFR of 40% to 65% of normal non-pregnant GFR values in first trimester

(measured by inulin clearance) and a decrease in GFR of approximately 15% to 20% of this rise late in the third trimester.<sup>14,15</sup> In this study, the relatively low GFR in the normal pregnant individuals was still higher than the GFR of non-pregnant. This can be partially explained by

the physiological decline in late pregnancy towards non-pregnant GFR and the creatinine clearance which had been corrected with the body surface area to ease the comparisons and so led to reduction in its values.

Hynad M et al reported that the ERPF significantly increases during early pregnancy. It reaches a peak increment in mid-trimester of 50% to 85% and then shows a small decline during the third trimester but does not go below normal non-pregnant values and is unrelated to posture.<sup>16</sup>

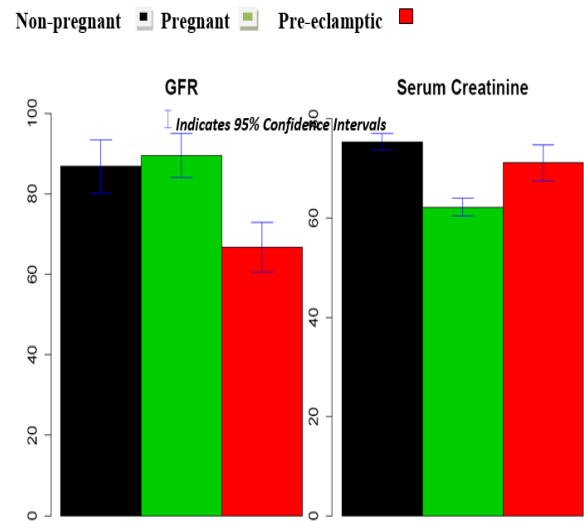
In pre-eclampsia the mean GFR was significantly lower than that of non-pregnant and of normal pregnant women. This may be due to the marked renal impairment (glomerular endotheliosis) which accompanies pre-eclampsia.<sup>17</sup> Lafayette et al reported a similar significant decline in GFR of pre-eclamptic cases compared to the normal pregnant (control) group. In contrast, renal plasma flow and oncotic pressure were similar in the two groups.<sup>18</sup> The control non-pregnant group of this study was active which may have increased their serum creatinine and uric acid leading to weak correlation with the GFR (Figure 1).



**Figure 1: Histogram of GFR in normal pregnant and pre-eclamptic subjects.**

In the second half normal pregnant women, their serum creatinine levels dropped when compared with non-pregnant subjects. This may add to the evidence that serum creatinine level is decreased with the hemodilution that accompanies pregnancy (normal range values, in pregnancy, of serum creatinine is 40-80  $\mu\text{mol/L}$ ).<sup>9,18</sup> In another theory Lindheimer et al observed that the glomerular hyperfiltration of pregnancy reduced the serum creatinine level from about 0.5mg/dl to 0.4mg/dl (44 $\mu\text{mol/L}$  to 35 $\mu\text{mol/L}$ ) and that the hyperfiltration persisted till term. They stated that serum creatinine is an imperfect marker, as a marked reduction (40%-50%) in renal function is needed, before a rise in plasma creatinine into the abnormal range is noticed.<sup>2,19</sup> However, the serum creatinine levels increased in the pre-

eclamptic women and this may indicate that the renal impairment reduces the creatinine renal filtration. This increase may have been due to renal involvement but was not to values above the non-pregnant one. The mean serum creatinine of the pre-eclamptic cases was significantly lower when compared to that of non-pregnant women; but significantly higher compared to normal pregnant women. There was an overlap between the values in the three groups, so a case may be pre-eclamptic but still with low serum creatinine value (Figure 2). This may decrease the value of its use as a precise indicator of early GFR changes in normal second half pregnancy and pre-eclampsia. Serum creatinine levels did not correlate with GFR changes in pre-eclamptic cases.



**Figure 2: Means and confidence intervals for GFR (ml/min/1.73m<sup>2</sup>), serum creatinine ( $\mu\text{mol/L}$ ), in non-pregnant, pregnant and pre-eclamptic.**

In clinical practice, exogenous substances such as inulin or isotopes are used to find out GFR. On the basis of endogenous serum creatinine levels, a number of formulae have been advised to estimate GFR values. Creatinine clearance method was used in this study.

Though Hynad M declared that the 24-hour creatinine clearance is the best clinical measurement of GFR, creatinine clearance rates tend to overestimate GFR due to the secretory component of creatinine excretion. Despite these problems, creatinine clearance still remains the most useful measure of GFR in clinical practice.<sup>16</sup> The creatinine clearance needs a complete collection of 24-hour urine for accuracy. Searching in-depth in literature, the first author found that the accurate equation to calculate the GFR from creatinine clearance (Ccr) is equation C.<sup>10</sup> In this study it was found that the corrected creatinine clearance values were higher when using equation B than when using equation C for GFR. Commonly, in physiological laboratory teaching in Sudan, the students are generally taught that the GFR

equals the creatinine clearance rate using the creatinine clearance equations (See equations A and B).<sup>20</sup>

Delange JR et al reported that there is a recent campaign for standardization of creatinine measurement which has been promoted to allow the widespread use of formulae for estimating the GFR. But studies still show disappointing interassay variation of serum creatinine results, new calibration traceable to an Isotope Dilution Mass Spectrometry (IDMS) reference measurement procedure are now expected to be used for serum creatinine.<sup>21</sup>

## CONCLUSION

In this study, the GFR decreased at term in normal pregnancy and even more in pre-eclampsia. This may add to the reported evidence that there is a reduction in the GFR at term and pre-eclampsia. Serum creatinine levels did not correlate with GFR changes in pre-eclamptic cases. Using different equations for calculating GFR from creatinine clearance yielded different values. It can be concluded from the above mentioned facts that it is mandatory in practical physiology to teach the students how to differentiate between creatinine clearance measurement and GFR calculations. Pre-eclampsia is associated with major organs dysfunction especially the kidneys. GFR decreases in pre-eclampsia and its reduction may be very severe and desire immediate intervention to prevent acute renal failure in pre-eclamptic cases.

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