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Afr. J. Biomed. Res. Vol. 21 (May, 2018); 161- 167

Research article

Progesterone and 17β-Estradiol Have No Relationship with Renal Clearance of Creatinine During Normal Pregnancy and The Puerperium

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ABSTRACT

This study was carried out, to determine the association between the steroid hormones concentration increase and creatinine clearance during pregnancy and to make observations on the pattern of change in renal function in the late puerperium. This study included 330 apparently healthy normotensive female subjects, made up of seventy each trimesters of pregnancy with seventy (70) women at six weeks post-partum. Fifty (50) non-pregnant women of child bearing age served as controls. Blood and urine samples were collected from each woman during the first, second and third trimesters of pregnancy and during the late puerperium. Serum and urine creatinine, were determined by colorimetric methods. Serum electrolyte profile was determined by Ion Selective Electrode method using automated machine, while the hormonal assays were done using Elecsys 2010 autoanalyzer. The results of both creatinine clearance and the hormonal assay showed significant increase during pregnancy. However, the correlation analysis did not reveal any significant relationship among groups. There were significant differences in the changes observed in other parameters within the trimesters and the puerperium. The increase in creatinine clearance above the normal level during the postpartum period, despite the rapid clearance of the hormones shows that renal function became more efficient, in order to clear excess fluid and electrolytes that the body accumulated during pregnancy. Therefore, the increase in progesterone and 17β-estradiol may not have direct roles in the increase in creatinine clearance during pregnancy.

Keywords: *Progesterone, 17β-Estradiol, Relationship, Creatinine clearance, Normal pregnancy, Puerperium*

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Received: August 2017; Revised version Accepted: January, 2018

Abstracted by:
Bioline International, African Journals online (AJOL), Index Copernicus, African Index Medicus (WHO), Excerpta medica (EMBASE), CAB Abstracts, SCOPUS, Global Health Abstracts, Asian Science Index, Index Veterinarius

INTRODUCTION

The female body undergoes major but transient changes during pregnancy, parturition, and postpartum that affect the genital organs and the hormonal system, the cardiovascular system, salt and water balance (Risberg 2009). Disturbances in the cardiovascular system and the regulation of fluid balance can lead to changes in blood pressure and to hypo- or hypertension. Imbalance in salt and fluid regulation is common and can cause oedema (Risberg 2009).

Estrogen (E2) and progesterone (P4) are steroid hormones implicated principally in the control of female reproductive functions by genomic and non-genomic mechanisms (Brunette and Leclerc 2001; 2002). Among their other actions, E2 and P4 can also modulate Na+ and Cl- reabsorption along the mammalian nephron and alter the physiological hydroelectrolyte balance (Johnson and Davis 1976). It is known that extracellular volume increases in women during the pre-ovulatory phase of the menstrual cycle when estrogen levels are rising (Stephenson and Kolka 1988). "These findings could be associated with the actions of E2 and P4 on renal function, leading to electrolytes retention (Stetchenfeld *et al*., 2005).

Maternal hormones may influence hemodynamic changes in pregnancy. Mean arterial pressure is decreased in the mid-luteal phase of menstruation compared with the mid-follicular phase in association with a decrease in vascular resistance and rise in cardiac output (Chapman *et al*., 1997). The report of Cheung and Lafayette, (2013) showed that, progesterone increases renal plasma flow and glomerular filtration rate, but it cannot account for the magnitude of increase seen in pregnancy.

The aim of this work was to determine the association between the steroid hormones concentration and renal clearance of creatinine during pregnancy and to make observations on the pattern of change in renal function in the late puerperium.

MATERIALS AND METHODS

Subjects: A total of three hundred and thirty (330) apparently healthy normotensive female subjects made up of seventy each at first (8^{th} -10^{th} week), second (20^{th} week) and third (32^{nd} week) trimesters of pregnancy respectively with seventy (70) women at six weeks post partum and fifty (50) non pregnant women of child bearing age as controls who were randomly selected, between the ages of 18 and 42 years (27.88 ± 4.9 years) were studied.

Place and Duration of Study: The study was carried out in the antenatal clinic of Bingham University Teaching Hospital (BUTH), Jos. The study procedure was well explained to each participant and written informed consent was obtained from each of them. Blood and urine samples were collected from each woman. Blood collection was done between 8.00a.m and 9.00 a.m. on visiting days. All protocols employed in this study complied with the guidelines and regulations of BUTH ethical committee.

Exclusion Criteria: Questionnaire was applied on each woman for biodata and medical history to exclude pregnant women with medical history of kidney disease, diabetes, hypertension and other chronic illnesses.

Blood sample collection: 5mls of blood was collected by venipuncture into plain vacutainer tube with minimal stasis. The blood was allowed to clot at room temperature, and centrifuged at 3000 rpm for 5 minutes. The serum was separated into clean dry well labeled sample bottles and kept at -70^0C in aliquots until they were analyzed.

Collection of urine samples: The women were given a 2 L-container each for 12 hours urine collection and were instructed on how to collect the urine sample. Also, fresh urine samples were collected from the women into twenty milliliters monovette containers for urinalysis. The urine collection was done before blood collection.

BIOCHEMICAL MEASUREMENTS

Measurement of serum and urine creatinine: Creatinine concentrations were determined by modified Jaffee's reaction by Bartels and Bolumer, (1972).

Measurement of serum progesterone and 17β- estradiol: Serum progesterone and 17β-estradiol concentrations were measured by Electrochemiluminescence immunoassay (ECLIA) on Elecsys 2010 Auto analyzer

pH determination using hand held pH meter (Model MI4152. Microelectrodes Inc. NH, USA).

Measurement of urine volume: The volume of the 12hour urine collected was measured, using a clean dry 2Litres glass (measuring cylinder).

Measurement of serum electrolytes concentrations: Serum concentrations of sodium, potassium, chloride, and bicarbonate were determined, by a high speed high precision fully automated Ion Selective Electrode (ISE) method on ISE 6000 SFRI Medical Diagnostics, France

Statistical Analysis:
The biochemical data were subjected to some statistical analysis as the Mean (X), standard deviation (SD), standard error of mean (SEM) and analysis of variance (ANOVA) followed by a Fisher's Least significant difference post- hoc test to determine pair-wise difference among group means using Statistical Package for Social Sciences (SPSS) version 17. The results were expressed as Mean ± standard error of mean (SEM). Statistical significance was accepted at a level of p equal to or less than 0.05.

RESULTS

There was a reduction in blood pressure in the three trimesters of pregnancy when compared to the control values. Both the systolic and diastolic blood pressures of postpartum women were significantly higher ($p<0.001$) than those of the women in the three trimesters of pregnancy. (Table1)

Serum creatinine concentration was lowest in the second trimester of pregnancy. Although, there was an increase during the third trimester, the values were still significantly lower ($p<0.001$) when compared to the non–pregnant control and the 6 weeks postpartum period. (Table1)

Creatinine clearance showed significant increases ($p<0.001$) within the trimesters of pregnancy; the peak was at the second trimester and when compared with the non-pregnant women, the differences observed were also significant ($p<0.001$). Also, creatinine clearance declined in the third trimester significantly ($p<0.001$) but not to the non-pregnant level. There was a further reduction of the clearance during the 6 weeks postpartum period but the value remained significantly higher ($p< 0.01$) than the non- pregnant control level.

Volume of 12 hours urine collected increased significantly ($p< 0.05$) only in the first trimester. However, the volume was significantly reduced ($p<0.001$) during the 6 weeks postpartum period. Urinary pH reduced ($p<0$ 05) during the pregnancy trimesters. The 6 weeks postpartum value was significantly lower ($p<0.001$) than in both the pregnant and non-pregnant women (Table1)

Serum levels of progesterone and 17β-estradiol increased significantly ($p<0.001$) in the three trimesters of pregnancy. Also, the increases within the trimesters were significant ($p<0.001$). The levels declined drastically during the six weeks postpartum period to slightly below the non-pregnant control level (Table 3).

Serum sodium decreased significantly ($p<0.001$), in pregnancy when compared with the non-pregnant control women. The value remained low through to the postpartum period (Table 2.)

Table 1:
Changes in renal function during pregnancy and the 6 weeks postpartum period

	ABP (mmHg)	Serum Creatinine (µmol/L)	Urine Creatinine (mmol/L)	Creatinine Clearance (ml/min)	Urine Volume (ml)	Urine pH	Fractional Excretion of sodium (%)
Control	106/76	89.778 ± 14.37	4.756 ± 1.651	70.31 ± 31.72	872.5 ± 273.6	6.568 ± 0.456	1.26 ± 0.47
1st trimester	104/69	58.084 ± 7.402	5.314 ± 1.827	136.31 ± 51.1	1064.9 ± 339.5	6.654 ± 0.61	1.02 ± 1.02
2ndtrimester	104/66	50.011 ± 6.472	6.273 ± 2.826	164.32 ± 68.31	970.97 ± 293. 4	6. 484 ± 0.542	0.93 ± 0.5
3rd trimester	106/71	56.295 ± 10.113	5.887 ± 2.408	132.88 ± 36 961	983.1 ± 300.3	6.37 ± 0.447	0.85 ± 0.58
6weeks pp	117/77	77.101 ± 9.917	6.693 ± 2.245	103.95 ± 21.1	839.4 ± 314.6	6.078 ± 0.458	1.20 ± 1.08
F	19.77/17.72	120.32	4.33	21.29	4.493	10.53	2.031
P	.000	.000	.002	.000	.002	.000	.091
Post Hoc							
Control vs 1st	.643/.001	.000	.350	.000	.017	.518	.254
Control vs2nd	.491/.000	.000	.011	.000	.219	.071	.117
Control vs 3rd	.842/.010	.000	.059	.000	.168	.002	.047
Control vs 6wks pp	.000/.517	.000	.001	.006	.679	.000	.750

Table 2:
Showing the changes in the major electrolytes during pregnancy and the 6 weeks postpartum period

	Serum Sodium (mmol/L)	Serum Potassium (mmol/L)	Serum Chloride (mmol/L)	Serum Bicarbonate (mmol/L)
Control	140.9 ± 3.7	4.34 ± 0.38	107.9 ± 3.8	21.4 ± 2.7
1st trimester	135.9 ± 2.9	4.14 ± 0.91	104.8 ± 2.9	22.6 ± 4.2
2nd trimester	137.0 ± 2.72	4.08 ± 0.37	105.6 ± 2.9	21.3 ± 2.7
3rd trimester	136.5 ± 3.6	4.13 ± 0.37	106.5 ± 3.1	20.2 ± 2.0
6 wks pp	137.1 ± 3.38	4.12 ± 0.53	103.9 ± 2.7	26.4 ± 4.2
F	10.61	1.06	10.47	29.76
P	.000	.369	.000	.000
Post Hoc				
Control vs 1st trim.	.000	.165	.000	.017
Control vs 2nd	.000	.060	.004	.219
Control vs 3rd	.000	.057	.069	.168
Control vs 6wkspp	.000	.131	.000	.679

Table 3:
Showing the changes in hormonal levels during pregnancy and the 6 weeks postpartum period

	Progesterone	17β- Estradiol
Control	11.17 ± 4.77	236.41 ± 137.44
1st trimester	49.16 ± 7.97***	3121.24± 2076.6*
2nd trimester	94.03 ±32.77***,aaa	8678.05±4388.8***, aaa
3rd trimester	142.21± 73.19***	11648.58 ± 8325.1***
6weeks pp	0.34 ± 0.21ooo	39.44 ± 16.23ooo
F	121.524	64.630
P	.000	.002

*Values are presented as Mean± SEM, significant at ***P<0.001 vs control, aaap<0.001 vs 1st and 3rd trimesters, ooop<0 001vs 1st , 2nd and 3rd trimester*

Fractional excretion of sodium decreased during pregnancy but the difference was only significant ($p<0.05$) during the third trimester of pregnancy as shown in Table 3.

Serum potassium showed no significant difference in all the trimesters of pregnancy and the postpartum period when compared with the non-pregnant controls as shown in Table 2.

Serum chloride concentration showed a significant decrease ($p<0.001$), in the first and second trimesters and the postpartum when compared with the non-pregnant control. Also, the third trimester concentration was significantly ($p<0.05$) higher than the first trimester (Table 2).

Serum Bicarbonate decreased from the first trimester reaching the lowest during the third trimester which was significantly different ($p<0.001$) from the non -pregnant controls (Table 2).

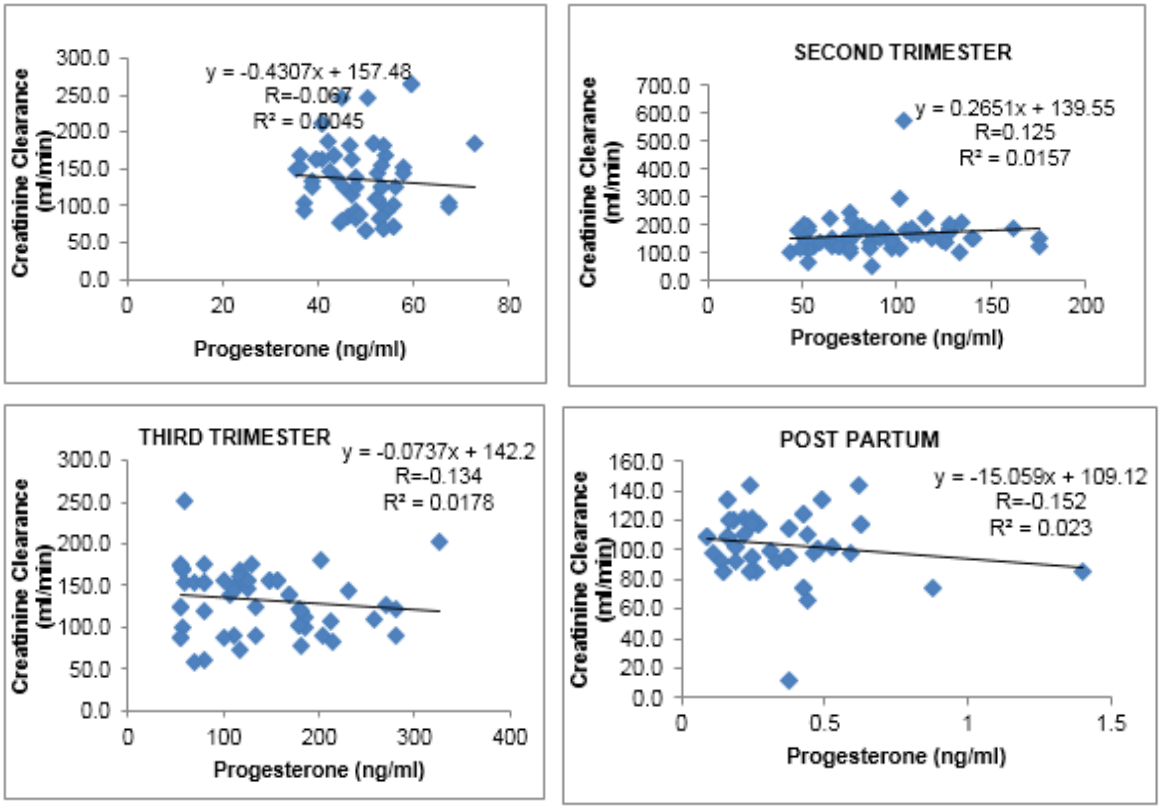

Figure 1:
Relationship between Creatinine clearance and progesterone concentration during pregnancy and postpartum partum period.

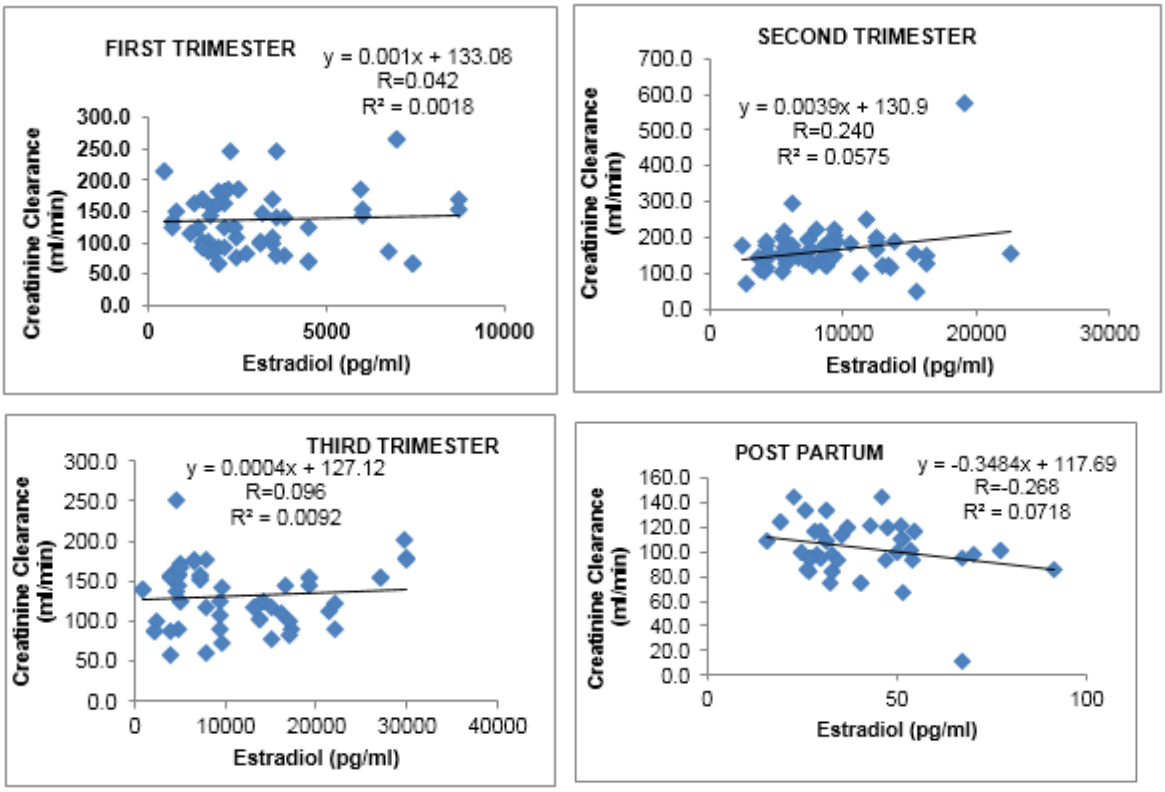

Fig. 2: Showing the relationship between Creatinine clearance and 17β- estradiol concentration during 1st to 3rd Trimesters of pregnancy and the postpartum period

However, the rise in bicarbonate during the postpartum period was significantly different ($p<0.001$) from the non-pregnant control and the pregnant women.

Figures 1 and 2: represents the correlation analysis carried out to determine the relationship between renal clearance of creatinine and the two pregnancy hormones studied. The results showed no correlation.

DISCUSSION

A decrease in blood pressure during pregnancy was observed, in conformity with some of the earlier studies (Indira and Srikanth 2015; Gaillard *et al*., 2011; Onah, 2002). Also, Fernanda *et al*., (2015) reported notable variation in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels during pregnancy. The decrease in blood pressure during pregnancy may be attributed to the increase in serum progesterone level which enhances relaxation of arterial smooth muscles and thus decreases peripheral vascular resistance (Barbagallo *et al*., 2001).

The differences observed in serum creatinine in the three trimesters were significant when compared to the values for non-pregnant controls and for the postpartum women. This result agrees with earlier reports that consequent to increased Glomerular Filtration Rate (GFR), serum creatinine begins to fall early in the first trimester, reaching its lowest level in the second trimester, and then increasing slightly towards term (Hussein and Lafayette 2014; Oguntayo *et al*., 2011; Eiya and Obika; 2010; August, 2005; Girling, 2000). Okpala *et al*., (2012) and Wolak *et al*., (2011) reported similar findings of low serum creatinine in early pregnancy. They also observed and suggested that women who had increased concentration of creatinine at 20 weeks of gestation may likely develop hypertension. This study extended beyond the third trimester of pregnancy to six weeks postpartum, the essence of which was to make observations on the pattern of change in renal function during the puerperium. The six weeks postpartum serum concentration of creatinine started to increase towards the non-pregnant level, but the value was still low because of the persistent elevation of renal clearance into the postpartum period. However, the result of this study was at variance with the re-evaluation done by Girling (2000), where he reported a higher value in the upper limit of creatinine concentration during pregnancy. The variation may be due to geographical location or ethnicity of subjects. This information is important for the clinical assessment of results from pregnant women in Nigeria, particularly in conditions such as pre-eclampsia where abnormalities of renal function may occur. Furthermore, it was observed that urinary excretion of creatinine increased in the first and second trimesters and then reduced slightly in the third trimester; this was shown in the third trimester increase in serum creatinine concentration. It may be as a result of the reduced GFR during the third trimester: This decrease in GFR probably contributed to the sodium retention in the third trimester, since there was a significant reduction in the fractional excretion of sodium in the third semester.

Similarly, progesterone and 17β- estradiol increased throughout pregnancy but the levels declined rapidly during the puerperium, at this time creatinine clearance was still high. Furthermore, the results of analyses carried out revealed a non-significant relationship (Table 4), meaning that these two pregnancy hormones may not have direct effect on renal function during pregnancy. Earlier reports indicated that in pregnancy, both the glomerular filtration rate and effective renal plasma flow (ERPF) increase by 50 - 70% (August, 2005). ERPF probably increases to a greater extent, and thus the filtration fraction is decreased during early and mid pregnancy (August, 2005). This result is similar to the observations of Lafayette *et al*., (1999); who reported a significant hyper filtration in postpartum women immediately after caesarian section compared with non-pregnant women. Hladunewich *et al*., (2003), reported a similar elevated GFR of 40 - 60% above non-gravid levels a week after delivery. The study reported here shows an elevated creatinine clearance of 47% 6 weeks after parturition. The hyper filtration appears to result primarily from depression of the mean glomerular intra-capillary oncotic pressure (π GC) (i.e. force opposing the formation of glomerular filtrate (Hussein and Lafayette 2014; Hladunewich *et al*., 2003).

The 12hours urine collection was employed in this study to reduce the error due to non compliance of women during longer periods of urine collection. The improvement in this method of collection is due to the fact that the women were at home mostly during the period. In this study, urinary volume increased significantly ($p<0.05$) in the first trimester of pregnancy when compared with that of non-pregnant and postpartum women. This agrees with the work done by Eiya and Obika (2010). The increase in urine volume may be as a result of increase in extracellular fluid especially plasma volume due to systemic vasodilation, which is the basic reason for the increased cardiac output and renal plasma flow (RPF) (Garland and Green, 1982).

Urine pH of the pregnant women when compared with the non-pregnant control showed no difference, but the postpartum values had the lowest pH, which was significantly different ($p<0.05$) from the value of control and pregnant women. However, the values fall within the normal range.

The result in this study showed a reduction in serum sodium (Na^+) concentration, throughout the period of pregnancy and during the postpartum period. The reduction in serum concentration of sodium is attributable to the increase in blood volume expansion during pregnancy. It is observed that among the factors that influence sodium and fluid balance is a physiological decrease in blood pressure that occurs during pregnancy, due to vasodilatation, resulting in a diminished effective circulatory volume, or relative underfilling (Schrier, 2006). Also it is possible that a substantial amount of retained sodium is sequestered in the fetal tissues and the placenta which causes the maternal plasma sodium concentration to remain low during pregnancy (Jellema *et al*., 2009). Furthermore, sodium and fluid retention is needed to accommodate the expanding maternal extracellular compartment and the fluid demands of the growing fetus. It is suggested that the reduction in sodium excretion noted in the third trimester is a reflection of the increasing sodium concentration in the blood with advancing pregnancy (Isichei *et al*., 1978). The serum sodium concentration was still low during the 6 weeks postpartum period probably due to the

persistent elevation of the renal clearance, which increased the fractional excretion of sodium as seen in this study.

The observation that there was no significant change in serum potassium concentration in this study was in agreement with the report of Isichei *et al*., (1978). Ekeke and Ebirim, (1986) and Shakhmatova *et al*., (2000) reported that potassium (K+) levels are either normal or on the average 0.3mEq/L lower than values in the non-pregnant state, despite significant increase in aldosterone levels. The ability to conserve potassium may be a result of elevated progesterone in pregnancy. High level of progesterone blocks much of the potassium wasting effect of elevated aldosterone. Glucocorticoids that increased 2-3 folds could also be partly blocked (Takacs, 1998). Another thought is that the baby and placenta take potassium preferentially over the mother because they take it from the plasma that the body strives to keep constant (Takacs, 1998).

We observed a slight decrease in chloride (Cl-) concentration from the first trimester which was significantly different from the non-pregnant controls. Serum level of chloride follows the same pattern like that of sodium generally (Isichei, *et al*., 1978). The decrease in serum chloride observed in the postpartum women may be due to the chloride shift as a result of the increase in serum bicarbonate. To keep the total anion concentration constant, chloride reabsorption is increased when bicarbonate reabsorption is decreased and vice versa

Serum bicarbonate (HCO3-) in the pregnant women reduced significantly only at the third trimester, but the concentration increased significantly during the postnatal period. This may be attributed to a general increase in the number of cations and anions compared with the antepartum values. The changes also appear to be due to the effects of increased progesterone on the respiratory center which cause modest hyperventilation accompanied by a fall in pCO2 during gestation. The reduction in pCO2 is accompanied by a decline in plasma bicarbonate concentration of approximately 4mmol/L (Podymow *et al*., 2010; Baker, 2006).

The result of this study is suggestive of an increased renal function during pregnancy that confirms what has been reported earlier on. It is also clear that the increase in hormonal concentration during pregnancy is one of the factors that may affect renal function; notwithstanding, there was no correlation between the hormones and renal creatinine clearance. This shows that progesterone and 17β-estradiol may not have direct roles in the creatinine clearance increase during pregnancy. However, the increase in creatinine clearance above the normal level during the postpartum period, despite the rapid clearance of the hormones shows that renal function became more efficient, in order to clear excess fluid and electrolytes that the body accumulated during pregnancy.

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