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Evaluation of changes in renal functions of pregnant women attending ante-natal clinic in Vom Plateau State, North-Central Nigeria

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ABSTRACT

The concentrations of serum uric acid, urea and creatinine were determined in 75 pregnant women categorized into 3 groups of 25 each, based on their trimesters of pregnancy and 25 non-pregnant women used as control. In the first trimester, the mean values of uric acid, urea and creatinine are 122 µmol/L, 3.6 mmol/L and 88 µmol/L respectively. There was a significant ($p<0.05$) decrease in the levels of uric acid and creatinine but no significant ($p>0.05$) difference in the level of urea, when compared with the control levels of 308 µmol/L, 113 µmol/L and 4.11 mmol/L respectively. In the second trimester, the values of uric acid, urea and creatinine were 199 µmol/L, 3.49 mmol/L and 82 µmol/L respectively. There was a significant ($p<0.05$) decrease in the levels of uric acid and creatinine but the decrease in the level of urea was not significant ($p>0.05$). In the third trimester of pregnancy, the values of uric acid, urea and creatinine were 360 µmol/L, 3.29 mmol/L and 61 µmol/L respectively. There was a significant ($p<0.05$) decrease in the levels of creatinine and a significant ($p<0.05$) increase in the level of uric acid, but no significant ($p>0.05$) difference in the level of urea when compared with the controls. The progressive decrease in the levels of creatinine through the 3 trimesters of pregnancy suggests an increase in glomerular filtration rate, probably due to increased cardiac output, renal blood flow and changes in fluid distribution, while the progressive increase in the levels of uric acid through the trimesters of pregnancy suggests an impairment in uric acid excretion, may be with concomitant increase in renal tubular re-absorption of uric acid, thereby leading to hyperuricaemia.

Key words: Glomerular filtration rate, pregnant women, trimesters, uric acid, urea, creatinine.

INTRODUCTION

Pregnancy is the carrying of one or more embryos or foetuses by mammals including humans inside their wombs. Human pregnancy lasts approximately 40 weeks between the time of last menstrual cycle and birth. Gestation which is the period of pregnancy measured in weeks is divided into three time intervals or trimesters known as 1st, 2nd, and 3rd trimesters. The first trimester period; which is 0 – 13 weeks, carries the highest risk of miscarriage. In the second trimester; which is 13 – 26 weeks, the development of the foetus can begin to be monitored and assessed. The third trimester of pregnancy; which is 26 – 40 weeks, marks the beginning of viability [2].

In pregnancy, a woman undergoes dramatic physiological and hormonal changes. The kidney also undergoes tremendous anatomical and physiological changes [2]. Changes in fluid distribution produces an increase in

glomerular filtration rate (GFR) and lower plasma creatinine. The plasma volume increases during pregnancy sometimes by as much as 50%; these changes are accompanied by alteration in the concentration of many plasma constituents [6]. The large amount of estrogen, progesterone, placental lactogen and corticosteroids produced during pregnancy affect various metabolic, physiological and endocrine systems. An increased resistance to angiotensin, a predominance of lipid metabolism over glucose utilization and an increased synthesis by the liver of thyroid and steroid-binding proteins are some characteristics of pregnancy. Physiological changes occurring in pregnancy involves nearly every organ system and the kidney is not an exception. As a result of these changes, many of the laboratory reference intervals of non-pregnant women are not appropriate for pregnant women [2].

The kidneys are the primary means of eliminating waste products of metabolism that are no longer needed by the body. These include urea (from metabolism of amino acids), creatinine (from muscle creatinine), uric acid (from nucleic acid metabolism) and metabolism of various hormones. The free creatinine is a waste product of creatine metabolism, which is present in all body fluids and secretions, and freely filtered by the kidney glomerulus [11]. The functions of the kidney (usually two in mammals) also include regulation of water, electrolytes balance and regulation of acid-base balance [18]. The renal system undergoes marked changes in function during pregnancy due to hormonal effects, increased metabolic load of the foetus and outflow obstruction of the ureters by the enlarging uterus. The glomerular filtration rate increases by up to 50 % in pregnancy, which is an indication of increased renal function [10]. The increase in renal blood flow and glomerular filtration rate is attributable to increased cardiac output, increase in progesterone and aldosterone. As a result of increase in glomerular filtration rate, the clearance of urea, uric acid and creatinine increases and their plasma levels are lowered in pregnancy [12].

The lowering of the normal range of values of urea and creatinine during pregnancy has clinical significance, because a normal urea or creatinine level (using non-pregnant women standard) in a pregnant female may actually indicate an underlying renal disease [4]. The factors associated with increased peri-natal mortality and pre-term labour are impaired renal functions [13]. Renal function can be evaluated by the determination of urea, creatinine and uric acid levels in serum/plasma. The effect of renal failure on body fluids include generalized oedema, acidosis, high concentration of protein nitrogen, especially concentrations of urea, creatinine and other nitrogenous end products of amino acid or protein metabolism; a condition known as ureamia, which results from the failure of the kidneys to maintain adequate excretory, regulatory and endocrine functions [11]. So, the clinical chemistry laboratory has an important role in the management of pregnancy [1]. In addition, there seems to be dearth of information on the values of renal function tests of pregnant women in Plateau state, North-central Nigeria.

This study was therefore initiated to determine the levels of serum uric acid, creatinine and urea at different trimesters of pregnancy and evaluate the risk associated with changes in renal functions of pregnant women attending ante-natal clinic at Vom Christian Hospital, Vom, Plateau state, North-Central Nigeria.

MATERIALS AND METHODS

Materials

Chemicals and reagents used include 14 % Sodium Carbonate, 50 % Acetic acid, conc.H_2SO_4 , phosphoric acid, Diacetyl monoxime thiosemicarbazide, phenyl mercuric acid, 10 % Sodium tungstate, Lithium carbonate, N/12 H_2SO_4 , Phosphotungstic acid, $FeCl_3.6H_2O$, distilled water, Analar grade picric acid, 0.75 N Sodium hydroxide and other common laboratory reagents. The instruments used include spectrophotometer, refrigerator, water bath, centrifuge and other common laboratory apparatus.

Study Population

A total of 100 subjects were used for this study; 75 were pregnant women attending ante-natal clinic in Vom Christian Hospital, Vom, Plateau state, Nigeria while the other 25 women were randomly selected non-pregnant women in the community, which served as control. The pregnant women were divided into three groups of 25 each, based on the trimester of their pregnancies. Relevant information about pregnancy and health status of the subjects was obtained, after they gave their informed consent.

Collection of samples

A 5 ml blood was collected by venous puncture using a 5 ml sterile syringe and needle. The blood was dispensed into clean dry tubes, allowed to clot for about 15 minutes at room temperature, then centrifuged at 3000 rpm for 5 minutes and the serum was harvested into clean dry screw-capped bijou bottles.

Methods for biochemical assay

Estimation of serum uric acid

Serum uric acid was assayed by phosphotungstic acid method. Preparation of reagents was done using standard laboratory procedure and the reagents used were of analytical grade. The technique for uric acid estimation has two stages. In stage I, 8 ml N/12 H_2SO_4 was mixed with 1 ml serum and 1 ml 10 % sodium tungstate, then spinned in a centrifuge at 3000 rpm for 5 minutes. In stage II, 3 ml of supernatant was added to the tube labeled test, 3 ml uric acid standard was added to the test tube labeled standard and 3 ml distilled water was added to the test tube labeled blank. Then, 1 ml of 14 % sodium carbonate and 1 ml of phosphotungstic acid were added to each of test, standard (std) and blank test tubes. They were left for 15 minutes at room temperature and absorbance was read at 680 nm against reagent blank. The concentration of uric acid was calculated using the expression,

$$\text{Uric acid (µmol/l)} = \frac{A_{test}}{A_{std}} \times \text{Conc. of std (600 µmol/l)}$$

where A represent absorbance.

Estimation of serum urea

The method of estimation of serum urea using thiosemicarbazide is the standard Diacetyl monoxime method. There are 2 stages in this technique; in stage I, test tubes were labeled test, standard and blank. Then 10 ml of distilled water was added to the tubes labeled test and standard, followed by 0.1 ml serum placed in the tube labeled test while 0.1 ml urea standard was added to the tube labeled standard and each was thoroughly mixed. In stage II, 1 ml of diluted serum was transferred into another tube labeled test, followed by 1 ml of distilled water, 2 ml urea acid reagent and 2 ml urea colour reagent. To another tube labeled standard, 1 ml diluted standard was placed, followed by 1 ml distilled water, 2 ml each of urea acid and urea colour reagents. To the tube labeled blank, 2 ml distilled water was added, followed by 2 ml each of urea acid and urea colour reagents. All the tubes contents were thoroughly mixed, then placed in a boiling water bath at 100^{o}C for 20 minutes; removed, allowed to cool and absorbance was read at 520 nm against reagent blank. The concentration of urea was calculated by the expression,

$$\text{Urea (mmol/l)} = \frac{A_{test}}{A_{std}} \times \text{Concentration of standard (10 mmol/l)}$$

Estimation of serum Creatinine by Jaffe's method

This technique also has 2 stages. In stage I, test tubes were labeled test, standard and blank. To the test, 3 ml distilled water, 1 ml of serum, 1 ml 10 % sodium tungstate and 1 ml 2/3N H_2SO_4 were added. To the blank was added 4 ml distilled water, 1 ml 10 % sodium tungstate and 1 ml 2/3N H_2SO_4. Each tube content was mixed and centrifuged for 5 minutes at 3000 rpm. In stage II, 3 ml of each supernatant from stage I was added to fresh test tubes labeled test and blank while 3 ml of creatinine standard was added to tube labeled standard. To the test, standard and blank was added 1 ml each of 0.75 N NaOH and Picric acid. These were mixed thoroughly and allowed to stand for 15 minutes at room temperature, then optical densities of test and standard were measured using spectrophotometer at 520 nm, after zeroing with blank. The concentration of creatinine was calculated by the expression,

$$\text{Creatinine (µmol/l)} = \frac{A_{test}}{A_{std}} \times \text{concentration of standard (530 µmol/l)}$$

Statistical analysis

Data was presented as mean±standard deviation, and analyzed statistically using Analysis of Variance (ANOVA). Then where applicable, Duncan Multiple Range test was used to determine level of significance.

RESULTS

The results of the experiments were presented in tables. Table 1 shows the mean levels of serum uric acid, urea and creatinine in pregnant women attending ante-natal clinic in Vom Christian Hospital, at various trimesters of pregnancy and non-pregnant women as control. These results showed that there was a progressive decrease in the levels of serum creatinine and urea, while there was progressive increase in the levels of uric acid across the 3 trimesters of pregnancy. There was a significant ($p<0.05$) decrease in the levels of serum creatinine from the 1st to 3rd trimester of pregnancy but the significant ($p<0.05$) decrease in the levels of uric acid is only for 1st and 2nd trimesters while there was a significant ($p<0.05$) increase in the level of uric acid in the 3rd trimester of pregnancy,

when compared with the control. There was a progressive but not significant (p>0.05) reduction in the level of serum urea from the 1st to the 3rd trimester of pregnancy.

Table 1: Levels of serum uric acid, urea and creatinine in pregnant women at Vom Christian hospital

Parameters	Control	1st trimester	2nd trimester	3rd trimester
Serum Uric acid (µmol/l)	308.0 ±26	122.0 ±23*	199.0 ±32*	360.0 ±27*
Serum Urea (mmol/l)	4.11 ±0.71	3.60 ±0.72	3.49 ±0.80	3.29 ±0.78
Creatinine (µmol/l)	113 ±10.5	88 ±13.4 *	82.0 ±8.9*	61.0 ±7.50*

Values are means±SD, where SD=standard deviation, n =100. Values with asterisk(*) are significantly different from the control at p<0.05.

Table 2 shows the age distribution of pregnant women across three trimesters, attending ante-natal clinic at Vom Christian hospital and the control. This shows that the highest percentage of pregnant women (33 %) were from age group, 26 – 30, while the lowest percentage of pregnant women (6 %) were from age group, 36 – 40.

Table 2: Age distribution of pregnant women attending ante-natal clinic at Vom Christian hospital

Age group	Pregnancy stages and percentage age of subjects				
	1st trimester	2nd trimester	3rd trimester	Control	% Age
16 – 20	7	4	8	8	27
21 – 25	3	3	5	2	13
26 – 30	9	11	7	6	33
31 – 35	4	6	3	8	21
36 – 40	2	1	2	1	6

Mean age = 25.7 years, Range = 16 – 40, standard deviation = 6.22

DISCUSSION

The clinical laboratory has an important role to play in the management of pregnancy [1]. During pregnancy, a woman undergoes several physiological and biochemical changes such as haematological, hormonal, renal function etc. As a result of these changes, many of the laboratory reference intervals for non-pregnant women are not appropriate for pregnant women [10]. The laboratory determination of serum creatinine, urea and uric acid can be a reliable means of assessing the kidney function of pregnant women worldwide and evaluating the risk to the life of pregnant mothers and their foetuses, as a result of changes in renal function during pregnancy.

Urea is the main waste product of protein breakdown. It is synthesized in the liver from ammonia which is toxic to the body, but formed as a result of deamination of amino acids [3]. The decrease in serum urea of pregnant women in all trimesters even though not significant might be due to hydration, a rise in glomerular filtration rate (GFR), increased anabolic rate and demand of the developing foetus on the protein of pregnant mothers. A rise in the GFR was thought to account for the increased excretion of urea. As GFR increases without substantial alteration in urea production, due to limited intake of protein, concentration of this molecule decreases in plasma. The alteration in protein metabolism in late pregnancy suggests that amino acids are conserved for tissue synthesis. The sum total of plasma amino acids decline in pregnancy is between 15 -25 %, reflecting enhanced placental uptake and increased anabolic rate. It is a well known fact that the level of urea in urine acutely decreases when dietary protein is restricted, which is an indication of reduced plasma urea [22]. It appears therefore that as GFR increases in normal pregnancy, in addition to increased anabolic rate, serum concentration of urea decreases.

Creatinine is a muscle metabolite excreted by the kidney in the urine. When formed, creatinine diffuses passively into the blood stream where it is removed by the glomerular filtration action of the kidney, thus the level of creatinine in the bloodstream is reasonably constant [11]. The progressive significant (p<0.05) decrease in the levels of serum creatinine from the 1st to the 3rd trimester of pregnancy may be due to increase in glomerular filtration rate which occurs during pregnancy. The increase in glomerular filtration rate (GFR) results in an increase in the clearance rate of urea and creatinine but a decrease in urea and creatinine levels in the serum [19]. This observation is in agreement with the studies by [9], who reported that in pregnancy there is increased cardiac output and renal blood flow and physiological increase in glomerular filtration rate for the clearance of creatinine; so most pregnant patients who have serum creatinine at the upper limit of normal, defined by laboratory tests for non-pregnant individuals, should be viewed with marked suspicion of renal impairment. Serum creatinine is probably the most widely used indirect measure of GFR and one of the means of assessing kidney function. In several renal failures, the plasma concentration of creatinine is raised. Creatinine is freely filtered, so the serum creatinine levels depend

on the GFR. The GFR increases in normal pregnancy, so the serum concentration of creatinine decreases. It appears that changes in fluid distribution might produce an increase in GFR and lower plasma creatinine, although these have been found to increase progressively with gestation period; as it was reported that the plasma volume increases during pregnancy, sometimes by as much as 50 % and these changes are accompanied by alteration in the concentration of many plasma constituents including creatinine [6].

The significant ($p<0.05$) decrease in serum uric acid level of the pregnant women in their 1st and 2nd trimesters of pregnancy may be due to decrease in renal tubular threshold, with increase in cardiac output, renal blood flow and glomerular filtration rate. This is in agreement with [9], who reported that the renal tubular threshold is lowered in pregnancy, which results in an increased excretion of uric acid while cardiac output and renal blood flow are increased. These lead to an increased GFR, with resultant decrease in concentrations of serum urea, creatinine and uric acid. Pregnancy increases the glomerular filtration rate by 20 weeks of gestation and increases the clearance of uric acid, urea and creatinine [10]. The significant ($p<0.05$) increase in serum uric acid level seen in the third trimester of pregnancy may be due to increased tubular re-absorption of uric acid and decreased urate clearance by the proximal convoluted tubules. It was reported by [7] that in late pregnancy, tubular renal function decreases, leading to a decrease in glomerular filtration rate while [8] reported that pre-eclamptic hyperuricaemia is a result of decreased urate clearance by the proximal convoluted tubules of the kidney. Hyperuricaemia is an increase in concentration of plasma uric acid and has been associated with increasing symptoms of pre-eclampsia [20].

Pre-eclampsia is a common disorder of pregnancy characterized by high blood pressure and proteinuria, posing a serious health risk to mother and foetus. Increased serum uric acid is an early and characteristic feature of pre-eclampsia, which helps to differentiate the disorder from essential and other chronic forms of pre-existing hypertension which complicate pregnancy [14]. In pre-eclampsia of pregnancy, there is impaired glomerular filtration rate with resultant increased tubular re-absorption of uric acid, leading to impaired uric acid clearance [5]. It was earlier reported that glomerular filtration rate increases in normal pregnancy, thus the decrease in both renal blood flow and glomerular filtration rate are contrary to changes which occur in normal pregnant women [21]. According to [16], the production of uric acid is the same in pre-eclampsia as in normal pregnancy, so it appears the changes in serum uric acid during pregnancy might be due to an altered renal handling of the uric acid itself and not alteration in it's production [7]. The implication of an increase in serum uric acid was observed in 20 pregnant women complicated by pre-eclampsia and 22 normal pregnant women at 23 – 28 weeks of gestation. The mean serum uric acid level in women with pre-eclampsia was significantly higher than in the normal pregnant women [17]. It was also shown by [15], that elevated level of serum uric acid could be attributed to the well-documented decline of GFR in pre-eclampsia. However, we could not establish if the pregnant women with hyperuricaemia have pre-eclampsia, due to the limitation that this study did not include determination of blood pressure and serum protein levels.

CONCLUSION

The renal system undergoes marked changes in function during pregnancy due to hormonal effects, the increased metabolic load of the foetus and the outflow obstruction of the ureters by the enlarging uterus. Thus, the decrease in levels of creatinine, urea and uric acid may be due to increase in renal blood flow and glomerular filtration rate caused by increase in cardiac output and increase in the activities of progesterone, aldosterone, deoxycorticosterone and placental lactogen [13]. The decrease in uric acid levels in the 1st and 2nd trimesters of pregnancy, progressive decrease in the levels of creatinine and urea in all trimesters might be attributed to increase in glomerular filtration rate, which occurs in normal pregnancy. However, the elevated serum uric acid level in the 3rd trimester of pregnancy may be abnormal but not sufficient to conclude that there is renal impairment and pre-eclampsia, as other renal function tests showed values which decrease progressively and are within the reference ranges. Therefore, more studies need to be conducted to determine if the increase in serum uric acid in the later stages of pregnancy might result in renal impairment. Clinical chemistry laboratories should be encouraged to set reference ranges for biochemical parameters of renal function tests in pregnancy, as they vary from those of adult non-pregnant females.

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