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Original article

Effect of Pregnancy on the Metabolism of Creatinine, Urea and Uric Acid among Pregnant Women at the Volta Regional Hospital

Ahmed Tijani Bawah[1*], Francis A. Osei Kuffour[1], Michael Asamoah Boateng[1], Mohammed Mustapha Seini[2], Paul Amoah[3], Francis Abeku Ussher[4], Huseini Alidu[1]

[1]Department of Medical Laboratory Sciences, School of Allied Health Sciences, University of Health and Allied Health Sciences, Ho, Ghana
[2]Laboratory Department, Greater Accra Regional Hospital, Accra, Ghana
[3]Laboratory Department, Volta Regional Hospital Ho, Ghana
[4]Department of Medical Laboratory Sciences, Faculty of Health and Allied Science, Koforidua Technical University, Koforidua, Ghana.

ABSTRACT

Background: This paper looks at the low concentration of urea, uric acid and creatinine in pregnant women and argues that the causes may be due to physiological changes in the metabolism of these serum markers of kidney function. During pregnancy, physiological and anatomical changes occur resulting in increased renal workload. As a result of these changes, comparison of plasma levels of these biochemical markers to non-pregnant levels is inappropriate hence this study was aimed at evaluating the changes in the metabolism of these serum markers among pregnant women in the Ho municipality and to compare their reference intervals in both pregnant and non-pregnant women.**Methodology**: This case - control study involved 90 pregnant women and 90 aged-matched non-pregnant women who served as controls. Five milliliters of venous blood was obtained from each participant from which sera were obtained and concentrations of creatinine, urea and uric acid determined across the trimester intervals, using SELECTRA PRO S chemistry analyzer. **Results**: Creatinine and urea ($p<0.0001$) were significantly lower in the cases than the controls and uric acid was also significantly lower in the cases than the control ($p<0.0185$). Furthermore, uric acid concentration increased from the second to the third trimester, though the increase was not statistically significant.**Conclusion**: There is progressive decrease in the concentration of urea, creatinine and uric acid during normal pregnancy with a slight increase in the concentration of uric acid during the third trimester.

KEYWORDS: Urea, Creatinine, Uric Acid, Pregnancy

INTRODUCTION

Human pregnancy takes about 40 weeks to complete starting from the last menstrual cycle to the time of delivery of the baby and comprises three time intervals known as first, second, and third trimesters. The first trimester starts from first day of conception up to 13th week and miscarriages are most likely to occur at this stage. Second trimester is from the 13th week to the 26th week, where the movement of the fetus may also be felt by monitoring and assessment by ultra sound. The third trimester starts from the 26th week to the end of pregnancy which is usually around the 40th week and marks the beginning of viability [1, 2]. At the time of pregnancy, the pregnant woman's body undergoes substantial physiological and anatomical alterations making it possible to nurture and accommodate the developing fetus and these alterations which commence after conception affects every organ system [3].

This physiological phenomenon with many biochemical alterations (ranging from alterations in fluid and electrolyte concentrations to more complex modifications in cortisol and calcium metabolism), help in the nurturing and survival

of the developing fetus [4]. During the first half of pregnancy, there is increase in cardiac output, accompanied by marked increase in intravascular and extracellular volume [5]. This is accompanied by enlargement of the kidneys due to fluid retention and failure of urine to properly drain from the kidney to the bladder, which is attributable to proliferation in kidney's interstitial fluid volume and vascular system rather than proliferation in the number of nephrons [6].

This hydronephrosis which may be observed in pregnancy may be due to increased levels of progesterone and sudden changes in hormonal and hemodynamic environment during pregnancy [7]. This enlargement of the kidneys is prominent in the right kidney as a result of the angle at which it crosses the iliac and ovarian vessels at the point of its entry to the pelvis [8, 9], and becomes more pronounced as the pregnancy advances through the trimesters due to fluid retention which predisposes the woman to urinary stasis, culminating in the increased risk of urinary tract infections [10]. Structural changes in the kidneys during pregnancy is also influenced by both hormonal and mechanical factors where elevated progesterone concentration in plasma creates force of contraction on the uterus leading to a compression effect exerted by the weight of the uterus as the pregnancy advances [4]. Hormonal and mechanical forces are thought to be responsible for ureteral dilation as early as 6 weeks of gestation [11].

Even before the onset of conception, hormonal changes influence renal function during the menstrual cycle especially in midluteal phase where there is increase in renal plasma flow (RPF) and glomerular filtration rate (GFR) as a result of increase cardiac output [8]. There is elevation in GFR and RPF due to marked vasodilation which is a characteristic of renal physiologic changes [11]. Subsequently, as a result of renal vasodilation, RPF and GFR both increase, compared to non-pregnant levels, by 40–65% and 50–85%, respectively [3, 6]. There is an increase in renal blood flow of 50% resulting in an increase in the size of the kidneys and eventually a raised GFR from 100 to 150 ml/min by the second trimester leading to the increase in the clearance of creatinine, urea and drugs [12].

Glomerular filtration rate is good in assessing renal disease by estimating urine or plasma clearance of substances [13]. The GFR may increase by up to 50% in pregnancy above non-pregnant levels, primarily due to elevations in cardiac output and RPF [2, 6]. Notwithstanding the increase in RPF, the pressure within the glomerulus remains unchanged due to compensatory effects on the afferent and efferent arterioles, but this only occurs in a normal kidney. Any pre-existing disease in the kidney will be accelerated, and usually accompanied by worsening in renal function [9]. In most women without complicated pregnancy, these changes resolve after delivery with minimal residual effects [3].

Furthermore, the handling of water and electrolytes by the renal tubules are altered, leading to lower serum osmolality, decline in serum sodium levelsand mild increases in glucosuria and proteinuria [6]. Physiologically, there will be increase in protein excretion during pregnancy because of increase GFR and increase in the permeability of the glomerular basement membrane and when this proteinuria becomes severe *de novo* or as a result of worsening of preexisting hypertension, then this will be pointing to underlying glomerular disease or preeclampsia [14]. The increased vascularity of the kidneys makes a renal biopsy beyond 32 weeks of pregnancy risky [9]. However, Renal biopsy is preferred in cases where accurate histological diagnosis will significantly change clinical management during pregnancy [15].

Therefore, in a situation of suspected renal impairment, biochemical means of assessing renal function is the preferred method, especially in Ghana where these methods are readily available in our health facilities. Factors such as nutrition, genetics and mother's lifestyle influence the imbalance of metabolites in pregnant women [4]. Renal impairment is a common complication of pregnancy [8]. Biochemical parameters reflect these changes and are clearly distinct from the non-pregnant state [4]. Assessment of renal function during pregnancy should therefore take into consideration of these changes. Urea, Uric acid and creatinine are part of panel of biochemical parameters usually employed in the assessment of renal function.

Urea is the major nitrogen containing metabolic product of protein catabolism in humans. It is synthesized in the liver from ammonia and formed as a result of deamination of amino acid and excreted by the kidneys [2, 16]. The factors that can influence the uptake of urate by the kidneys are: plasma concentrations, volemia and RPF modulators [17].

Many organs in the body including the kidneys are able to synthesize creatinine compound endogenously from the amino acids methionine, arginine and glycine by two enzymatically mediated reactions. This begins in the kidney with L-arginine: glycine aminotransferase (AGAT), an enzyme which initiate the transamination of arginine and glycine to form guanidinoacetic acid and ornithine. The second enzyme glycine N-methyltransferase (GAMT) causes methylation of guanidinoacetic acid which occurs with S-adenosylmethionine as the methyl donor [18]. Creatine is then transported in blood to the muscles, brain and other organs where it is phosphorylated to phosphocreatine. Inter conversion of phosphocreatine and creatine occurs in the muscle following muscular contraction. A fraction (between 1% and 2%) of free creatine in muscles spontaneously and irreversibly converts to creatinine, the anhydride waste product [16]. The creatinine then diffuses passively into the bloodstream where it is excreted through the urine [2].

Uric acid is the main product of catabolism of the purine nucleosides; adenosine and guanosine[16]. Plasma concentrations of uric acid increase with age with relatively smaller concentrations in women [17]. It is transported in the blood from the liver to the kidney, where it is filtered. Reabsorption of about 98% of the uric acid from the glomerular filtrate occurs in the proximal tubules while small amounts are secreted by the distal tubules into the urine. About 70% of uric acid is excreted through kidney and the remainder sent to the gastrointestinal tract where it is degraded by bacterial enzymes [19]. Conditions such as dilutional effect of an expanding plasma volume, decreased production, and increased renal excretion due to pregnancy-induced increase in the GFR causes a reduction in the concentration of serum uric acid, creatinine and urea [20].

Successful outcome of pregnancy requires frequent monitoring of biochemical and hematological parameters to

avoid complications throughout the trimesters of pregnancy [1].

The determinations of serum concentrations of urea, creatinine and uric acid are reliable in assessing kidney function of pregnant women globally [2], however, the biochemical changes in renal function accompanying normal pregnancies in Ghana as a whole and Ho in Volta Region in particular are not well documented. It was therefore important to evaluate the levels of these biochemical parameters at various stages of pregnancy so as to elucidate their usefulness in assessing the kidney function during pregnancy.

MATERIALS AND METHODS

This study was carried out among pregnant women attending antenatal clinic at the Volta regional Hospital, Ho, Ghana. It was a prospective and case - control study in which serum creatinine, urea and uric acid of 90 pregnant women were analyzed during the first trimester (11-13 weeks), second trimester (24- 28 weeks) and third trimester (34 weeks and above) and compared to 90 aged- matched non-pregnant controls. Participants were 18 years and above, consented to take part in the study and signed informed consent form. Participants with human immunodeficiency virus infection, impaired liver function and those with preexisting renal disease, systemic diseases such as systemic lupus erythematosus (SLE) and diabetes mellitus were excluded.

Socio-demographic information, obstetric history (parity, gravidity) of the selected participants according to the various trimesters were obtained from their folders and knowledge on the topic and other relevant information such as employment and marital status were obtained directly from the participants by way of interview.

The University of Health and Allied Sciences' Research Ethical Committee (Protocol number: UHAS-REC/A.5 [66] 17-18) reviewed the consenting process. Each participants'5 mL of venous blood sample was collected at each trimester using a disposable syringes and needles into a properly labeled gel separator tubes with the gel serving as clot activator at the antenatal clinic of the Volta Regional Hospital. Blood samples were centrifuged at 3,000 rpm for 5 minutes and the sera were separated and aliquoted into well-labeled Eppendorf tubes and frozen at -21^{o}C until analysis within one week. Serum creatinine, urea and uric acid were estimated using SELECTRA PRO S chemistry analyzer (Van Rensselaerweg 4, NL 6956 AV Spankeren, The Netherlands).

RESULTS

A total of 180 participants took part in the study with minimum and maximum ages of participants being 18 years and 41 years respectively with 73 participants employed in the formal sector while the remaining 107 engaged in the informal sector. Majority (149) of the participants were married, while 25 of them were single and 6 participants cohabiting (Table 1).

Table 1: Demographic information of the study respondents

Parameter	Frequency	Percentage
Total respondents	180	100
Status		
Pregnant	90	50.00
Non-pregnant	90	50.00
Marital status		
Single	25	13.90
Co-habiting	6	3.30
Married	149	82.80
Age (Years)		
<20	12	6.67
20-29	72	40.00
30-39	87	48.33
≥40	9	5.00
Career category		
Formal	73	40.83
Informal	107	59.17

Data is presented as figure and percentage.

In this study, the biochemical parameters usually employed in the assessment of renal impairment were analyzed. Creatinine and urea were significantly lower in the cases than the controls ($p<0.0001$) and uric acid was also significantly lower in the cases than the control ($p<0.0185$) (Table 2). When the biochemical parameters were compared across the various trimesters, there were significant differences between the controls and the first, second and third trimesters of the cases for creatinine and urea.

However, when the uric acid levels were compared between the controls and the various trimesters of the cases, there

was no significant difference in the first trimester (p>0.05) but significant differences were shown in the second and third trimester (p>0.05) (Table 3).

Comparison of the biochemical parameters across the trimesters revealed that, no significant differences existed between the controls and creatinine levels for first and second as well as second and third but there was significant difference between the first and third trimester (p<0.0106).

Table 2: General comparison of the serum creatinine, urea and uric acid between the controls and the cases

Parameter	Control	Case	*P- value*
Creatinine (µmol/l)	81.9 ± 14.02	61.89 ± 9.55	<0.0001
Urea (mmol/l)	3.39 ± 0.79	2.07 ± 0.73	<0.0001
Uric Acid (µmol/l)	227.42 ± 64.35	196.55 ± 60.28	0.0185

Data is presented as mean ± SD. P-value of < 0.05 is statistically significant.

On the other hand, when the urea levels were compared between the various trimesters there was no significant difference between the first and the second trimesters, however, there were significant differences between the second and third (p<0.0348) as well as between the first and the third (p<0.0013). Uric acid did not show any significant difference across the trimesters (Table 4).

The results of this study indicates lower reference interval for urea, creatinine and uric acid as compared to the reference interval currently being used at the Volta Regional Hospital (Table 5).

Table 3: Comparison of the main serum parameters between the controls and the cases across the trimesters

Parameters	Control (90)	Cases (90)		
		First trimester	Second trimester	Third trimester
Creatinine (µmol/l)	81.90±14.08	65.54 ± 12.34*	61.61 ± 6.55*	58.52 ± 7.70*
Urea (mmol/l)	3.39±0.79	2.36 ± 0.72*	2.12 ± 0.63*	1.74 ± 0.70*
UricAcid (µmol/l)	227.42 ± 64.35	201.76 ± 71.63	181.45 ± 41.38*	206.45 ± 62.79

Data is presented as mean ± SD. Values with (*) are significantly different between the Control and the respective trimester; p value<0.05.

Table 4: Comparison of serum creatinine, urea and uric acid levels across trimester interval

Parameters	**Trimester Interval**		
	$1^{ST} – 2^{ND}$	2^{ND} - 3^{RD}	$1^{ST} – 3^{RD}$
Creatinine (µmol/l)	0.1292	0.0997	0.0106*
Urea (mmol/l)	0.1606	0.0348*	0.0013*
Uric Acid (µmol/l)	0.1839	0.0737	0.7882

Data presented as trimester interval and their corresponding p-value. Values with asterisk (*) are significant within that trimester interval.

Table 5: Comparison of urea, creatinine and uric acid levels and the reference ranges used at the VRH.

Parameter	**Study reference interval**	**Reference interval at VRH**
Creatinine (µmol/l)	45 – 84	53 – 115
Urea (mmol/l)	1.12 - 3.93	2.10 - 7.10
Uric Acid (µmol/l)	112 - 338.20	150 – 350

Data presented as lower and upper limit for the various for serum parameter range.

DISCUSSION

The physiological state of pregnancy brings about a lot of changes which affect the metabolism of various biochemical parameters. These changes are largely thought to provide conducive environment for the growing fetus but may affect the health of the woman and could also lead to problems with metabolism and excretion of biochemical markers of renal impairment. Furthermore, during pregnancy cardiac output and renal blood flow are increased together with

physiological increase in GFR resulting increased clearance of creatinine [6], hence pregnant patients with serum creatinine level closer to the upper limit of reference interval for the "normal'' population, should be examined further for possible renal impairment.

To this end, a slight rise in creatinine level during pregnancy may indicate progression of renal disease and thus serum creatinine has greater predictive ability compared with urea for the determination of the adverse outcomes of kidney disease [5, 10, 12].

The gradual decrease in the concentration of creatinine in plasma from the first to the third trimesters of pregnancy is likely to be as result of increase in GFR associated with pregnancy but not a reduction in its plasma concentration. The increase in GFR may be due partly to upsurge in the concentration of aldosterone which increases the blood volume, in some instances, up to 50% and increase renal blood flow [4] resulting in an increase in the rate at which creatinine is cleared from plasma.

In this study, creatinine concentration was significantly reduced among the pregnant women compared to the non-pregnant controls. This is in consonant with one study which reported significantly lower creatinine levels in the cases as against the control [2]. Some report indicated about 50% increase in glomerular filtration rate during pregnancy [3], and this could lead to increase in creatinine excretion. Creatinine is freely filtered and its level falls in normal pregnancy due partly to a pregnancy-induced increase in GFR on one hand and on the other hand due to hemodilution from plasma expansion culminating in the decrease in serum creatinine concentration [9]. Consequently, the reduction in serum creatinine is ancillary to plasma volume expansion, renal vasodilation, hyperfiltration, and increased glomerular basement membrane permeability [15].

In this study there was significant decrease in the urea concentration across the various trimesters. This is similar to a study which showed a general decrease in urea level between pregnant women and controls though the decrease was not statistically significant [2]. This decrease might be as a result of hydration, a rise in GFR, increase anabolic rate and increased demand of the fetus on the maternal protein [2]. The rise in glomerular filtration rate that normally occurs in pregnancy results in lower levels of urea [5]. As GFR increases without significant increase in urea synthesis, its concentration decreases in plasma [5]. In late pregnancy, there is alteration in protein metabolism suggesting that amino acids are preserved for tissue synthesis and evidence points to enhanced metabolic rate and increased placental uptake [2], consequently serum concentration of urea declines.

There was generally statistically significant decrease in uric acid level between the controls and the pregnant women during the first trimester. This is in consonant with a study in which there was a decline in uric acid level during the first trimester between the pregnant women and the controls [2]. Paradoxically, the uric acid level in this study increased though not statistically significant as the pregnancy progressed to the third trimester. This is similar to a study which showed a general increase in uric acid level as the pregnancy progressed from the second to the third trimester [21].

During the late stages of pregnancy more profoundly in the third trimester, tubular reabsorption of uric acid increases dramatically which increases serum uric acid concentration in addition to decrease in the clearance of uric acid from the proximal and distal tubules [1]. The increase in concentration of uric acid at the late stage of pregnancy may also be secondary to improved fetal production, reduced binding to albumin and elevated tubular re-absorption with decreasing renal clearance of the uric acid [21]. There is a gradual decrease in serum uric acid concentration in normal pregnancy up to 16 weeks of gestation. The uric acid levels then tend to stabilize between 17 and 28 weeks of pregnancy and start increasing during the third trimester [21].

CONCLUSION

Normal pregnancy is associated with progressive decrease in urea and creatinine levels from the first trimester to the third trimester while uric acid decreases in first half of pregnancy followed by increases from the second trimester to the third trimester. The upsurge in uric acid concentration from the second to the third trimester of pregnancy may be attributable to the dramatic increase in tubular re-absorption and fetal production.

The absence of reliable data on reference intervals for urea, creatinine and uric acid among pregnant women in Ghana call for the establishment of these reference ranges using larger sample size and should cover all the ten regions of the country. This is because the physiological and anatomical changes that come with pregnancy especially those related to the kidney means that the laboratory reference intervals of non-pregnant women are not suitable for pregnant women.

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Competing interest: The authors declare that they have no competing interests.

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*Corresponding author: Dr. Ahmed Tijani Bawah
E-Mail:ahmed024gh@yahoo.com