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Liver and kidney function tests in normal and pre-eclamptic gestation - a comparison with non-gestational reference values

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Abstract

Objective : To compare liver and kidney function tests in pre-eclampsia and in uncomplicated pregnancy and to relate the results to physiological reference values.
Design: Prospective cross sectional study.
Setting: Antenatal clinic and antenatal labour wards, Harare Hospital, Zimbabwe.
***Subjects*:** 38 pre-eclamptic and 72 normal women of similar parity, *gravida* and gestational age.
Main Outcome Measures: Serum albumin, total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT) and gamma-glutamyl transaminase (GGT) were used as indices of hepatic function. Serum creatinine, urea and uric acid were used to assess renal function.
Results: Albumin, bilirubin and ALT did not show any differences between the pre-eclamptic and normotensive pregnant women. The activities of the following enzymes, ALP ($p<0.001$), AST ($p=0.001$) and GGT ($p<0.01$) were significantly elevated in pre-eclamptic women. The renal indices, creatinine, urea and uric acid were significantly raised in pre-eclampsia ($p<0.001$). No significant differences were observed in the haematological parameters, haemoglobin (Hb), white blood cell count (WBC), red blood cell count (RBC), mean corpuscular volume (MCV) and platelet count. Almost all the biochemical and haematological parameters were lower in normal pregnancy compared to the physiological reference values used in our maternity unit.
Conclusion: Liver and kidney function is modified by normal pregnancy. However, the majority of the liver and kidney function tests between pre-eclamptic and normal pregnancy exhibited significant differences. The physiological reference values that are currently in use are different from those of women with uncomplicated pregnancies and may not be entirely suitable for management of pre-eclampsia which has hepatic and renal involvement.

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Introduction

Normal pregnancy is associated with immense changes in various metabolic processes which induce major physiological adaptations in the pregnant individual. It has been reported that hepatic and renal abnormalities occur in a considerable number of pregnancies complicated by pre-eclampsia.[1-3] These abnormalities may result in poor maternal and foetal outcomes[4-6] Generally, non-pregnant derived female reference ranges are used to identify liver and kidney dysfunction, without making any allowances for the physiological changes that occur in normal pregnancy. This raises the question whether these reference ("normal") values should be used as standards for accurate interpretation of results from pregnant subjects.

Pre-eclampsia, the most common medical complication of the second half of pregnancy, is a complex multi-organ disorder that is characterized by hypertension, oedema and proteinuria, most frequently observed in the *primigravida*. It contributes significantly to maternal and neonatal mortality and morbidity. The manifestations of pre-eclampsia arise from reduced organ perfusion due to intravascular coagulation, vasoconstriction and diminished maternal blood volume. Liver and kidney function, including clotting ability are affected in individuals afflicted by this disorder[7-9]

Since no allowances are made for the "pregnancy effect" in pre-eclampsia, our major objective was to compare hepatic and renal function tests in women afflicted by pre-eclampsia and in normal pregnant women and also to compare the means of these parameters to the local non-pregnant reference means, using universal biochemical tests. As pre-eclampsia may affect the haemostatic system, we also performed a full blood count on all participants.

Materials and Methods

The study was conducted at Harare Maternity Hospital, a tertiary level hospital. The women were recruited from the antenatal clinic and the antenatal labour wards. Women who had two consecutive blood pressure readings of >140/90 mmHg at four hours apart and a urine sample exhibiting proteinuria on a dipstick were considered to be pre-eclamptic. Women with essential hypertension, *Diabetes mellitus*, a history of hepatic disease, renal disease or urinary tract infections were excluded from the study. Assuming that abnormal hepatic or renal function tests occurred 10 times more frequently in women with pre-eclampsia than in normotensive women, a sample size of 38 women was needed to have a power of 90% with a 95% confidence interval of detecting a 25% difference. We therefore, elected to choose two unmatched normotensive women for each pre-eclamptic woman recruited into the study. Both groups of women gave their written consent in order to participate in the study.

Venous blood samples were withdrawn from the participants and a sample was collected in a plain tube for biochemical analysis and in an EDTA anticoagulant vial for haematological studies. The blood pressure measurements were carried out by a midwife using a conventional sphygmomanometer. The principal laboratory assays were the liver function tests: serum albumin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT) and total bilirubin. Other parameters included the renal parameters, serum creatinine and urea as well as uric acid. The above biochemical assays were carried out on the Cobas Mira Plus autoanalyzer using Randox kits (Randox Laboratories Ltd, United Kingdom). Full blood count (FBC) analysis was carried out on the EDTA samples on a Coulter-JS analyzer, using reagents supplied by the manufacturer of the autoanalyzer (Coulter Electronic Ltd, United Kingdom). Sample preparation and analysis was carried out within two hours of sample collection and all assays were performed at 37°C.

Normally distributed data was analyzed by analysis of variance (ANOVA) and non-parametric data by Kruskal-Wallis analysis using the Epi-Info 6.0 statistical package. Results are expressed as means with standard deviation (SD), unless otherwise stated. The level of statistical significance in this study was set at 5%.

Results

We enrolled 110 women, 38 pre-eclamptic and 72 normotensive participants. The baseline characteristics of the normotensive and pre-eclamptic women are shown in Table I. The mean age of women with pre-eclampsia was 27 years (range, 16 to 39), and that of women with uncomplicated pregnancy was 25 years (range, 15 to 45) (p=0.05). Both groups of women shared similar parity, *gravida* and gestation (not statistically significant, 0.91, 0.89 and 0.83 respectively). The mean systolic blood pressure and SD was 165 (20) and 118 (11) mmHg, whereas, the mean diastolic blood pressure and SD was 109 (13) and 74 (8) mmHg for the pre-eclamptic and normotensive women respectively. As expected, the blood pressure parameters were significantly elevated in pre-eclampsia ($p < 0.001$).

Table I : Baseline characteristics, means with standard deviation (SD) in pregnant women.

Characteristic (Mean + SD)	Normotensive (n=72)	Pre-eclamptic (n=38)	p-value
Age (yrs)	25 (6)	27 (6)	0.05
Systolic BP (mmHg)	118 (11)	165 (20)	<0.001
Diastolic BP (mmHg)	74 (8)	109 (13)	<0.001
Parity	1.4 (1.6)	1.4 (1.6)	0.91
Gravida	2.7 (1.6)	2.7 (1.8)	0.88
Gestation (weeks)	32 (6)	32 (5)	0.83

The means, standard deviations and p-values of the liver function, renal function and haematological tests are shown in Table II. No significant differences between pre-eclamptic and normal pregnancy were observed for

albumin, total bilirubin and ALT (p=0.73, 0.46 and 0.16 respectively). All the other enzymes associated with the liver were significantly elevated in pre-eclampsia, ALP 281 vs 171 IU/L (p<0.001), AST 32 vs 22 IU/L (p<0.001) and GGT 18 vs 12 IU/L (p<0.01).

Serum uric acid, an end product of purine metabolism, was significantly raised in hypertensive women, 359 vs 208 μmol/L (p<0.001). The two indices for assessing renal function, serum creatinine and urea, showed significant elevation in pre-eclampsia, 71 vs 52 μmol/L and 3.7 vs 1.9 mmol/L respectively, with a p value <0.001 (Table II). In contrast, none of the haematological parameters (Hb, platelet count, MCV and WBC) were significantly different between normotensive pregnant women and those diagnosed with pre-eclampsia (Table II).

Table II: Biochemical and haematological parameters, means with standard deviation (SD) in pregnancy.

Parameter	Normotensive (n=72) Mean + SD	Pre-eclamptic (n=38) Mean + SD	p value
Liver Function Tests			
Albumin (g/L)	33 (3)	33 (4)	0.73
Total Bilirubin (umol/L	13 (12)	12.7 (7)	0.46
ALP (U/L)	171 (90)	281 (152)	<0.001
ALT (U/L)	13 (8)	16 (13)	0.16
AST (U/L)	22 (11)	32 (17)	<0.001
GGT (U/L)	12 (8)	18 (13)	<0.01
Renal Function Tests			
Creatinine (umol/L)	52 (9)	71 (24)	<0.001
Urea (mmol/L)	1.9 (0.07)	3.7 (1.8)	<0.001
Uric acid (mol/L)	208 (68)	359 (109)	<0.001
Haematological Tests			
Haemoglobin (g/L)	11 (2)	11 (2)	0.88
Platelets (x 103/ml)	248 (56)	238 (74)	0.46
MCV (%)	80 (8.9)	78 (7.6)	0.22
WBC (x 103/ml)	8.8 (4.2)	8.1 (3.9)	0.44

The means of the liver and kidney function parameters in pre-eclamptic, normotensive and non-pregnant women are shown in Table III. There was insufficient information from the laboratory-derived data to do a statistical comparison of their data with ours. The physiological mean values of ALP and AST were 97% and 10% higher in non-pregnant women compared to normotensive pregnant women. However, the means of most of the biochemical parameters were lower in normal pregnancy compared to non-pregnant women, 20%, 19%, 35%, 46%, 33%, 57% and 13% for albumin, total bilirubin, ALT, GGT, creatinine, urea and uric acid respectively.

Discussion

The most striking finding in this study is the lower mean values of almost all biochemical and haematological parameters in women with uncomplicated pregnancy compared to the non-gestational reference means. The lower values can be explained by the physiological

Table III: Comparison of liver and renal function study parameters in pregnant women and reference values.

Parameter	Pre-eclamptic Mean + SD	Normotensive Mean + SD	Laboratory reference Mean + SD
Albumin (g/L	33 (4)	33 (3)	41 (6)
Total bilirubin (umol/L)	**12.7 (7)**	**13 (12)**	**16 (7)**
ALP (U/L)	281 (152)	171 (90)	87 (27)
ALT (U/L)	16 (13)	13 (8)	20 (9)
AST (U/L)	32 (17)	22 (12)	20 (5)
GGT (U/L)	18 (13)	12 (8)	22 (7)
Creatinine (umol/L)	71 (24)	52 (9)	78 (22)
Urea (mmol/L)	3.7 (1.8)	1.9 (0.7)	4.4 (1.2)
Uric acid (umol/L)	359 (109)	208 (68)	240 (50)

haemodilution of pregnancy as well as increases in renal glomerular filtration rate.[10,11] Another important finding is the significantly elevated liver and renal biochemical parameters in pre-eclampsia signifying some dysfunction in the two organs. Most of these physiological changes characteristic of pre-eclampsia should be considered as a failure of the compensatory responses that take place in normal pregnancy.

There is scanty and conflicting information regarding the limits to be used in defining abnormal liver and kidney function values in pregnancy.[3,12,13] Furthermore, the comparison data is mainly derived from reference ranges of non-pregnant women. It is quite feasible that these reference values are not suitable for interpreting accurately results obtained from pregnancies complicated by pre-eclampsia, as obvious physiological changes associated with normal pregnancy are often ignored. As the syndrome of pre-eclampsia can have an unpredictable fluctuating course, it is imperative to have stringent pregnancy based biochemical reference ranges for accurate interpretation of results and effective management of this disease.

The elevation of ALP in normal pregnancy especially during the last two trimesters has been known about for decades and is attributed partly to placental and bone activity.[14,15] In our study the significant rise (64%) of total ALP activity in pre-eclamptic women, compared to the normal pregnant women of similar gestational age must be ascribed to the effects of pre-eclampsia. The rise in ALP activity could be due to cholestasis which increases the synthesis of hepatic ALP and its subsequent regurgitation into plasma. We recommend further investigations to identify the specific isoenzyme(s) associated with the elevation of ALP in pre-eclampsia in this population.

Measurement of GGT activity is a more sensitive marker of hepatic cholestasis and, the enzyme is more likely to be elevated when there is liver cell damage accompanied by minor cholestasis. The concomitant significant rise (50%) in GGT activity (comparable to ALP activity) in pre-eclamptic women reinforces the concept of intrahepatic cholestasis. Increases in GGT levels have been reported elsewhere.[10,16] The rise in GGT was not due to alcohol abuse as women who consumed alcohol were ineligible for

inclusion in this study. However, caution must be exercised in interpreting this, as our assay measured total GGT activity. There is a need to develop routine assays for determining specific GGT isoenzymes.

Hepatocellular damage is characterised by an elevation of several enzymes, in particular ALT and AST. The significant increase in AST activity without a corresponding significant elevation in ALT activity in our study is difficult to explain. The two enzymes are raised in liver cell damage, ALT is more liver specific than AST and rises to a greater extent in acute hepatocellular injury. Significantly increased levels of these transaminases in pre-eclampsia have been reported by several workers.[6,17,18] Since there was a significant elevation of all the renal function tests in this study, this represents some dysfunction of the kidney, and the raised levels of total AST activity could in part be attributed to the renal isoenzyme, rather than hepatocellular damage. This is supported by the fact that the bilirubin levels were not significantly affected.

The most significant elevations in biochemical parameters were observed in renal function tests. There was a 37% increase in serum creatinine and a 95% increase in serum urea levels in women diagnosed with pre-eclampsia when compared to women with uncomplicated pregnancy. Measurement of plasma creatinine is very effective in detecting early renal disease, as its endogenous production remains constant. The significant increase of creatinine, a sensitive marker of renal function, is a well documented phenomenon in gestational hypertension.[3,6,19,20] Kidney dysfunction, represented by the significant changes in renal function parameters, warrants further investigation to ascertain its effect on pregnancy outcome in pre-eclampsia. The mean serum uric acid level in the pre-eclamptic women was much higher than in normal pregnancy or in the upper physiological reference limit. Therefore, serum uric acid levels seem to be a very sensitive marker of pre-eclamptic effects in this population. Hyperuricaemia of pre-eclampsia is related to the decline in uric acid clearance by the kidney, due to alterations in glomerular and tubular function.[21-23]

Women who had their pregnancies complicated by pre-eclampsia exhibited no significant differences in the haematological parameters under study, except that the platelet count, MCV and WBC were lower than in normal pregnancy. The fact that the platelet count was not significantly lowered is supported by the AST, ALT and blood pressure results which suggests that the majority of the women had mild to moderate pre-eclampsia. Some workers have reported little, if any change in platelet behaviour during pregnancy from the non-pregnant state.[24,25] However, Hayashi *et al.* found significant decreases in platelet count in women with pre-eclampsia compared to uncomplicated pregnancy.[9]

This study has established that significant hepatic and renal function deviations occur in pre-eclamptic pregnancy, and that most values of liver and kidney function tests are lower in pregnancy than the physiological reference ranges used at our obstetric unit. Despite the fact that the majority of the biochemical parameters did not exceed the upper physiological reference limits, it must be accepted that their distinct and significant deviations are due to disease. Therefore, use of reference ranges derived from normal pregnancy can only provide a more accurate diagnostic assessment of this serious disorder. A large longitudinal study should be carried out to derive pregnancy specific reference ranges for liver and kidney function tests

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