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Evaluation of some Marker Enzymes, Prostaglandins, C-Reactive Protein and Plasma Total Protein, in Pregnancy Induced Hypertension among women in Ekiti State, Nigeria

OYEYEMI A. O[1*] AND ASAOLU M. F[2]
[1*]Department of Biochemistry, Ekiti State University, Ekiti State, Nigeria,
[2] Department of Biochemistry, Ekiti State University, Ekiti State , Nigeria.

ABSTRACT
This study was carried out to evaluate the levels of some marker enzymes, Prostaglandins, C-Reactive protein and Total protein in women with pregnancy induced hypertension (PIH) and normotensive pregnant women in Ekiti state, Nigeria. The patients were got and nurtured at the university teaching hospital and Federal medical Centre located in different towns within the state. The results obtained revealed no significant change ($p<0.05$) in the activities of the enzymes; Acid Phosphatase(ACP), Aspartate Aminotransferase (AST), Alanine aminotransferase (ALT), Lactate Dehydrogenase (LDH) in both normotensive and hypertensive pregnancy. However, Alkaline phosphatase showed a significant decrease ($p<0.05$) in patients with PIH. Prostaglandins assayed for revealed a significant increase ($p<0.05$) in both normotensive and hypertensive pregnant patients, but patients with PIH showed a higher significance. It was also observed that C-reactive protein significantly increased ($p<0.01$) in pregnant women with PIH. The results further revealed a significant decrease ($p<0.05$) in the level of Total Protein in women with PIH only. This study reveals that PIH is associated with reduced levels of Total Plasma Protein and raised levels of C-Reactive Protein and Prostaglandins. Also, it can be said from the result that PIH does not bring about significant changes in the activities of the marker enzymes examined apart from alkaline phosphatase which was implicated.
Keywords: Marker Enzymes, Prostaglandins, C-Reactive Protein, Total Protein, Pregnancy Induced Hypertension(PIH), Acid phosphatase(ACP), Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT),Aspartate Aminotransferase (AST), Lactate dehydrogenase(LDH).

INTRODUCTION

Maker enzymes are enzymes confined to a particular organelle, cell or cellular compartment. They are cell biomarkers used to characterize a cell type , they are also used in the isolation of the target cellular components. Some of this marker enzymes are Alkaline phosphatase(ALP), Acid phosphatase(ACP), Alanine amino transferase (ALT), Aspartate aminotransferase(AST), Lactate dehydrogenase (LDH). All of these enzymes could have their activities raised or lowered in the plasma as a result of different factors which could be a pointer to a disease condition, organ damage, or physiological changes. So, the activities of all of the enzymes have clinical significance.

Pregnancy refers to the period from conception to the expulsion of the foetus. The Pregnancy period affects various physiologic and endocrinology systems. It's a natural state that sets up great changes throughout the whole body and most of these changes subside quickly after delivery (GuiceBooth,2005) Pregnancy can be complicated by at least two distinct types of hypertension. The first one is chronic hypertension, which is usually characterized by blood pressure greater than 140/90mmHg. The second type is Pregnancy Induced Hypertension (PIH), previously called pre-eclampsia and toxemia. PIH is a complication that results to the development of hypertension after about twenty (20) weeks of gestation in a woman who had previously been normotensive (with no pre-existing renal disease). A patient with PIH will begin her pregnancy with a normal blood pressure but it will rise sometime in the third trimester in typical cases, but earlier in severe cases. A rise in the blood pressure by 30/50 (e.g. from 90/50mmHg to 120/70mmHg) over the course of the pregnancy is a diagnostic criterion, even though the final pressure may seem normal (Courtney,2006, Sibai et al, 2007, Asaolu et al, 2010). In United States, the incidence of PIH reveals that, approximately 10% of pregnancies are characterizes by pre-clampsia. Black women have higher rates of pre-eclampsia complicating their pregnancies compared with other racial groups (Chobanian et al, 2003).

PIH is a much more dangerous condition than chronic hypertension, because there is much more alteration in the maternal body than just high blood pressure. There is a whole chemical shift of maladaptive reactions that can even lead to seizures and death in the pregnant patient (Chesley, 1987). PIH is one of the major causes of maternal death throughout the world. There is the belief that Pill contributes extensively to still births, neonatal morbidity and death (Mannisti et al, 2013). It has been suggested that one or more of the protective mechanisms are either deficient or fails to functions properly or even gets out of control (Cunmigham et al, 2005).

PIH is characterised by swelling of the body especially the ankles and legs, a
condition known as oedema, hyper reflexia, or exaggerated deep tendon reflexes

(the knee-jerk, for instance), hyperproteinuria or spilling protein in the urine). Many complications go with PIH relating to the offspring (Gutman and Gutman 1970, Hollegaard et al, 2013). The expectant mother's kidneys are especially vulnerable, affecting filtration, worsening the swelling and resulting in the loss of protein in the urine. The proteinuria in PIH may also due to pathological damage to the glomerular cells and almost always occurs after hypertension, 60% of the protein is albumin. The blood vessels develop abnormalities of constriction, affecting blood pressure and the reflexes become hyperactive (Guice Booth, 2005).

As at the moment, the exact cause of PIH is unknown, and currently there is no sure way to prevent the hypertension (Hajjar et al, 2003; Gross et al 2007).

Hence this area is still of great interest and in need of utmost attention of the populace. However, possible causes have been suggested to include; auto immune disorders, blood vessel problems, diets, genes and some of the risk factors for PIH include first pregnancy, multiple pregnancy (twins or more) ,obesity, women older than 35years, past history of diabetes, high blood pressure or kidney disease, women whose sisters and mothers had PIH (Onusco, 2003).

Prostaglandians (PGs) are lipid signal substances derived from essential fatty acids together with thromboxanes (TX) and prostacyclins (PGI_2), they form the prostanoid class of fatty acid derivatives. The Prostanoid class is a subclass of eicosanoids. PGs act in a manner similar to that of hormones by stimulating target cells into action. However, they differ from hormones in that they act locally, near the site of synthesis and are metabolised very rapidly.Prostaglandins act in virtually all tissues and body fluids of mammals, although with considerable qualitative and specie variation. Unlike many other biologically active substances, prostaglandins are formed immediately prior to release and are not stored in the body. Biosynthesis and release of PGs from tissues occur so readily in response to a variety of physiological and pathological stimuli that it would appear that any distortion of cell membrane is an adequate trigger mechanism. Numerous chemical trials with PGs of the E and F groups, given by various routes have confirmed the fact that they have oxytocin-Iike activity. It has been demonstrated repeatedly that the PGs exert a powerful effect associated with interruption of pregnancy at different stages of gestation, depending upon the route and duration of PG administration (Karim et al, 1970).

ALP catalyses hydrolysis of phosphoric acid mono- esters. It is found in most tissues but mainly in the bone (osteoblasts), liver (bile canaliculi), intestine(epithelium) , kidney and placenta.

ACP catalyzes the hydrolysis of mono-esters of acid at an acidic pH. It is concentrated in the prostate gland (at 100-300 times the concentration found in other tissues), leucocytes, red blood cells and platelets.

L-aspartate and 2-oxoglutarate is catalyzed by AST to form L-glutamate and oxaloacetate. In terms of tissue specificity the heart has the highest concentration of AST, followed by liver, skeletal muscle, pancreas, erythrocytes and spleen.

L-alanine and 2-oxoglutarate is catalyzed by ALT to form L-glutamate and pyruvate. The predominant source is the liver, but molecular isoforms are also found in kidney, heart, skeletal muscle and pancreas.

LDH catalyzes the formation of pyruvate from lactate in an NAD dependent reaction. The enzyme is ubiquitous but the highest concentrations are found in heart, skeletal muscle, Liver, kidney and erythrocytes.

Plasma total protein is a biochemical test for measuring the total amount of protein in blood plasma or serum. Results of total protein test gives information on one's general health status with regards to one's nutrition, and/or conditions involving major organs such as kidney and liver. Krusha et al, 2014 reported that there are relationships and links in the result got for these markers enzymes determined in this study.

C-reactive protein (CRP) is found in blood, the levels of which rise in response to inflammatory CRP in an acute phase protein (Asaolu et al 2009,). CRP is synthesized by the liver in response to factors released by macrophages and fat cells. It's physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via the carrier (CLQ) complex (Thompson et al,1999). Measuring CRP level is a screen for infections and inflammatory diseases (Zacho eta al ,2008).

MATERIALS AND METHOD

Grouping

The present study was carried out at Ekiti State University teaching Hospital (EKSUTH) Ado Ekiti, Ekiti State Nigeria. A total of 120 women were examined in this study. Their blood samples were collected with the help of medical personnel in the University Teaching Hospital, Ado Ekiti, Ekiti State, Nigeria. These subjects were divided into four groups.

Subjects in group 1 comprise of forty (40) hypertensive pregnant women (test) with symptoms of PIH brought into the hospital for management and treatment. Twenty (20) each of the forty subjects were in their 2nd and 3rd trimester of pregnancy respectively. The subjects were monitored up to three to six days after delivery.
Group 2 comprise of randomly selected 40 normotensive pregnant women in their 2nd and 3rd trimesters of pregnancy respectively. This served as control for group 1.
Group 3 was made up of 20 hypertensive non-pregnant and non-user of contraceptive therapy women randomly selected. Lastly, group 4 comprise of 20 normotensive non-pregnant women who are non-users of contraceptive therapy. They were randomly selected and age-matched with group 3.

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Blood sampling

Blood samples were drawn from all the subjects following a fast of 6-12 hours. Plasma was separated by centrifuging the blood at 3000rpm for 10minutes at 4^0c. The plasma was used for the evaluation of the levels of the enzymes, C –Reactive Protein, Total Proteins and Prostaglandins.

Biochemical assay

The plasma levels of the enzymes; alanine amino transferase (ALT), aspartame amino transferase (AST), LDH, alkaline phosphatase (ALP) and acid phosphatase was determined using the method Reitman and Frankel (1956). Measurement of the various prostaglandins and C- Reactive proteins (CRP) , in the plasma of the subjects was determined by the method of ELISA described by Engrall and Perlman (1971). Determination of total protein in all the samples collected from all the subjects was carried out using Biuret method described by Peters et al. 1982. Plasma albumin was determined using dye binding method known as Bromocresol Green (BCG) method as described by Doumas et al.1971.

Statistical Analysis

Data got from the present study were presented as mean value ± SD. The statistical significance was evaluated by students "t" test and Anova.

RESULTS AND DISCUSSION

TABLE 1: The levels of marker enzymes, prostaglandins, CRP and Total Protein in normotensive and hypertensive pregnancies(2nd trimester)

PARAMETERS	NNPW A	HNPW B	NPW C	HPW D
ALT(IU/L)	8.1±3.11	9.02±7.00	8.12±3.02	8.89±2.95
AST(IU/L)	12.6±3.10	13.4±6.40	12.99±2.81	12.15±1.80
LDH(IU/L)	2.0±0.15	2.15±0.20	3.15±1.0	4.2±1.0
ACP(IU/L)	11.10±8.40	11.89±5.00	12.10±2.8	12.0±2.14
ALP(IU/L)	17.30±2.40	18.01±5.50	20.77±2.5	17.25±2.13
$PGF_{2\alpha}$ (pg/ml)	4.99±1.1	5.10±1.0	5.91±1.2	6.01±1.5
Total PGE(pg/ml)	2.80±1.0	2.91±1.5	3.6±1.2	4.91±1.5
CRP(mg/L)	1.15±1.72	1.20±2.10	1.89±1.0	2.5±1.50
Total Protein(g/dl)	7.0±0.39	6.89±0.15	7.67±1.6	5.21±1.25
SBP(mmHg)	98.7±10.42	161±13.45	105.5±7.87	159±10.90
DBP(mmHg)	67.15±10.18	107±12.45	65.9±6.70	105±11.42

TABLE 2: The levels of marker enzymes, prostaglandins, CRP and Total Protein in normotensive and hypertensive pregnancies(3rd trimester)

PARAMETERS	NNPW A	HNPW B	NPW C	HPW D
ALT(IU/L)	8.1±3.11	9.62±6.80	8.89±3.10	9.45±2.80
AST(IU/L)	12.6±3.10	13.84±6.20	13.05±2.50	14.18±1.72
LDH(IU/L)	2.0±0.15	2.23±0.31	3.04±1.4	5.01±1.14
ACP(IU/L)	11.10±8.40	12.05±4.50	12.95±2.40	13.3±2.61
ALP(IU/L)	17.30±2.40	19.00±5.10	23.14±2.30	18.10±2.41
$PGF_{2\alpha}$ (pg/ml)	4.79±1.0	5.99±1.0	9.4±1.4	12.2±1.5
Total PGE(pg/ml)	2.85±1.1	3.0±1.5	6.8±1.5	7.20±1.2
CRP(mg/L)	1.15±1.72	1.41±2.00	2.01±1.1	3.01±1.40
Total Protein(g/dl)	7.04±0.39	7.02±0.22	8.14±1.2	4.68±1.62
SBP(mmHg)	98.7±10.42	161±13.45	109±8.10	161±11.10
DBP(mmHg)	67.15±10.18	107±12.45	66.5±7.42	106±10.95

TABLE 3: The levels of marker enzymes, prostaglandins, CRP and Total Protein in normotensive and hypertensive pregnancies(3-6 days post-partum)

PARAMETERS	NNPW A	HNPW B	NPW C	HPW D
ALT(IU/L)	8.1±3.11	9.62±6.80	9.00±2.89	9.05±2.65
AST(IU/L)	12.6±3.10	13.84±6.20	12.65±2.62	14.00±1.60
LDH(IU/L)	2.0±0.5	2.23±0.31	2.10±1.21	2.87±1.02
ACP(IU/L)	11.10±8.40	12.05±4.50	12.05±2.05	13.11±2.24
ALP(IU/L)	17.30±2.40	19.00±5.10	21.20±2.10	18.90±2.15
$PGF_{2\alpha}$(pg/ml)	5.0±1.5	4.80±1.0	8.5±1.2	10.0±1.2
Total PGE(pg/ml)	3.11±1.0	3.1±1.5	5.9±1.5	6.40±1.5
CRP(mg/L)	1.15±1.72	1.41±2.00	1.21±1.0	1.89±1.02
Total Protein(g/dl)	7.04±0.39	7.02±0.22	7.49±1.0	4.78±1.02
SBP(mmHg)	98.7±10.42	161±13.45	104±4.91	151±4.24
DBP(mmHg)	67.15±10.18	107±12.45	66±3.58	96±7.89

KEYS:

NNPW-Normotensive non- pregnant women NPW-Normotensive pregnant women

HNPW-Hypertensive non-pregnant women HPW-Hypertensive pregnant women

ALT- Alanine amino transferase AST- Aspartate amino transferase

LDH -Lactasste dehydrogenase ACP- Acid phosphatase

ALP- Alkaline phosphatase PG- Prostaglandins

CRP- C- Reactive Proteins SBP- Systolic Blood Pressure

DBP -Diastolic Blood Pressure

The results of all the parameters determined in this study with normotensive and hypertensive pregnant women are shown in the all the Tables .Table 1 shows the result determined at the 2nd trimester of pregnancy while Table 2 and Table 3 show the results at 3rd trimester and 3-6 days after delivery respectively. The levels of the marker enzymes; ALT, AST, ACP show no significant ($p<0.05$) change at all the stages of pregnancy in both normotensive and hypertensive pregnancies. This is in line with what the literature says that the factors responsible for significant changes in the plasma levels of the enzyme are cases that involves liver disorder, kidney disorder, or bone problems (Anderson et al, 1999 and Datolli et al,2007).PIH is different from all of the conditions that are known to cause changes in the levels of the enzymes. However, a significant increase ($p<0.05$) was found in ALP as seen from Tables 1 and 2 as the pregnancy gets more matured. The reason for this can be as a result of the production of ALP by the placenta during the pregnancy . Hence there will be more availability of ALP. Also, considering the levels of ALP in Table 2 which are 23.14±2.30 and 18.10±2.41 for normotensive and hypertensive pregnancy respectively, ALP showed a higher significant increase in normotensive patient compared with the hypertensive patients. It is reported that there is always a decrease in the production of ALP whenever there is low protein assimilation utilization in the body, and this is expected since PIH is associated with Proteinuria (Brown et al,2000 and Chen et al,2006). Results obtained in Table 3 for ALP which was 3-6 days after delivery, shows a significant reduction ($p<0.01$) of ALP level for both normotensive and hypertensive pregnancy. This is expected because the placenta which also produces ALP must have been terminated following delivery. Lactate dehydrogenase (LDH) was observed to be increasing in both normotensive and hypertensive pregnancy has shown in the Tables. It can be said that PIH does not have effect on the level of the enzyme.

A higher level of C-reactive was observed in both normotensive and hypertensive pregnancies, as compared with the non-pregnant subjects in Tables1&2. However, a significant increase ($P < 0.05$) was only found in hypertensive pregnancy. Table 2 shows a value of 3.07±1.0g/L for hypertensive pregnancy against a value of 2.01+1.1 seen in non-pregnant women. CRP is reported to be produced principally by the liver into the blood as a result of inflammation (Kristensen et al,2009). Hence, it is expected that a pregnant person can have a slightly higher CRP level. However, the significant increase seen in PIH subjects reveals that the patients body go through a greater inflammation which is as a result of not just the pregnancy but the PIH attached to the pregnancy as a condition. The literature also revealed that patients with hypertension, undergoing surgery or having cancer, and other forms of conditions will have higher level of CRP released into the blood. However, results obtained in Table3 show that PIH is associated with a lot of inflammation, and Oedema is one of the symptoms found. This result agrees with the work of Kristiansen et al (2009). CRP decreases in all the pregnant subjects after delivery since the state of pregnancy which was the source of inflammation has been terminated.

Total Protein which was determined in all the subjects was found from the results obtained in table 1&2 to significantly decrease ($P < 0.05$) in PIH subjects both at 2nd and 3rd trimesters. However, no significant change was found in normotensive pregnant subjects and non-pregnant subjects. The results obtained in this study for the Total Protein is expected because, PIH has been said to be associated with proteinuria (Lindheimer et al, 2010). Hence, with much loss of protein in the urine, there can be a significant decrease level in the blood after sometime. Table3 shows an insignificant increase ($P < 0.05$) of total protein level in PIH patients. This is because after delivery PIH effect drastically reduces until it varnishes .

Prostaglandins as seen in the results from the tables revealed a significant increase ($P<0.05$) in both the normotensive and hypertensive pregnant women as the pregnancy moves from 2nd trimester to 3rd trimester. The reason for the increase in the levels of the PGs (PGE & $PGF_{2\alpha}$), as seen in the pregnant women is undoubtedly as a result of the pregnancy and the growth of the foetus which is a kind of stress on the physiology of the body system. This is in line with literature that PGs increases in levels as a result of stimuli on the body system (Elwood et al,1980 and Mitchell et al, 1978). Comparing the PG levels of hypertensive pregnant women to the normotensive pregnant ones, it was observed (as shown in the tables) that there was an insignificant higher levels ($P<0.05$) of the PG levels in the hypertensive ones. This is in agreement with the literature that hypertension may not necessarily be a factor that causes increase in the production of PGs (Bygdeman,1980 and Samuelson 1973).

Table 3 reveals the post-partum result of the PGs. The levels of the PGs reduces significantly ($P<0.01$). This is because following delivery, the production of PG will diminish. The highest production of PGs is usually experienced prior to delivery, since PGs perform roles in uterine contraction during delivery like Oxytocin (Jenkin , 1992).

CONCLUSION

It can be deduced from the result obtained from this research work that, all the marker enzymes studied apart from ALP are not implicated in Pregnancy Induced Hypertension. However Prostaglandins, C- Reactive Proteins and Total Proteins are greatly implicated in PIH. Thus a further research all of these parameters can help proffer solution to or manage the problem of PIH among women.

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