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**Status of Liver Enzymes in Women on Hormonal Contraceptives in Maiduguri****Mamza, Y.P.\*, Bwala, E.P., Musa, A.H., Zakari, F.***Department of Medical Laboratory Science, Faculty of Allied Health Sciences, College of Medical Sciences University of Maiduguri, Nigeria**Author for Correspondence\*: ymamza@yahoo.com***Abstract**

Estrogens and oral contraceptives are both associated with several liver-related complications. The aim of this study was to evaluate the status of liver enzymes in women on hormone-based contraceptives attending the family planning unit of the University of Maiduguri Teaching Hospital (UMTH). One hundred and eighty women participated in this study of which hundred (100) were on hormonal contraceptives and eighty (80) were non-contraceptives users (controls). Phenolphthalein monophosphate method was used for the measurement of alkaline phosphatase (ALP) activity while Reithman and Frankel method was used for the measurement of Aspartate aminotransferase (AST) and alanine amino transferase (ALT) activity. Data obtained were analyzed using Statistical Package for Social Science (SPSS) version 16.0. The mean values of ALP and AST activity were significantly ( $p < 0.05$ ) higher in contraceptive users as compared to the controls ( $25.52 \pm 11.39$  vs  $11.65 \pm 10.26$ ) IU/L versus ( $39.21 \pm 23.65$  vs  $13.64 \pm 10.10$ ) IU/L respectively. The means of ALP, AST and ALT activity was significantly ( $p < 0.05$ ) higher in short-term contraceptives users when compared with long-term users ( $27.78 \pm 12.75$  versus  $21.50 \pm 6.96$ ,  $49.72 \pm 21.41$  versus  $22.47 \pm 16.38$  and  $13.59 \pm 12.02$  versus  $8.19 \pm 4.30$ ) IU/L respectively. A significant ( $p < 0.05$ ) negative correlation ( $r = -0.26$  and  $r = -0.35$ ) was observed between duration of use of contraceptives, ALP and AST activity respectively. Considering therefore the fact that the liver plays a central role in the metabolism of oestrogen and progestogens it becomes obvious

that these substances can act directly or indirectly on the liver to produce a variety of biological effects which have both physiological and pathological significance.

**Keywords:** *Hormonal contraceptives, Liver enzymes, Maiduguri*

**Introduction**

Liver is an essential organ that has many functions in the body including making proteins and blood clotting factors, manufacturing triglycerides, cholesterol, glycogen synthesis and bile production (Wedro, 2016).

The liver plays an important role in detoxification by converting ammonia, a bile product of metabolism in the body into urea that is excreted in the urine by the kidneys. The liver metabolizes most drugs including alcohol and is responsible for breaking down insulin and other hormones in the body (Wedro, 2016).

It metabolizes most drugs including contraceptives. Thus, it can be vulnerable to various drug induced liver injuries (DILIs). The liver is also the site of many drug interaction. One drug may speed or slowdown the rate at which liver metabolizes other drugs, intensifying or hindering its clinical effect. Many drugs that interact with oral contraceptives can be explained by metabolic events within the liver. Drug interaction may worsen if DILIs is present (AFP, 2011).

Inflamed or injured liver cells leak higher than normal amounts of certain chemicals including

liver enzymes into the blood stream which can result in elevated liver enzymes most commonly found are: alanine transaminase (ALAT), aspartate transaminase (Lee *et al.*, 2012). Blood test pertaining to liver, are measurement of some of the other enzymes found in the liver in addition to ASAT and ALAT which are the not sensitive and widely used liver enzymes (amino transferases) alkaline phosphatase, 5-nucleotidase and gamma glutamyl transpeptidase are few of the other enzymes located in the liver the most (Davis, 2016). The focus of this work is mainly on the most common liver enzymes which are ASAT, ALAT and alkaline phosphatase.

Contraception prevents unintended pregnancy and limited access to primary health care services contributes to high rates of unintended pregnancy in women with low incomes (Baird and Glansier, 1993). Unintended pregnancy poses significant health risks to women and their families. It is associated with higher rates of domestic violence, maternal drug and alcohol use during pregnancy and low birth weight (Santelli *et al.*, 2003). In developing countries, the practice of birth control is less widespread and strongly influenced by the levels of socioeconomic development, religious and cultural traditions (Santelli *et al.*, 2003). In all these nations however, the extent of birth control practice is increasing as education becomes more widely available and family planning programme becomes part of the national health services. Based on estimates of married women of reproductive age during the year 2000, more than 75 million women worldwide use oral contraceptives and more than 27 million women use hormonal injectable and implants (Santelli *et al.*, 2003). These preparations are either progesterone, estrogen or both (Colditz *et al.*, 1995). After child birth, most women can begin using progestin-only contraceptives immediately (Nabulsi *et al.*, 1993) whereas estrogen-containing methods can safely be initiated 6 weeks to 6 months post-partum for women who are breast feeding and three weeks post-partum for women who are not breast feeding (Epstein, 2003).

Women on hormonal contraceptives often experience certain physiological changes such as

increased menstrual flow, weight gain, nausea, vomiting etc and available literature has laid much emphasis on the effect of hormonal contraceptive on the different metabolites in the body (Petitti, 2003) but the extent to which these contraceptives lead to some changes especially after short, mid and long-term use have not been thoroughly investigated. There are several studies which have reported that hormonal contraception (HC)-pills and injectables-moderately increase the risk of cervical cancer as well as being a risk for all stages of cervical cancer (Epstein, 2003). A more limited body of evidence indicates that hormonal contraceptives taken in early pregnancy cause no significant increase in the risks of miscarriage or foetal growth problems (Santelli *et al.*, 2003). Moreover, most of these preparations, since they are xenobiotics are metabolized in the liver and may have certain adverse effects on the normal physiology and biochemistry of the liver (Karam, 2001). The ingestion of this synthetic hormones has been shown to produce profound effect on the liver although the effects are more physiologic than pathologic (Epstein, 2000). Therefore, knowledge of the metabolic changes caused by the use of hormonal contraceptives will go a long way in keeping the clinicians informed on the resultants modifications in the body system.

### Materials and methods

This study was carried out in University of Maiduguri Teaching Hospital (UMTH). A total of 180 subjects were recruited for the study. This consisted of 100 hormonal contraceptives users attending the family planning unit of University of Maiduguri Teaching Hospital, and 80 non-hormonal contraceptives users (Controls). Subjects that were not on hormonal based contraceptives were excluded from the study. Inform consent was sought from each subject before enlistment in the study. Ethical approval was obtained from the ethical committee of University of Maiduguri Teaching Hospital. A simple random sampling technique was used to select all patients on hormonal base contraceptives. Five milliliters (5mls) of blood sample was collected from the anticubital vein using vacutainer needle. The samples were centrifuged at 4000 revolution per minute for 10 minutes. The serum was separated into cryovials

and preserved in a refrigerator at about 2-8 degrees Celsius prior to analysis.

AST and ALT were determined by dinitrophenyl hydrazone coupling colorimetry method as described by Reitman and Frenkel (1957). Alkalinephosphatase was determined by phenolphthalein monophosphate method as described by Klein and Babson (1960). Data obtained were analyzed using the Statistical Package for Social Science (SPSS) version 16.0 for windows. Student 't' test was used to compare the means. Karl Pearson correlation coefficient was used to determine the correlation between duration of use and liver enzymes activities. A p-value of equal or less than 0.05 ( $p \leq 0.05$ ) was considered as statistically significant.

### Results

The means of serum alkaline phosphatase activity and aspartate aminotransferase activity were significantly ( $p < 0.05$ ) higher in contraceptives users as compared to controls (25.52±11.39 vs 16.65±5.86, 39.21±23.65 IU/L vs 12.68±8.67) IU/L respectively. No significant

difference ( $p > 0.05$ ) was observed in the mean values of age and alanine amino transferase activity of the contraceptives users when compared with the control subjects (table 1).

There were sixty- four (64), 0-12 months contraceptive users termed the short-term users and thirty- six, >12months contraceptive users termed as the long-term users. The mean values of alkaline phosphatase activity, Aspartate amino transferase activity and Alanine amino transferase activity were significantly ( $p < 0.05$ ) higher in short term users as compared to long term users respectively (table 2).

In determining the association between duration of use and the liver enzymes, a negative and significant ( $p < 0.05$ ) correlation was observed between duration of use and ALP activity, duration of use and AST activity ( $r = -0.26$ ,  $r = -0.35$ ,  $p < 0.05$ ) respectively, while a negative but not significant ( $p > 0.05$ ) correlation ( $r = -0.15$ ,  $p > 0.05$ ) was observed between duration of use and ALT activity (table 3). The scatter plots are shown in figures 1,2 and 3 respectively.

**Table 1: Comparison of mean values of age and biochemical variables in contraceptives users and control subjects**

Variables	Subjects (n=100)	Controls (n=80)	t-value	p-value	Remark
Age (Years)	28.91 ± 6.51	29.10 ± 7.01	-1.19	0.85	NS
ALP (IU/L)	25.52 ± 11.39	16.65 ± 5.86	6.75	0.00	S
AST (IU/L)	39.91 ± 23.65	12.68 ± 8.67	10.66	0.00	S
ALT(IU/L)	11.65 ± 10.26	13.64 ± 10.10	-1.303	0.194	NS

All values were expressed as mean ± SD

Key S=Significant, NS= Not significant

**Table 2: Comparison of Mean values of biochemical variables in contraceptives users according to duration of use**

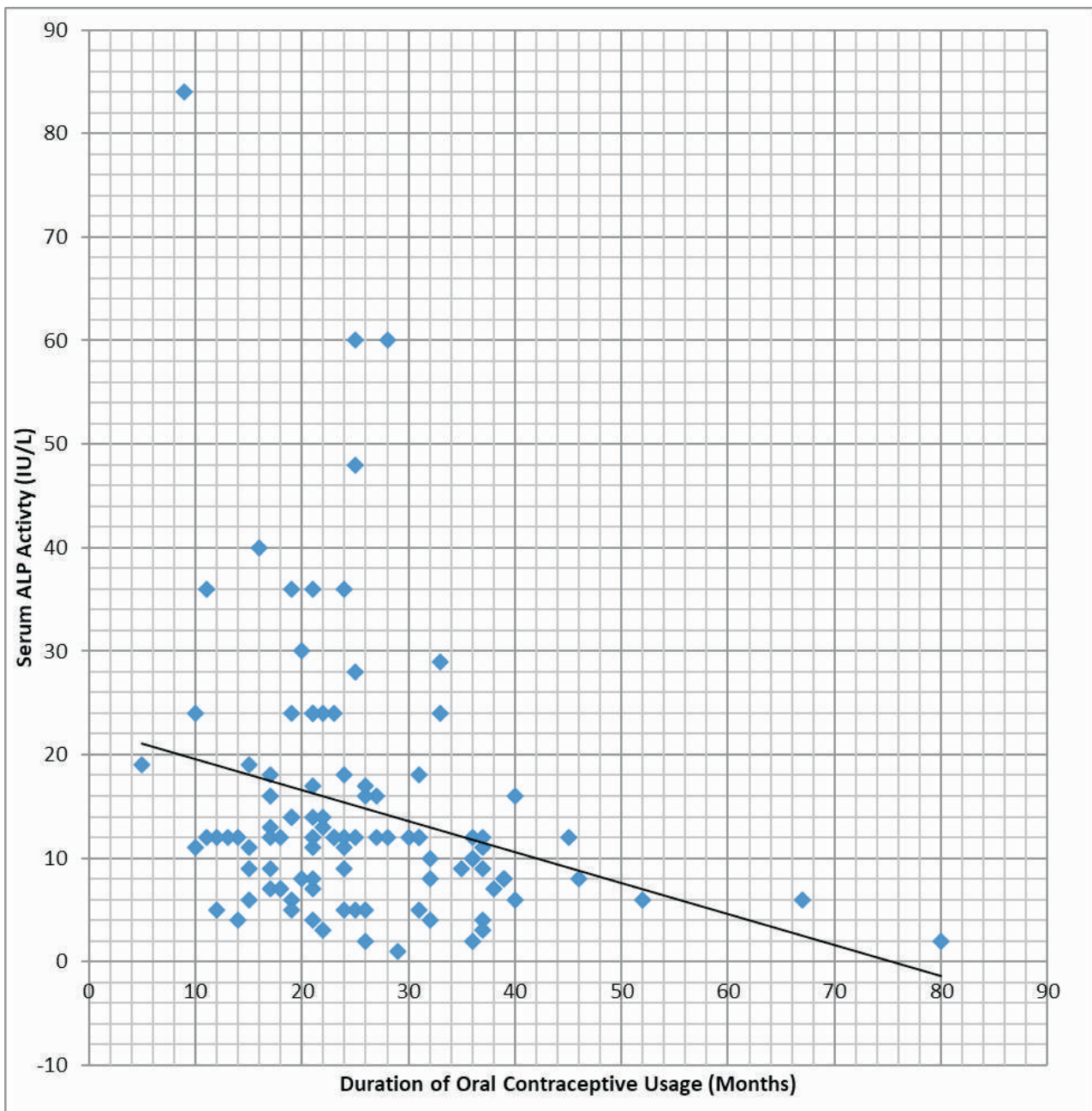
Biochemical Variables	0-12 Months	>12 Months	t-value	p-value	Remark
ALP (IU/L)	27.78 ± 12.75	21.50 ± 6.96	-3.19	0.02	S
AST (IU/L)	49.72 ± 21.41	22.47 ± 16.38	7.12	0.00	S
ALT(IU/L)	13.59 ± 12.02	8.19 ± 4.30	3.25	0.02	S

All values were expressed as mean ± S.D

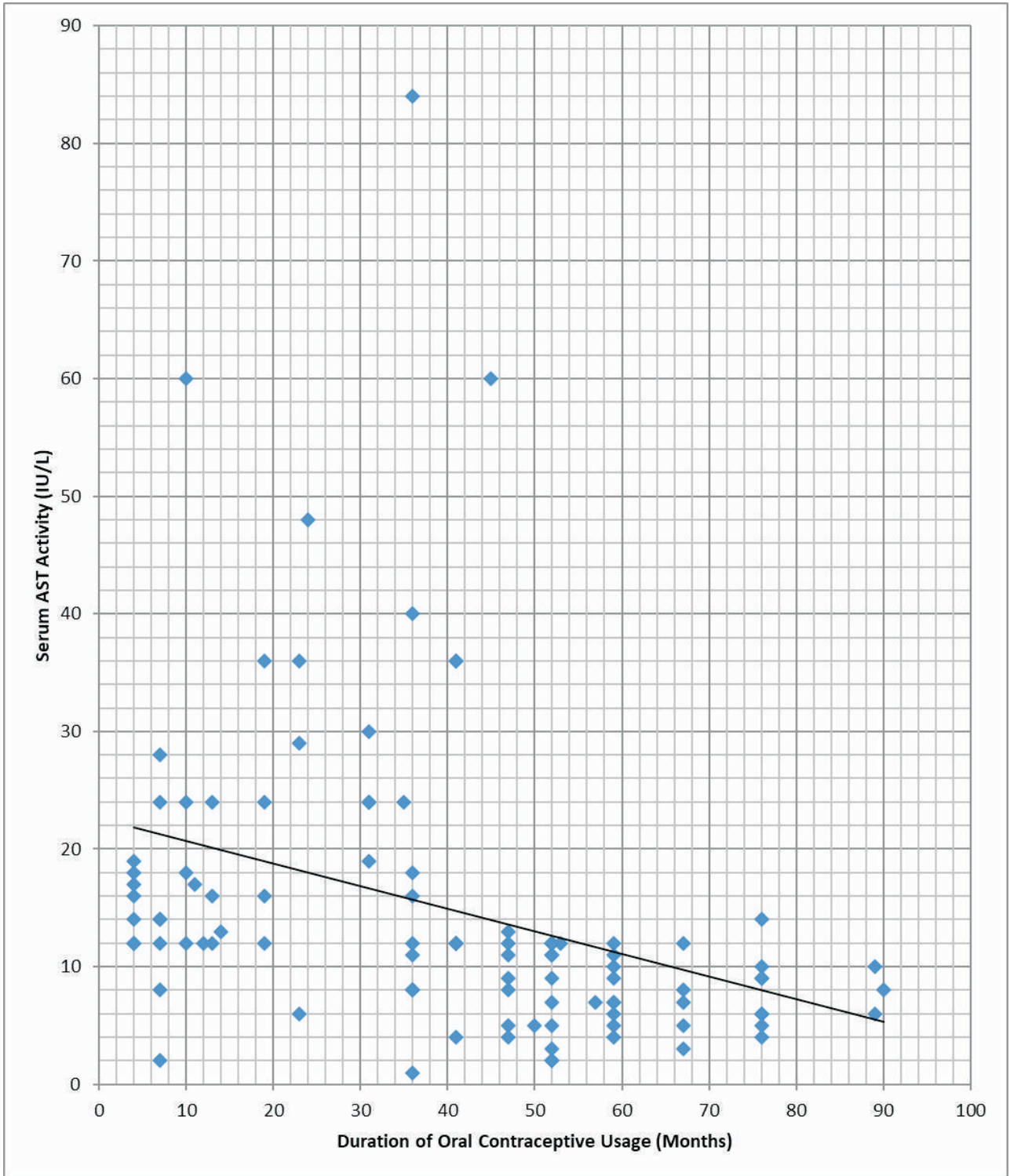
**Table 3: Correlation between duration of contraceptive use and ALP,ASAT and ALAT activity**

Variables	r-value	p-value	Remark
Duration and ALP activity (IU/L)	-0.26	0.009	S
Duration and AST activity (IU/L)	-0.35	0.009	S
Duration and ALT activity (IU/L)	-0.15	0.129	NS

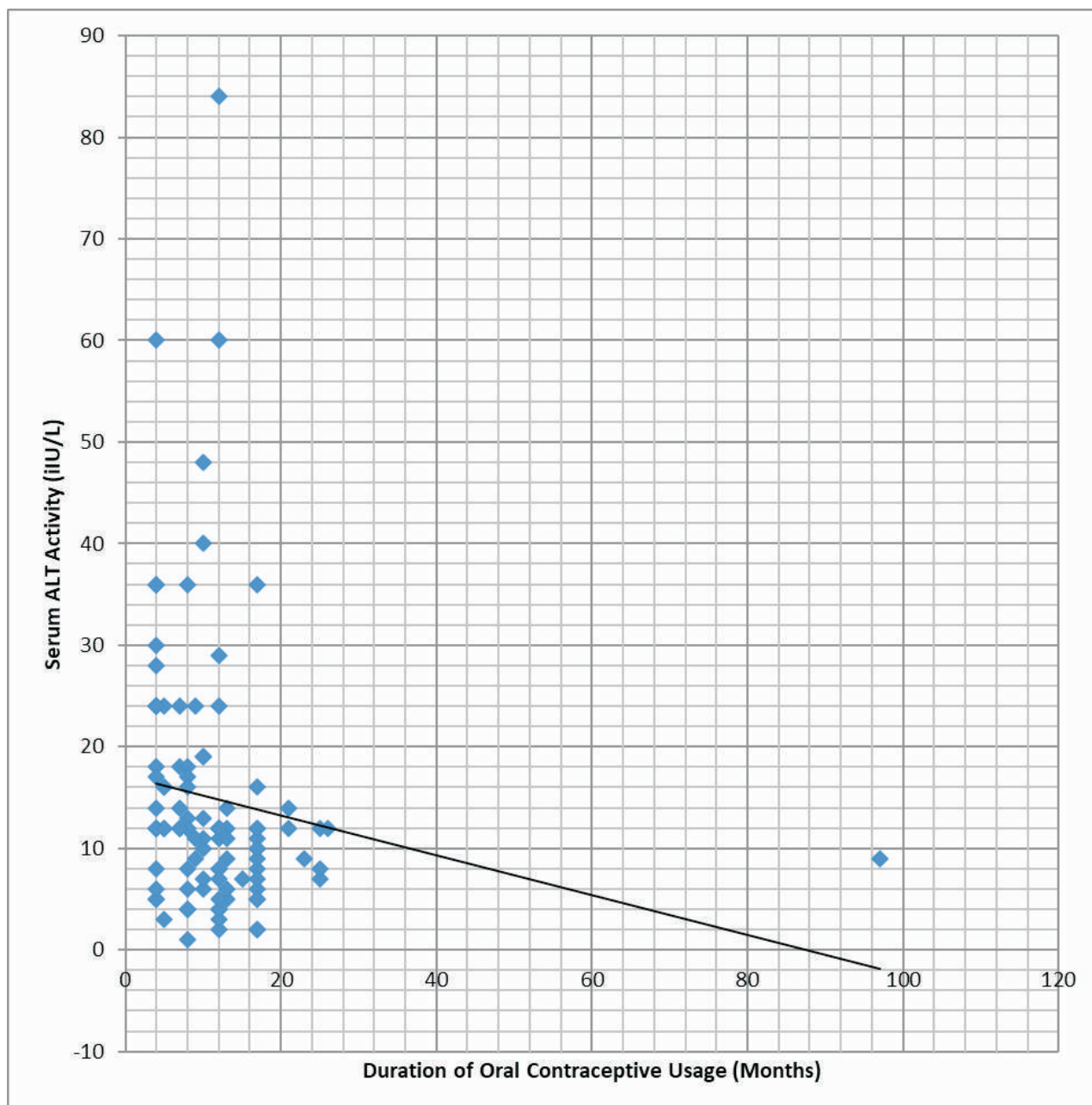
Key S=Significant, NS=not significant



**Figure 1: Scatter plot between Duration of contraceptive use and serum ALP Activity**



**Figure 2: Scatter plot between Duration of contraceptive use and serum AST activity**



**Figure 3: scatter plot between duration of contraceptive use and serum ALT activity.**

**Discussion**

The liver metabolizes most drugs including alcohol and most contraceptives. It is responsible for breaking down insulin and other hormones in the body. Thus, it is vulnerable to various drug induced liver injuries (AFP, 2011; Wedro, 2016). Injured liver cells leak higher than normal amount of certain chemicals and liver enzymes into the blood streams which can result in elevated liver enzymes most commonly found are Alanine amino transferase (ALT), Aspartate amino transferase (Lee *et al.*, 2012). The serum AST, ALT and ALP activity in hormonal

contraceptives users and those not on any contraceptives used as the control subjects were determined in this study and the activities of these enzymes were related to non-users, and to duration of use of the contraceptives in those women on the hormonal base contraceptives.

In this study, it was observed that the mean of serum alkaline phosphatase and aspartate amino transferase were significantly higher in contraceptives users as compared to controls. This finding is similar to that of Ekhatu *et al.* (2014), who reported that the increase in

activities of these enzymes could be ascribed to cellular degeneration of myocardial, neuronal and liver cells.

The mean values of AST, ALT and ALP were significantly higher in contraceptives users according to duration of use as compared to the control subjects. This finding concurred with that of Ebele *et al.* (2009), who reported a significant increase in AST, ALT and ALP activity of short-term contraceptives users as compared to control groups and suggested that liver function is affected by short term use of contraceptives. The effects are not observed in continuous use and short lived. Increase in plasma activity of these enzymes may occur soon after starting the treatments with hormonal contraceptives (Reichling and Kaplan 1988). There was a negative and significant correlation between duration of use of contraceptives and APL, and AST activity.

From this research work, it was also observed that serum ALP, AST and ALT activities were lower in long- term contraceptives users. This finding is similar to that of Ebele *et al.* (2009), which suggest a possible regression of effects following a mid- term or long-term use. Nabulsi *et al.* (1993) observed that increase in the liver enzymes are not marked and also, they are usually short lived, reverting to normal although there is continued administration of the contraceptives, but otherwise becoming normal again in most women soon after stopping the use. This can also be related to the observed effects in the carbohydrate intolerance, which is seen to develop in women who are early users of hormonal contraceptives, since the liver is a major organ involved in carbohydrate metabolism. These effects also do not progress during prolonged administration but usually returns to normal when the administration is stopped.

There was no significant difference in the mean value of ALT activity of contraceptives users and the control subjects and correlation between duration of use and ALT activity was not significant. This may be due to short-lived effects of these contraceptives on the liver enzymes since alanine amino transferase is more

specific to the liver. Karam (2001) observed that these effects are more physiological than pathological since they are not marked and short lived. This finding is similar to study performed by Ray Kim *et al.* (2008) who reported that in acute hepatocellular injury, serum AST levels usually rise immediately, reaching a higher level than ALT initially due to higher activity of AST in the hepatocytes and its release with the liver injury.

### Conclusion

Considering therefore the fact that the liver plays a central role in the metabolism of oestrogen and progestogens it becomes obvious that these substances can act directly or indirectly on the liver to produce a variety of biological effects which have both physiological and pathological significance. In view of this it is recommended that serum liver enzymes be included as screening test especially for women who have recently started the use of hormonal contraceptives and those with history of hepatic disease should be well monitored shortly after the commencement of contraceptive use.

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**Conflicts of interest:** There are no conflicts of interest.

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