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Effects of Duration of Use of Hormonal Contraceptives on Liver Function

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Abstract: Liver function test (AST, ALT, ALP, total and conjugated bilirubin) were assayed in serum samples of 180 apparently healthy women attending the family planning clinic in UNTH, who were on hormonal contraception. The test subjects were divided into three groups based on short, mid and long term use of the contraceptives while a group of 30 patients that have not started the use of contraceptives were used as control. The mean values in the activities of AST, ALT and ALP were significantly increased, while a significant decrease was observed in the mean values of total and conjugated bilirubin in the women on short term use ($p<0.05$) whereas, a non significant difference ($p>0.05$) was observed in the women in mid term and long term use. When comparison was done between the short term users and both the mid term and long term users, statistically significant changes were observed ($p<0.05$), but when mid term and long term users were compared, no significant change was observed ($p>0.05$). The result shows that only short term use of hormonal contraceptives appear to have an effect on liver function, suggesting a possible regression of effect following mid or long term use.

Key words: Effects, hormonal contraceptives, duration, liver function

INTRODUCTION

Contraception can be defined as birth control through deliberate or intentional prevention of conception (Epstein, 2003). 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, >75 million women world wide use oral contraceptives and >27 million women use hormonal injectables 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

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(Petitti, 2003), but the extent to which these contraceptives led to some changes especially after short, mid and long-term use have not been thoroughly investigated. Questions have also been raised whether hormonal contraceptives may increase a woman's risk of acquiring STI's, perhaps by inducing cervical ectopy and thereby increasing susceptibility to cervical infection (Mohllajee *et al*., 2006). 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 fetal 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 these synthetic hormones has been shown to produce profound effects on the liver, although these effects are more physiologic than pathologic and they often become normal soon after stopping treatment (Epstein, 2003). Important alterations in the hepatic drug excretion and metabolism also occur since estrogens in the amounts used in hormonal contraceptive agents delay the elimination of drug and reduce the flow of bile (Karam, 2001). Increase in plasma AST and ALT may occur soon after starting treatment with hormonal contraception, ad this may be due to induction of the hepatic isoenzymes, though these increases are not marked (Reichling and Kaplan, 1988). A knowledge of the metabolic changes caused by short, mid and long term use of these preparations are important, as they will go a long way in keeping the clinicians informed on the resultant modifications in the system which might be attributed to hormonal contraceptive treatment.

MATERIALS AND METHODS

Subjects: The subjects included a total of 240 apparently healthy female patients within the age range of 20-45 years, attending the family planning clinic at UNTH Enugu. The subjects were divided into 3 groups of 60 women each, based on the duration of use of hormonal contraceptives. Those that have used the preparation for 1-6 months were grouped as short term users, while those that have used it for 7 months to 2 years were the mid term users. The long term users comprised of those who have used it for more than 2 years whereas 60 women who have not used the contraceptive at all were used as control. Informed consent was given by all the subjects before participation in the study.

Sample collection and preparation: Five mL of venous blood was collected from each subject, through a clean venepuncture from the antecubital vein and placed into a sterile plain tube. The samples were collected without undue pressure on either the arm or the plunger of the syringe. The samples were allowed to clot and then centrifuged at 3000 rpm for 5 min to separate the serum. The separated clear serum was transferred into sterile tubes and used for the analysis.

Analytical methods

Bilirubin estimation: Total and Conjugated bilirubin was assayed using the method of Powell W.N (Burtis *et al*., 1996). Bilirubin reacts with diazo-reagent to form a purple compound, azobilirubin and the intensity of the colour which was proportional to the concentration of bilirubin was estimated at 540 nm wave length with Beckman spectrophotometer.

Assay of liver enzymes: Aspartate and alanine transaminases (AST and ALT) were assayed by the Reitman and Fankel method (Burtis *et al*., 1996) using Beckman Spectrophotometer, whereas the method of King Armstrong was employed for the estimation of alkaline phosphatase (ALP) activity (Cheesbrough, 2002).

Statistical analysis: Data was analyzed separately using paired t-test and results were expressed as mean ±Standard Deviation (±SD).

RESULTS

The results show the mean±SD and the p-values of total bilirubin, conjugated bilirubin, AST, ALT and ALP of women on short term, mid term, long term use of hormonal contraceptives and the control subjects.

Table 1 shows the Mean±SD of the women on short-term use of the contraceptives. From the Table 1, the total bilirubin, conjugated bilirubin, AST, ALT and ALP of the short-term users (6.5±3.3, 3.0±1.9 mmol L^{-1}, 17.2±2.7 μ L^{-1}, 13.6±2.4 mmol L^{-1} and 56.9±15.6 μ L^{-1}) was significantly different ($p<0.05$), when compared with the control (11.6±2.8, 5.6±1.5 mmol L^{-1}, 11.9±3.8, 10.3±4.2 and 49.1±17.7 μ L^{-1}, respectively).

There was however, a non-significant difference ($p>0.05$) in the mean values of the assayed parameters in the mid-term users (10.9±3.7, 4.9±2.1 mmol L^{-1}, 11.6±3.8, 9.4±3.4 and 47.4±12.7 μ L^{-1}) when compared to the control (11.6±2.8, 5.6±1.5 mmol L^{-1}, 11.9±3.8, 10.3±4.2 and 49.1±17.7 μ L^{-1}) in the same order Table 2.

Table 3 shows the values for the long term users of hormonal contraceptives. From the Table 3, the values for

Table 1: The liver function parameters in the short-term users of hormonal contraceptives and the control subjects

No. subjects	Short-term users (n = 60)	Control (n = 60)	p-value
Total Bilirubin mmol L^{-1}	6.5±3.30	11.6±2.80	<0.05*
Conj. Bilirubin (mmol L^{-1})	3.0±1.90	5.6±1.50	<0.05*
AST (μ L^{-1})	17.2±2.70	11.9±3.80	<0.05*
ALT (μ L^{-1})	13.6±2.40	10.3±4.20	<0.05*
ALP (μ L^{-1})	56.9±15.6	49.1±17.7	<0.05*

* = Statistically significant

Table 2: The liver function parameters in the mid-term users of hormonal contraceptives and the control subjects

No. subjects	Mid-term users (n = 60)	Control (n = 60)	p-value
Total Bilirubin (mmol L^{-1})	10.9±3.70	11.6±2.80	>0.05
Conj. Bilirubin (mmol L^{-1})	4.9±2.10	5.6±1.50	>0.05
AST (μ L^{-1})	11.6±3.80	11.9±3.80	>0.05
ALT (μ L^{-1})	9.4±3.40	10.3±4.20	>0.05
ALP (μ L^{-1})	47.4±12.7	49.1±17.7	>0.05

Table 3: The liver function parameters in the long-term users of hormonal contrtaceptives and the control subjects

No subjects	Long-term users (n = 60)	Control (n = 60)	p-value
Total Bilirubin (mmol L^{-1})	11.4±3.10	11.6±2.80	>0.05
Conj. Bilirubin (mmol L^{-1})	5.6±1.80	5.6±1.50	>0.05
AST (μ L^{-1})	11.2±4.10	11.9±3.80	>0.05
ALT (μ L^{-1})	10.1±4.10	10.3±4.20	>0.05
ALP (μ L^{-1})	48.3±12.7	49.1±17.7	>0.05

Table 4: The liver function parameters in the short-term and mid-term users of hormonal contraceptives

No. subjects	Mid-term users (n = 60)	Short-term users (n = 60)	p-value
Total Bilirubin (mmol L^{-1})	10.9±3.7	6.5±3.30	<0.05*
Conj. Bilirubin (mmol L^{-1})	4.9±2.1	3.0±1.90	<0.05*
AST (μ L^{-1})	11.6±3.8	17.2±2.70	<0.05*
ALT (μ L^{-1})	9.4±3.4	13.6±2.40	<0.05*
ALP (μ L^{-1})	47.4±3.7	56.9±15.6	<0.05*

* = Statistically significant

Table 5: The liver function parameters in the short-term and long-term users of hormonal contraceptives

No. subjects	Long-term users (n = 60)	Short-term users (n = 60)	p-value
Total Bilirubin (mmol L^{-1})	11.4±3.10	6.5±3.30	<0.05*
Conj. Bilirubin (mmol L^{-1})	5.6±1.80	3.0±1.90	<0.05*
AST (μ L^{-1})	11.2±4.10	17.2±2.70	<0.05*
ALT (μ L^{-1})	10.1±4.10	13.6±2.40	<0.05*
ALP (μ L^{-1})	48.3±12.7	56.9±15.6	<0.05*

* = Statistically significant

Table 6: The liver function parameters in the mid-term and long-term users of hormonal contraceptives

No. subjects	Long-term users (n = 60)	Mid-term users (n = 60)	p-value
Total Bilirubin (mmol L^{-1})	11.4±3.10	10.9±3.70	>0.05
Conj. Bilirubin (mmol L^{-1})	5.6±1.80	4.9±2.10	>0.05
AST (μ L^{-1})	11.2±4.10	11.6±3.80	>0.05
ALT (μ L^{-1})	10.1±4.10	9.4±3.40	>0.05
ALP (μ L^{-1})	48.3±12.7	47.4±12.7	>0.05

the long-term users (11.4±3.1, 5.6±1.8 mmol L^{-1}, 11.2±4.1, 10.1±4.1 and 48.3±12.7 μ L^{-1}) was also non-significantly different (p>0.05) in comparison with the control.

When comparison was drawn between the mid-term and short-term users, there was a statistically significant difference (p<0.05), as also seen in the comparison between the short-term and long-term users (Table 4 and 5).

However, a statistically non significant difference was observed when the mid term users were compared to the long term users, as shown in Table 6 (p>0.05).

DISCUSSION

The results of this analysis show that the increase in serum AST, ALT and ALP and the decrease in the total and conjugated bilirubin in women on short term use was significant (p<0.05). This is in agreement with the work of Reichling and Kaplan (1988), who suggested that the increase in plasma activity of these enzymes may occur soon after starting the treatment with hormonal contraceptives though, they were not able to state whether these increases were reverted with continuous use of these preparations.

It was also observed that there was no significant increase or decrease in the serum AST, ALT, ALP, total and conjugated bilirubin in the women on mid term and long term use of these contraceptives (p>0.05). This suggests a possible regression of effects following a mid or long term use. Nabulsi *et al.* (1993) observed that the increases in these 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 treatment. This can also be related to the observed effects in the degree of carbohydrate intolerance which is seen to develop in women starting to take 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 treatment is stopped (Nabulsi *et al.*, 1993).

Since the effects caused by these hormonal contraceptives are not marked and are short lived, it can be suggested that the effects of these preparations are more physiologic than pathologic (Karam, 2001).

CONCLUSION

This study shows that liver function is affected by a short-term use of hormonal contraceptives. These effects are not observed with continuous use and can be said to be short-lived.

This study therefore, suggests that this class of contraceptives do not necessarily lead to a pathologic condition on the liver with prolonged use of the preparations.

RECOMMENDATIONS

Further research is thus, recommended to determine the possible effects or otherwise of other methods of contraception on the liver function.

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