Niger. J. Physiol. Sci. 28(December 2013)205–210
www.njps.com.ng

Niger. J. Physiol. Sci.

Impact of alcohol consumption and cigarette smoke on renal function and select serum elements in female subjects using combined oral contraceptive

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Summary: Drugs and life style choices such as alcohol consumption and smoking are capable of independently altering levels of essential trace elements as well as tissue or organ function. The purpose of the study is to determine how differences in degree of exposure to cigarette smoke and alcohol consumption will alter serum magnesium (Mg), Cobalt (Co) and Manganese (Mn) levels in female subjects using combined oral contraceptives. Thirty female subjects who have used combined oral contraceptive for at least 5 years as well as 30 age-matched control women who are using rhythm method as birth control method were recruited from drinking joints/bars by random sampling technique. Serum trace element concentrations were determined using atomic absorption spectrometry and K^+, Na^+, albumin, globulin, total protein, urea and creatinine were also determined. Data obtained were analyzed using Student't' test, Pearson's correlation coefficient and Multivariate Analysis of Variance (MANOVA). Na^+ was significantly higher in combined oral contraceptive users compared with controls ($p<0.05$), whereas Mg was decreased ($p<0.05$). Co, Mn, urea, creatinine, total protein, albumin, globulin, K^+ were not significantly different in combined oral contraceptive users compared with the controls ($p>0.05$). MANOVA results revealed that binge drinkers/smokers group recorded a significant lower ($p<0.05$) magnesium level than the passive smokers/social drinkers group and controls. The results of this study suggest that subjects using combined oral contraceptive, consuming alcohol and exposed to cigarette smoke may be at greater risks of diseases linked with magnesium depletion.

Keywords*:* combined oral contraceptive; magnesium, renal function, alcohol, cigarette

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Manuscript Accepted: August, 2013

INTRODUCTION

The Combined Oral Contraceptive Pill (COCP) also known as the birth-control pill, or "the Pill", is one of most popular birth control methods in the developing world (Dorea and Miazaki, 1999). It is a combination of an estrogen and a progestin hormone similar to those found naturally in a woman's body. The history of oral contraceptive began in the 1930s when scientists discovered that high doses of androgens, estrogens or progesterone inhibited ovulation (Goldzieher and Rudell, 1974; Goldzieher, 1982; Perone, 1993; Goldzieher, 1993). The pill alters a number of metabolic processes in the body one of which serves as the basis or mechanism of its action, specifically it suppresses the release of gonadotropins. Combined oral contraceptives depress follicular development and prevent ovulation (Rivera et al. 1991; Loose and Stancel, 2006; Glasier, 2006). It is estimated that over 100 million women use oral contraceptive as a form of birth control worldwide with 12 million of them being in the United States of America (USA) alone (Trussell, 2007; Mosher et al., 2004).

Users of high dose combined oral contraceptive have significantly high**er** level of glucose than the control; this invariably translates to abnormal Oral Glucose Tolerance Tests (OGTT) (Oyelola et al., 1991). The use of Oral Contraceptive (OC) steroids is also associated with high blood pressure. Olatunji and Soladoye (2008) investigated the role of Renin-Angiotensin System (RAS) or Sympathetic Nervous System (SNS) in the development of oral contraceptive-induced hypertension in female rats. These workers observed that there was an association between oral contraceptive-induced high blood pressure and cardiac hypertrophy, enhanced pressor response to angiotensin II and preserved pressor response to sympathetic activation and therefore suggested that oral contraceptive-induced hypertension and cardiac hypertrophy may be mediated by renin-angiotensin system rather than sympathetic nervous system. Szlendak-Sauer et al.

(2009) reported that administration of a low dose oral contraceptive containing 20 microg ethinyloestradiol and 3.0 mg drospirenone did not influence the electrolyte equilibrium and renal function after 12 cycles of use. Lip et al. (1997) on the other hand, found that malignant hypertension in young women were related to previous hypertension in pregnancy but not oral contraception. Epidemiologic studies have revealed an increase in mortality rate from cardiovascular diseases in people with lower magnesium levels and both smoking and oral contraceptive use independently cause magnesium depletion.

Having earlier established in a past study (Iyanda et al., 2012) the negative effect of oral contraceptive/alcohol/smoking administration on hepatic cells, this study is embarked upon to determine the impact of alcohol consumption and cigarette smoke on renal function and serum magnesium, cobalt, manganese levels in female subjects using combined oral contraceptive as the birth control method. In addition to this, it may also help to identify if lifestyle choices such as smoking and alcohol consumption may prone subjects to a more harmful effect of this agent. Such that it may help to predict if subjects in smokers\binge drinkers group are at greater risk of diseases associated with alteration in levels of Mg, Mn, and Co than subjects in passive smokers\social drinkers group.

MATERIALS AND METHODS

Thirty apparently healthy female subjects between 24 and 39 years of age, who have been using combined oral contraceptive for more than 5 years and subjected to different degrees of cigarette smoke and alcohol ingestion were recruited at selected drinking joints in Ibadan metropolis, Nigeria. Another group of 30 women, within the age range 24 and 42 years constituted the control group; the women in the control group were utilizing the rhythm method as the birth control method. Twenty subjects constituted the non-alcohol/non-cigarette smoke exposed combined oral contraceptive users. Exclusion criteria included history of renal diseases and disorders associated with alteration in the levels of Co, Mg, and Mn. Others were ingestion of agents capable of altering trace element levels as well as recent history of trace element supplementation. This is a cross sectional study which employed simple random sampling technique for the selection of subjects for both alopecia and control groups. The purpose of the study was described to the women, who gave their informed consent. Each woman filled or was assisted in filling a detailed questionnaire which was administered by a well trained person. Information on age of subjects, duration of exposure to combined oral contraceptive, duration and degree of exposure to alcohol and cigarette smoke, drug history, history of pathologic conditions were obtained. All procedures were in accordance with the Helsinki Declaration of 1975 (Revised).

From the ante-cubital vein of each subject ten milliliter (10ml) of blood was collected in non-anticoagulant bottles, stored at 4°C for two hours and centrifuged at 3000 r.p.m. for ten minutes to obtain serum. The serum obtained was immediately stored at -20°C until the time required for analysis. Total protein, albumin, and globulin were analyzed in the serum of these subjects. Total protein was estimated using the Biuret method, (Kingsley, 1982) albumin-the standard Bromocrescol green method; urea –the diacetyl monoamine oxidase method; Na^+ and K^+-standard flame photometry. Atomic absorption spectrometric technique was employed for the estimation of magnesium; Buck Scientific 205 Atomic Absorption (Buck Scientific, East Norwalk, Connecticut, USA) was used for this purpose.

Reagents were of high-purity analytical grade (Merck, Darmstadt, BDH, Chemicals Ltd). Hitachi 902 Automated machine supplied by Roche Diagnostic, Germany was used for the estimation of urea, creatinine, total protein, albumin and globulin.

The level of significance between serum levels of these parameters in the combined oral contraceptive users and controls was determined using SPSS package version 15. Student't' test was used to determine the significant differences between mean values of analyzed parameters in COC users and control subjects and Multivariate Analysis of Variance (MANOVA) for the different sub-groups of combined oral contraceptive users; namely binge drinkers\smokers and social drinkers\passive smokers sub-groups. Pearson's correlation coefficient was employed to ascertain association between parameters. $P<0.05$ was considered significant.

RESULTS

The mean±SEM (mean±standard error of mean) of sodium, potassium, total protein, albumin, globulin, urea, creatinine and copper in both oral contraceptive exposed and control subjects are presented in Table 1. Of the two electrolytes analyzed, only Na^+ was significantly increased ($p<0.05$) while K^+ was not significantly different ($p>0.05$) in the exposed group compared with the control group. Moreover, total protein, albumin and globulin were not significantly increased in oral contraceptive exposed group compared with controls ($p>0.05$). No significant difference was observed for either of the renal indices; urea and creatinine when oral contraceptive exposed subjects were compared with controls ($p>0.05$). The results of manganese, cobalt, and magnesium are shown in Table 2. The essential trace elements manganese and cobalt were also not significantly altered when both groups wereelements

Table 1: Mean ± SEM of biochemical parameters of oral contraceptive-users and control groups.

	Oral Contraceptive	Control
K^+ (mmol/L)	5.75±1.56	4.44±0.17
Na^+(mmol/L)	139.65±0.89*	135.30±1.54
Total protein (g/L)	67.20±1.59	71.25±1.66
Albumin (g/L)	34.20±1.48	37.05±1.74
Globulin (g/L)	33.20±1.69	34.20±1.74
Urea (mmol/L)	3.59±0.24	3.96±0.36
Creatinine (µmol/L)	86.06±5.67	84.84±4.01

Mean ± SEM: mean±standard * p<0.05 is considered significant

Table 2: Mean±SEM of age, duration of exposure & select elements of oral contraceptive users and controls

	Oral Contraceptive	Control
Age (years)	31.55±1.21	31.90±1.36
Exposure (years)	6.65±0.41	--
Cobalt (nmol/L)	5.43±0.84	5.93±1.19
Magnesium (mmol/L)	0.35±0.02*	0.75±0.01
Manganese (nmol/L)	8.23±0.23	7.97±0.31

Mean ± SEM: mean±standard error of mean. *p<0.05 is considered significant.

Table 3: Mean±SEM of some parameters in different sub-groups of oral contraceptive users and control group

	Smokers\binge drinkers	Passive smokers\social drinkers.	Non-alcohol\non-smoking group	Control group	F	P
Na^+ (mmol/L)	138.30±1.49	141.00±0.86	138.02±0.94	135.30±1.54	3.67	0.032
Cobalt (nmol/L)	5.09±0.45	5.77±1.02	5.43±0.34	5.94±0.51	0.14	0.724
Magnesium (mmol/L)*	0.32±0.02	0.39±0.03	0.46±0.03	0.75±0.01	105.44	0.004
Manganese (nmol/L)	8.11±0.34	8.35±0.47	7.46±0.61	7.97±0.31	1.58	0.206

Mean ± SEM: mean±standard error of mean. *significant difference at p <0.05

Table 4: Correlation among age of subjects, duration of exposure & biochemical parameters in oral contraceptive exposed subjects.

	Age	Dur. Expo.	K^+	Na^+	Tot. Prot.	Album	Glob	Urea	Mg	Mn
Age	-									
Dur. Expo.	0.480	-								
K	–0.084	–0.126	-							
Na	0.261	0.040	0.271	-						
Tot. Prot	0.308	0.271	0.312	0.309	-					
Albumin	0.085	0.585	0.045	0.264	0.316	-				
Globulin	0.099	–0.350	0.265	–0.141	0.370	–0.343	-			
Urea	–0.277	0.146	–0.213	–0.306	–0.044	0.012	–0.094	-		
Mg	0.062	–0.272	0.468	–0.173	–0.376	–0.187	0.229	–0.239	-	
Mn	–0.173	–0.055	–0.159	–0.046	–0.490	–0.160	–0.070	0.179	–0.051	-

Numbers with an underline are statistically significant at the p < 0.05 level.

manganese and cobalt were also not significantly altered when both groups were compared (p>0.05). The level of Mg was significantly decreased in the oral contraceptive group compared with controls (p<0.05).

Table 3 shows the mean±SEM of magnesium, cobalt and manganese levels of different sub-groups of oral contraceptive users, with smokers/binge drinkers exhibiting a much lower level of magnesium than both passive smokers/social drinkers and controls (F=5.856; P=0.034). The results of the correlation study of different variables e.g. age, duration of exposure and the biochemical parameters are shown in Table 4 below. Positive correlation exists only between age and duration of exposure; duration of exposure and albumin; Mg and K^+ as well as Mn and urea.

DISCUSSION

The ability of oral contraceptives (OC) to induce hypertension has been reported through results obtained from a number of studies, Olatunji and Soladoye (2008) have suggested that the development of the OC-induced hypertension and cardiac hypertrophy is mediated by renin angiotensin system (RAS) rather than sympathetic nervous system (SNS). Renin is an aspartyl protease secreted by the juxta-glomerular apparatus; its secretion is in response to a reduction in renal blood flow, possibly mediated by the mean pressure of afferent arterioles

and beta-adrenergic. Among other functions, this enzyme stimulates the cells of the zonal glomerulosa to synthesize and secrete aldosterone, a hormone which stimulates sodium retention. The elevation in the level of serum sodium observed in oral contraceptive users in this study agrees with the report of Olatunji and Soladoye (2008), although this did not translate into a decrease K^+ level. Moreover, in agreement with our study is the observation of Cherney et al. (2007) in which minimal systemic as well as renal changes were recorded for women exposed to oral contraceptives compared with controls even when these coexisted with elevated angiotensin II**.** Both of our renal indicators; urea and creatinine were not significantly different in combined oral contraceptive group compared with control subjects.

Subjects in combined contraceptive group were found to have serum magnesium levels which were significantly lower than the controls; this report is in agreement with the observation of Olatunbosum et al. (1974) who noted that women using OCs were found to have significantly lower serum magnesium levels in a controlled study. In another report from a preliminary study carried out by Blum et al. (1991), blood levels of magnesium decreased in women taking OC containing ethinyl estradiol and levonorgestrel. We also observed significant differences in the levels of Mg between the passive smokers/social drinkers and the binge drinkers/smokers, with the binge drinkers\smokers recording a much significantly lowered level than the passive smokers, an indication that smoking contributed to the depletion in magnesium level of the combined oral contraceptive group. Micronutrient deficiency occurs from increased absorption of harmful components of cigarette smoke and increased oxidative stress (Cogswell et el., 2003).

Magnesium deficiency in these patients accompanied by elevation in calcium level which had earlier been identified as a common feature of oral contraceptive use, as reported by Werbach, (1997); Wynn, (1975); Berg et al., (1998) may aggravate calcium/magnesium imbalance for which oral contraceptive use is noted. These two in association with Na^+ and K^+ are responsible for rapid depolarization, a plateau and a rapid slow repolarization process necessary for the transmembrane action potential of cardiac muscle cells. The depletion in Mg level observed in these subjects therefore may affect the physiologic role of these two elements, especially contraction of the heart muscle in a regular rhythm, thereby leading to irregular heart beat.

The significant decrease in magnesium level in these subjects is also likely to impair the breakdown of fats into fatty acids; consequently causing accumulation of fats, some of which may lodge on damaged arterial points, a condition capable of increasing risks of contracting major degenerative heart diseases e.g. arteriosclerosis, as well as hypertension, myocardial infarction, cardiac dysrhythmias and coronary vasospasm. To support its association with these conditions, magnesium supplementation has been reported to, among other things improve myocardial metabolism; inhibits calcium accumulation and myocardial cell death. Magnesium supplementation also enhances vascular tone, reduces cardiac arrhythmias and improves lipid metabolism, as well as reduces vulnerability to oxygen-derived free radicals; this means that the subjects in the binge drinkers/smokers group with greater depletion in magnesium level may be at greater risks of generating higher level of oxygen-derived free radicals. Non-significant difference was observed in the levels of cobalt and manganese in the oral contraceptive group compared with controls, although Holt (1998) has identified that OCs may interfere with manganese absorption (Holt, 1998).

Oral contraceptives are metabolized by the hepatocytes, and just like a number of other xenobiotics, its constant and chronic administration to a subject has been reported to cause a significant increase or decrease in the levels of some hepatocyte-derived biomolecules. For example fibrinogen was found to be altered in women exposed to oral contraceptive (Famodu and Osadebe, 2002). In addition, a significant increase in the levels of total protein and globulin has also been reported in women on oral contraceptives (Obisesan et al., 2002) an observation which is in contrast to ours. This study recorded a non-significant difference ($p>0.05$) in total protein and globulin levels unlike the results obtained from the study of Obisesan et al. (2002). The significant increase in globulin level in past studies, (Berg et al., 1998; Obisesan et al., 2002; Adekunle et al., 2002) was specifically linked to increase in IgG immunoglobulin, a condition which they identified as an immunoprotective effect of oral contraceptive. Our results translate to the fact that OC did not alter the humoral immunity and therefore the immunoprotective effects of OC were abolished in these subjects. Interaction among the different agents (e.g. oral contraceptive, alcohol, cigarette smoke, etc) these subjects were exposed to, might have also contributed to the difference in the globulin levels of our study compared to those of Adekunle et al., (2002) and Obisesan et al.(2002). Especially as drug interactions resulting sometimes from induction of some enzymes of the CYP enzyme system, in the liver have been reported to alter the effect of certain agents. Drugs such as rifampicin, phenytoin, and

carbamazepine as well as broad spectrum antibiotics, such as ampicillin and doxycycline, have been reported to alter the efficacy of many oral contraceptives and its effects on other tissues. Moreover, hard drugs like barbiturates have also been identified as capable of affecting result outcome in users of oral contraceptive and organ function (Archer and Archer, 2002; Dickinson et al., 2001; De Rossi and Hersh, 2002). The results of a non significant difference in albumin level in the oral contraceptive group compared with controls is in agreement with the result of Adekunle et al., (2002) who used another kind of hormonal contraceptive-UniplantR, an observation which probably is an indication that the synthetic ability of the liver was not altered by exposure to oral contraceptive in these subjects.

The results of this study suggest that cigarette smoke and alcohol modulate the effect of oral contraceptive on serum magnesium level as a significant decrease was observed for this category of subjects, with greater depletions observed in smokers than passive smokers. This possibility of an increased risk of contracting major degenerative heart diseases may necessitate therefore an increase in nutrient requirement values for this category of subjects. Slight increase in recommended daily allowance of magnesium which hitherto had been put at 250-350 mg per day per an adult female subject may be necessary because apart from the heart, magnesium deficiency has deleterious effect on other tissues. Indirectly it may cause kidney failure and the spasm of an artery resulting from a decrease in magnesium level can consequently lead to angina pectoris or even a heart attack. In addition, since combined oral contraceptive is a combination of estrogen and progestin hormone, there may be the need to determine if progestin oral contraceptive will feature the same degree of alteration.

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