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Evaluation of the Effects of Hormonal Contraceptives on Liver and Kidney Function

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Abstract

Hormonal contraceptives (HCs) are widely used for birth control. There are reported adverse effects associated with HCs and liver and kidney function in people on hormonal contraceptives. Limited studies exist to establish these reports; it is however crucial to elucidate any potential associations between these medications with liver and kidney dysfunction. This study aims to evaluate the impact of hormonal contraceptives on liver and renal function. For this study, a total of 50 participants were used; 25 of the total participants are women of reproductive age, using hormonal contraceptives, while the other 25 participants are women of reproductive age, not using hormonal contraceptives. The participants were recruited from Orita-Obele and Arakale health centers, Akure, Ondo State. The results showed a significant increase ($p<0.001$) in both creatinine and urea levels when compared to the control, but no significant increase ($p>0.05$) in both sodium and potassium ion concentrations. A significant increase ($p<0.0001$) in aspartate aminotransferase (AST), alanine transferase (ALT) activity, along with a significant increase ($p<0.01$) in bilirubin level, were observed in the case when compared with the control group. The results suggest that the alterations observed in kidney and liver function of subjects on hormonal contraceptives may indicate potential impairment. Understanding these interactions is crucial for ensuring the safe use of hormonal contraceptives and managing any potential risks to liver and kidney health, thereby guiding clinicians in prescribing these medications and monitoring their effects.

Keywords: Liver function, renal function, hormonal contraceptives, creatinine, urea.

INTRODUCTION

Contraception is the intentional prevention of pregnancy which enables individuals to manage fertility, reduce unintended pregnancy, abortions, pregnancy-related morbidity and death [1]. This can involve a variety of methods, including hormonal methods (like pills and injections), barrier methods (such as condoms), intrauterine devices (IUDs), and natural methods (like withdrawal and abstinence). A report in Nigeria gave overall contraceptive prevalence as 16.6% for traditional methods and 12.2% for modern methods [2]. The primary goal of contraception is to enable individuals and couples to control their reproductive health, thus allowing for family planning, spacing of births, and preventing unintended pregnancies. Hormonal contraceptives (HCs) are artificial birth control methods which enables sexual activity without the risk of pregnancy [3]. They inhibit ovulation by regulating pituitary production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which act as reproductive signals for ovulation in women [4]. Hormonal contraceptives can be classified into two main classes; Combined contraceptives (contains both estrogen and progestin e.g oral contraceptives) and Progestogen-only contraceptives (also known as short-

acting hormonal method), which consist of either progesterone or a synthetic analogue (progestin) [5].
Given the widespread use of hormonal contraceptives for family planning and reproductive health purposes, recent clinical report highlighted women on hormonal contraceptive with signs of dysfunction such a urinary changes, fatigue, muscle cramps and high blood pressure. It is crucial to elucidate any potential associations between these medications with liver and kidney function. The kidney plays a vital role in sustaining normal cellular functions and homeostasis [6]. This study was conducted to investigate how oral and injectable hormonal contraceptives affect Creatinine and Urea levels, with some select electrolytes concentration, serving as a pointer to any form of pathology.
The liver is essential for metabolism of drugs among which are hormonal contraceptives which have estrogen and progesterone as active ingredients [7]. Oral contraceptives may influence liver health by either directly contributing to liver disorders or aggravating pre-existing hepatic conditions. These hormones whether naturally occurring or synthetic can interact with liver function in ways that lead to both normal physiological responses and potentially harmful effects [8].

MATERIALS AND METHODS

Study Participants

For this study, a total of 50 participants were used; 25 of the total participants are women of reproductive age, using hormonal contraceptives, while the other 25 participants are women of reproductive age, not using hormonal contraceptives. The participants were recruited from Orita-Obele health and Arakale health centers, Akure, Ondo State.

Data collection

A data collection form (questionnaire) which contained items on demographic characteristics, anthropometric characteristics, duration of exposure, type of hormonal contraceptives used, common side effects experienced, diet/physical activity were used for subjects' recruitment. The data collection was all done by personal interview and informed consent form was obtained from all participants after educating them on the benefits and relevance of the study. Ethical approval was obtained from University of Medical Sciences, ethic committee.

Biochemical analysis

Blood samples were withdrawn from each subject by venipuncture. Blood samples collected were further analyzed.

Determination of kidney function: The serum samples were analyzed for creatinine and urea using the following methods:

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The serum samples were analyzed for creatinine and urea using the following methods:

Determination of creatinine:

It was determined in the serum using colorimetric method [9]. Creatinine in alkaline solution reacts with picric acid to form a coloured complex. The amount of the complex formed is directly proportional to creatinine concentration.

$$\text{Concentration of creatinine in serum} = \frac{\triangle \text{ sample x 177}}{\triangle \text{standard}} = \mu\text{mol/l}$$

Determination of Urea:

Serum samples were analyzed using a method by [10]. Urea in the serum is hydrolysed to ammonia in the presence of urease. The ammonia is then measured photometrically by Berthelot's reaction.

The method is based on the following reaction:-

$$\text{Urea} + H_2O \xrightarrow{\text{urease}} 2NH_3 + CO_2$$

$$NH_{3\,+\,\text{hypochorite}\,+\,\text{phenol}} \longrightarrow \text{indophenol (blue compound)}$$

Determination of electrolyte concentration:

Potassium ions: Potassium ions in the serum were determined using a method by [11]. Potassium ions in a protein –free alkaline medium react with sodium tetraphenylboron to produce a finely dispersed turbid suspension of potassium teraphenylboron. The turbidity produced is proportional to the potassium concentrate and read photometrically.

Sodium ions:

Sodium ions in the serum were determined using a method by [11]. Sodium reacts selectively with chromogen producing a chromophore whose absorbance varies directly as the concentration of sodium in the test samples.

Determination of liver function:

The activity of Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) in the serum were measured by adopting the method by [12] using Randox test kits.

Determination of Aspartate aminotransferase (AST):

AST is measured by monitoring the concentration of oxaloacetate hydrazine formed with 2,4- dinitrophenylhydrazine.

α-oxoglutatrate + L-aspartate →L- glutamate + oxaloacetate

Determination of Alanine aminotransaminase (ALT):

ALT in samples reacts with alanine to transfer an amino group to another substrate producing glutamate and pyruvate.

ALT
Alanine + α- ketoglutarate ↔ glutamate + pyruvate

Statistical analysis

The data obtained were statistically analyzed with Shapiro-wilk test for normality using GraphPad prism 9.0) and the test of homogeneity of variance. An unpaired t-test was then performed to compare the means between the control and subjects using hormonal contraceptives. The results were presented as mean ± standard error of mean (SEM). Differences between means of case and control values at $p<0.001$ at 99.9% confidence interval for kidney function and liver function parameters were considered significant.

RESULTS

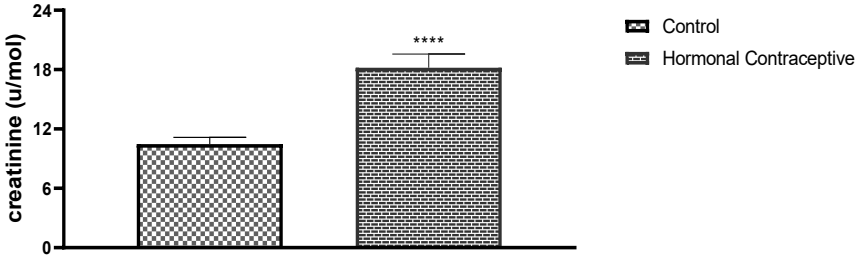

Figure 1: Effects of hormonal contraceptives on creatinine level. ****p<0.0001; significantly different vs control

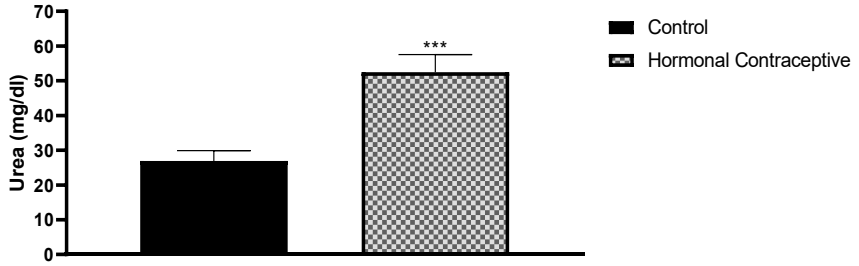

Figure 2: Effects of hormonal contraceptives on urea level. ***p<0.001; significantly different vs control.

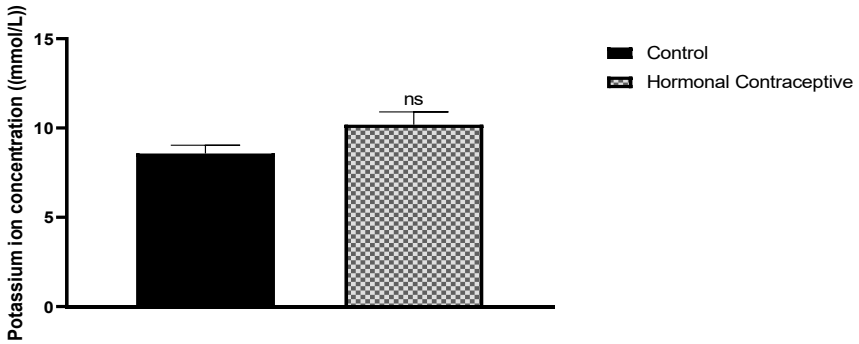

Figure 3: Effect of hormonal contraceptives on Potassium ion concentration level.. NS- not significant

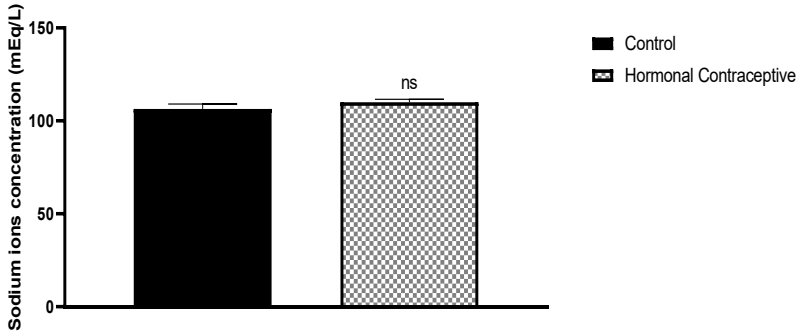

Figure 4. Effect of hormonal contraceptives on Sodium ion concentration level. *P*>0.05 vs control. NS- not significant.

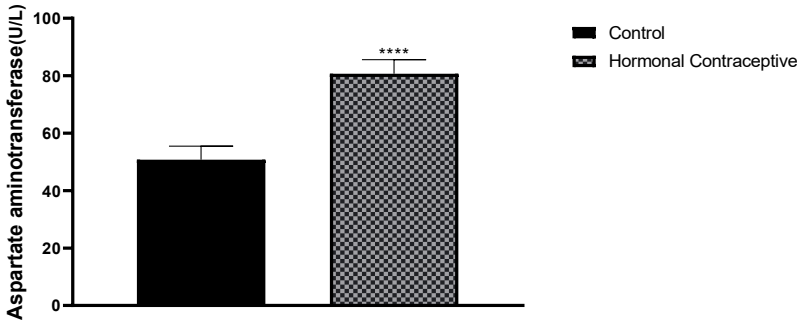

Figure 5. Effects of hormonal contraceptives on aspartate aminotransferase level. ****p<0.0001; significantly different vs control.

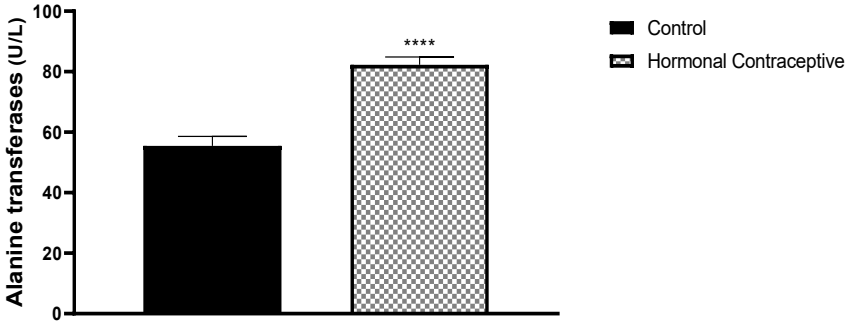

Figure 6. Effects of hormonal contraceptives on alanine transferase level.. ****p<0.0001 vs control

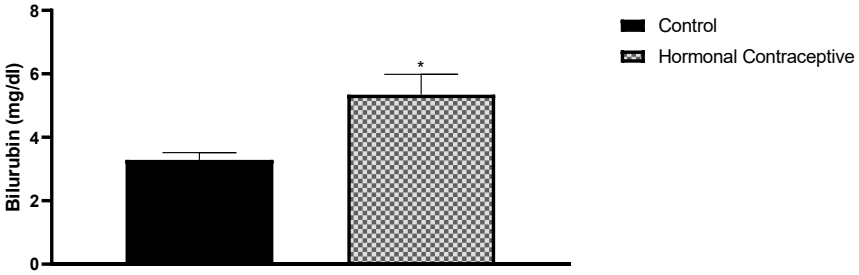

Figure 8: Effects of hormonal contraceptives on Bilurubin level. **p<0.01; significantly different vs control

DISCUSSION

This study evaluated the effects of hormonal contraceptives on liver and kidney function and select electrolytes (Na^+ and K^+). A significant increase (p<0.0001) was observed in Creatinine and Urea levels with no significant difference (P>0.05) in Na^+ and K^+ concentrations in test subjects (those on hormonal contraceptives) when compared with control subjects (those not on hormonal contraceptives). These are consistent with studies conducted by [13, 14, 15] who reported significant increase in the serum concentrations of Urea, and Creatinine, although there were conflicting reports in the concentrations of electrolytes (Na+ and K+) reported.

Contrary to this study, Eqbal *et al.,* [6] reported no significant difference (P>0.05) in the level of Urea, Sodium and Potassium between the three study groups considered while Creatinine showed a significant increase (p <0.01) in combined oral contraceptives group compared with injectable contraceptives and control groups. Al-Jomard and Al-Youzbaki, [16] also observed a contrary report where there were no significant difference (p>0.05) in the level of urea, although a significant increase (p <0.05) in the level of creatinine were observed in women on oral contraceptives when compared with women who do not use oral contraceptive.

The kidney had been observed to be one of the most estrogen-responsive organs, hormonal contraceptives however contains estrogen and progestin and they have been shown to increase urea and creatinine levels by influencing renal function through several mechanisms [15, 17]. Estrogen can influence renal hemodynamics by causing vasodilation of the renal arteries, potentially altering the glomerular filtration rate. While this might initially seem beneficial, prolonged exposure to high levels of estrogen can lead to maladaptive responses, including glomerular hyperfiltration followed by a decline in kidney function [18]. Hormonal contraceptives increase the risk of thromboembolic events, including renal vein thrombosis. Thrombosis can impair renal perfusion and filtration, leading to decreased excretion of urea and creatinine and their subsequent accumulation in the blood [19].

The probable explanation for the lack of significant difference in sodium and potassium ion concentrations observed in this study likely stems from the body's intrinsic regulatory mechanisms, particularly those controlling fluid and electrolyte homeostasis. Estrogen and progestins contained in hormonal contraceptives, can interact with the renin-angiotensin-aldosterone system (RAAS), however, the effects of these hormones are usually mild and can be compensated by aldosterone and antidiuretic hormone, both of which play a critical role in maintaining electrolyte balance [20].

Furthermore, from this study, a significant difference (p<0.0001) was observed in the activity and concentration of aspartate aminotransferase (AST), alanine transferase (ALT), and Bilirubin (p<0.01) in test subjects when compared with the control group respectively. This is in agreement with a study by Chan *et al.,* [21], who reported that hormonal contraceptive users were observed to have a statistically significant higher mean value of liver enzymes assessed compared to non-user control groups. Odinga *et al.,* [22] also reported impairment on the functionality and the integrity of the liver on administration of oral contraceptives over a long period, dose dependent. Also in tandem with this study, Mamza *et al*., [23], observed and reported significant increase in AST and ALT activity of short- term contraceptives users compared to control group and suggest that liver function is affected by short term use of contraceptives.

Hormonal contraceptives had been reported to induce the metabolic activities of the hepatocytes; larger doses of hormonal contraceptives cause adaptive changes by increasing the level of metabolic enzymes [24, 25]. A probable mechanism is that HCs are able to enhance oxidative stress (OS) [25]. This is due to the necessity to metabolize the hormone load from the HCs with the help of liver enzymes. In the same vein, the significant (p<0.01) increase in the mean value of bilirubin observed in this study is suggestive of hepatobiliary complications, which are most likely induced by the prolonged use of hormonal contraceptives with the subsequent inhibition of the hepatic excretory function, thus leading to increased serum bilirubin [7].

CONCLUSION

The use of hormonal contraceptives resulted in a significant increase of creatinine and urea levels among women using hormonal contraceptives while no significant difference was observed in the levels of Na^+ and K^+ concentration when compared to control.

However, hormonal contraceptives were shown to induce increase in liver enzyme activity and the mean value of bilirubin were higher among hormonal contraceptive users than respective control.

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