# LEVONORGESTREL AND ETHINYLESTRADIOL ON KIDNEY FUNCTION

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## ABSTRACT

### BACKGROUND

Despite the modifications on Oral Contraceptive Pills (OCPs) in term of content and dosage to lessen their side effect, paucity of information existed on the effect of COCP on kidney function.

### AIM OF STUDY

Hence, this study investigates the effect of COCP containing 0.15mg levonorgestrel (a progestogen) and 0.03mg ethinylestradiol (an estrogen) on kidney biochemical parameters and electrolytes.

### METHODS

The study involves 15 female rabbits divided into three groups (A, B and C). Group A served as the control, while B and C served as the test groups and were administered the COCP per body weight human doses for 7 days and 14 days respectively. At the end of the study, blood sample was obtained for the determination of plasma creatinine, urea, Na, Cl and K using standard laboratory procedures.

### RESULTS

Results showed significant increase ($p<0.05$) in plasma creatinine, urea and K+ but a decreases in plasma Na+ and Cl- in the tests compared to the control.

### CONCLUSION

Considering the observed changes in the parameters herein studied, COCPs usage is not without impact on kidney function and may cause homeostasis dysfunction and hence the need for further studies.

## KEY WORDS

Estrogen, Progestogen, Electrolyte, Creatinine, Urea.

## INTRODUCTION

The World Health Organization in 1998 and other studies estimated that over 100 million women worldwide are on oral contraceptive pills (OCPs) [1]. Hitherto, it is know that many women discontinuation it uses primarily because of issues concerning cycle control, weight gain, water retention, perimenstrual symptoms, and hypertension [2,3] venous and arterial cardiovascular complications [4-6] nausea, breast tenderness, irregular menstrual bleeding and thrombosis [7-10]. These side effects are of great clinical importance and have over the years resulted in many important changes in the composition and use of these preparations to reduce the side effects.

Of greater concern, is the fact that despite extensive clinical experience, many metabolic effects of OC treatment remains to be explored. In fact, there are only few studies evaluating body composition and OCP usage. Indeed, the questions about metabolic effects of OCPs and weight gain are of particular relevance to females during OCP treatment. Recently, our findings reported that levonorgestrel and ethinylestradiol containing COCP elicit anti-obesity properties and potentials for weight management in both the obese and non-obese rabbits [11]. In fact, natural and synthetic female sex hormones have been reported to have various effects on water and electrolyte balance; a function of the kidney know to be critical for normal cellular function and maintaining adequate blood and plasma volume (PV) and osmolality [12].

This finding lead to the curiosity of what the consequence of this COCP containing levonorgestrel and ethinylestradiol may have on kidney function considering it physiological role. The goal of this study was to evaluate the effects of levonorgestrel and ethinylestradiol containing COCP on kidney function indicated by some selected parameters and electrolytes.

## METHODS

*EXPERIMENTAL ANIMALS*: Fifteen adult female rabbits were obtained from Aduwawa market in Benin City, Nigeria, and transported to the experiment site where they were housed in a well-ventilated room under a 12/12 hours light/dark cycle and fed feed (Vital feed (Grower pellets produced by Grand Cereals Ltd, a subsidiary of UAO Nigeria PLC, Jos, Plateau State), grass and water ad libitum.

*DRUG OF STUDY:* COCP tagged AVA 30ED (containing Levonorgestrel 0.15mg and Ethinylestradiol 0.03mg) was purchased from a Pharmacy store in Ekpoma, Nigeria. AVA 30 ED is a combined oral contraceptive consisting of 21 hormonal tablets and 7 non-hormonal tablets. Because of the small amount of hormone contents, it is considered as a combined low-dose oral contraceptive preparation.

*EXPERIMENTAL GROUPING:* The rabbits were divided into three groups (A, B and C) of 5 rabbits each; A served as the control, while B and C served as the test groups treated for 7 days and 14 days respectively.

*DRUG ADMINISTRATION*: Each day a tablet was dissolved in 100ml distilled water and the appropriate dose per kg was measured out for oral administration via an oro-gastric tube using a 2ml syringe. The dose was determined based on comparative dosage per body weight proportion akin to humans.

*SAMPLE COLLECTION*: At the end of the experiment and 24 hours after the last administration of COCP, blood samples were collected from each rabbits by means of cardiac puncture using 5ml hypodermic syringe and needles under mild chloroform anesthesia.
Sample analysis: The collected blood sample was immediately sent to the biochemical laboratory for analysis. Serum urea and creatinine level were analysis as described by Baker et al. [13] serum potassium, sodium and chloride were analyzed using standard method as described by Tsalev and Zaprianov [14].

*DATA ANALYSIS*: The mean ± standard deviation was determined and one-way analyses of variance was performed using SPSS version 17 soft ware. The significance level was set at $p<0.05$.

## RESULTS

Table 1 shows the variations in selected kidney function parameters of rabbits treated with COCP containing 0.15mg levonorgestrel and 0.03mg ethinylestradiol synthetic hormones. COCP was observed to significantly increase ($p<0.05$) urea and creatinine in a manner that is dependent on period of ingestions compared to the control (group A). Furthermore, on electrolytes with kidney function significant indicated by K, Cl and Na, COCP was observed to have a significantly ($P<0.05$) time dependent impact on K, Cl and Na levels. Specifically, the impact on K level was a time dependent increase in the test groups while Cl was a time dependent decrease compared to the control. Although Na was observed to reduce significantly with COCP ingestions when compared to the control (136.00±1.41mmol/L), however, it increases with increased period of ingestion but the difference was statistically not significant (see table 2).

## DISCUSSION

The two most influential female sex hormones; estrogen and progesterone, change in concentration across the menstrual cycle and are governed by OCP usage [12]. In the present investigation, it was observed that COCP, containing 0.15mg levonorgestrel (a progestogen) and 0.03mg ethinylestradiol (an estrogen), significantly increases creatinine outputs suggesting an increase in muscle metabolism. This is sequel to the fact that creatinine is produced and excreted at a constant rate which is proportional to the body muscle mass [15]. The mean significant increase in creatinine in this study is in line with the study by Oelker et al. [16] who studied an oral contraceptive containing an antimineralocorticoid progestogen, drospirenone, but contradicts the study by Surasak et al. [17] who reported no significantly changed in mean serum creatinine following 6 cycles of OCPs ingestion containing Drospirenone. Although depressed levels of plasma creatinine are rare and not clinically significant, its plasma elevation is indicative of under excretion, suggesting kidney impairment and as such regarded as the most useful endogenous marker in the diagnosis and treatment of kidney disease and measured primarily to assess kidney function [18,19]. This effect on creatinine may be the progestegen content reason own to a report by Smith and Sizto [20] that high progestogen increases serum creatinine.

Our findings on electrolytes with kidney function significance showed that COCP containing 0.15mg levonorgestrel (a progestogen) and 0.03mg ethinylestradiol (an estrogen), significantly increases plasma Na+ and K but decreases plasma Cl-. This finding is in accordance with several other previous studies [16,17] where a different oral contraceptive containing drospirenone as progestogen. This effect on electrolytes showed by OCPs suggests that the COCP used in this study may alter the fluid nature of extra cellular fluid. Thus understanding the interactions between OCP and the fluid regulatory system is crucial. In fact, female sex hormones have been reported to influence sodium and water distribution and thus fluid compartment volumes and dynamics [12] and may not be unrelated to the hypertensive effect of OCPs previously reported by several studies. The mechanism behind this effect of the COCP used in this study may be explained by the fluid retention potentials by activating the renin-angiotensin- aldosterone system, enhances vasodilation, capillary permeability and lower operating set point of plasma osmolality by estrogens [21-25]. Progesterone on the other hand has also been noted to antagonizes estrogenic effect [22] by competing directly with the same mineralocorticoid receptor as aldosterone, which may cause a transient natriuresis [26].

Our findings therefore suggest that levonorgestrel and ethinylestradiol containing COCP, may deregulate hemostatic. Similar assertion has been reported in the study of Klipping et al. [27], who studied two combined oral contraceptives containing ethinyl estradiol 20 microg combined with either drospirenone or desogestrel on hemostatic parameter and found changes in hemostatic parameters such as increase in activation markers for thrombin (clotting activation), fibrin (fibrinolytic activation) turnover, in (pro)coagulatory, and in (pro) fibrinolytic parameters as well as a decrease in PAI-1 antigen levels. He then concluded that these suggested that the overall balance between factors influencing hemostasis were maintained on an up-regulated level in both study groups [27].

## CONCLUSION

Judging by the results from this study, it is commendable that further animal researches and human studies be investigated on, as levonorgestrel and ethinylestradiol containing COCP may not be without effect on kidney function. There is also a need to access the effect of other OCPs on kidney function and other body organs.

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