
Effect of Combined Oral Contraceptive Pills on Renal Function Tests

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Abstract

Background: Controversy exists regarding the adverse and beneficial effects of oral contraceptive use. Microalbuminuria is associated with increased risk of renal and cardiovascular disease. There are very little studies to determine the effects of combined oral contraceptive pills (COCs) on renal function tests including detection of microalbuminuria in hormonal contraceptive users at least in our locality.

Objective: To evaluate the effects of COCs on serum urea, creatinine and electrolytes level and creatinine clearance and to detect microalbuminuria (MAU) in COCs users and in relation to the blood pressure (BP) changes and duration of their usage in Mosul City.

Subject & Methods: This is a case control study in which a total of 47 healthy married women, age range between 19-35 years, from those who were attending AL-Batool and AL-Khansa Family Planning Centers in Mosul from the period of 15th Oct 2010 to the 15th of Apr 2011, who were taking Microgynon tablets which are one of monophasic, second generation COCs (each contains 0.03 mg of ethinyl estradiol and 0.15 mg levonorgestrel) for a period ranged between 3 months to 5 years and these were considered the users group. Another 51 healthy married women who did not use any hormonal contraceptives and were drawn from the same population and matched for age, body mass index (BMI) with the users group and they were considered as the non users groups. Blood samples (5ml) and urine samples (5ml) were obtained from COCs users and non-user groups. The sera obtained from the blood samples were used for the estimation of serum urea, serum creatinine by commercial kits. Serum electrolytes level was measured using OPTI LION Stat Electrolyte Analyser. Creatinine clearance was calculated using Cockcroft and Gault equation. The urine samples were used for the detection of microalbuminuria using *i*-chroma reader system.

Results: This study demonstrated that using of COCs caused a significant increase in the mean of systolic BP (SBP) and diastolic BP (DBP) in comparison to the nonuser group. There was a significant higher level of serum creatinine and a significant lower level of creatinine clearance in the COCs users group as compared with the nonusers group, but non significant differences in the level of serum urea. Also there is a significant increase in the mean of MAU level of the COCs users group in comparison to the nonusers group. There were a non significant positive correlation between SBP and MAU level and DBP and MAU level among COCs users. There were non significant variations in the renal function tests among COCs user group according to duration of use except that for MAU, there was a significant positive correlation between MAU and duration of usage of COCs.

Conclusion: The use of COCs is independently a cause of a significant increase (although within normal range) of BP and MAU but non significant variations in the renal function tests among COCs users group according to duration of usage except that for MAU, there was a significant positive correlation between MAU and duration of usage of COCs and the changes of MAU is irrespective to the BP changes. These data suggest that the use of hormonal contraceptives (HC) may be deleterious from a renal and cardiovascular disease point of view.

Key words: Combined oral contraceptive pills, urea, creatinine, microalbuminuria

Introduction

Oral contraceptives (birth control pills) are medicines taken by mouth to help in preventing pregnancy, contain artificially made form of two hormones naturally produced in the body (estrogen and progesterone) so called COCs¹. They are the most effective, safe, reliable and popular form of reversible contraception².

Hormonal contraceptives (HC) have been used for more than four decades. Much attention has been drawn to the thromboembolic and cardiovascular adverse events associated with these agents. Moreover, the incidence of this adverse effect may also be related to the estrogen and progestin content of the oral contraceptive^{3,4}.

However the epidemiological and pathophysiological data on HC use and the renal outcome, e.g. albuminuria and renal function, are limited. Interestingly, some studies have described an association between the use of HC and albuminuria^{5,6,7}. Microalbuminuria is a marker for early vascular endothelial damage⁸ and are related to an increased risk of progressive renal failure and excess cardiovascular morbidity and mortality in subjects with and without diabetes^{9,10,11,12}.

The mechanism of the effect of HC on urinary albumin excretion (UAE) is still unknown, although there are studies showing that it may be related to a systemic haemodynamic effect, i.e. an increase in BP^{13,14} or a specific renal effect^{15,16}.

There is currently no evidence to suggest that HC use predisposes women to renal disease. However, studies on the association between HC and renal outcome have so far been conducted in hypertensive⁶ or diabetic populations⁵. In the general population data are scarce. Three studies have proposed that the use of HC may be associated with an increased risk of microalbuminuria, independent of BP^{6,7,17}.

The aim of this study was to assess the effect of COCs on renal function tests (serum urea, serum creatinine, creatinine clearance, serum electrolytes and the detection of microalbuminuria), and in relation to the blood pressure changes and duration of use of these hormonal contraceptive users in comparison to non users aged matched healthy women as control.

Subjects and Methods

The approval of the study protocol by an ethic committee has been obtained from the local health

committee of Ministry of Health and College of Medicine - University of Mosul – Iraq.

The study was conducted in the largest two centers of Family Planning in Mosul city: Al-Batool Family Planning Center and Al-Khansa Family Planning Center. From 15th October 2010 to the 1st of April 2011. This study included 47 apparently healthy women who were attending Al-Batool Family Planning Center and Al-Khansa Family Planning Center and having the following inclusion criteria: Age range between 19-35 years old and their body mass index (BMI) < 25. All married but not pregnant, nor lactating but were fertile at the time of study and having regular menstrual cycle. Apparently healthy, were not use any other medications at the time of study. Neither smoker nor alcoholic.

These women were taking combined oral contraceptive pills (COCs), called Microgynon of Schering AG Company of Pharmaceutical Division-Federal Republic of Germany (each tablet contains 0.03 mg Ethinylestradiol (EE) and 0.150 mg Levonorgestrel (LNG)) for more than 3 months.

The non-users group included 51 women, from those, attending Al-Batool Family Planning Center, women works at Colleges of Medicine and Pharmacy, University of Mosul, who had the same criteria as the users group except that they were not using any hormonal contraceptives, instead they used either a barrier method or mechanical methods and they were volunteered for comparison.

Five ml of venous blood were withdrawn, using a disposable syringe from the contraceptive users and non users. The separated serum was kept frozen at – 20°C to be analyzed thereafter for:

- 1- Serum urea concentration was measured using a kit supplied by Biomerieux (France).
- 2- Serum creatinine was measured using a kit supplied by SYRBIO company (Syria) diagnostic reagents for laboratories under license of EURO BIO laboratories PARIS-France.
- 3- Determination of Creatinine clearance (Crcl) was calculated using the Cockcroft and Gault

equation¹⁸. They utilize serum creatinine concentration ($\mu\text{mol/l}$), sex, age (year) and weight (Kg) as follow:

$$\text{Crcl} = \frac{[140 - \text{Age (year)}] \times \text{weight (kg)} \times 0.85 (\text{female})}{\text{Serum creatinine } (\mu\text{mol/l})}$$

- 4- Serum sodium and Potassium were measured using the OPTI LION Stat Electrolyte Analyser using Opti Medical Systems, Inc.

OPTI-LION Operator's Manual PD7200. Roswell, GA: OPTIMedical. 2007).

Flourescence immunoassay technology for quantitative measurement of microalbumine in human urine¹⁹ was performed by *i*-chroma reader system.

Statistical analysis: Standard statistical methods were used to determine the mean and standard deviation (SD). Unpaired student t-test was used to compare the results for measured biochemical parameters between hormonal contraceptive users and non-users. Linear regression analysis [Pearson correlation coefficient (r)] was performed for finding the degree of association between different parameters. ANOVA Test (Analysis of Variance) was used to identify the variation in the different variables in relation to the duration of hormonal contraceptive user groups. P-value of < 0.05 was considered to be statistically significant.

Results

A total number of 47 women who used COCPs were included in this study, with mean age $\pm$ SD of (30.46 $\pm$ 3.40) years, those have been considered to represent the exposed group (COCPs users) group. Another 51 women with mean age $\pm$ SD of (29.05 $\pm$ 4.50), who did not use or used non hormonal contraceptives such as condom or IUCDs and were considered to represent the non exposed group (Non-Users) group.

Table (1): demonstrates that using of COCPs caused a significant increase in the mean of SBP and DBP in comparison to the nonuser group.

Table 1: Comparison between mean of SBP and DBP of COCPs users, and nonuser groups

Parameters	Mean $\pm$ SD		P-Value
	COCPs Users (n=47)	Non-Users (n=51)	
SBP (mmHg)	122.9 $\pm$ 18.2	112.3 $\pm$ 9.9	0.00
DBP (mmHg)	79.2 $\pm$ 14.3	74.2 $\pm$ 7.8	0.03

Table (2) shows a significant higher level of serum creatinine and a significant lower level of creatinine clearance in the COCPs users group as compared with the nonusers group, but non

significant differences in the level of serum urea. Also there is a significant increase in the mean of MAU level of the COCPs users group in comparison to the nonuser group.

Table 2: Comparison of renal function tests between COCPs users and nonusers groups

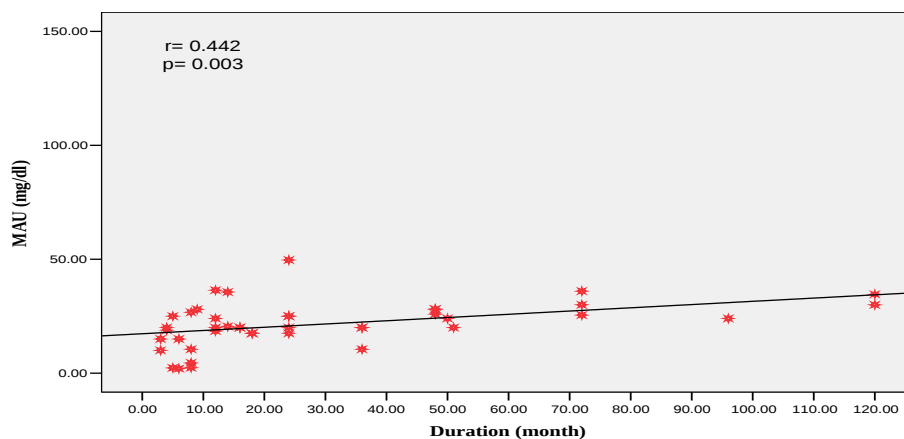
Parameters	Mean $\pm$ SD		P-Value
	COCPs Users (n=47)	Non-Users (n=51)	
Urea (mmol/L)	4.9 $\pm$ 3.5	4.61 $\pm$ 0.96	(NS)
Creatinine (μ mol/L)	73.4 $\pm$ 18.5	63.4 $\pm$ 8.6	0.001
Cr.Cl (ml/min)	88.7 $\pm$ 20.6	99.6 $\pm$ 14.3	0.003
Sodium (mmol/L)	138.5 $\pm$ 3.9	138.6 $\pm$ 2.6	(NS)
Potassium (mmol/L)	4.45 $\pm$ 0.65	4.3 $\pm$ 0.33	(NS)
MAU (mg/L)	21.52 $\pm$ 9.79	6.89 $\pm$ 3.27	0.000

There were non significant variations in the mean of renal function tests among COCPs users group according to duration of use Table (3), except for

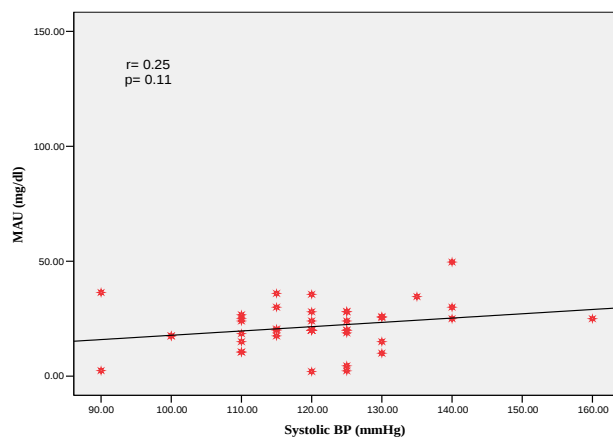
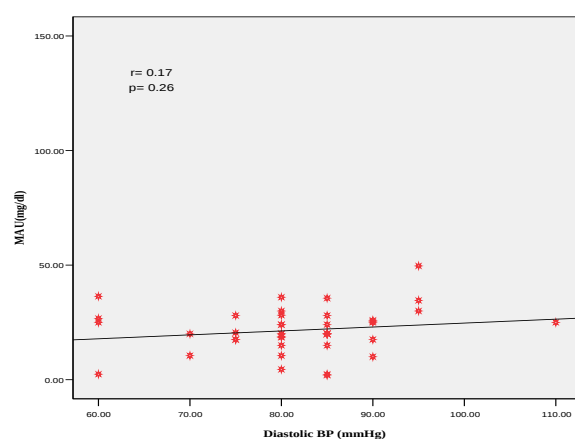
MAU, there was a significant positive correlation between MAU and duration of usage of COCPs Figure (1).

Table 3: Comparison between renal function tests among COCPs users group according to duration of use

Parameters	(Mean $\pm$ SD) (N=47)			P-value
	COCPs Users $\leq$ 1yr (N=14)	COCPs Users 1< yr<5yr (N=20)	COCPs Users $\geq$ 5yr (N=13)	
Urea (mmol/L)	4.45 $\pm$ 1.09	5.72 $\pm$ 0.36	4.66 $\pm$ 0.82	NS
Creatinine (μ mol/L)	71.01 $\pm$ 12.71	70.92 $\pm$ 18.24	79.87 $\pm$ 23.53	NS
Cr.Cl (ml/min)	86.75 $\pm$ 17.22	93.74 $\pm$ 21.33	83.30 $\pm$ 22.83	NS
Sodium(mmol/L)	139.00 $\pm$ 4.26	137.89 $\pm$ 3.56	139.07 $\pm$ 4.36	NS

**Figure 1:** Relationship between MAU level and duration of usage among COCPs users

There is a non significant positive correlation between SBP and MAU level and DBP and MAU level among COCPs users Figure (2,3).

**Figure 2:** Relationship between SBP and MAU level among COCPs users**Figure 3:** Relationship between DBP and MAU level among COCPs users

Discussion:

The hormonal contraceptive used in this study was "Microgynon" tablets, which is one of the monophasic, second generation COCPs (0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel), because COCPs are the most commonly used method of contraception in Iraq, as it was found that oral pills represent the most popular, about 36% of current users use oral pills²⁰. Also, in another study done in Mosul City²¹, found that the most common type of contraceptive methods used was the oral pills, (42.6%) (including COCPs in 32.3% and progesterone only pills (POPs) in 10.3%) of the users.

Since the introduction of hormonal contraceptives in the early 1960s, repeated attention has been focused on the possible beneficial and harmful side effects²². Among the possible impact, much attention has been drawn to the thromboembolic and cardiovascular adverse events associated with these agents but the results of these studies, however, are controversy.

This study showed a higher mean SBP and DBP in women using COCPs compared with the non users, this is in agreement with other studies^{14,16,17,23,24} but the study of Blumenstein *et al.*,²⁵ fail to support the hypothesis of a causal relationship between OC use and elevated BP in black women.

When compared with earlier studies, a decreased cardiovascular morbidity was recently observed in OC users, possibly because of a tendency to refrain (abstain) from OC in smoking older women and the reduction in dosages of both estrogen and progestogen components to about one fifth to one sixth²⁶. Nevertheless, data from the Nurses' Health Study II suggested that even COCPs with lower doses of estrogen increase the risk of hypertension, and that the risk increases with duration of use and with increased progestin potency²⁷.

Regarding the renal function tests this study found a significant increase in the mean value of serum creatinine of COCPs women compared with non users group but still within normal range and consequently there is a significant decrease in the mean value of estimated creatinine clearance that is calculated using Crockroft Gault formula. Serum urea showed non significant changes in the mean value of COCPs group when compared with the nonuser group, and this result is in agreement with Brito *et al.*,²⁸ who confirmed that the monophasic oral contraceptive with (30 µg ethinylestradiol and 150 µg desogestrel) is a safe and effective oral contraceptive with unaffected serum urea and creatinine level.

Another studies^{6,7} demonstrated that oral contraceptive use are associated with an elevated creatinine clearance, which are in disagreement with this study. The study of Pinto-Sietsma²⁹ has been shown that, as in persons with diabetes, glomerular filtration rate (measured as creatinine clearance and

using the Cockcroft and Gault formula) is elevated in subjects without diabetes with microalbuminuria, but more so in subjects with high normal urinary albumin excretion (15-30 mg/24 h), which is in disagreement with this study.

The results of this study show no significant changes in the serum electrolytes (sodium and potassium) level which is in agreement with the study of Brandle *et al.*,³⁰ on the kidney function of 28 healthy women not taking contraceptives and 46 healthy women (aged 20–28 y) on one of three different types of oral contraceptive (combination preparations) were investigated [Minulet®/Femovano®, Marvelon®, Diane®]. They found that endogenous creatinine clearance was significantly increased. The potassium excretion rate was significantly elevated in some type of COCPs and the sodium excretion rate was significantly increased in other type.

An increase in renin substrate and activation of the renin–angiotensin–aldosterone system (RAAS) have been observed among effects of oral contraceptives, leading to vasoconstriction and sodium and water retention^{24,31} but this would not cause any significant changes in serum sodium or potassium concentration, which is in agreement with this study. Although water retention is not always reflected clinically, it frequently results in a weight increase in some oral contraceptive users, depending on individual sensitivity. Therefore, oral contraceptives containing reduced doses of ethinylestradiol and progestogens that have an antimineralocorticoid effect are a logical clinical choice to minimize water retention and its related side effects³².

The results of this study revealed that there were a significant increase in the mean level of MAU in women using COCPs in comparison to the non users and this result is in agreement with results of other studies^{6,7,17}. Similar results were observed in a recent study in a diabetic population⁵. While Brandle *et al.*,³⁰ found that besides their various effects on renal tubular function, oral contraceptives are able to increase the glomerular filtration rate and in all groups on oral contraceptives the albumin excretion rate was numerically but not significantly elevated.

Although the mean value of albumin in urine (spot urine) in our COCPs study group is considered within the normal range but it is high normal value according to the classification of Jong and Curhan³³, who defined the concentration of microalbuminuria in overnight urine albumin (ug/min) as 20 to <200 mg/L, less than 10 mg/L as normal and between 10 to >20 as high normal.

In women, regardless of menopausal status, estrogen preparations remained after adjustment for age, hypertension, diabetes, obesity, hyperlipidemia, and smoking, factors considered to be associated with microalbuminuria⁷. It has been suggested that microalbuminuria reflects generalized vascular

endothelial dysfunction⁸. However, based on our data, it is not possible to conclude whether there is a direct effect on the vascular endothelium, or whether it is secondary to unknown effects of oral contraceptive use on vascular endothelial function and structure. An alternative explanation is that estrogens induce glomerular hyperfiltration, which via a greater tubular load of albumin, and perhaps in combination with an altered tubular albumin handling, could lead to an elevated albumin excretion⁷. Because microalbuminuria is an early marker for increased risk of cardiovascular disease^{11,12} so users of estrogen preparations may have an increased risk for cardiovascular morbidity and mortality. However, the reassuring finding of the study of Atthobari *et al.*,¹⁷ is that these unfavourable effects of HC are reversible after withdrawal, even after many years.

This study found that there were no significant correlations between MAU and SBP nor DBP, this is in agreement with the study of Hillege *et al.*,¹² and de Jong *et al.*,³⁴ who concluded that microalbuminuria is associated with an enhanced risk for cardiovascular mortality and probably also with an enhanced risk for progressive renal failure not only in diabetic patients but also in hypertensive and in non-diabetic, non-hypertensive subjects as well as Ribestein *et al.*,⁶ Monster *et al.*,⁷ and Atthobari *et al.*,¹⁷ approved that the higher prevalence of microalbuminuria in COCPs compared with nonusers is independent whether or not arterial pressure was elevated.

This study found that there were non significant variations in the mean of all renal function tests among COCPs user group according to duration of use, except that there were significant variations in the mean of MAU according to duration of use. Various short term studies and cross-sectional epidemiological studies have shown an association of HC use and urinary albumin loss^{5,6}. Other studies, for example, using data of the first screening of the PREVEND cohort, showed that women receiving HC had a 90% increased risk for microalbuminuria compared with non-users⁷ and the follow up study of Atthobari *et al.*,¹⁷ found that the long term use of HC is associated with worsening of BP, UAE and GFR which is in agreement with this study. The result of these studies suggested a controversy regarding the effect of HC on renal function tests in relation to duration of use.

Conclusion:

The use of COCPs on women aged 19-35 years is independently a cause of a significant increase (although within normal range) of BP and MAU but non significant variations in the mean of renal function tests among COCPs users group according to duration of usage except that for MAU, there was a significant positive correlation between MAU and duration of usage of COCPs and the changes of

MAU is irrespective to the BP changes. These data suggest that the use of HC may be deleterious from a renal and cardiovascular disease point of view.

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