

Effects of combined oral contraceptive pills on thyroid function tests in Mosul City

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ABSTRACT

Background: There are very little studies to determine the effects of combined oral contraceptive pills (COCPs) on thyroid function tests in hormonal contraceptive users at least in our locality.

Objective: To evaluate the effects of COCPs on serum level of thyroid stimulating hormone (TSH), free triiodothyronine (FT₃) and free tetraiodothyronine (thyroxine) (FT₄) and in relation to the duration of their usage in Mosul City.

Design: A case control study.

Subject & Methods: This study was conducted during the period from September 2008 to March 2009. A total of 78 healthy married women, age range between 19-30 years, from those who were attending AL-Batool and AL-Khansa Family Planning Centers in Mosul, who were taking Microgynon tablets which are one of monophasic, second generation combined oral contraceptive pills (COCPs) (contain 0.03 mg of ethinyl estradiol and 0.10 mg levonorgestrel) (N=48) for a period ranged between 3 months to 6 years and these were considered the users group. Other 40 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) were obtained from COCPs users and non-user groups. The sera obtained from the blood samples were used for the estimation of serum TSH, FT₃, FT₄ using Menividus analytic device.

Results: This study revealed non significant differences in TSH, FT₃ and FT₄ serum levels between COCPs users and non users and no correlation between serum TSH, FT₃ and FT₄ levels and duration of hormonal contraceptives usage.

Conclusion: This study supported that the free thyroid hormone tests are the tests of choice in assessing thyroid function of women taking COCPs and concluded that COCPs can be regarded as a safe drugs in women using these types of hormonal as far as thyroid function is concerned.

الخلاصة

الخلفية: يوجد دراسات قليلة جدا لتقرير تأثير حبوب منع الحمل المشتركة على وظيفة الغدة الدرقية وعلى الأقل في منطقتنا.

الهدف: لتقييم تأثير حبوب منع الحمل المشتركة على مستوى مصل الدم للهرمون المحفز للغدة الدرقية (تي اس اج)، الثايرونين الثلاثي اليود الحر (اف تي ثري) والثايروكسين الحر (اف تي فور) وعلاقته بفترة

استخدامها في مدينة الموصل.
تصميم الدراسة: تصميم دراسة حالة.

الطرق المتبعة والأشخاص: اجريت هذه الدراسة بين الفترة من أيلول ٢٠٠٨ ولغاية آذار ٢٠٠٩ تم أخذ مجموع ٧٨ امرأة سليمة تتراوح أعمارهن بين (١٩ - ٣٥) سنة ممن كن يراجعن مركزي تنظيم الاسره في مستشفى البتول والخنساء في الموصل وممن يستعملن إما حبوب منع الحمل المشتركة "مايكروجينون" والتي تحتوي على أثينايل أسترادايول (٠,٠٣ ملغم) وليفونورجيستريل (٠,١٥ ملغم) وهو واحد من حبوب موانع الحمل الهرمونية الأحادية ومن الجيل الثاني (عددهن ٤٨) لفترة تتراوح بين ثلاثة أشهر إلى خمس سنوات ، هؤلاء النساء تم اعتبارهن " مجموعة مستعملي موانع الحمل الهرمونية " ومقارنتهن مع ٤٠ امرأة متزوجة سليمة أخرى من نفس الفئة العمرية والطول والوزن ممن لا يستعملن موانع الحمل الهرمونية وتم اعتبارهن كمجموعة ضبطت أو سيطرة. تم سحب دم بمقدار ٥ س من كلا المجموعتين تم استخدام عينات مصل الدم المأخوذ من نماذج الدم لقياس الفحوصات الكيمياوية بواسطة العدد اليدوية التجارية باستعمال جهاز المنى فايدز التحليلي. تم قياس ضغط الدم بوضعية الجلوس باستخدام المضغوط وتم حساب مقياس كثافة الجسم من قسمة الوزن (كغم) على مربع الطول (متر).

النتائج: أظهرت هذه الدراسة فرق غير مميز إحصائياً في مستوى مصل الدم للهرمون المحفز للغدة الدرقية (تي اس ا) ، الثايرونين الثلاثي اليود الحر (اف تي ثري) والثايروكسين الحر (اف تي فور) بين مستعملات حبوب منع الحمل المشتركة مقارنة بغير المستعملات وعدم وجود علاقة بين مستوى مصل الدم لهرمونات الغدة الدرقية (تي اس ا) ، (اف تي ثري) و (اف تي فور) وفترة استخدام موانع الحمل الهرمونية. **الاستنتاج:** هذه الدراسة دعمت أن اختبار الهرمونات الحرة لوظيفة الغدة الدرقية هو الاختبار الأفضل في تقييم وظيفة الغدة الدرقية لدى مستعملات حبوب منع الحمل المشتركة واستنتجت أن حبوب منع الحمل المشتركة تعتبر من الأدوية الأمينه بالنسبة لوظيفة الغدة الدرقية لدى مستعملات هذا النوع من موانع الحمل الهرمونية.

It has been reported that estrogen increase serum thyroxin-binding globulin (TBG) concentration because this hormone may enhances hepatic production of TBG¹ and decrease TBG clearance^{١,٢}, thus increasing serum total tetraiodothyronine (thyroxine) (TT_٤) and to a lesser extent total triiodothyronine (TT_٣)^{١,٣}. As a result, increased TT_٤ and TT_٣ are seen in states of excessive estrogen and/or progestin, such as pregnancy, hormonal replacement therapy (HRT) and oral contraceptives usage^{٤,٥}. This phenomenon may cause problems in clinical diagnoses when TT_٤ or TT_٣ is used for these patients.

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 COCPs^٦. They are the most effective, safe, reliable and popular form of reversible contraception^٧.

The results of a study done by Duijkers et al.^٨ on healthy women

aged ١٨-٤٠ years used either vaginal ring delivering ٠,٠١٥ mg ethinyl estradiol and ٠,١٢ mg of etonogestrel per day, or COCPs containing ٠,٠٣ mg ethinyl estradiol and ٠,١٥ mg levonorgestrel for six cycles, found that both the vaginal ring and the oral contraceptive have no clinically relevant effects on carbohydrate metabolism, adrenal or thyroid function tests.

Other study^٩ about the effects of sex-steroid administration on the pituitary-thyroid axis in trans sexuals, concluded that estrogens do not affect T_٣/T_٤ ratio, irrespective of the route of administration. Whereas Shifren et al.^{١٠} suggested that in comparison with COCPs, transdermal route exerted minimal effects on the total and free concentrations of T_٤, T_٣ and their binding proteins. In contrast to what would be expected theoretically the study done by Grüning et al.^{١١} found that FT_٣ values decreased significantly during COCPs usage while TSH and TT_٤ were unaffected.

In a recent cohort study done by Sängner et al.^{١٢} in ٥٩ women ingested

this monophasic COCPs for 13 cycles, the serum concentrations of TBG were elevated by about 60% , likewise, an increase in TT₃ and TT₄

The aim of this study is to assess the effect of COCPs Microgynon (0.03 mg Ethinylestradiol (EE) and 0.02 mg Levonorgestrel (LNG)) on thyroid function tests (TSH, FT₄ and FT₃), and in relation to the duration of use by these hormonal contraceptive users in comparison to non users aged matched women as control.

Subjects and Methods

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 September 2008 to March 2009. This study included 48 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 19-30 years old and their body mass index (BMI) < 30. 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 (COCPs), called Microgynon (Schering, Germany). Each tablet contains 0.03 mg Ethinylestradiol (EE) and 0.02 mg Levonorgestrel (LNG) for more than 3 months.

The non-users group included 40 women, from those, attending Al-Batool Family Planning Center, women works at Colleges of Medicine and Pharmacy,

by 30-40%, but non significant changes in free T₄ were found.

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 blood was allowed to clot in a plain tube at room temperature and then the serum was separated by centrifugation at 3000 rpm for 10 minutes and then kept frozen at -20°C to be analyzed thereafter. Serum TSH, FT₄ and FT₃ were measured, using the ELFA technique (enzyme linked fluorescent assay), and TSH, FT₄ and FT₃ kits (Ref. 30, 31 and 32 respectively) from biomerieux, France were used.

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. $P < 0.05$ was

considered to be statistically significant.

The approval of the study protocol by an ethic committee has Health and College of Medicine, University of Mosul, Iraq.

Results

A total number of 48 women who used COCPs were included in this study, with mean age ± SD of 30.56±3.50, those have been considered to represent the exposed (COCPs users) group. Another 50 women with mean age ± SD of

been obtained from the Local Health Committee, Ministry of

29.0±3.0 years, 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.

No significant differences between the mean serum TSH, FT3 and FT4 levels in the COCPs users compared with the non users (Table 1)

Table 1: Comparison between mean serum levels of measured thyroid hormones of COCPs users and non-user groups

Parameters	Mean±SD		P-Value
	COCPs Users (n=48)	Non-Users (n=50)	
FT3 (Pmol/L)	4.74±0.90	4.68±0.81	NS
FT4 (Pmol/L)	11.64±1.03	11.83±1.70	NS
TSH (Pmol/L)	1.74±0.94	1.71±0.82	NS

No significant differences in the mean serum TSH, FT3 and FT4 levels among COCPs users group according

to duration of use has been demonstrated in Table 1.

Table 2: comparison between mean serum levels of measured thyroid hormones among COCPs users group according to duration of use

Parameters	(Mean ± SD) (n=48)			F-value	P-value
	COCPs Users ≤ 1yr (n=17)	COCPs Users 1<yr<2yr (n=20)	COCPs Users ≥ 2yr (n=11)		
FT ³ (Pmol/L)	4.67±0.09	4.73±0.97	4.70±0.40	0.049	NS
FT ⁴ (Pmol/L)	11.03±1.00	11.69±1.02	11.60±1.78	0.092	NS
TSH(Pmol/L)	1.67±0.9	1.79±0.82	1.72±0.07	0.183	NS

Discussion

The hormonal contraceptive used in this study was "Microgynon" tablets, which is one of the monophasic, second generation COCPs (0.02 mg ethinly estradiol and 0.10 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 pills¹⁷. Also, in another study done in Mosul City¹⁸, 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 users¹⁸.

Since the introduction of hormonal contraceptives in the early 1960s, repeated attention has been focused on possible beneficial and harmful side effects¹⁹. Among the possible impact, the relation between

hormonal contraceptive use and thyroid function tests has been studied but the results of these studies, however, have been equivocal. This study found that there were no significant changes in the mean serum levels of TSH, FT³ and FT⁴ among COCPs users in comparison to the non-users, which is in agreement with many studies^{8,12,16}, who found no significant differences in thyroid parameters in women taking COCPs containing ethinly estradiol and levonorgestrel in comparison to the control. In a recent cohort study done by Sanger *et al.*,¹⁹ in 29 women ingested this monophasic COCPs for 12 cycles, the serum concentrations of TBG were elevated by about 60% , likewise, an increase in TT³ and TT⁴ by 30-40%, but non significant changes in free T⁴ were found.

Other two studies^{19,18} in agreement with our results and

concerning thyroid reference levels, concluded that the use of oral contraceptives was a significant predictor for variation in TT^{ξ} and TT^{ν} concentrations due to estrogen-evaluation of thyroid diseases owing to their capacity to modulate the limits of thyroid hormone distinct reference intervals.

The present study showed no correlation between serum TSH, FT^{ν} and FT^{ξ} levels and duration of hormonal contraceptive usage which indicates that the effects of contraceptives on thyroid tests is time independent. In line with this, Sanger *et al.*,¹¹ observed that during hormonal contraceptive usage, a steady state in the effects on thyroid hormones and androgen parameters was reached within 3 months and that the changes in the various hormonal parameters did not substantially differ between conventional and extended-cycle regimen.

In the present study, the free hormones (FT^{ν} & FT^{ξ}) were evaluated instead of the routinely measured total forms (TT^{ν} & TT^{ξ}) in Iraq, since total test is a measure of bound and free hormone, and the change in the level of thyroid hormone binding protein, as in subjects using oral contraceptives, produce corresponding changes in the total T^{ξ} , even though levels of physiologically active free T^{ξ} are unchanged^{1,5,19}; thus a patient may be physiologically normal but has an abnormal total serum hormonal level. So, FT^{ν} and FT^{ξ} in the serum can be measured directly, avoiding the hazard of interpreting total levels^{11,21}. Furthermore, because the free rather than bound thyroid hormone is subjected to homeostatic control by the hypothalamic-pituitary-thyroid axis²², estimation of free thyroid hormone

mediated TBG-induced hepatic synthesis, where as FT^{ξ} and FT^{ν} were insignificantly affected and that the use of contraceptives should be considered in diagnostic concentrations are theoretically preferable to TT^{ξ} and TT^{ν} tests, indicating that free serum thyroxine is the test of choice in assessing the functional thyroid status of women taking oral COCPs or HRT^{2,23}.

In conclusion, COCPs can be regarded as a safe drugs in women using these hormonal contraceptives as far as thyroid function is concerned and the use of free thyroid hormone tests should be followed instead of measuring the total thyroid hormone in assessing thyroid function of women taking hormonal contraceptives.

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