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 ٢٠٠٢ to March ٢٠٠٣. A total of ٨٧ healthy married women, age range between ٩١-٥٣ 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 ٠.٣٠ mg of ethinyl estradiol and ٠.٥١ mg levonorgestrel) (N=٨٥) for a period ranged between ٣ months to ٦ years and these were considered the users group. Other ٤٠ 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 (٥ml) 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.
It has been reported that estrogen increase serum thyroxin-binding globulin (TBG) concentration because this hormone may enhances hepatic production of TBG\(^1\) and decrease TBG clearance \(^1\), thus increasing serum total tetraiodothyronine (thyroxine) (TT\(_4\)) and to a lesser extent total triiodothyronine (TT\(_3\)) \(^2\). As a result, increased TT\(_4\) and TT\(_3\) are seen in states of excessive estrogen and/or progestin, such as pregnancy, hormonal replacement therapy (HRT) and oral contraceptives usage \(^3\). This phenomenon may cause problems in clinical diagnoses when TT\(_4\) or TT\(_3\) 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 \(^4\). They are the most effective, safe, reliable and popular form of reversible contraception.

The results of a study done by Duijkers et al. \(^5\) on healthy women aged 18-40 years used either vaginal ring delivering 0.15 mg ethinyl estradiol and 0.12 mg of etonogestrel per day, or COCPs containing 0.03 mg ethinyl estradiol and 0.15 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\(^6\) about the effects of sex-steroid administration on the pituitary-thyroid axis in trans sexuals, concluded that estrogens do not affect T\(_3\)/T\(_4\) ratio, irrespective of the route of administration. Whereas Shifren et al. \(^7\) suggested that in comparison with COCPs, transdermal route exerted minimal effects on the total and free concentrations of T\(_4\), T\(_3\) and their binding proteins. In contrast to what would be expected theoretically the study done by Grüning et al., \(^8\) found that FT\(_3\) values decreased significantly during COCPs usage while TSH and TT\(_4\) were unaffected.

In a recent cohort study done by Sänger et al. \(^9\) in \(5^\) women ingested
this monophasic COCPs for \( \text{\textdegree} \) cycles, the serum concentrations of TBG were elevated by about \( 56\% \), likewise, an increase in \( \text{TT}^3 \) and \( \text{TT}^4 \) by \( \eta \)-\% by \( \eta \)-\% but non-significant changes in free \( \text{F}^4 \) were found.

The aim of this study is to assess the effect of COCPs Microgynon (\( 0.30\text{mg} \) Ethinylestradiol (EE) and \( 0.051\text{mg} \) Levonorgestrel (LNG)) on thyroid function tests (TSH, \( \text{FT}^4 \) and \( \text{FT}^3 \)), 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 \( 2002 \) to March \( 2004 \). This study included \( 84 \) 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 \( 19-50 \) years old and their body mass index (BMI)< \( 35 \). 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 \( 0.3 \text{mg} \) Ethinylestradiol (EE) and \( 0.05 \text{mg} \) Levonorgestrel (LNG) for more than \( 3 \) months.

The non-users group included \( 4 \) 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 blood was allowed to clot in a plain tube at room temperature and then the serum was separated by centrifugation at \( 1000 \text{ rpm} \) for \( 15 \) minutes and then kept frozen at \( -20\text{C} \) to be analyzed thereafter.

Serum TSH, \( \text{FT}^4 \) and \( \text{FT}^3 \) were measured, using the ELFA technique (enzyme linked fluorescent assay), and TSH, \( \text{FT}^4 \) and \( \text{FT}^3 \) kits (Ref. \( 03004 \), \( 03104 \) and \( 03204 \) 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 been obtained from the Local Health Committee, Ministry of Health and College of Medicine, University of Mosul, Iraq.

Results
A total number of 84 women who used COCPs were included in this study, with mean age ± SD of 39.9±4.9 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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean±SD</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COCPs Users (n=84)</td>
<td>Non-Users (n=41)</td>
</tr>
<tr>
<td>FT₃ (Pmol/L)</td>
<td>4.74±0.9</td>
<td>4.8±0.8</td>
</tr>
<tr>
<td>FT₄ (Pmol/L)</td>
<td>11.44±1.53</td>
<td>11.9±1.75</td>
</tr>
<tr>
<td>TSH (Pmol/L)</td>
<td>1.74±0.92</td>
<td>1.7±0.82</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>(Mean ± SD) (n=٨٤)</th>
<th>F-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COCPs Users</td>
<td>COCPs Users</td>
<td>COCPs Users</td>
<td></td>
</tr>
<tr>
<td>≤ ٥ yr (n=٦)</td>
<td>&gt;٥&lt;٥ yr (n=٥٢)</td>
<td>≥ ٥ yr (n=٧١)</td>
<td></td>
</tr>
<tr>
<td>FT٣(Pmol/L)</td>
<td>٤.٤١±٠.٩٩</td>
<td>٤.٧٥±٠.٩٧</td>
<td>٤.٧١±٠.٩٨</td>
</tr>
<tr>
<td>FT٤(Pmol/L)</td>
<td>١١.٥٣±١.٨٠</td>
<td>١١.٧٩±١.٨٢</td>
<td>١١.٨٠±١.٨٠</td>
</tr>
<tr>
<td>TSH(Pmol/L)</td>
<td>١.٧٧±٠.٣٤</td>
<td>١.٧٩±٠.٣٣</td>
<td>١.٧٢±٠.٣٣</td>
</tr>
</tbody>
</table>

Discussion

The hormonal contraceptive used in this study was "Microgynon" tablets, which is one of the monophasic, second generation COCPs (٠.٣٠ mg ethinly estradiol and ٠.٥١ 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 ٦٣% of current users use oral pills٤. Moreover, in another study done in Mosul City٣، found that the most common type of contraceptive methods used was the oral pills, (٤٦.٢%) (including COCPs in ٦٧.١% and progesterone only pills (POPs) in ٦٦.٧%) of the users٧.

Since the introduction of hormonal contraceptives in the early٦٩، repeated attention has been focused on possible beneficial and harmful side effects٨. 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, FT٣ and FT٤ among COCPs users in comparison to the non-users, which is in agreement with many studies٨،٩، 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 Sänger et al.، in ظ٩ women ingested this monophasic COCPs for ٣١ cycles, the serum concentrations of TBG were elevated by about ٥٦%، likewise, an increase in TT٣ and TT٤ by ٠.٣-٠.٤%， but non significant changes in free T٤ were found.

Other two studies٩، 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\textsubscript{4} and TT\textsubscript{3} concentrations due to estrogen-mediated TBG-induced hepatic synthesis, whereas FT\textsubscript{4} and FT\textsubscript{3} were insignificantly affected and that the use of contraceptives should be considered in diagnostic concentrations are theoretically preferable to TT\textsubscript{4} and TT\textsubscript{3} tests, indicating that free serum thyroxin is the test of choice in assessing the functional thyroid status of women taking oral COCPs or HRT. In conclusion, COCPs can be regarded as a safe drug 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.

References

1. Sandy HJ, Cheng WC, Jang MW, Tsai KS. Effects of long-term use of raloxifene, a selective estrogen receptor modulator, on thyroid function test profiles. Am Assocat Clin Chem \(1002\); \(74\): \(5681\) - \(5686\).


3. Muller AF, Verhoeff A, Mantel MJ, De Jong FH, Berghout A. Decrease of free thyroxine levels after controlled ovarian hyperstimulation. J Clin Endocrinol Metab \(1891\); \(6\) (\(4\)): \(861\) - \(867\).

4. Swanson MA, Custer TR, Suey CM. Free thyroxine and free thyroxine index in women taking oral contraceptives. Clin Nucl Med \(1981\); \(6\) (\(1\)): \(38\) - \(41\).

5. Nelson JC, Yoo EW, Wilcox RB. Accuracy issues in free thyroxine...
testing methods Semin Perinatol 10;5:93-9.


Thesis in Community Medicine, College of Medicine, University of Mosul.