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Comparison of TSH between Combined Oral Contraceptive Pill Users and Non-user Women: A Cross-sectional Study

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Abstract

Background: *Normal thyroid function is mandatory for healthy life. Normally there is a fine balance between the free and bound thyroxine in the body that can be altered by combined oral contraceptive pill which contain estrogen and progesterone. And this alteration is clearly assessed by thyroid stimulating hormone (TSH).* ***Objectives:*** *The aim of this study was to estimate and compare the thyroid-stimulating hormone (TSH) among the oral contraceptive pill users and non-user women in Rajshahi City.* ***Methods:*** *This cross-sectional comparative study was carried out from January 2022 to December 2022 in the Department of Physiology, Rajshahi Medical College, Rajshahi. The study was conducted on 120 married women aged 18-40 years. Among them 60 women were combined oral contraceptive pill users and 60 women were COCP non-users. TSH parameter was estimated using the auto analyzer machine. Data were analyzed by SPSS software, version 24 and p value < 0.05 was considered statistically significant for all tests.* ***Results:*** *The mean age of COCP user women was 30.22 ± 7.30 years and the COCP non-user women was 32.63 ± 7.81 years. COCP user women with mean BMI 26.57 ± 2.94 kg/m2 compared with COCP non-users with BMI of 24.54 ± 2.67 kg/m2. The mean TSH value in COCP user women was found 1.92 ± 0.83 µIU/ml and in COCP non-user women was 1.50 ± 0.76 µIU/ml and it was statistically significant ($p < 0.01$).* ***Conclusion:*** *The present study had showed an increased level of TSH in combined oral contraceptive pill user women group than COCP non-users group. Present study findings indicated the tendency to develop subclinical hypothyroidism among COCP users. Routine monitoring of thyroid function status is a time demanding issue as widespread use of combined oral contraceptive now-a-days. Early detection of hypothyroidism might reduce complications and give women a healthy life.*

Keywords: *Combined oral contraceptive pill, Thyroid stimulating hormone.*

Introduction

In 2022, Bangladesh was the eighth most populous country in the world, with an estimated population of 167 million. Bangladeshi population is equivalent to 2.11% of the total world population. The country's population density, roughly 1,265 people per square kilometer, is also one of the highest in the world (1). About 40% of the total population is under the age of 15 and about 50% of the population is within reproductive age. Bangladesh cannot achieve sustainable development without continued efforts to curb population growth. It is a positive issue that choice of contraceptive methods has considerably increased over recent years in Bangladesh. Now contraceptive prevalence rate (CPR) is 62% that was only 8% in 1975 (2). Oral pill is the most widely used (27%) method, followed by injectables (12.4%), condoms (6.4%), female sterilization (4.6%), male sterilization (1.2%), implants (1.7%) and IUDs (0.6%) (2). As the most common form of effective and reversible contraception, the prevalence of use of birth control pills among women aged 15–45 is 17% and 27.3% among all methods of contraception in the Bangladesh (2). Moreover, use of birth control pills declined as age increased: 54% of users of contraceptives are under 20 years old, 35% are 20–40 years old and only 11% are 40–45 years old (3).

Among birth control pill combined oral contraceptive pill (OCP) is commonly used in Bangladesh due to free Government supply named as Sukhi from community clinic to tertiary level hospital. It was first designed to inhibit ovulation and thus used for birth control (4). Over time, combined OCP is used not only for prevention of unwanted pregnancies but also as treatment for abnormal uterine bleeding, endometriosis, menstrual and hormonal disorders etc. Additionally, long- term use of combined OCP (≥10 years) could significantly decrease the risk of ovarian and endometrial cancer (5).

However, COCP can also bring many adverse effects including increased risk of hypertension, thromboembolic events, breast cancer, serious autoimmune diseases and especially endocrine related dysfunctions (6,7). Among endocrine dysfunctions, thyroid disorders are important. The thyroid gland produces hormones–predominantly the prohormone T4 and a small amount of the bioactive hormone T3 that play a role in normal growth, energy metabolism and reproduction (8,9). Most T3 is produced by deiodination of T4 in peripheral tissues through the action of deiodinases. Thyroid secretion is controlled primarily by thyroid stimulating hormone (TSH) secreted by anterior pituitary gland. The effects of thyroid hormones depend on the amount of hormone that reaches the tissues, their activation and the availability of specific hormone receptors in the nucleus and cytoplasm of the cells. Under normal conditions, the levels of free thyroid hormones are adjusted by appropriate stimulation or suppression of hormone secretion and elimination mechanisms. The total serum concentration is usually maintained at a level proportional to the thyroid-binding globulin (TBG) concentration and appropriate to maintain a constant level of the free form of the hormone (10,11). In combined oral contraceptive pill, there are two components oestrogen and progesterone. The proportions of these two components vary based on formulation time to time. The oestrogenic component of the OCP is capable of increasing various liver proteins such as thyroid binding globulin (TBG), sex hormone-binding protein (SHBG) and coagulation factors. As a result, increased TBG alter the delicate balance of free and bound thyroid hormone in our body because free T4 is bound to the increased TBG and there is less free T4 in our body for performing function. TBG has more affinity to T4 than T3 and represents over 70% of the total hormone bound to proteins (12). On the other hand, the role of progesterone is to modulate oestrogen-dependent effects mainly through their anti-androgenic action. As both progesterone and thyroid are members of the steroid hormone superfamily, they compete each other for binding with the receptors of steroid (13).

Therefore, in short time use of combined oral contraceptive pill, individuals develop subclinical

hypothyroidism and longtime use of combined OCP individuals develop hypothyroidism. Hypothyroidism refers to the common pathological condition of thyroid hormone deficiency. If untreated, it can lead to serious adverse health effects and ultimately death. Because of the large variation in clinical presentation and general absence of symptom specificity, the determination of hypothyroidism is pre-dominantly biochemical. Clinical manifestations of hypothyroidism range from no signs or symptoms to life threatening (14). Despite these plausible hypothetical relationships between the physiologies of the thyroid axis and combined oral contraceptive pill, there were few studies of thyroid function in relationship to exogenous oestrogen and progesterone. In Bangladesh, there were few studies regarding relationship between the thyroid function and combined oral contraceptive pill use. Therefore, this study might be useful to generate new data on effect of combined oral contraceptive pill on TSH in our population.……

Materials and Methods

This cross-sectional type of comparative study was conducted in the Department of Physiology, Rajshahi Medical College, Rajshahi from January 2022 to December 2022 to find out the association between combined oral contraceptive pill use and thyroid stimulating hormone level among the married women in Rajshahi City. The study population was married women aged 18 to 40 years in Rajshahi city. A purposive sampling technique was used and the final sample size was 120. 60 women aged 18 to 40 years under combined OCP were included in one group and similar numbers of women aged 18 to 40 years without under combined OCP were included in another group purposively. The selection was from neighbours, relatives and stuff who were resident of Rajshahi and women who were attend in Maternity and Child Welfare Centre of Rajshahi for services. Consulting with the guide and reviewing the previous published literature, the questionnaire was developed for the study. Prior to data collection, respondents were briefed about the purpose of the study and their informed written consent was taken. After taking informed written consent, complete history taking and physical examination were done and recorded in preformed data sheet. Then blood sample was obtained from median cubital vein in antecubital fossa making the subject to sit comfortably in a chair. Through a sterile DISPOVAN syringe under sterile precautions, about five milliliters of blood was collected in EDTA coated vacutainers. The sample was then analyzed for the TSH parameter by using auto-analyzing machine.

Results

The mean age of the COCP user women was 30.22 ± 7.30 years and the COCP non-user women was 32.63 ± 7.81 years (Table-01).

Table 1: Distribution of the respondents according to age (n=60 in each group).

Age in years	COCP user women	COCP non-user women
	Frequency (%)	
< 25 years	14 (23.30)	14 (23.30)
25-35 years	30 (50.00)	21 (35.00)
> 35 years	16 (26.70)	25 (41.70)
Total	60 (100.00)	60 (100.00)

$\overline{X}$±SD = 30.22 ± 7.30 years, range = (18 – 42) years in COCP user women.

$\overline{X}$±SD = 32.63 ± 7.81 years, range = (18 – 42) years in COCP non-user women.

The occupational status of the women revealed that among the COCP user women, majority (76.70%) of the respondents were housewife, 18.30% were NGO worker and only 5% were Govt. service holder. Similarly, in the COCP non-users group, majority (75%) of the women were housewife, 13.30% were NGO worker and remaining 11.70% were Govt. service holder. In both groups, housewife respondents were proportionately higher (Figure-I).

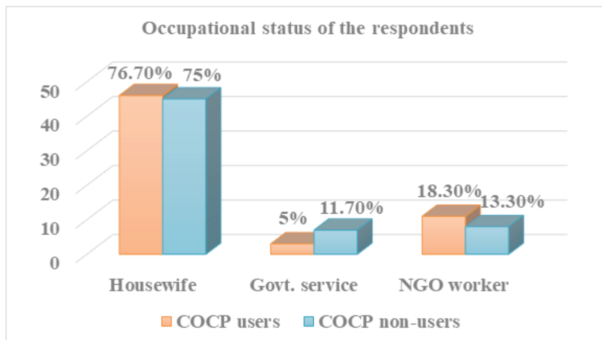

Fig I. Distribution of the respondents on the basis of occupational status (n=60 in each group).

The mean BMI of the COCP user women was 26.57 ± 2.94 kg/m^2 and the COCP non-user women was 24.54 ± 2.67 kg/m^2 (table-02).

Table 2: Distribution of individuals with a single abnormal lipid parameter (n=80)

BMI (kg/m^2)	COCP user women (n=60)	COCP non-user women (n=60)
	Frequency (%)	
Underweight (< 18.5)	0 (0.00)	4 (6.70)
Normal (18.5 to 24.9)	21 (35.00)	27 (45.00)
Overweight (25 to 29.9)	30 (50.00)	29 (48.30)
Obese (30 to 39.9)	9 (15.00)	0 (0.00)
Total	60 (100.00)	60 (100.00)

$\overline{X}$±SD = 26.57 ± 2.94 kg/m2 in COCP user women.

$\overline{X}$±SD = 24.54 ± 2.67 kg/m2 in COCP non-user women.

In COCP users group, 100% of the women had normal TSH and in the COCP non-users group, most (96.70%) of the women had normal and only 3.3% had low level of TSH (Table-03).

Table-03: Estimation of TSH in COCP users and non-user women (n=60 in each group).

Parameter	Group	Below the normal ranges	Normal ranges	Above the normal ranges
		Frequency (%)		
TSH	COCP users	0 (0)	60 (100)	0 (0)
	COCP non-users	2 (3.3)	58 (96.70)	0 (0)

TSH level in COCP user women was higher than the COCP non-user women and it was statistically significant (p < 0.01) (Table-04).

Table-04: Comparison of TSH level between COCP users and non-user women (n=60 in each group).

Group	TSH (µIU/ml) mean ± SD	TSH (µIU/ml) Range	t-value	p-value
COCP user women	1.92 ± 0.83	0.88 to 4.20	2.90	< 0.01
COCP non-user women	1.50 ± 0.76	0.09 to 3.50		

(Data were analyzed by **Unpaired t-Test** and were presented as **mean ± SD.** p value < 0.05 was considered as significant.)

There was statistically significant positive correlation between serum TSH level and duration of COCP use among pill user women (p < 0.001) (Figure-II).

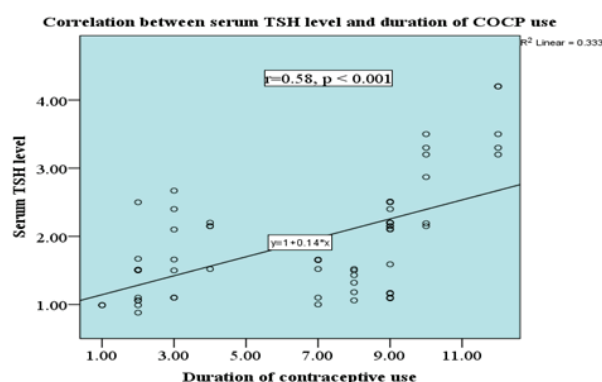

Fig II. Scatter diagram showing correlation between serum TSH level and duration of COCP use (n=60).

Discussion

The use of hormonal contraceptives is more common and has exponentially increased day by day. No substance used is without side effects, that is why it is necessary to know the possible side effects of combined oral contraceptive pill. Due to use of combined oral contraceptive pill that contain both estrogen and progesterone can alter that delicate balance of free and bound thyroid hormone in the body. The estrogen in birth control pills increases the amount of thyroid binding proteins that is available for binding of thyroid hormone. So, there is less functioning thyroid hormones in the body.

In the current study, among COCP users group, 50% of the respondents were overweight, 35% had BMI within the normal range and 15% were obese. On the other hand, in the COCP non-users group, 48.30% of the women were overweight, 45% women had BMI within the normal range and only 6.70% were underweight. The mean BMI of the COCP user women was 26.57 ± 2.94 kg/m^2 and the COCP non-user women was 24.54 ± 2.67 kg/m^2. These findings were not similar with a study done by Qiu et al (15). where in pill users group 35.90% had BMI within the normal range, 31.30% were obese, 28.40% were overweight and 4.40% were underweight. On the other hand, 40.30% of pill non-user women were obese, 28.80% were both overweight and normal weight and 2.10% were underweight. These dissimilarities might be due to food habit and life style varies in different geographical areas.

In the current study, serum TSH in COCP user women was 1.92 ± 0.83 µIU/ml and in non-user women was 1.50 ± 0.76 µIU/ml and it was statistically highly significant ($p < 0.01$). Similar findings were also found in a study that was done by Knudsen et al (16). in Denmark where serum TSH was 1·24 mU/l in non-users of oral contraceptive pill and 1·35 mU/l in users of pill and it was statistically significant ($p < 0·01$). Berair and Abdalla (17) in Sudan reported that TSH level in pill user women was 6.40 ± 1.46 mIU/L and in pill non-user women was 1.88 ± 0.87 mIU/L and it was statistically significant ($p < 0.05$) which findings were also in accordance with our study findings. Similar findings also found with the studies done by Weeke and Hansen (18), Kuhl et al. (19), Rumsey et al. (20), Zaninovich et al. (21) and Muller et al. (22). But findings were not similar with a study done by Al-Youzbaki and Mahmood (23) in Iraq where free TSH level in COCP user women was 1.74 ± 0.94 Pmol/L and in COCP non-user women was 1.71 ± 0.82 pmol/L and it was statistically non-significant ($p > 0.05$). High blood levels of estrogen signal the liver to increase the production of thyroid-binding globulin (TBG). This is an inhibitor protein that binds to the thyroid hormone, reducing the amount of free T3 and free T4 available for use by cells. In response, thyroid gland cranks up production of TSH to compensate for the deficit.

Contradictory findings were also found in the studies done by Duijkers et al. (24), Khalil (25) and Wiegratz et al. (26) where there were no statistically significant different of serum TSH level between COCP pill users and non-user women. Study to study

dissimilarities might be due to duration of contraceptive use which was not same among the women.

In this study, there was statistically significant positive correlation between serum TSH level and duration of COCP use among pill user women ($p < 0.001$). These findings were in accordance with a study done by Al-Youzbaki and Mahmood (23). But contradictory findings were found in a study done by Berair and Abdalla (17) where there was statistically non-significant positive correlation between serum TSH level and duration of COCP use. In the current study there was statistically non-significant positive correlation of total T3 & T4 level with duration of COCP use among pill user women ($p > 0.05$). Similar findings were found in a study done by Berair and Abdalla (17).

In the present study, OCP users showed non-significantly lower FT4, FT3 but significantly higher TSH level than the non-OCP users. It indicates a tendency to develop subclinical hypothyroidism among the OCP users. Consequently, regular screening of thyroid function is necessary among the OCP users.

So, the use of oral contraceptives is a predictor for variation in thyroid hormone concentrations due to estrogen mediated TBG-induced hepatic synthesis which is clearly understood by measuring TSH level. The use of contraceptives should be considered in diagnostic evaluation of thyroid diseases owing to their capacity to modulate the limits of thyroid hormone distinct reference intervals.

Conclusion

Present study concluded that long term OCP intake causes increased TSH level among the COCP users which is an indicator of a tendency to develop subclinical and clinical hypothyroidism.

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