Original Article

Menstrual Patterns of Reproductive Age Group Women and Their Association with Thyroid Dysfunctions

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ABSTRACT

Objective: This study was designed to evaluate the menstrual cycle patterns including cycle-specific characteristics and explore their relationship with thyroid hormones by measuring the levels of urine hormones in premenopausal women.

Study Design: Prospective Cohort Study

Place and Duration of Study: This study was conducted at the District Head Quarter Hospital Swabi from August 2021 to August 2022.

Materials and Methods: This prospective cohort study was conducted to evaluate the menstrual patterns and thyroid association among reproductive women. Data was collected by a pre-designed questionnaire and clinical diagnosis of thyroid performed by physicians. Menses were defined as two consecutive days of bleeding proceeding by three consecutive days of spoting. For monitoring, menstrual cycle patients were asked to submit their first urine void sample and kept their daily menstrual diaries for at least three menstrual cycles. We used univariate analysis for the distribution of each hormone. The log method was used to transform the TSH into a normal distribution. A linear mixed random effect model was used for those results reporting single outcomes.

Results: This study recruited 140 women with irregular menstrual patterns. Out of 140, a total of 52 cases of oligomenorrhea, 12 cases of neuropathic, 43 cases of polymenorrhagia, and 33 cases of menorrhagia were detected. These women reported a total of 423 cycles. We recruited cases between the age range of 18 to 45 years. A high association was observed between total T4 and Pd3G and E13G throughout the follicular and luteal phases. At various timeframes, we observed a high association of total and free T3 with high E13G concentrations. These T3 levels were also associated with Pd3G.

Conclusion: We observed that thyroid hormone levels were associated with several menstrual cycles. Across the menstrual cycle, a positive correlation between T4 and T3 indicates the effect of hormones on the female reproductive system.

Key Words: Menstrual cycle, Thyroid dysfunctions, Hormones

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INTRODUCTION

Menstrual cycle function plays an important role in reproductive health and fertility. The menstrual cycle is defined by the complex endocrine axis which is responsible for controlling ovaries and endometrium and represents the underlying hormonal milieu of the reproductive system of women. Therefore, the mestrual cycle is a major indicator of reproductive health and provides a pathway for epidemiologic research.[1,2]

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The Gonadotropins network and sex steroid hormones constitute the hypothalamic-pituitary-gonadal system. This system controls thyroid functions.[3] However, the association between thyroid functioning and female reproductive physiology is still debatable. The incidents of thyroid disorders are more prevalent in females than males. Thyroid disorders fluctuate the estrogen levels affect the menstrual patterns leading to menopause.[4] Incidents of menstrual disturbances are more highly reported in women suffering from hypothyroid and hyperthyroid than in euthyroid women.[5] Previous studies observed oligomenorrhea and menorrhagia in patients of hypothyroid whereas hypomenorrhea is highly reported in hyperthyroid women.[6-9] However, associations between thyroid disorders were found in clinical-based studies while very limited research reported an association with thyroid hormones. Furthermore, these studies were based on self-reported menstrual outcomes and integrated different outcomes as menstrual "disturbances" or "irregularities.[8,10] Therefore, the results of these studies are not strong enough to clarify the relationship between menstrual

patterns and thyroid functions. To fill this gap this study was designed to evaluate the menstrual cycle patterns including cycle-specific characteristics and explore their relationship with thyroid hormones by measuring the levels of urine hormones in premenopausal women.

MATERIALS AND METHODS

This prospective cohort study was conducted to evaluate the menstrual patterns and thyroid association among reproductive women in Gynaecology Department of DHQ sawabi hospital from August 2021 to August 2022. For this study, all the premenopausal women were eligible however, lactating or pregnant women were excluded. All the participants who were currently on thyroid medication were also excluded. Data was collected by a pre-designed questionnaire and clinical diagnosis of thyroid performed by physicians. This pre-designed questionnaire entailed information on thyroid medication used by participants and the menstrual cycle. Menses were defined as two consecutive days of bleeding proceeding by three consecutive days of spoting. For monitoring, menstrual cycle patients were asked to submit their first urine void sample and kept their daily menstrual diaries for at least three menstrual cycles.[11] Three menstrual cycles were defined as weeks for oligomenorrhea while diaries enlisted information about cramps, bleeding, stress, medication, and exercise habits. Urine samples were used to measure the estrogen and progesterone metabolites, estrone 3-glucuronide (E13G), and pregnanediol 3-glucuronide (Pd3G) within 17 days of the ovulation window. For measuring these parameters we used double-antibody time-resolved fluoroimmunoassays. At the research laboratory of our institution we analyzed the thyroid-stimulating hormone (TSH), total and free thyroxine (T4), and total and free triiodothyronine (T3) by using an immunoassay analyzer. For this purpose, the blind control method was used to strengthen the results. The self-reported bleeding intensity was measured by using a scale ranging from 0 to 4 grades throughout menses. We used the definition of Baird et al[12] for hormonal outcomes.

Statistical Analysis: All the data from the questionnaire and laboratory tests were transferred to the excel sheets for performing statistical analysis. We used univariate analysis for the distribution of each hormone. The log method was used to transform the TSH into a normal distribution. A linear mixed random effect model was used for those results reporting single outcomes. This linear effect model helps us in measuring individual correlations among multiple menstrual cycles per woman. We adjusted age and thyroid hormones as fixed effects for measuring the association between each thyroid and menstrual cycle outcomes. Coefficient Beta analysis was used for comparing the 3-day GM outcomes while the medium was treated as a reference because a previous study mentioned that both hypothyroid and hyperthyroid patients suffer from menstrual cycle disruption. An association between thyroid hormones and E13G and Pd3G was observed by fitting the linear mixed model. All these tests were performed by using the statistical package for Social Science (SPSS) version 23.0.

RESULTS

This study recruited 140 women with irregular menstrual patterns. Out of 140, a total of 52 cases of oligomenorrhea, 12 cases of neuropathic, 43 cases of polymenorrhagia and 33 cases of menorrhagia were detected. These women reported a total of 423 cycles. We recruited cases between the age range of 18 to 45 years. Women with experience of 1-2 (45%) pregnancies had high irregular menstrual patterns than others. We observed that 55.7% were obese, 63.5% never do any kind of exercise and 44.2% had moderate levels of stress. Detailed findings were presented in Table 1. In table 2, we presented different mean levels of total triiodothyronine, thyroxine, and Thyroid-stimulating hormone concerning the menstrual cycle, bleeding length, bleeding intensity, follicular phase length, and luteal phase. We observed that bleed length decreased with age obese women had longer cycles than others. We observed high FSH in women aged 41–54. No association of thyroid hormones was found with cycle length. However, we observed a significant association of free T4 levels with decreased cycle length. This association was observed due to variations in follicular phase length. No association of thyroid hormones was found between bleeding intensity while body mass index was independently associated (Table 2). Correlation Beta analysis was performed in table 3. A high association was observed between total T4 and Pd3G and E13G throughout the follicular and luteal phases. At various timeframes, we observed a high association of total and free T3 with high E13G concentrations. These T3 levels were also associated with Pd3G.

Table No.1: Characteristics of premenopausal women

	Total number of participants	Mean TSH (μIU/ml)	Mean Total T4 (μg/dl)
Age			
41-45	19 (13.5%)	1.56	9.7
36-40	40 (28.5%)	1.68	9.2
31-35	33 (23.5%)	1.6	9.33
26-30	28 (20%)	1.31	9.71

18-25	20 (14.2%)	1.41	8.26
Parity			
0 prior pregnancies	56 (40%)	1.29	8.6
1-2 prior pregnancies	64 (45.7%)	1.65	9.1
3 or more prior pregnancies	20 (14.2%)	1.54	9.2
Body Mass Index			
Normal	24 (17.1%)	1.59	8.8
Overweight	39 (27.8%)	1.41	9
Obese	78 (55.7%)	1.29	9.4
Weekly excercise			
0 times	89 (63.5%)	1.33	9.3
1-3 times	31 (22.1%)	1.59	8.78
> 3 times	20 (14.2%)	1.48	8.9
Stress			
Low	29 (20.7%)	1.52	8.9
Moderate	62 (44.2%)	1.41	8.35
High	49 (35%)	1.41	9.86

Table No.2: Clinical presentation of Thyroid hormones

	Mean Cycle length	Mean bleeding length	Mean bleeding intensity	Mean follicular phase length	Mean luteal phase length
Total tri-iodothyronine					
High	30.5	5.6	2.2	16.4	12.6
Medium	31	5.6	2.2	18.1	12.9
Low	29.1	5.7	2.3	17	13.4
Total thyroxine					
High	30	5.6	2.2	16.3	12.7
Medium	30.9	5.7	2.3	18.1	13
Low	30	5.6	2.2	16.3	13.1
Free triiodothyronine					
High	30.7	5.9	2.3	17.7	12.6
Medium	30.4	5.6	2.2	17.2	13.1
Low	29.6	5.4	2.2	16.6	13.2
Free thyroxine					
High	32.1	5.7	2.2	19	13
Medium	31.1	5.7	2.2	17.9	13
Low	28.2	5.5	2.3	15.4	12.9
Thyroid-stimulating hormone					
High	29.7	5.6	2.1	16.7	12.9
Medium	30.5	5.6	2.2	17.5	13
Low	30.4	5.7	2.3	17.5	12.9

Table No.3: Coefficient beta analysis

	FSH (mIU/mg Cr) in early follicular	FSH (mIU/mg Cr) in late luteal	Pd3G (µg/mg Cr) luteal phase	Pd3G (µg/mg Cr) in mid luteal phase	E13G (ng/mg Cr) in follicular phase	E13G (ng/mg Cr) in luteal phase
Total triiodothyronine						
High	-0.1 (-3.8, 3.6)	-0.6 (-3.9, 2.8)	1.0 (-1.6, 3.5)	1.2 (-1.0, 3.4)	9.2 (-1.5, 19.8)	6.6 (-1.3, 14.5)
Medium	7.5 (5.0, 10.0)	4.3 (2.1, 6.5)	9.8 (8.1, 11.5)	8.4 (6.9, 9.8)	35.5 (29.6, 41.5)	28.7 (23.4, 34.0)
Low	1.9 (-1.1, 4.8)	1.6 (-1.1, 4.2)	-0.8 (-3.1, 1.5)	-1.0 (-2.8, 0.7)	-2.9 (-10.5, 4.7)	-4.0 (-11.1, 3.1)
Total thyroxine						

High	1.0 (-1.4, 3.3)	0.7 (-1.3, 2.7)	2.2 (0.7, 3.8)	2.2 (1.0, 3.4)	7.4 (2.3, 12.4)	3.2 (-2.0, 8.4)
Medium	8.1 (6.0, 10.2)	4.8 (2.9, 6.6)	9.5 (8.1, 10.9)	7.9 (6.7, 9.0)	34.3 (29.4, 39.2)	28.5 (23.9, 33.2)
Low	-0.8 (-3.5, 1.8)	-0.9 (-3.3, 1.4)	-1.4 (-3.2, 0.4)	-0.9 (-2.3, 0.6)	-0.6 (-6.8, 5.5)	-0.9 (-7.1, 5.2)
Thyroid-stimulating hormone						
High	-0.7 (-3.1, 1.7)	-0.4 (-2.6, 1.7)	0.7 (-1.0, 2.4)	0.6 (-0.8, 2.0)	-3.5 (-9.0, 2.0)	-0.3 (-5.5, 5.0)
Medium	8.4 (6.4, 10.3)	4.9 (3.1, 6.6)	9.6 (8.2, 11.0)	8.2 (7.1, 9.4)	38.0 (32.7, 43.3)	30.1 (25.7, 34.4)
Low	0.2 (-1.3, 1.7)	0.0 (-1.4, 1.3)	-0.2 (-1.3, 0.8)	-0.2 (-1.1, 0.7)	1.0 (-5.0, 7.0)	-0.9 (-4.1, 2.4)

DISCUSSION

In this prospective cohort, thyroid hormones were examined to evaluate their effect on menstrual patterns. In this study, we found a positive association of high T4 with elevated levels of Pd3G and E13G throughout the menstrual cycle while low T4 levels were correlated with Pd3G, especially at the follicular phase. Meanwhile, several times during the menstrual cycle, we observed a positive correlation of total and free T3 with Pd3G and E13G levels. We observed that T4 was associated with the length of the menstrual cycle and similar findings were observed while adjusting the covariates. In the current study associations between cofounders and hyperthyroidism were observed in 3-day hormonal outcomes. Evaluation and interpretation of thyroid hormones and their association with menstrual cycle function are hard. However, many clinical studies observed menstrual disruption in women suffering from thyroid disorders. One of the studies observed elevated estrogen levels during pregnancy which leads to boosting total T4 due to thyroxine-binding globulin (TBG).[13]

In the current study, serum samples were collected before monitoring the menstrual cycle. These serum samples were used to measure the thyroid hormones so there is a great possibility that enhanced levels of pre-existing TBG increased the T4 concentration and resulted in a positive correlation of E13G and Pd3G. Therefore, we failed to produce meaningful results to explain the relationship. Comparing our results with International literature one previous study revealed high free T4 in the progesterone therapy group than in the placebo group.[14] This study observed a positive correlation between progesterone and thyroxine due to similar metabolic pathways. Both of these hormones are involved in maintaining basal temperature and energy expenditure. Albumin is the main carrier of both these hormones however, only 10% thyroxine was transported by albumin.[15] The positive correlation between T4 and E13G was observed in our study. These results are parallel to the previous studies which observed increased plasma estrogen levels in hyperthyroid women during their menstrual cycle.[16,17] One of the hypothesis claim that elevated T4 hormones also enhanced the sex hormones binding globulin.[5] These sex hormones enhanced estrogen levels and reduced clearance rates.[17] In hyperthyroid women, many studies reported increased amounts of androgen production and estrogens. Our study revealed similar results despite the variations in sample size as the study design. Similar levels of thyroid hormone and urinary estrogen metabolites were observed[18] but our study shows contradictory results when measuring plasma or serum estradiol concentrations.

Previous studies also reported the influence of behavior and environmental toxicants that affect thyroid functions. A disturbance in thyroid functions also menstrual cycles and the reproductive system.[19,20] However, in this study, BMI was not strongly associated with thyroid functions. In the current study, 89% of participants were exposed to persistent organic pollutants (PBB). These results were detected in their blood samples. These results indicate a direct and causal relationship between thyroid hormones and menstrual patterns when compared with other studies. This prospective cohort study monitored many menstrual cycles and has an edge over other self-reported studies. Observations over multiple cycles reduced the chances of misclassification and validate the results. However, our study has many limitations including a small sample size. In our study, we also observed two perimenopause cases. One of the women had a small menstrual cycle while one was amenorrhea however both these cases showed hormonal evidence of ovulation and eliminating both findings does not affect our overall results. We did not measure serum reproductive hormones. Our study was not able to detect the independent association of thyroid hormones due to low statistical power.

CONCLUSION

In conclusion, we observed that thyroid hormone levels were associated with several menstrual cycles. Across the menstrual cycle, a positive correlation between T4

and T3 indicates the effect of hormones on the female reproductive system.

Author's Contribution:

Concept & Design of Study:	Amina Bibi
Drafting:	Tabassum Ali, Tariq Mahmood
Data Analysis:	Tabassum Ali, Tariq Mahmood
Revisiting Critically:	Amina Bibi, Tabassum Ali, Sara Gul
Final Approval of version:	Amina Bibi

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Harlow SD, Ephross SA. Epidemiology of menstruation and its relevance to women's health. Epidemiologic Reviews 1995;17:265–286.
2. Small CM, Manatunga AK, Klein M, Feigelson HS, Dominguez CE, McChesney R, et al. Menstrual cycle characteristics: associations with fertility and spontaneous abortion. Epidemiol 2006; 17:52–60.
3. Dittrich R, Beckmann MW, Oppelt PG, Hoffmann I, Lotz L, Kuwert T, et al. Thyroid hormone receptors and reproduction. J Reproductive Immunol 2011;90:58–66.
4. Adlersberg MA, Burrow GN. Focus on primary care. Thyroid function and dysfunction in women. Obstetrical and Gynecological Survey 2002;57: S1–7.
5. Krassas GE, Pontikides N, Kaltsas T, Papadopoulou P, Batrinos M. Menstrual disturbances in thyrotoxicosis. Clin Endocrinol 1994;40:641–644.
6. Krassas GE, Pontikides N, Kaltsas T, Papadopoulou P, Paunkovic J, Paunkovic N, et al. Disturbances of menstruation in hypothyroidism. Clin Endocrinol 1999;50:655–659.
7. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocrine Reviews 2010;31:702–755.
8. Joshi JV, Bhandarkar SD, Chadha M, Balaiah D, Shah R. Menstrual irregularities and lactation failure may precede thyroid dysfunction or goitre. J Postgraduate Med 1993;39:137–141.
9. Thomas R, Reid RL. Thyroid disease and reproductive dysfunction: a review. Obstet Gynecol 1987;70:789–798.
10. Krassas GE. Thyroid disease and female reproduction. Fertility and Sterility 2000;74:1063–1070.
11. Jukic AM, Weinberg CR, Wilcox AJ, McConnaughey DR, Hornsby P, Baird DD. Accuracy of reporting of menstrual cycle length. Am J Epidemiol 2008;167:25–33.
12. Baird DD, Weinberg CR, Zhou HB, Kamel F, McConnaughey DR, Kesner JS, et al. Preimplantation urinary hormone profiles and the probability of conception in healthy women. Fertility and Sterility 1999;71:40–49.
13. Kaplan MM. Clinical perspectives in the diagnosis of thyroid disease. Clin Chem 1999;45:1377–1383.
14. Sathi P, Kalyan S, Hitchcock C, Pudek M, Prior J. Progesterone therapy increases free thyroxine levels—data from a randomized placebo-controlled 12-week hot flush trial. Clin Endocrinol 2013; 79:282–287.
15. Oppenheimer JH. Role of plasma proteins in the binding, distribution and metabolism of the thyroid hormones. New Engl J Med 1968;278:1153–1162.
16. Ridgway EC, Longcope C, Maloof F. Metabolic clearance and blood production rates of estradiol in hyperthyroidism. J Clin Endocrinol Metabolism 1975;41:491–497.
17. Akande EO, Hockaday TD. Plasma oestrogen and luteinizing hormone concentrations in thyrotoxic menstrual disturbance. Proceedings of the Royal Society of Med 1972;65:789–790.
18. Southren AL, Olivo J, Gordon GG, Vittek J, Brener J, Rafii F. The conversion of androgens to estrogens in hyperthyroidism. J Clin Endocrinol Metabolism 1974;38:207–214.
19. Zoeller TR. Environmental chemicals targeting thyroid. Hormones (Athens) 2010;9:28–40.
20. Asvold BO, Bjoro T, Nilsen TI, Vatten LJ. Tobacco smoking and thyroid function: a population-based study. Archives of Internal Med 2007;167:1428–1432.