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To Compare TSH, T3, T4 Levels in Patients with Menstrual Disturbances with Normal Healthy Fertile Females

Dr. Gurmanpreet[1], Dr. Hardeep Singh Gill[2*]

[1]Professor, Department of Biochemistry, M. M Institue of Medical Sciences and Research, Sadopur, Haryana, India
[2]Professor, General Surgery, M. M Institue of Medical Sciences and Research, Sadopur, Haryana, India

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***Corresponding author:** Dr. Hardeep Singh Gill
Professor, General Surgery, M. M Institue of Medical Sciences and Research, Sadopur, Haryana, India

Abstract **Original Research Article**

Thyroid disorders may influence reproductive performance in a variety of ways ranging from abnormal sexual development to menstrual irregularities to infertility. A close interplay exists between thyroid hormone and normal steroid action and secretion, which are necessary for normal ovarian function and thus fertility. In the present study, a total of 100 patients were studied. Out of these 100 patients, 50 patients were with a history of menstrual disturbances and 50 patients of reproductive age group with normal menstrual cycle and with proven fertility were taken as control. It is concluded from the present study that abnormal thyroid profile is associated with menstrual disturbances.

Keywords: Menstrual disturbances, Thyroid disorders, Infertility, hyperthyroidism, hypothyroidism, thyroxine, triidothyronine.

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INTRODUCTION

Infertility and sterility are synonymous terms meaning inability to conceive. The term sterility is usually used to depict the absolute state of inability to conceive. The incidence of infertility among women aged 15-44 years in India has increased slightly over the past 30 years reaching 10.2%. The prevalence of infertility is estimated at between 12-14% and has remained stable in recent years [1]. There is a general view that about 8-10% of married couples, of reasonable age, having normal sexual relationship, fails to produce children. Irregular menses, once thought to be of harmless occurrence, are no more considered to be benign. Normal menstrual cycles indicate on overall healthy reproductive system and its abnormalities require evaluation. Oligomenorrhea and amenorrhea generally means anovulation and causes infertility. Menstruation is dependent on the proper functioning of the chain made up of hypothalamus, pituitary, ovary and uterus. Pituitary hormones FSH, LH, PRL and thyroid hormones are required for the normal development of ova and need to be investigated in cases of chronic anovulation, oligmenorrhea and amenorrhea.

Thyroid hormones play an important role in fertility of females

Berson [2] reported that the synthesis of hormonally active materials by the thyroid gland proceed via a sequence of discrete reactions. They may be categorized as:

1. Active transport of iodide into the thyroid gland.
2. Oxidation of iodide and iodination of tyrosine residues by the oxidized iodide within thyroglobulin to yield hormonally inactive iodotyrosines.
3. Coupling of iodotyrosines form the hormonally active iodothyronins i.e. T_3 and T_4.

Larsen *et al*., [3] reported that thyroid hormones synthesized by thyroid gland are transported in serum bound to 3 proteins, thyroxine binding globulin (TBG), Transthyritin and albumin. Although TBG is present in low abundance in serum it has a high affinity for thyroid hormones and is responsible for transport of the majority of thyroxine (68%) and triidothyronine (80%).

The cause of infertility may vary from one geographic and social area to another. The major cause of infertility includes ovulatory dysfunction (15%), tubal and peritoneal pathology (35%), male factors (35%) and rest are unexplained causes (10%). Ovulatory dysfunction which accounts for 15% cases of infertility is based on hormonal events that characterize the normal ovulatory menstrual cycle. Infertility of each partner is a relative state and complex interaction between the

hormones ultimately determines the fertility potential of the couple [4].

Thyroid disorders may influence reproductive performance in a variety of ways ranging from abnormal sexual development to menstrual irregularities to infertility. A close interplay exists between thyroid hormone and normal steroid action and secretion, which are necessary for normal ovarian function and thus fertility. Thyroid problems, either too much thyroid hormones (hyperthyroidism) or too little (hypothyroidism) can interrupt cycles. Hypothyroidism can result in excess prolactin. Most women with hypothyroidism fail to produce eggs and they may be diagnosed as case of hypothyroidism for the first time during fertility evaluation.

Granner *et al*., [5] demonstrated that TSH is secreted in response to thyrotrophin releasing hormone (TRH), released from the hypothalamus. TSH release is primarily affected by TRH, which in turn is regulated by thyroid hormones T3 and T4. But TSH release is also inhibited by somatostatin. The most sensitive indicator of primary hypothyroidism is an elevated TSH level. They also reported that it is the beta subunit which determines the biological specificity of the heterodimer of TSH. TSH binds to the plasma membrane receptors and activates adenyl cyclase. The consequent increase of cAMP is responsible for thyroid hormone biosynthesis.

The rarity of pregnancy in hypothyroid women is generally explained by a high prevalence (>70%) of anovulation [6].

Pregnancy in women with hypothyroidism is considered extremely rare. Infertility rates are high in hypothyroid women and if they become pregnant the abortion rate is also high [7].

Singh *et al*., [8] found oligomenorrhea as the prominent menstrual abnormality. A large number of traditional investigations and bioassay of hormones have been practiced in the diagnosis of menstrual disorders and infertility for a long time. So by doing the thyroid profile (T3, T4 and TSH) in all the cases of menstrual disturbances, infertility and in repeated pregnancy losses will help in diagnosis and treatment in time.

Normal blood levels of thyroid hormone are essential for growth and development of tissues and for the maintenance of tissue and organ function. Changes of thyroid hormone levels can adversely affect fertility [9].

Bals-Pratsch *et al*., [10] established a relationship between thyroid dysfunction and sterility in women. In 118 infertile women endocrinological investigations and thyroid sonography was performed. In control group, containing 50 fertile females, same investigations were done. The incidence of biochemical immunological thyroiditis was not significantly different in study and control group. But thyroid volume was significantly higher. Goiter was diagnosed in 52% fertile females. Subclinical hypothyroidism (<12.5 mIu/ml) was found in 29 patients. During follow up of 12-24 months, 10 women with goiter conceived spontaneously after initiation of iodine or L-thyroxine treatment. This data supports that TSH levels are associated with infertility in women.

Arojoki *et al*., [11] studied hypothyroidism among infertile women in Finland. The main aim of study was to evaluate the occurrence of hypothyroidism with infertility. For this purpose the records of 335 women, presenting for the first time with infertility, were reviewed. Thyroid stimulating hormone levels, in conjugation with serum prolactin, were measured. In the TSH screening test 4% exhibited elevated serum TSH levels ranging from 5.7-32 mIu/L. The relative occurrence of abnormal TSH levels in infertile women, indicate a significant relation of Thyroid stimulating hormone with infertility.

AIM AND OBJECTIVE

To compare TSH, T3, T4 levels in patients with menstrual disturbances with normal healthy fertile females.

MATERIAL AND METHODS

The present study was conducted in the Department of Biochemistry in collaboration with Department of Obstetrics and Gynaecology, in our hospital. A total of 100 patients reporting to the OPD of Obstetrics and Gynaecology were studied.

Out of 100 patients, 50 patients were with a history of menstrual disturbances, 50 patients of reproductive age group with normal menstrual cycle and with proven fertility were taken as control.

A detailed history of the patients was taken in view to include all other factors of infertility (tubal factors, male factors, etc.) and a detailed history of menstrual disturbances was taken. Complete general physical examination with reference to breast development, distribution of hair and secondary sexual characters etc. was done. Informed consent was taken from every patient before including her in the study.

Routine investigations were carried out in all the patients:

Hemoglobin: Acid haematin method using Sahli's hemoglobinometer.
TLC: Thomas-Ziess haemocytometer with improved Neubar counting chamber.
DLC: Studying peripheral blood film stained with Leishmann stain.
Blood sugar: Asatoor and King Method **[12].**
Blood urea: Diacetyl Monocrome Method (DAM) method **[13]**

Serum: Jaffe Reaction (Method of Brod and Sirota, 1948)
Creatinine: Urine Complete Examination

Special investigations:
Specimen collection: 5 ml of blood taken under aseptic conditions from the patient and serum was separated by centrifugation.

T_3: The T_3 ELISA kit was used for quantitative measurement of T_3 in human serum as plasma [14].

Principle:
The T_3 is estimated by competitive enzyme immunoassay. The essential reagents required for a solid phase enzyme immunoassay include immobilized antibody, enzyme-antigen conjugate and native antigen. Upon mixing immobilized antibody, enzyme-antigen conjugate and a serum containing the native antigen, a competition reaction results between the native antigen and the enzyme-antigen conjugate for a limited number of insolubilized binding sites. After equilibrium is attained the antibody bound fraction is separated from unbound antigen by decantation or aspiration. The enzyme activity in the antibody bound fraction is inversely proportional to the native antigen concentration. By utilizing several different serum references of known antigen concentration, a dose response curve can be generated from which the antigen concentration of an unknown can be ascertained.

Contents of the kit and reagent preparation:

1.	Microwell plate:	1 microtitre plate 6 x 8 well strips coated with goat antimouse pAB.
2.	Enzyme conjugate:	Triodothyronine horse radish peroxidase conjugate.
3.	Assay reagent:	Buffer containing bottle
4.	Substrate solution:	TMB substrate
5.	Stop solution:	Contain sulphuric acid
6.	T_3 standards:	6 standards
7.	Concentrations:	0, 0.5, 1.0, 2.5, 5.0 and 10.0 ng/ml

Procedure:
1. 50 µl each of standard controls and samples were dispensed into the microtitre wells coated with goat-antimouse Ab.
2. 50 µl of assay reagent was added to each well.
3. Incubation was done for 30 minutes at room temperature.
4. 50 µl of enzyme conjugate was added to each well.
5. Incubation was done for 30 minutes at room temperature.
6. Reaction solution from all the wells was aspirated.
7. Washed with 300 µl of wash buffer and washing was repeated by draining the buffer completely five times.
8. 100 ml of TMB substrate was added to each well.
9. It was incubated for 10 minutes at room temperature.
10. 100 µl of stop solution was added to each well.
11. Absorbance of each well was read with ELISA reader at 450 nm against air.

Reference values:
The serum T3 reference values are 0.49-2.02 ng/ml.
T_4: The T_4 ELISA kit was used for quantitative measurement of T_4 in human serum or plasma [14].

Principle:
It is competitive enzyme immunoassay. Upon mixing immobilized antibody, enzyme-antigen conjugate and a serum containing the native antigen, a competition reaction results between the native antigen and the enzyme antigen conjugate for a limited number of antibody combining sites immobilized on the well. After equilibrium is attained the antibody bound fraction is separated from unbound antigen by decantation or aspiration. The enzyme activity in the antibody bound fraction is inversely proportional to the native antigen concentration. By utilizing several different serum references of known antigen concentration, a dose response curve can be generated from which the antigen concentration of an unknown can be ascertained.

Contents of the kit and reagent propagation:

1.	Microtitre plate:	1 microtitre plate 6 x 8 strips coated with antibody
2.	Enzymes conjugate:	Peroxidase enzyme conjugate
3.	Substrate solution:	TMB substrate
4.	Stop solution:	containing sulphuric acid
5.	T_4 standards:	6 standards
6.	Concentrations:	0, 25, 50, 100, 175 and 250 nmol/L

Procedure:
1. 10 µl each of standard control and samples were dispensed into the microtitre wells coated with antibody.
2. Incubation was done for 5 minutes at room temperature.
3. 100 µl of peroxidase conjugate was added into each well.

4. Incubation was done for 80 minutes at room temperature.
5. Reaction mixture from all the wells was aspirated.
6. Washed with 300 µl of wash buffer and washing was repeated by draining the buffer completely five times.
7. 100 µl of TMB substrate was added into each well.
8. It was incubated for 10 minutes at room temperature.
9. 100 µl of stop solution was added into each well.
10. Absorbance of each well was read with ELISA reader at 450 nm against air.

References values:

The serum T4 reference values are – 48-116 nmol/L.

TSH: The TSH ELISA kit was used for quantitative measurement of TSH in human serum or plasma **(14).**

Principle:

The TSH ELISA is a solid phase sandwich ELISA method. The samples and the anti-TSH-HRP conjugate are added to the wells coated with Mab to TSH beta subunit. TSH in the patient's serum binds to anti-TSH-Mab on the well and the anti-TSH second antibody then binds to TSH. Unbound protein and HRP conjugate are washed off by wash buffer. Upon the addition of the substrate the intensity of the colour is proportional to the concentration of TSH in the samples. A standard curve is prepared relating colour intensity to the concentration of the TSH.

Content of the Kit and Reagents preparation:

1. Microwell plate: 1 microtiter plate 6 x 8 well strips coated with anti-TSH-HRP conjugate.
2. Enzyme conjugate: Anti TSH-HRP conjugate.
3. Concentrated wash solution: Phosphate buffer.
4. Substrate solution: TMB substrate.
5. Stop solution: contain sulphuric acid.
6. TSH standards: 7 standards
7. Concentrations: 0, 0.2, 0.5, 2.5, 5.0, 10.0, 20.0 mIU/ml.

Procedure

1. 50 µl each of standard control and samples were dispensed into the microtiter wells coated with anti TSH-HRP conjugate.
2. 100 µl of enzyme conjugate was added to each well.
3. Incubation was done for 60 minutes at 37°C.
4. Reaction solution from all the wells was aspirated.
5. Washed with 300 µl of wash buffer and washing was repeated by draining the water completely six times.
6. 100 µl of TMB substrate was added to each well.
7. It was incubated for 20 minutes at room temperature.
8. 100 µl stop solution was added to each well.
9. Absorbance of each well was read against air with ELISA reader at 450 nm within 30 minutes.

Reference values

The serum TSH reference values are: 0.39-6.16 mIU/ml.

RESULTS

Table 1

Groups	No. of Patients
Control	50
Menstrual disturbances	50

The study was conducted on 100 patients attending the Outpatient Department of Obstetrics and Gynaecology. Control Group 1 comprised of 50 normally menstruating females between the age of 15-35 years Group II comprised of 50 patients of menstrual disturbances.

Table 2: Age Wise Distribution of Study and Control Group

Age (in years)	Menstrual Disturbances Group		Control Group	
	No. of cases	%age	No. of cases	%age
15-20	12	24%	7	14%
21-25	12	24%	19	38%
26-30	14	28%	14	28%
31-35	6	12%	10	20%
36-40	6	12%	0	0%
Total	50	100%	50	100%
Range				
Mean	25.86		25.98	
± SD	6.60		4.71	
't'	0.011			
'p'	0.09			
Significance	NS			

Table 2 shows that mean age of study group was 25.86 ± 6.60 years and of control group was 25.98 ± 4.71 years. Statistical analysis showed that there was no significant difference in age ($p > 0.05$). Hence both the groups were comparable.

Table 3: Routine Investigations In Study And Control Group

	Control			Menstrual Disturbances			't'	'p'	Sig.
	Range	Mean	± SD	Range	Mean	± SD			
Hb (gm%)	8-11.2	9.59	0.98	8.2-11.0	9.65	0.71	0.35	0.05	NS
TLC/ cumm	6500-10800	8613.40	1527.72	7600-10500	8983.0	1110.40	1.39	0.05	NS
N (%)	62-80	70.26	3.86	64-75	69.5	3.16	1.08	0.05	NS
L (%)	15-36	25.32	4.52	20-32	26.14	3.19	1.05	0.05	NS
M (%)	0-6	2.46	1.83	0-4	1.86	1.07	1.90	0.05	NS
B (%)	0-6	1.62	1.46	0-4	1.58	0.97	1.94	0.05	NS

In all 100 patients and 50 control, routine investigations were carried out as per Performa. Table 3 shows that both the groups were comparable. All routine investigations were within normal range.

Table 4: Routine Investigations in Study and Control Group

	Control			Menstrual Disturbances			't'	'p'	Sig.
	Range	Mean	± SD	Range	Mean	± SD			
FBS (mg%)	70-96	85.14	6.29	68-96	84.40	7.19	0.55	0.05	NS
Urea (mg%)	20-36	28.58	4.74	20-36	29.56	4.39	1.07	0.05	NS
Creatinine (mg%)	1.0-1.6	1.22	0.20	1.0-1.8	1.22	0.20	0.00	0.05	NS

In all 100 patients and 50 control, routine investigations were carried out as per Performa. Table 4 shows that both the groups were comparable. All routine investigations were within normal range.

Table 5: Comparison of T3 in Menstrual Disturbances and Control Group

Group	No. of Cases	Range (ng/ml)	Mean ± SD		't'	'p'	Sig.
Control	50	0.66-1.91	1.22	0.36	0.92	0.05	NS
M. Disturbances	50	0.25-2.62	1.31	0.60			

Table 5 show that mean levels of T3 in study group was 1.31 ± 0.60 ng/ml and that of control group it was 1.22 ± 0.36 ng/ml. Statistical analysis shows that the difference in values is non-significant in both the groups ($p > 0.05$).

Table 6: Comparison of T4 in Menstrual Disturbances and Control Group

Group	No. of Cases	Range (nmol/L)	Mean ± SD		't'	'p'	Sig.
Control	50	4.72-10.90	8.17	1.56	1.53	0.05	NS
M. Disturbances	50	3.01-14.68	7.62	2.00			

Table 6 shows that mean levels of T4 in study group was 7.62 ± 2.00 nmol/L and that of control group it was 8.17 ± 1.56 nmol/L ($p > 0.05$). On statistical analysis it was found that difference is non-significant in both the groups.

Table 7: Comparison of TSH in Menstrual Disturbances and Control Group

Group	No. of Cases	Range (mIU/ml)	Mean ± SD		't'	'p'	Sig.
Control	50	0.38-4.75	1.88	1.11	2.21	0.05	S
M. Disturbances	50	0.18-40.00	4.53	8.44			

Table 7 shows the mean levels of TSH in study group was 4.53 ± 8.44 mIU/ml while that of control group it was 1.88 ± 1.11 mIU/ml. Statistical analysis shows that difference in the mean values in study group was significant when compared with the control group ($p < 0.05$).

DISCUSSION

The reproduction is controlled by a interaction between gonadotrophins, steroid hormones and hypothalamic pituitary ovarian axis. An imbalance in any of these processes can result in menstrual disturbances.

The purpose of this study was to test the hypothesis which states that, endocrinal abnormalities are associated with menstrual disturbances.

In the present study, study group included total of 100 patients out of which 50 patients were with the

history of menstrual disturbances when normal menstrual cycle is defined as that with a length of 22 to 40 days and moderate bleeding for 3 to 7 days. 50 patients with same age group, normal menstrual cycles and with proven fertility were taken as control.

Age

In the present study, the mean age in menstrual disturbances group ranged between 15-40 years with a mean of 25.86 ± 6.60 years when compared with the mean age in the control group which was 15-35 years with mean of 25.98 ± 4.71 years. Both the groups were comparable in terms of age. The age group taken in present study was also comparable to the various studies done which are included in the review.

Routine Investigations:

Routine investigations like hemoglobin, TLC, DLC, blood urea, fasting blood sugar and serum creatinine were carried out in both the study group as well as the control group. All the routine investigations were within the normal range. Both the groups were comparable in terms of the routine investigations.

Body Mass Index (BMI)

Body Mass Index (BMI) was calculated in all the 100 cases. Maximum patients fell in the normal range 19-24.9 kg/m^2. Mean value of BMI in the menstrual disturbances group was 23.42 ± 2.25 kg/m^2 while in control group mean was 22.90 ± 1.83 kg/m^2. Statistical analysis showed that BMI values were non-significant in study group as compared to control group.

The menstrual pattern is influenced by thyroid hormones directly through impact on ovaries and indirectly through impact on SHBG, PRL, GnRH secretion and coagulation factors. Treating thyroid dysfunction can reverse menstrual disorders thus improving fertility. In fertile females, the prevalence of autoimmune thyroid disease (AITD) is significantly higher compared to parous age matched women [15].

A large number of traditional investigations and bioassays of hormones have been practiced in the diagnosis of menstrual disorders for a long time. Doing thyroid profile i.e T_3, T_4 and TSH, will help in diagnosis and treatment in time in all cases of menstrual disturbances [8].

The present study was performed to investigate the significance of thyroid profile i.e T_3, T_4 and TSH as a factor in menstrual disturbances. Similar studies have been performed by various other investigators.

Joshi and Bhandarkar [16] studied values of thyroid hormone in menstrual disturbances. He concluded that in women with menstrual irregularities in the perimenopausal age, if thyroid dysfunction is detected, pharmacotherapy may be a superior alternative to surgical interventions like hysterectomy.

Krassas *et al*., [17] investigated disturbances of menstruation in hypothyroidism. The conclusion of the study was that hypothyroidism in women is less frequently associated with menstrual disturbances than was previously described. Also, menstrual irregularities tend to be more frequent in severe hypothyroidism in comparison with mild cases, although this finding was not statistically significant.

Krassas *et al*., [18] studied thyroid disorders in females with menstrual disturbances. They concluded that in women of fertile age, hypothyroidism results in changes in cycle length and amount of bleeding that is oligomenorrhea, amenorrhea, polymenorrhea or menorrhagia. His study found 40 (23.4%) out of 171 hypothyroid female patients had irregular cycles.

Sharma and Parmar [19] made an attempt to evaluate the role of thyroid hormones T_3, T_4 and TSH in infertility and menstrual disturbances. They found that in women with primary sterility and menstrual disturbances although T_4 and TSH levels were within normal limits, the levels were higher as compared to normal women. T_3 concentrations were slightly lower in these women.

Poppe *et al*., [20] investigated the prevalence of subclinical hypothyroidism in women of infertile couples. They demonstrated that in infertile females thyroid abnormalities are significantly more frequent than in fertile controls.

The present study was performed to investigate the role of thyroid hormones in menstrual irregularities using endocrinal examination. Triidothyronine levels were measured in females with menstrual disturbances to see the incidence of hypothyriodism in them. In the study, T_3 levels ranged between 0.25-2.62 ng/ml with the mean of 1.31 ± 0.60 ng/ml in menstrual disturbances group while in that of control group the range was between 0.66 ± 1.91 ng/ml with the mean of 1.22 ± 0.36 ng/ml. On comparison the difference was insignificant.

The T_4 levels in the study ranged between 3.01-14.68 nmol/L with the mean value of 7.62 ± 2.00 nmol/L in menstrual disturbances group. While that of control, the range was between 4.72 – 10.90 nmol/L with the mean value of 8.17 ± 1.56 nmol/L. On comparison they were significantly decreased. So our study again emphasized on the fact that hypothyroidism is associated with reduced pregnancy rates which is consistent with most of the other studies already done.

In the study group, TSH levels ranged between 0.18-40.0 mIU/ml with the mean of 4.53 ± 8.44 mIU/ml while in that of control group the values ranged between 0.38-4.75 mIU/ml with the mean of 1.88 ± 1.11 mIU/ml. On comparison the levels were significantly increased. So our study again emphasized on the fact that hypothyroidism is associated with menstrual

disturbances which is consistent with most of other studies already done.

SUMMARY

The present study was conducted with an aim to test the hypothesis that deranged thyroid profile is associated with menstrual disturbances.

The study was carried out in our Hospital. Total 100 patients were taken. Out of 100, 50 patients were with a history of menstrual disturbances. Control included 50 patients, within reproductive age group with normal menstrual cycle and with proven fertility.

1. The mean age of study group i.e. menstrual disturbances group was 25.86 ± 6.60 years. Mean age of control group was 25.98 ± 4.71 years. Both the groups were comparable with control on the basis of age.
2. Routine investigations like Hb, TLC, DLC, blood urea, serum creatinine and fasting blood sugar were carried out in both the groups. All the investigations were within normal range and comparable in both groups.
3. Serum T_3 levels were measured in both the groups. Mean T_3 levels were 1.31 ± 0.60 ng/ml in menstrual disturbances group. When compared with the mean value of control group which was 1.22 ± 0.36 ng/ml, it was seen that T_3 levels were non-significant in patients with menstrual disturbances.
4. Serum T_4 (Thyroxine) levels were measured to know the effect of T_4 concentration on menstrual disturbances group. Mean values of T_4 were 7.62 ± 2.00 nmol/L in menstrual disturbances group. On comparison with the mean levels of T_4 in control group which were 8.17 ± 1.56 nmol/L, it was found that T_4 levels were non-significantly decreased in patients with menstrual disturbances.
5. Serum TSH levels were measured to see the effect of thyroid stimulating hormones on reproduction. TSH levels were significantly higher in study groups than in control group. Mean level of TSH were 4.53 ± 8.44mIU/ml in menstrual disturbances group. The control group having mean value of 1.88 ± 1.11mIU/ml. On comparison TSH levels were found to be significantly increased in the study group.

It is concluded from the present study that abnormal thyroid profile is associated with menstrual disturbances.

CONCLUSION

To conclude, our findings support the hypothesis that women with menstrual disturbances have disturbances in the hypothalmic-pituitary-ovarian axis compared with their fertile counterparts. So, abnormal thyroid profile plays a significant role in the etiology of menstrual disturbances.

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