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Original Article

Pharmacology Section

Effect of Hypothyroidism on Menstrual Cycle Pattern and Fertility at a Tertiary Care Centre in South India

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ABSTRACT

Introduction: Thyroid disorders are very common in females and are known to prevent ovulation. Thyroid disorders can impact menstrual cycles and causes menstrual irregularities and infertility in females.

Aim: To determine effects of hypothyroidism on menstrual cycle pattern and prevalence of subfertility among women having thyroid dysfunction.

Materials and Methods: This cross-sectional study was conducted in Department of Obstetrics and Gynaecology in collaboration with Department of Endocrinology in Government Medical College, Datia Madhya Pradesh, India from July 2019 to June 2021. A total of 205 patients aged 18-45 years were taken. Among them, 116 and 89 patients were of hypothyroid and euthyroid respectively. After properly selecting patients, detailed history of their menstrual cycles was taken and effect of thyroid dysfunction on menstrual irregularities was assessed. The collected data were evaluated and analyzed using Statistical Package of the Social Sciences (SPSS).

Results: A total of 205 patients participated in present study. Mean age was 35+/-5 years. Among 205 subjects, 116 were hypothyroid and 89 were euthyroid. Among the hypothyroid subjects, 72 (62.1%) had normal menstrual cycles, 23 (19.8%) had history of oligomenorrhea, 12 (10.3%) had polymenorrhea, and 9 (7.7%) had amenorrhea, while among the thyroid subjects, 76 (85.4%) had normal menstrual cycle, 6 (6.7%) had oligomenorrhea, 5 (5.6%) had polymenorrhea, and 2 (2.2%) had amenorrhea, with statistically significant differences ($p<0.001$). The proportions of primary 13 (11.2%) and secondary 9 (7.7%) subfertility were significantly higher among hypothyroid subjects compared with thyroid subjects ($p<0.05$). The prevalence of subfertility was 7 (7.8%), 10 (14.28%), and 12 (26.08%) among the thyroid, overtly hypothyroid, and subclinical hypothyroid subjects, respectively.

Conclusion: In this study, effects of thyroid dysfunction were presumably significant on menstrual cycle pattern and fertility; therefore, thyroid status should be assessed in all patients with menstrual disorders and appropriate treatment should be initiated early.

Keywords: Oligomenorrhea, Polymenorrhea, Subfertility

INTRODUCTION

Hypothyroidism is a commonly encountered clinical syndrome that results from the reduced secretion of Thyroxin (T4) and Tri-iodothyronine (T3) by the thyroid gland irrespective of the cause. The prevalence of hypothyroidism is 1/100 but increases to 5/100 if patients with subclinical hypothyroidism are included [1,2]. Many permanent or temporary conditions can reduce thyroid hormone secretion and cause hypothyroidism. About 95% of hypothyroidism cases occur because of problems that originate from the thyroid gland. In such cases, the disorder is referred to as primary hypothyroidism [3]. The most important causes of primary hypothyroidism are Hashimoto's thyroiditis, radioactive iodine treatment, thyroid surgery, medications and iodine deficiency. Less common causes are pituitary disorders, De Quatrain thyroiditis and pregnancy [4].

Thyroid disorders are common among women. Hypothyroidism is ten times more common in females than in males, which is particularly common in iron deficient areas [5]. Goiter and iodine deficiency disorders are common in India [6]. There are various changes in thyroid physiology in different phases of life in women [7]. These changes are considered to be responsible for variety of reproductive disorders in females ranging from menstrual irregularities to infertility [8]. Thus, these changes should be carefully understood in managing thyroid disorders in women. These changes are especially important during pregnancy and in postmenopausal women because the consequences of thyroid disease are quite different [9].

The prevalence of hypothyroidism among women of reproductive age (20-40 years) varies between 2% and 4% [8]. Several factors may affect the prevalence, such as age and dietary iodine intake [10]. The effect of hypothyroidism on menstrual cycle length and blood flow was known since 1950s [11]. Mild hypothyroidism, which manifests only as an elevated serum Thyroid Stimulating Hormone (TSH) concentration, can cause infertility by causing menorrhagia, an ovulatory cycles and luteal phase dysfunction. Menstrual abnormalities may precede clinical symptoms and signs of hypothyroidism. Hypothyroidism is often associated with ovulatory dysfunction due to variety of interactions between thyroid hormones and female reproductive system. Both hyperprolactinemia, due to increased thyrotrophic releasing hormone production, and altered pulsatile Gonadotropin Releasing Hormone (GNRH) secretion, leading to delayed luteinising hormone response and inadequate corpus luteum development, have been reported [12].

Hypothyroidism alone, without hyperprolactinemia, may directly interfere with normal hypothalamic pituitary ovarian function, and result in menstrual cycle dysfunction. In less severe forms of hypothyroidism, menorrhagia is common. Long standing or severe hypothyroidism, particularly if accompanied by hyperprolactinemia, is often associated with amenorrhea [13].

Timely management of thyroid dysfunction can cure the menstrual irregularities hence improves the fertility. In areas with iodine deficiency, approximately 10% of infertile women have mild hypothyroidism and approximately half become pregnant after starting thyroxin therapy [14]. Because of various implications of hypothyroidism on ovulatory function, screening is recommended for any women with ovulatory dysfunction. Infertility is a global health problem and hypothyroidism

is one of the reversible causes [15]. Thus far, no such study has been conducted in India. Hence present study aimed to determine the effects of thyroid dysfunction on menstrual cycle pattern and subfertility and the prevalence of subfertility among women of reproductive age with subclinical thyroid disease.

MATERIALS AND METHODS

This was a cross-sectional study conducted in Department of Obstetrics and Gynaecology in collaboration with Department of Endocrinology in Government Medical College, Datia, Madhya Pradesh, India. from July 2019 to June 2021. Study was done after getting approval from Institutional Ethics Committee with IEC no-ECR/662/Inst/OR/2019.

Inclusion criteria: Patient aged between 18-45 years with symptoms of thyroid dysfunction and abnormal thyroid hormone level, who were not on thyroxin replacement therapy and intrauterine contraceptive device were included. Person with normal thyroid hormone level were also included for comparison.

Exclusion criteria: Patient with palpable pelvic pathology or known thyroid disorders and patient on any medication like aspirin, heparin, steroids, lithium, and amiodarone were excluded from study.

Total 205 subjects were enrolled using simple random sampling and sample size was calculated based on Cochran formula ($n_0=Z^2pq/e^2$) in present study. These 205 subjects were divided into two groups:

Group 1: In present study 116 subjects with hypothyroidism were included in group 1.

Group 2: Total 89 subjects with euthyroidism were enrolled in group 2.

Euthyroidism is defined as normal thyroid hormone production and serum levels as mentioned below. Hypothyroidism is the condition in which thyroid hormones are deficient below the hormone reference value except TSH which increases in hypothyroidism [16]. Hormone reference values: TSH: 0.5 to 5.5 mIU/L, Free T3: 1.7 to 4.2 pg/mL, Free T4: 0.3 to 5.5 micro-IU/mL [17]. In the present study two types of hypothyroidism were observed-

Subclinical hypothyroidism: A mild form of hypothyroidism where the only abnormal hormone level is an increased TSH level.

Overt hypothyroidism: Clear hypothyroidism characterised by an increased TSH and a decreased T3 and T4 level.

Study Procedure

After properly selecting the patients, detailed menstrual history regarding abnormality (scanty, absence or increased) for more than three months and history of presence of any symptoms of thyroid dysfunction like fatigue, weight gain and palpitation for more than three months was taken. Abnormality in menstrual history was categorized into following subtypes: Polymenorrhea- menstruation interval lasting less than 21 days, Oligomenorrhea- menstruation interval of more than 35 days and Amenorrhea- an abnormal absence of menstruation [18].

Effects of hypothyroidism on menstrual pattern and fertility was determined by blood tests for thyroid levels, FSH, LH and prolactin level in blood and any pelvic pathology, IUD in ultrasonography.

Subfertility: Any form of reduced fertility with prolonged time of unwanted non-conception. Further divided into 2 types: Primary subfertility- any form or grade of reduced fertility in couples unsuccessfully trying to conceive without ever having had a live birth and Secondary subfertility- any form or grade of reduced fertility in couples unsuccessfully trying to conceive after previously having had a live birth [19].

STATISTICAL ANALYSIS

Collected data was evaluated and then processed using SPSS 26.0 version software (IBM Corp., Armonk, NY, USA). Unpaired T-test was used to compare both the groups.

RESULTS

A total of 205 patients participated in present study. Mean age was 35±5 years. Among 205 subjects, 116 were hypothyroid and 89 were euthyroid. Among the patients with hypothyroidism, 72 (62.1%) had normal menstrual cycles. However, 23 (19.8%) had history of oligomenorrhea, 12 (10.3%) had polymenorrhea, and 9 (7.7%) amenorrhea. On the other hand, among the euthyroid patients, 76 (85.4%) had normal menstrual cycles. Among them, 6 (6.7%) had oligomenorrhea, 5 (5.6%) had polymenorrhea, and 2 (2.2%) had amenorrhea. The proportion of abnormal menstrual history was found to be significantly high among the hypothyroid patients 44 (37.9%) compared to euthyroid patients 13 (14.6%) (p<0.001) [Table/Fig-1].

Variables	Group 1 (Hypothyroid, n=116) n (%)	Group 2 (Euthyroid, n=89) n (%)	Total (n=205) n (%)	p-value
Normal	72 (62.1%)	76 (85.4%)	148 (72.19%)	p<0.001 (Highly significant)
Abnormal menstruation	44 (37.9%)	13 (14.6%)	57 (27.8%)	
Polymenorrhea (Frequent menses, <21 days)	12 (10.3%)	5 (5.6%)	17 (8.3%)	
Oligomenorrhea (Scanty menses, >35 days)	23 (19.8%)	6 (6.7%)	29 (14.1%)	
Amenorrhea (Absence of menses)	9 (7.7%)	2 (2.2%)	11 (5.3%)	

[Table/Fig-1]: Percentage of abnormal menstrual pattern in thyroid and hypothyroid subjects.
Unpaired t-test; p<0.001 (highly significant), p<0.005 (significant), p>0.005 (not significant)

The proportions of primary 13 (11.2%) and secondary 9 (7.7%) subfertility were higher among group 1 patients compared to group 2 patients who showed proportions of primary and secondary subfertility of 2 (2.2%) and 5 (5.6%), respectively [Table/Fig-2].

Subfertility	Group 1 (Hypothyroid) (n=116) n (%)	Group 2 (Euthyroid) (n=89) n (%)	Total (n=205) n (%)	p-value
No subfertility	94 (81%)	82 (92.1%)	176 (85.9%)	p=0.004 (significant)
Primary subfertility	13 (11.2%)	2 (2.2%)	15 (7.3%)	
Secondary subfertility	9 (7.7%)	5 (5.6%)	14 (6.8%)	

[Table/Fig-2]: Number of subfertility cases among hypothyroid and euthyroid subjects.
Unpaired t test. p<0.001 (highly significant), p<0.005 (significant), p>0.005 (not significant)

In present study out of total 116 patients with hypothyroidism 70 had overt hypothyroidism and 46 had subclinical type of hypothyroidism. Subfertility was more in hypothyroid patients even in subclinical state compared to euthyroid patients. Subfertility was present in 7 (7.8%) among thyroid patients and in 10 (14.28%) among patients with overt hypothyroidism and 12 (26.08%) among patients with subclinical hypothyroidism. No subfertility was seen in 176 subjects with 82 (92.1%) normal thyroid status, 60 (85.7%) overt hypothyroidism and 34 (73.9%) subjects with subclinical thyroid status [Table/Fig-3].

	Thyroid status			
Subfertility	Normal (n=89) n (%)	Overt (n=70) n (%)	Subclinical (n=46) n (%)	Total (n=205) n (%)
No subfertility	82 (92.1)	60 (85.7)	34 (73.9)	176 (85.85)
Subfertility	7 (7.8)	10 (14.28)	12 (26.08)	29 (14.14)

[Table/Fig-3]: Number of subfertility cases among thyroid, overt, and subclinical-Hypothyroid subjects.

DISCUSSION

Out of 116 hypothyroid patients, 22 were found with subfertility and out of 89 euthyroid patients, 7 were found with subfertility. This shows that incidence of subfertility was more among hypothyroid patients. Proportions of primary 13 (11.2%) and secondary 9 (7.7%) subfertility were higher among patients with primary hypothyroidism compared to those with euthyroidism. Joshi JV et al. detected primary and secondary subfertility in 6.2% of overtly hypothyroid women [20]. Thyroid dysfunction is implicated in wide variety of reproductive disorders starting from menstrual irregularities to infertility [21].

Hypothyroidism in adult women often results in changes in cycle length and blood flow. In previous series, menorrhagia (increased blood flow) was the most prevalent symptom and occurred in 48 (60%) of women with overt hypothyroidism [22]. In India, Joshi JV et al. found 68.2% of menstrual abnormalities in hypothyroid women (15/22) compared with 12.2% of healthy controls (6/49) [20]. Menstrual abnormalities may precede clinical symptoms and signs of hypothyroidism. It was interesting to note presence of menstrual irregularities in 44% of euthyroid cases and this study shows abnormalities in menstrual cycle can occur even in euthyroid cases when it is associated with goiter. The most common manifestation was oligomenorrhea [12]. In a more recent study conducted by Krassas GE et al., the frequency of menstrual irregularities was 40 (23.4%) among 171 hypothyroid patients and was significantly higher than the 17 (8%) among 214 normal controls [23]. In the present study, the proportion of abnormal menstrual history was found to be significantly high among patients with hypothyroidism 44 (37.9%) compared to those with euthyroidism and goiter 13 (14.6%). Among the hypothyroid patients, 72 (62%) had normal menstrual cycles. However, 23 (19.8%) had history of oligomenorrhea, 12 (10.3%) had polymenorrhea, and 9 (7.7%) had amenorrhea. However, among the euthyroid patients, 76 (85.4%) had normal menstrual cycles. Among them 6 (6.7%) had oligomenorrhea, 5 (5.6%) had polymenorrhea, and 2 (2.2%) had amenorrhea. The proportion of abnormal menstrual flow was found to be high among the hypothyroid patients 30 (37.9%) compared to euthyroid patients 13 (14.6%). All these results correlate with the findings of the above studies [20,23]. Out of 116 hypothyroid patients, 22 were found with subfertility and out of 89 euthyroid patients, 7 were found with subfertility. This shows that incidence of subfertility is more among hypothyroid patients.

A study done by Kaur T et al., showed that out of 100 patients with menstrual irregularities, 14 had hypothyroidism [24]. A study done by Sharma N and Sharma A showed the presence of hypothyroidism in 22% patients of Dysfunctional Uterine Bleeding (DUB) and hyperthyroidism in 14% patients of DUB [25]. Study done by Pahwa S et al., showed presence of hypothyroidism in 22% of cases and study done by Padmaleela K et al., showed presence of thyroid disorders in 26.5% of dysfunctional uterine bleeding [26,27]. Gowri M et al.,in their study showed hypothyroidism in 17.6% of women with DUB and presence of subclinical hypothyroidism in 2.7% of women and presence of hyperthyroidism in 4.7% of women with menstrual irregularities. All these results are similar to present study [28].

Using thyrotrophic releasing hormone test, Bohnet HG et al. showed 11% of infertility is due to low functioning of thyroid [29]. Abalovich M et al., showed higher prevalence of subclinical hypothyroidism (13.9%) in 244 infertile women [30]. Lincoln SR et al., showed elevated TSH levels in 16 out of 704 infertile women [31]. These studies show us association of Subclinical Hypothyroidism (SCH) with infertility is not consistent. This can be explained by different cut-offs which are used to define upper limit of normal of TSH concentration in above mentioned studies [29-31].

Limitation(s)

Study was done at a single center involving 205 patients. Study should be done in more centers like a multicentric study involving many patients. Studies focusing on the association between subclinical hypothyroidism and subfertility were poorly controlled.

CONCLUSION(S)

In this study, the effects of hypothyroidism were significant on the menstrual cycle and subfertility; therefore, thyroid status should be assessed in all patients with menstrual disorders to avoid unnecessary interventions and to initiate appropriate treatment for early stage SCH in infertile women. Further research on this subject should be encouraged on many patients before drawing a definitive conclusion.

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