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Thyroid Disorders and Menstrual abnormalities: A Prospective Evaluation

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ABSTRACT

Introduction: Regular menstruation is an important health indicator in women. Menstrual abnormalities affect up to one third of women globally and are the major reason for gynaecological consultations worldwide [1,2]. Abnormal uterine bleeding (AUB) is an umbrella term that includes heavy, irregular, and intermenstrual bleeding and disorders of cycle length-those more or less frequent than the normal range of 24–38 days [1,3]. Menstrual disorders have profound impact on women's physical and psychological health with a negative effect quality of life [4,5].

Materials And Methods: Patients were considered as euthyroid if the thyroid stimulating hormone (TSH), T3, and T4 were within normal range (TSH- 0.25-5 ulu/ml, T3 - 0.617-1.623 ng/ml, T4 - 4.65-9.3 ug/ml). According to result of thyroid function tests (TFT), patients were labelled as hypothyroid, hyperthyroid or euthyroid. Hypothyroidism was diagnosed based on elevated thyroid-stimulating hormone (TSH) levels (>4.0 mIU/L) and/or reduced free thyroxine (T4) levels, in accordance with standard diagnostic criteria. Hyperthyroidism was defined as a TSH level below 0.4 mIU/L with elevated free T4 or free triiodothyronine (T3).

Results: All women from endocrinology OPD had thyroid abnormality. Out of 100 patients with irregular menstruation presenting in gynaecology OPD (Group B), 33% (n=33) had thyroid abnormality. 25% (n=25) had hypothyroidism and 8% (n=8) had hyperthyroidism). 67 (67%) women with irregular menstruation were euthyroid. In women with thyroid disorder (n=133) (group A=100 + group B=33), prevalence of menstrual abnormality (n=113/133) was 85.0%. In women with hypothyroidism (n=106), irregular menstruation was present in 84.9% women (n=90/106). In women with hyperthyroidism (n=27), irregular menstruation was present in 85.18% women (n=23/27). Normal menstrual cycles were observed in 20/133 (15%) women with thyroid disorders.

Conclusion: To conclude, our study reinforced some key fact about thyroid disorders and menstrual cycles. Physicians and endocrinologists must specifically enquire about menstrual pattern in women presenting to them with suspected thyroid disorders as they may not reveal this problem because of shyness, embarrassment, or cultural restraints. Gynaecologists should also maintain high index of suspicion for thyroid disorders in women presenting with irregular menstruation. It should also be remembered that menstrual abnormality may precede other symptoms of thyroid disorder. Essentially, both hypo- and hyper-thyroidism can lead to menstrual disturbances. Thyroid disorders are easily treatable with cost effective medications and can possibly alleviate the need for hormonal treatment and unnecessary surgical interventions for abnormal bleeding.

Keywords: Thyroid Disorders, Menstrual Irregularities, Abnormal Uterine Bleeding (AUB), Hypothyroidism, Hyperthyroidism.

INTRODUCTION

Regular menstruation is an important health indicator in women. Menstrual abnormalities affect up to one third of women globally and are the major reason for gynaecological consultations worldwide [1,2]. Abnormal uterine bleeding (AUB) is an umbrella term that includes heavy, irregular, and intermenstrual bleeding and disorders of cycle length-those more or less frequent than the normal range of 24–38 days [1,3]. Menstrual disorders have profound impact on women's physical and psychological health with a negative effect quality of life [4,5]. The causes of AUB are described by an acronym PALM-COEIN with each letter denoting cause- polyp, adenomyosis, malignancy (structural causes) and coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not otherwise classified (non-structural causes)[6]. Of these aetiologies, ovulatory dysfunction is one of the most common causes of irregular menstruation in women of reproductive age [7,8]. Ovulatory dysfunction is linked with endocrinopathies, such as polycystic ovarian syndrome (PCOS), hyperprolactinaemia, thyroid disorders as well as extremes of weight, mental stress and excessive exercise [9,10]. One of the major recognisable systemic causes of menstrual disorders is thyroid dysfunction. Thyroid hormones affect the function virtually every system in the body including reproductive system both sexes [11]. In India, thyroid disorders are among the most common endocrine disorders. Prevalence of hypothyroidism is higher in India (7-11%) compared to Western world (2-5%) whereas prevalence of hyperthyroidism in India is reported to be 1-2% [12,13]. Female sex is an independent risk factor for thyroid dysfunction, possibly due to autoimmune nature of thyroid disorders, and both the thyroid disorders are approximately 4 to 5 times more common in females [12,14]. Most common cause of hypothyroidism is autoimmune Hashimoto thyroiditis, whereas that of hyperthyroidism is Graves' disease, toxic nodular goitre and subacute thyroiditis [13]. Hypothyroidism even in subclinical form complicate reproductive function. Thyroid abnormalities have a proven role in numerous reproductive pathologies such as PCOS, subfertility, infertility, endometrial dysfunctions including abnormal menstruation, obstetrical problems such as abruption, preeclampsia, abortions, and adverse neonatal outcomes [15].

Menstrual disturbances are 2 to 3-fold more frequent in thyroid disorder than in the normal population and irregular menstrual cycles may precede other symptoms of thyroid disorders [16]. The hypothalamus – pituitary – gonadal axis and the hypothalamus – pituitary – thyroid– axis in women is closely interlinked [17]. Thyroid hormones affect upstream metabolic signals at the hypothalamic-pituitary level, downstream sex steroid secretion at gonadal level and biological availability of sex steroids through alterations in binding proteins and transport [11,15]. Thyroid hormone receptors are present in the ovaries on oocytes and granulosa cells as well as in endometrium and myometrium [11,15]. In hyperthyroid women, levels of estrogen, sex hormone binding globulin (SHBG) and androgens are increased along with decreased clearance of estrogens and androgens. Luteinizing hormone (LH) levels in both the follicular and luteal phases are higher in hyperthyroid women and are known to return to normal after optimal treatment with antithyroid drugs [16]. Oligomenorrhea, hypomenorrhea, amenorrhea, and anovulation are frequently noted with hyperthyroidism [11,15,16]. Hypothyroidism in women is characterized by decreased levels of estrogens, SHBG and androgens with increased metabolic clearance of androstenedione. Though LH and follicular stimulating hormone (FSH) levels may be normal, a blunted or delayed LH response to gonadotropin releasing hormone (GnRH) is observed [14,16]. Levels of progesterone is either decreased or normal in both the conditions [16]. Hypothyroidism results in changes in cycle length and amount of bleeding. Menorrhagia is likely due to breakthrough bleeding because of anovulation [14]. Increased endometrial thickness is a frequent finding in these women [18]. Hypothyroidism even in subclinical form may result in excessive menstrual bleeding and severe blood loss. Alterations in the sex steroid metabolism disappear when a euthyroid state is restored [16]. Endometrial fibrinolysis plays an important role in normal menstruation and limitation of menstrual blood loss [1]. Hypothyroid status shifts the balance of haemostatic system to a hypo coagulable and hyper fibrinolytic state, whereas hyperthyroid status leads to a more prothrombotic state [19]. Thyroid hormones are also known to affect shedding of endometrium through their pathophysiologic role in bleeding disorders. Defects in haemostasis factors (such as decreased levels of factors VII, VIII, IX, and XI) that occur in hypothyroidism may also contribute to polymenorrhea and menorrhagia [14,16].

Since thyroid dysfunction is an important treatable cause of menstrual disorder, thyroid evaluation is must in these women. Cost effective medical treatment is readily available for these conditions. Treatment of thyroid disorders cures the cause of abnormal menstruation while other commonly employed remedies (hormonal therapy) merely treat a symptom. The results are usually rewarding as patient can be virtually symptom free with adequate treatment. Scanty data is available evaluating the resolution of menstrual complaints after regular treatment of hypothyroidism and virtually none in case of hyperthyroidism Recognizing the current gaps in knowledge about prevalence of different menstrual abnormalities and their response to treatment, we uniquely designed this study at both gynaecologists' and endourologists' clinic, to explore

the relationship between thyroid profile and menstrual irregularities in women of reproductive age and to assess the impact of clinical management on the menstrual outcomes.

MATERIALS AND METHODS

Study design and setting

This was a prospective study done in women of reproductive age group attending Endocrine and Gynaecology clinic at a tertiary care hospital from Western India. The study was approved by Institutional ethics committee. Written informed consent was sought from all the study participants. Study was conducted in accordance with principles of Declaration of Helsinki and other applicable local or national regulations.

Participants

In this study, we included women in the age group 15 to 45 years, with body mass index within 18 to 25, with newly detected treatment naïve thyroid disorder i.e. hyperthyroidism or hypothyroidism (group A) or menstrual abnormality (Group B). The included women participants also agreed to maintain a strict menstrual calendar and ready for regular uninterrupted treatment and follow up. Women having documented history of thyroid disorder and thyroid medication, women with organic disorders known to cause abnormal bleeding (e.g. PCOD, myoma, polyps), pregnancy, organic abnormality of thyroid (e.g thyroid nodules), abnormal level of other hormones (LH, FSH, prolactin), hormonal therapy, bleeding or coagulation disorders, anticoagulant therapy or any serious systemic illness were excluded.

Data collection

Data was collected from endocrinology and gynaecology clinics in the outpatient department**.** Group A included women newly diagnosed to have thyroid disorder (hypothyroidism and hyperthyroidism) in endocrine clinic (n=100). Group B included women coming to gynaecology clinic with menstrual dysfunction (n=100). Detailed history and examination findings were recorded including age, parity, menstrual disorders, family history, past medical and surgical history past and current treatment history. Urine pregnancy test followed by bleeding time, clotting time, ultrasonography of abdomen and pelvis was done. All the exclusion criteria were carefully ruled out.

Patients were considered as euthyroid if the thyroid stimulating hormone (TSH), T3, and T4 were within normal range (TSH- 0.25-5 uIu/ml, T3 - 0.617-1.623 ng/ml, T4 - 4.65-9.3 ug/ml). According to result of thyroid function tests (TFT), patients were labelled as hypothyroid, hyperthyroid or euthyroid. Hypothyroidism was diagnosed based on elevated thyroid-stimulating hormone (TSH) levels (>4.0 mIU/L) and/or reduced free thyroxine (T4) levels, in accordance with standard diagnostic criteria. Hyperthyroidism was defined as a TSH level below 0.4 mIU/L with elevated free T4 or free triiodothyronine (T3).

We ensured a systematic and methodical approach to evaluate the abnormal menstruation. Menstrual cycle details in terms of frequency, duration, and intensity were evaluated. Menstrual disorders were categorized as menorrhagia (> 80 ml blood loss and/or more than seven days), polymenorrhagia (cycle length < 21 days with heavy and longer periods i.e frequent & regular), menometrorrhagia (excessive and prolonged bleeding occurring at irregular and/or frequent intervals) [20].Oligomenorrhea (cycle length more than 35 days or less than ten periods per year i.e. irregular periods), hypomenorrhoea (scanty periods) metropathia (abnormal uterine bleeding due to persistence of the follicular phase of cycle.i.e. infrequent and irregular periods), and secondary amenorrhoea (complete cessation of menstruation for > 6 months).

Each patient was started on standard thyroid treatment in appropriate dose by an endocrinologist. Patient were followed up for 12 months with TFT and their menstrual pattern noted with the help of menstrual calendar and pictorial blood assessment chart with the scoring sheet. Patients were asked to record daily number of sanitary pads are lightly, moderately or completely saturated. Scores were assigned as :1 point for each lightly stained tampon, 5 for moderately saturated and 20 for completely soaked small clot had 1 point and large clot has 5 points. Points were tallied for each menses. Totals more than 100 points per menstrual cycle indicated greater than 80 ml objective blood loss [21]. Treatment doses changed according to response. Patients were contacted telephonically/messaging services weekly to ensure compliance.

Statistical analysis

Each participant data was reconciled from the data record forms into the Microsoft excel spreadsheet. Data was analyzed with descriptive statistics. Categorical data was presented with frequency and proportions. Continuous variables were represented with mean and standard deviation.

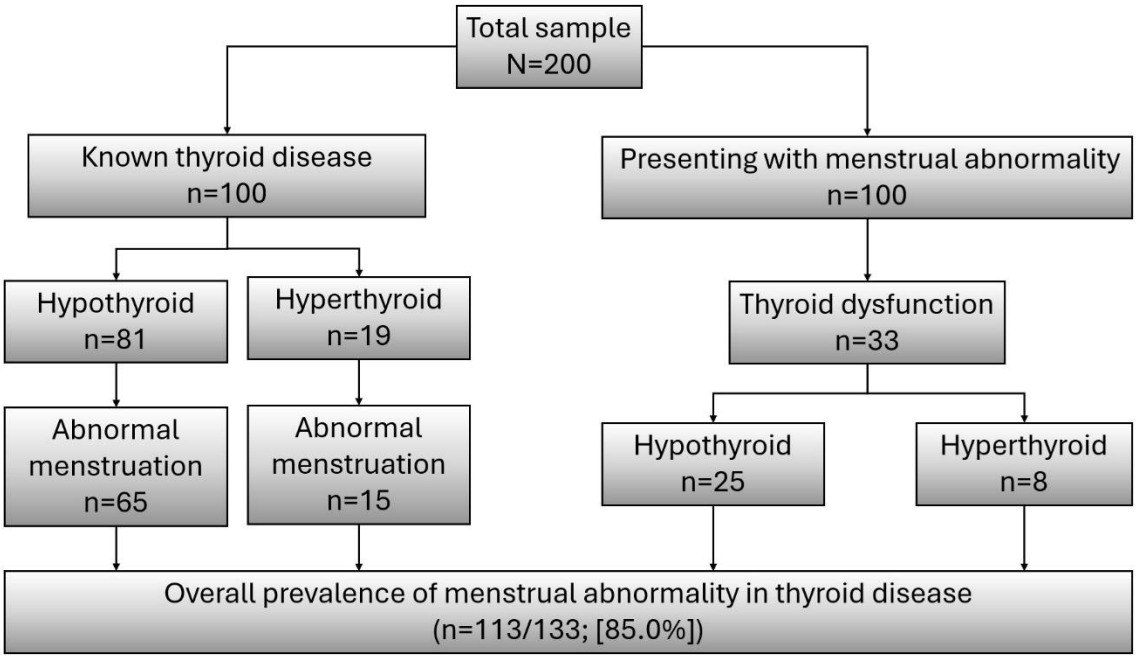
RESULTS

Patient disposition

We combined the data from group A and group B to assess the prevalence of irregular menstruation in women with thyroid disorders (**Figure 1**). All women from endocrinology OPD had thyroid abnormality. Out of 100 patients with irregular

menstruation presenting in gynaecology OPD (Group B), 33% (n=33) had thyroid abnormality. 25% (n=25) had hypothyroidism and 8% (n=8) had hyperthyroidism). 67 (67%) women with irregular menstruation were euthyroid. In women with thyroid disorder (n=133) (group A=100 + group B=33), prevalence of menstrual abnormality (n=113/133) was 85.0%. In women with hypothyroidism (n=106), irregular menstruation was present in 84.9% women (n=90/106). In women with hyperthyroidism (n=27), irregular menstruation was present in 85.18% women (n=23/27). Normal menstrual cycles were observed in 20/133 (15%) women with thyroid disorders.

Figure 1: Distribution of patient population



We divided women of reproductive age in three age groups (**Table 1**). For women with hypothyroidism, hyperthyroidism as well as for euthyroid women with irregular menstruation, most common age group was 25 to 35 years.

Table 1: Age group wise distribution of hypothyroid and hyperthyroid patients

Age (Yrs)	**Endocrine Clinic (Group A, n=100)**			**Gynecology clinic (Group B, n=100)**					**Total**
	Hypo-thyroid	Hyper-thyroid	Total	Euthyroid	Hypo-thyroid	Hyper-thyroid	Total thyroid disorder	Total	
15 – 25	22	5	27	23	6	3	9	32	59
25 – 35	32	9	41	31	12	4	16	47	88
35 – 45	27	5	32	13	7	1	8	40	53
Total	81	19	100	67	25	8	33	100	200

Thyroid abnormalities and menstrual disturbances

Overall, in women with thyroid disorders (n=133), menorrhagia was the commonest menstrual abnormality (44.3%) **(Table 2)**. Menometrorrhagia, metropathia and amenorrhoea were least common, being present in 3.7% women each with thyroid disorders.

Hypothyroidism

Out of 106 women with hypothyroidism (Table 2), menorrhagia was commonest (50.9%) followed by oligomenorrhoea (12.2%). Polymenorrhea, hypomenorrhoea and menometrorrhagia was present in 5.6%, 4.7% and 3.7% each. Metropathia was the least common abnormality in 2.8% women. 4.7% women had amenorrhoea whereas 15% women had normal cycles.

Hyperthyroidism

Out of 33 women with hyperthyroidism, hypomenorrhea was commonest (33.3%) followed by menorrhagia (18.5%). Polymenorrhagia and oligomenorrhoea was present in 11% women each. Menometrorrhagia was least common (3.7%). No hyperthyroid woman had amenorrhoea. Normal cycles were present in 14.8%.

Table 2: Abnormal menstruation and its relation to the thyroid abnormality

Menstrual disorder	Hypothyroid (n=106)	Hyperthyroid (n=27)	Total (n=133)
Menorrhagia	54 (50.9)	5 (18.5)	59 (44.3)
Polymenorrhagia	6 (5.6)	3 (11.1)	9 (6.7)
Menometrorrhagia	4 (3.7)	1 (3.7)	5 (3.7)
Oligomenorrhoea	13 (12.2)	3 (11.1)	16 (12.0)
Hypomenorrhoea	5 (4.7)	9 (33.3)	14 (10.5)
Metropathia	3 (2.8)	2(7.4)	5 (3.7)
Amenorrhoea	5 (4.7)	0	5 (3.7)
Total abnormal cycles	90 (84.9)	23 (85.2)	113 (85.0)

Response to treatment

We assessed improvement in menstrual complaints with treatment (**Figure 2**). At the end of 12 months, response to treatment of thyroid abnormality was 76.1% indicating achievement of normal menstruation in women. According to thyroid abnormality, response was achieved in 69 (76.7%) hypothyroid and 17 (73.9%) hyperthyroid women. **Table 3** shows the response to treatment in hypothyroid and hyperthyroid patients with each of menstrual abnormality. All patients with amenorrhoea and menometrorrhagia and 85% with menorrhagia and 83.3% with menometrorrhagia had normal menses at the end of 12 months. Lowest response to treatment was seen in women with oligomenorrhea (38.45%) and hypomenorrhoea (40%). In hyperthyroidism, menometrorrhagia and hypomenorrhoea (88%) patients returned to normal menstruation at 12 months.

Figure 2: Normalization of menstrual abnormality after treatment of thyroid abnormality

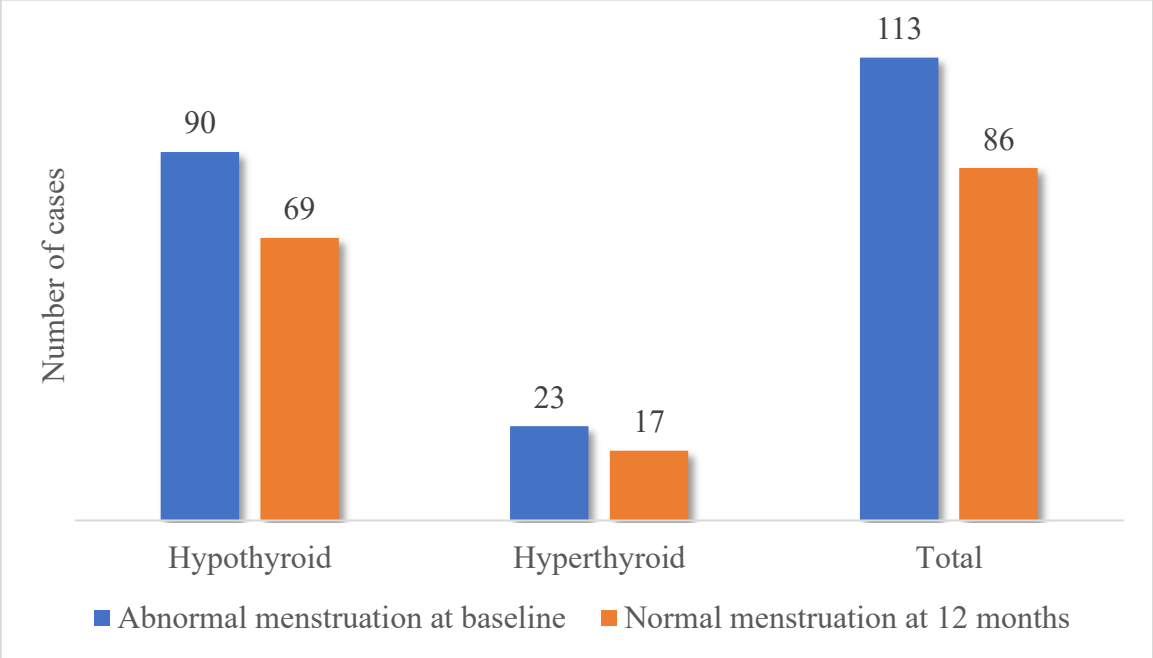


Table 3: Response to treatment of thyroid dysfunction at the end of 12 months

Menstrual abnormality	Hypothyroid		Hyperthyroid		Total	
	N	Normal menstruation	N	Normal menstruation	N	Normal menstruation
Menorrhagia	54	46 (85.1)	5	3 (60.0)	59	49 (83.0)
Polymenorrhagia	6	5 (83.3)	3	2 (66.6)	9	7 (77.7)
Menometrorrhagia	4	4 (100.0)	1	1 (100.0)	5	5 (100.0)
Oligomenorrhoea	13	5 (38.4)	3	2 (66.6)	16	7 (43.7)
Hypomenorrhea	5	2 (40.0)	9	8 (88.0)	14	10 (71.4)
Metropathia	3	2 (66.6)	2	1 (50.0)	5	3 (60.0)

Amenorrhoea	5	5 (100.0)	0	0	5	5 (100.0)

DISCUSSION

The highlight of the study was that it focused on both the specialities of endocrinology and gynaecology OPDs to distinctly assess the burden of thyroid disorders and menstrual abnormalities. We also ensured a comprehensive follow up of patients to assess post-treatment impact on menstruation in both the thyroid disorders. Overall prevalence of hypothyroidism and hyperthyroidism in our study was 79.7 % and 23.3%, respectively. Prevalence of menstrual abnormality was high (85%). A similar study by Koyadda et al. found high prevalence of hypothyroidism (83.93%) than hyperthyroidism (16.06%). However, a lower proportion of hypothyroid (30.6%) and hyperthyroid (7.5%) patients had menstrual complaints [22]. A Thyroid registry study by Sethi et al. which assessed the large database of hypothyroid patients in India observed that menstrual disturbances among all the women (n=730) who were not menopausal.[23]. A study by Krass et al noted that 23.4% women had irregular cycles in women with hypothyroidism [24]. Conversely, a study by Kakuno et al. reported a higher incidence (34.8%) of menstrual disturbances in severe hypothyroidism than mild-moderate cases (10.2%) [25].

In women with primary complaint of irregular menstruation, prevalence of thyroid disorders was 33% (25% hypothyroid and 8% hyperthyroid). Our findings are similar to other studies done in women with abnormal menstruation where majority of AUB cases associated with euthyroidism followed by hypothyroidism and lastly hyperthyroidism. Prevalences of thyroid disorders in abnormal menstruation has been studied across India with comparable results. Ajmani et al. in a study from Delhi observed 44% women with menstrual disorders having thyroid dysfunction (34% hypothyroid and 10% hyperthyroid) [26]. Other studies from Eastern, Southern and Western India have noted varying prevalence of hyperthyroidism (1.3%, 8.4% and 3%) and hypothyroidism (18%, 18.15% and 27%) in women with menstrual abnormalities. [27-29].

We observed that no menstrual abnormality was exclusive to either hypo or hyperthyroidism, with all of them having representation in both the thyroid disorders in varying frequency. In hypothyroidism, menorrhagia was the commonest form of irregular menstruation followed by oligomenorrhoea. A similar study by Joshi et al. also found menorrhagia to be the commonest (47.37%) followed by metrorrhagia (21%) [30]. Sethi et al. in Thyroid registry study reported menorrhagia in 99.58% women [23]. Other studies have also shown menorrhagia (32 to 55%) to be most common in hypothyroidism [26-30]. Menorrhagia in hypothyroidism is a result of infrequent or absent ovulation leading to deficient secretion of luteinizing hormone and a relative estrogen excess [29]. In hyperthyroidism, hypomenorrhoea (33%) was the commonest followed by menorrhagia (18.5%). Krass et al. observed that among patients with thyrotoxicosis 11% had hypomenorrhea, 7% had polymenorrhea and 2% had oligomenorrhea [31]. Padmaleela et al found menorrhagia in 42.8 % hyperthyroid women. Interestingly, none of our hyperthyroid patient had amenorrhoea which is a common finding associated with hyperthyroidism [11,14,25].

We also collected follow-up data to assess the impact of the treatment of either hypo or hyperthyroidism on abnormal menstruation. To our knowledge, this is the first study where comprehensive follow up of study participants was ensured to assess the post-treatment response in both the thyroid disorders. Improvement in steroid metabolism of sex hormones following euthyroid status is one of the important factors in regularization of menstruation [16]. In hypothyroid women, increase in estradiol, testosterone LH/FSH levels and decrease in TSH and prolactin levels is seen after achieving euthyroidism [32]. A study from Bachimanchi et al. evaluating hormonal changes after the treatment of hypothyroidism observed improvement in the levels of estrogen and prolactin [33]. Hypothyroid status shifts the balance of haemostatic system to a hypo coagulable and hyper fibrinolytic state, whereas hyperthyroid status leads to a more prothrombotic state [19]. Role of thyroid hormones in endometrial coagulation may be one of the probable mechanisms for the clinical benefits of restoring euthyroid status [15,16].

We observed that at the end of one year, 76.6% women with hypothyroidism and 73.4% women with hyperthyroidism returned to normal menstruation. Earlier, Menon et al. demonstrated a return to normal menstrual function post adequate treatment in 66% of hypothyroid and 75% of hyperthyroid women [34]. Krass et al. noted improvement in menstrual pattern in 60% hypothyroid women after levothyroxine treatment [24]. An Indian study evaluating spectrum of clinical symptomatology and its resolution following levothyroxine noted significant post treatment improvement [35]. A study by Dutta et al. which found prevalence of menstrual irregularities in women with severe hypothyroidism (TSH>40) to be 94.3%observed that treatment with levothyroxine resulted in normal menstruation in all the women who had amenorrhoea, menorrhagia, and menometrorrhagia whereas oligomenorrhoea was corrected in 94% women [36].

The strength of our study is that it was a prospective in design with an appreciable follow period to understand response to the treatment of thyroid dysfunction. However, study was limited by a restrictive sample which might limit the generalizability of our findings. We did not study the outcomes of women who had no response even after 12 months of

treatment. However, we made sure that they were appropriately evaluated and treated in routine OPD. Other supportive treatments for the irregular menstruation may have some confounding effects on treatment response.

CONCLUSION

To conclude, our study reinforced some key fact about thyroid disorders and menstrual cycles. Physicians and endocrinologists must specifically enquire about menstrual pattern in women presenting to them with suspected thyroid disorders as they may not reveal this problem because of shyness, embarrassment, or cultural restraints. Gynaecologists should also maintain high index of suspicion for thyroid disorders in women presenting with irregular menstruation. It should also be remembered that menstrual abnormality may precede other symptoms of thyroid disorder. Essentially, both hypo- and hyper-thyroidism can lead to menstrual disturbances. Thyroid disorders are easily treatable with cost effective medications and can possibly alleviate the need for hormonal treatment and unnecessary surgical interventions for abnormal bleeding.

DECLARATIONS

Funding: None.

Conflict of Interest: The authors declare no conflict of interest.

Ethical Approval: The study was conducted in accordance with applicable ethical standards and approved by the appropriate ethics committee where required.

Informed Consent: Informed consent was obtained from all participants involved in the study where applicable.

Author Contributions: All authors contributed to the study conception, design, data collection, analysis, manuscript preparation, and approved the final version of the manuscript.

Data Availability: Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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