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Abnormal Thyroid Stimulating Hormone Level and Heavy Menstrual Bleeding

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Abstract

Heavy Menstrual Bleeding is one of the common Gynaecological issues. There are several causes. Some of the women presented with these issues found to have underling thyroid abnormality which was not discovered earlier. This research tries to find the prevalence of the Thyroid Disorder among the women present with Heavy menstrual bleeding in Sri Lankan women.

Keywords

Heavy Menstrual Bleeding, TSH Levels, Thyroid Disorders

1. Introduction

The heavy menstrual bleeding is the most encountered problem during the reproductive life of most women. It is defined as excessive menstrual blood loss over several consecutive cycles [1] or menstrual bleeding that lasts longer than 7 days in adulatory women or more than 80 ml of blood loss [2] [3]. According to NICE guideline heavy menstrual bleeding is "excessive menstrual blood loss which interferes with the women's social, emotional, physical well-being and affects the quality of life, and which can occur alone or in combination with other symptoms" [4]. The prevalence of heavy menstrual bleeding varies. It has been reported to range between 4 and 50 percent, depending on the population under study and the methods used [5]. But those using objective measurement of blood loss [6] report around 10 per cent of more consistent prevalence.

Same time this condition severely affects the quality of life and result in significant morbidity. Also, the management causes a lot of expenditure. Heavy menstrual bleeding can be due to structural causes such as fibroids, polyps, ma-

lignancy, adenomyosis or Functional causes like coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and not yet classified. There may be other causes like thyroid diseases, pelvic infections, and arterio-Venus malformations. Abnormal thyroid functions are a well-known cause for heavy menstrual bleeding and sometimes it is undetected. Most of these women are treated several times before and have repeated medical managements and sometimes several admissions. Some of them required urgent blood transfusion as their haemoglobin levels were low. The thyroid status of a woman affects her reproductive life in several ways like interfering with ovulation, heavy and prolonged periods. The prevalence of thyroid diseases is high among the Sri Lankan population as our country is considered as endemic in thyroid diseases [7] and most of them are not diagnosed because they do not present in early stages. Alteration in menstruations is one of the manifestations of thyroid diseases. The prevalence of abnormal thyroid status in women with the history of heavy menstrual bleeding is unknown. Some of women with heavy menstrual bleeding have abnormal thyroid status. This observation makes me to do research in that women present with heavy menstrual bleeding in women without any underlying organic cause. So far no studies are conducted in Sri Lanka. In one Indian study, they found that "occult" menorrhagia has been found to be one of the early manifestations of sub clinical hypothyroidism. Most of the patients with hypothyroidism in their reproductive age present with menorrhagia in their early stage of the disease. Endometrial biopsy confirms that it is mostly proliferative endometrium [8].

The main objective of this study is to see whether the abnormal thyroid status was a risk factor for the development of heavy menstrual bleeding. Women present with menstrual bleeding investigated to exclude the common causes. But routine investigations for thyroid abnormalities are not recommended. If we find a strong correlation between heavy menstrual bleeding and thyroid abnormality, we can include in the initial assessment. This can lead to reduction in morbidity associated with the thyroid abnormality and significantly improve the quality of life not only in the menstrual aspects but also in various other aspects as well.

My hypothesis was "the abnormal thyroid status was a risk factor for the development of heavy menstrual bleeding without having the structural and functional causes". I expected an outcome of more than 3% - 4% of the general prevalence of the disease. If my study found a significant correlation between the thyroid abnormality and the heavy menstrual bleeding, we can incorporate the investigations for thyroid disorder in early stages in women presents with heavy menstrual bleeding where, other causes are excluded.

2. Objectives

The objective of my study was to test the hypothesis, whether the abnormal thyroid status is a risk factor for the heavy menstrual bleeding.

3. Materials and Method

3.1. Literature Review

Thyroid disorders usually cause menorrhagia by causing anovulatory dysfunctional uterine bleeding. It is associated with a wide range of molecular disturbances occurs in the endometrium, which appear to result in disturbance in the endometrial angiogenesis which will results in unpredictable vessel breakdown, increased vascular fragility and loss of the integrity of the epithelial, endothelial, and stromal supporting structures [9].

Krassas *et al.* had found that, prevalence of menstrual irregularities mainly oligomenorrhoea was 23% out of 171 hypothyroid patients, while oligomenorrhoea seen only 8% in 214 controls ($P < 0.05$). There were 12% of women in the entire hypothyroid group presents with amenorrhea, and no women among the control subjects. The study also showed a very important association between the severity of menstrual abnormalities and higher serum Thyroid stimulating hormone levels [9]. Also, they stated that the thyroid diseases are more common in women than men [10]. During the reproductive life they can cause variety of symptoms, the pattern menstrual cycle is influenced by thyroid hormones directly through impact on the ovaries and indirectly through impact on Prolactin Sex hormone binding globulin and Gonadotrophin releasing hormone secretion and coagulation factors, the menstrual irregularities occur in about 20% of patient's thyroid abnormalities [11].

Menorrhagia is more common in hypothyroid patients [12]. In the female reproductive system thyroid hormones have numerous interactions. Severe hypothyroidism is most associated with ovulatory dysfunction. Both altered Gonadotrophin releasing hormone pulsatile secretion and hyperprolactinemia, due to increased Thyroid releasing hormone production, leading to a delay in Luteinizing hormone response and inadequate corpus luteum, have been reported [13] [14]. The discovery of thyroid hormone receptors in human oocytes, [15] explains that the thyroid hormones are responsible for the some of the functions of the ovary. Thyroid hormones directly stimulate the progesterone production by the granulosa cells. It bring down this effect by synergize with the Follicular stimulating hormone-mediated Luteinizing hormone human chorionic gonadotrophin receptor [16]. Thyroid hormones involve on the differentiation of the trophoblast, which have been shown at in vitro studies [17]. Cramer *et al.* in their study they showed that serum Thyroid stimulating hormone levels were regarded as a significant predictor of failure of In-vitro Fertilization as women who produced oocytes that failed to be fertilized had a significantly higher level of Thyroid stimulating hormone levels [18]. Hypothyroidism may also impact on fertility through another pathway by decreasing Sex hormone binding globulin production and by altering the peripheral metabolism of estrogen. Abnormal feedback at the pituitary level may be resulted by both pathways. Hypothyroidism also led to menorrhagia by altered production of coagulation factors de-

creased levels of factors VII, VIII, IX and XI are seen Hypothyroid patients which is independent of the hormonal changes [19].

Mangalagowri *et al.* [20] concluded that the prevalence of thyroid diseases is high among Indian women as Sri Lanka geographically and culturally related India the prevalence may be like that. The results of studies involve on the incidence of infertility in patients with hypothyroidism are scarce. Most studies deal with the prevalence of infertility in cross-sectional studies of hypothyroid patients or in selected populations presenting at fertility clinics, ideally this should be evaluated prospectively by comparing the incidence with a matched control group. Joshi *et al.* [21] in their study found out that 2·4% of healthy control women had infertility compared to 21.6% of hypothyroid women and 5% of the euthyroid women who had goitre. However, in this study, the control population was not clearly defined, the number of patients was small and the thyroid antibody status unknown. Lincoln *et al.* [22] in their study, they measure the Serum TSH levels in 704 infertile women those without known thyroid disorder: 2·3% of them had an increased serum TSH level, representing both subclinical and overt hypothyroidism. The study did not have any control group; however, the prevalence of elevated serum TSH was equal to that of female population in the reproductive age.

Arojoki *et al.* [23], in their study in 299 infertile women, the prevalence of an increased serum TSH was 4% and that of overt hypothyroidism 3.3%. Women with ovulatory dysfunction (6.3%) had the highest percentage of an increased serum level of TSH, compared to 2.6% in the tubal infertility group, 4.8% in the idiopathic group and none in the patients with endometriosis group. The frequency of hypothyroidism between the different groups of infertility women did not show any statistical difference. In a study which was done by DL Wilansky *et al.* [24], in 67 menorrhagic, apparently euthyroid women they evaluate the functional status of the thyroid gland by testing the thyrotropin-releasing hormone. Out of sixty seven 15 patients showed mild primary hypothyroidism which is characterized by a small but significant elevation of basal levels of thyroid-stimulating hormone (5.9 ± 0.76 versus 2.4 ± 0.24 mU/L) and lowering of serum thyroxin levels (85 ± 4.2 versus 105 ± 3.0 nmol/L) to levels that were in spite of that within the normal range, they showed an exaggerated response of serum thyroid-stimulating hormone and thyroxin following administration of thyrotropin-releasing hormone. However, triiodothyronine levels did not show any significant change. It seems that the terms early and potential hypothyroidism appears to better describe the preliminary phases of hypothyroidism than do all other terms in current use. Menorrhagia disappeared within 3 to 6 months L-thyroxin treatment and did not reappear in 1 to 3 years of follow up in all patients with early hypothyroidism. This finding was also supported by a significant decline in random serum Thyroid-stimulating hormone levels and rise of thyroxin levels to those found in the group with a negative response to the thyrotropin-releasing hormone test, without any change in levels of triiodothyronine. Further systematic study of thyroid function in menorrhagia is needed.

Joshi *et al.*, in their study says that "Reproductive failure and lactation failure also preceded thyroid dysfunction or goitre. Reproductive dysfunction may therefore be considered as one of the presenting symptoms of thyroid disorders in women, keeping in mind both menstrual irregularities and lactation failure may also arise from other common or idiopathic origin. Especially 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" [25].

3.2. Design

Causes for heavy menstrual bleeding: Patients come to the gyn ecological unit, ward 12, included in the study. Many of them came to the clinic, and some of them were admitted directly to the hospital. A case-control study was conducted to see whether the abnormal thyroid status was a risk factor for the patient. The woman who gave the history of heavy menstrual bleeding underwent a thorough history and examination. Patients who were sexually active underwent a transvaginal scan and those who were sexually not yet active underwent a transabdominal scan. A speculum examination was done on all the women who were sexually active. A full blood count was done on all patients, and a urine HCG test was done to exclude pregnancy. A prothrombin time was done to exclude the coagulation abnormalities. The main purpose of these investigations was to exclude the common causes of heavy menstrual bleeding, like fibroids, polyps, coagulopathies, malignancy of the reproductive tract, pelvic infections, arterio-venous malformations, and some iatrogenic causes like the use of anticoagulants. Most of these investigations were routinely done on a patient who presented with a history of heavy menstrual bleeding. As the other causes were excluded, their thyroid status was checked by checking the thyroid stimulating hormone level using a third-generation assay. The results were compared with the age-matched control groups. The control group was selected from the healthy women who do not have a history of heavy menstrual bleeding and came to the family planning clinic, as well as from the MOH areas adjacent to the Colombo South Teaching Hospital. The control group also underwent the same investigations as the women with heavy menstrual bleeding.

3.3. Method

All the women, who presented either clinic or to the ward directly, with the history of heavy menstrual bleeding, were included in the study as the cases. To exclude the common causes of heavy menstrual all the patients underwent a series of investigations. All the women who had a probable cause for the conditions were excluded from the study. Appropriate age matched control group were selected from adjacent MOH areas who came to the family planning clinic. The control group women also underwent the same procedure and same investiga-

tions as the cases. In control group also the women with any underline asymptomatic pathology were excluded from the study. This study was carried out for 8 month period from June 2014 to January 2015.

3.4. Eligibility Criteria for the Study

Women who came with the history of heavy menstrual bleeding were included in the study as the cases for this study as the cases of this study as cases. The women come to the family planning clinic from the adjacent MOH area were included as the control.

3.5. Exclusion Criteria

- Women with miscarriages.
- Irrespective of the place all the women with the fibroid were excluded.
- Women with bleeding disorders.
- Women with cervical polyp.
- Women who suspected to have endometrial carcinoma.
- Women with the cervical pathology.
- Women who do not gave a written consent.
- Women who presented with signs of infection.

3.6. Sample Size Estimation

Based on previous meta-analysis on these aspects the expected prevalence of the thyroid abnormality among the women with the heavy menstrual bleeding is around "20%" the estimated sample size with the consideration of type one error and a power of study of "80%".

Formula for a different means,

"Eq. (1)" $n = r + 1$

$$n = \left(\frac{r+1}{r}\right)\frac{\sigma^2\left(Z_\beta + Z_{\alpha/2}\right)}{\text{difference}^2}$$

n = Sample size in the case group.

r = Ratio of case to control group is 2.

σ = Standard deviation of outcome variable is 10.0.

Z_β = Desired power typically 0.84 for 80%power.

$Z\alpha/2$ = Desired level of statistically significant typically.

"1.96"

$(\text{Difference})^2$ = effect size

By this equation there were 47 cases, and 94 controls were needed.

3.7. Outcome Measures

The primary outcome measure of this study was the measuring the Thyroid stimulating hormone level in both the cases and controls.

3.8. Statistical Analysis and Plan of Presentation of the Results

The results were analysed using SPSS program and using the t-test.

3.9. Ethical Consideration

Ethical approval for this case control study was obtained from the ethics review committee of the Colombo South Teaching Hospital Kalubowila. All the participants were given written information sheets which covers the purpose of the study and the investigations that they going to undergo. Informed written consent was taken from each participant following verbal explanation as well.

4. Results (Tables 1-8)

Table 1. Descriptive statistics.

	Number	Minimum	Maximum	Mean	Std. Deviation
Cases					
Age -years	47	23.00	45.00	35.3830	5.75422
Hb-g/dl	47	6.70	12.00	10.2085	1.12672
TSH uU/ml	47	2.00	4.9	3.4000	0.64133
Control					
Age -years	94	23.00	45.00	33.1809	5.80316
Hb-g/dl	94	9.00	14.00	11.3799	0.93636
TSH uU/ml	94	2.00	4.70	3.2032	0.57370

Explains the Minimum and Maximum, Mean and Standard deviation of age, Haemoglobin Level and TSH Level in both Cases and control.

Table 2. Description of the cases and control according to the parity.

Parity	Frequency	Valid Percent	Cumulative Percent
cases			
0	9	19.1	19.1
1	19	40.4	59.6
2	8	17.0	76.6
3	6	12.8	89.4
4	5	10.6	100.0
Total	47	100.0	
Control			
0	19	20.2	20.2
1	28	29.8	50.0
2	31	33.0	83.0
3	12	12.8	95.7

Continued

4	2	2.1	97.9
5	2	2.1	100.0
Total	94	100.0	

Illustrate the case and control according to the parity.

Table 3. Description of cases and control according to the ethnicity.

Ethnicity	Frequency	Percent	Cumulative Percent
Cases			
Sinhala	23	48.9	48.9
Tamil	14	29.8	78.7
Muslim	10	21.3	100.0
Total	47	100.0	
Control			
Sinhala	48	51.1	51.1
Tamil	28	29.8	80.9
Muslim	18	19.1	100.0
Total	94	100.0	

Illustrate the case and control according to the Ethnicity.

Table 4. Age category of both cases and control group.

	Frequency	Valid Percent	Cumulative Percent
<25 years	9	6.4	6.4
26 - 35 years	77	54.6	61.0
>36 years	55	39.0	100.0
Total	141	100.0	

Categorize the case and control according to the Age group.

Table 5. Thyroid stimulating hormone (TSH) level category whole group.

TSH uU/ml	Frequency	Valid Percent	Cumulative Percent
<3	44	31.2	31.2
3 - 4	80	56.7	87.9
>4	17	12.1	100.0
Total	141	100.0	

Categorize the case and control according to the THS Level.

Table 6. Haemoglobin category whole group.

Haemoglobin g/dl	Frequency	Valid Percent	Cumulative Percent
<10	32	22.7	22.7
10 - 12	89	63.1	85.8
>12	20	14.2	100.0
Total	141	100.0	

Categorize the whole group according to Haemoglobin Levels.

Table 7. One-Sample Test.

	Test Value = 0					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
TSH1	36.345	46	0.000	3.40000	3.2117	3.5883
TSH2	54.133	93	0.000	3.20319	3.0857	3.3207

TSH 1: TSH level for the cases group. **TSH 2**: TSH level for the control group. **t**: t value. **Df**: Degree of freedom. For the analysis one sample t-test can be used the calculated t-value for the cases group was 36.345 and the degree of freedom for the cases group was 46 the significance was 0 for the 2 tailed test the mean difference of the TSH level was 3.4 uU/ml 95% confidence interval (3.2117 - 3.5883). The calculated t-value for the control group was 54.133 and the degree of freedom for the control group was 93 the significance was 0 for the 2 tailed test the mean difference of the TSH level was 3.203 uU/ml 95% confidence interval (3.0857 - 3.3207).

Table 8. Group statistics.

TSH	HMB	N	Mean	St. Deviation	Std. Error Mean
	Yes	47	3.4000	0.64133	0.09355
	No	94	3.2032	0.57370	0.05917

TSH: Thyroid stimulating hormone level. **HMB**: Heavy menstrual bleeding. **Yes**: cases group. **No**: control group. **N**: Number. **Std. Deviation**: Standard Deviation. **Std. Error Mean**: Standard Error of Mean. The calculated standard Deviation of the cases group was 0.64133 with the standard Error of mean of 0.9355. The calculated standard Deviation of the control group was 0.57370 with the standard error of mean of 0.5917.

5. Discussion

Prentice states that there is "little evidence to link hypothyroidism with excessive menstrual loss". [26] His study also supported by a study involved in retrospective analysis of the records of 50 patients with myxoedema by Scott *et al.* [27]. In this cohort 28 women (56%) complained of menstrual disturbance, with the majority complaint being menorrhagia (occurring in 18 (36%) of the women). However, in both this studies which reported the women's perceived loss had an

improvement in the menstrual loss after treatment with thyroxin. And in more recent studies in which the menstrual loss was objectively measured treatment of hypothyroidism with thyroxin decreased menstrual blood loss [28]. Wilansky [24] performed TRH tests in 67 women with menorrhagia who had normal levels of thyroxin and thyroid stimulating hormone 22% had abnormal TRH tests and were treated with thyroxin. At follow-up all these treated women considered their menstrual loss to have returned to normal whilst of those with normal TRH tests, 56% still complained of menorrhagia.

All the available evidence supports a causative association between hypothyroidism and excessive menstrual loss. Prentice asserts that routine thyroid function tests are of no value in the investigation of women with menorrhagia. In this study that the mean age of the women with the menorrhagia is slightly higher than the control group women. The mean age for the cases is 35.383 years with the standard deviation of 5.75 years. The mean age for the control is 33.18 years standard deviation 5.80 years. The women in the cases group had mean haemoglobin level 10.20 g/dl standard deviation 1.126 g/dl. Women in the control group had a haemoglobin level 11.37 g/dl standard deviation 0.93 g/dl. This difference may be due to menorrhagia. That causes reduced haemoglobin level in the cases. In fact, some had frank anaemia. The Thyroid stimulating hormone level also shows variation between the two groups. The mean Thyroid stimulating hormone level for the cases group is 3.4 uU/ml standard deviation 0.64 uU/ml, the mean Thyroid stimulating hormone level for the control group is 3.20 uU/ml standard deviation 0.57 uU/ml this observation may be due to some association of the abnormal thyroid status in the development of heavy menstrual bleeding.

Majority of the women (40.4%) in the cases group had a parity of 1 in the control group majority had parity 2 (33%). Sinhalese comprise the majority in both groups followed by Tamils and the Muslims comprise the least group. This is like the national level but the percentage different than the national level this may be due to that the local community close to the Colombo south teaching hospital.

According to age whole group can be divided into three groups. Less than 25 years, between 26 to 35 years and above 36 years. The percentage wise these are 6.4%, 54.6% and 39%. The 26 to 35 years age group was many of the women in the study. This may be due to this age group of women commonly seek contraception as the control group women were selected from the women who attend the family planning clinic. According to the TSH level 31.2% had a value less than 3 uU/ml. TSH value was between 3 - 4 uU/ml in 56.7%. TSH value more than 4 uU/ml in 12.1% of the whole group.

Twenty-two point seven percentages of the study group women had haemoglobin level less then 10 g/dl. There come under anaemia. Sixty-three point one percents had the haemoglobin level between 10 and 12 g/dl.

The mean TSH level for the cases group was 3.40, (95% confident interval 3.211 - 3.588).

The mean TSH level for the control group was 3.20, (95% confident interval 3.085 - 3.321).

In this study the p-value calculated using two tailed t-test the calculated p-value was 0.067 which was more than p-value of 0.05. The 0.05 p-value regarded as significant. So, the null hypothesis was accepted thus the hypothesis was rejected. In other words, the abnormal thyroid hormone status is not a risk factor for the development of the heavy menstrual bleeding. However, the p-value close to 0.05 the difference was not with a higher difference. If a larger case this narrow difference could have been prevented. Study could have given significant results. This observation alone warrants a repeat study with a larger sample with a good power.

6. Limitations

I had hypothesized that the incidence of abnormal thyroid status among the women with the history of heavy menstrual bleeding would higher than the age matched control group. However, I did not observe this effect. In my study there may be several factors which could affect the outcome results.

- Women who had a history of heavy menstrual bleeding did not participate in the study as they were sexually not active and denies the consent for trans-Vaginal ultrasound scan examination.
- Women with the overt abnormal thyroid status were not encountered as this could be due to these patients were followed up in the medical clinics majority of them could have benefited by the treatment.
- Women with dual pathology did not come to the real category as the structural and functional causes were excluded, they might have excluded.
- Some proportion of women with the thyroid abnormality might have Amenorrhea those were missed during the study.
- Women with pregnancy have been excluded.
- Breastfeeding women with thyroid disorders were not come under this study.
- Only women who seek medical advice included in the study group. There might be some women with the heavy menstrual bleeding without seeking medical advice.
- If the study includes many women could increase the significance.
- The study was done in a short period of time if the study was done for a long time, it could increase the number of the cases and could have increase the power.
- Cases and the control were selected from the people who visited the hospital, so they did not represent the actual population.
- The heavy menstrual bleeding assessed by the clinical history alone but if assessed by objective measurement could have been more precise.

7. Conclusion

In this study I have found out that, Abnormal thyroid status was not a risk factor

for the development of heavy menstrual bleeding. But the calculated p-value is very close to 0.05 so the study needs to be repeated with more power.

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Recommendations

The study needs to be repeated with more samples.

The time should be more.

If possible as a multi centred study.

Better method of the sample selection technique.

Better objective method of assessing the cases.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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