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ORIGINAL ARTICLE

The Relationship between Thyroid Disorders and Prolactin level in the Blood of Premenopausal Women with Abnormal Uterine Bleeding

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ABSTRACT

Background: Abnormal uterine bleeding (AUB) is a common perimenopausal problem with numerous explanations and causes; thyroid disorders and hyperprolactinemia are part of these causes. This study aimed to find out the relationship between thyroid disorders and prolactin level in perimenopausal women with abnormal uterine bleeding. **Methods:** Cross sectional study was conducted on 63 patients aged from 40-55yr attending the outpatient clinic of Obstetrics and Gynecology Department Zagazig University hospital and Tallerak Central Hospital complaining from abnormal uterine bleeding. All women were subjected to examinations of the abdomen and Pelvic. The vagina was inspected with the use of a speculum. The bimanual examination was performed also. Laboratory investigation including Complete blood count, Liver function tests, Fasting blood glucose, Urine pregnancy test to exclude pregnancy. Specific investigations include thyroid gland hormones (TSH, free T3 and free T4) and serum prolactin. **Results:** There was negative non significant association between age, T3 (r=-0.14), TSH (r=-0.1) and Prolactin (r=-0.06). It also showed that there was positive significant correlation between abnormal uterine bleeding, hyperthyroidism (r=0.06) ($p<0.05$), hypothyroidism (r=0.1) ($p<0.05$), hyperprolactinemia (r=0.06) ($p<0.05$) and HMB (r=0.1) ($p<0.05$). This study showed that abnormal uterine bleeding in perimenopausal women is strongly associated with thyroid disorders and hyperprolactinemia. **Conclusions:** Abnormal uterine bleeding is strongly associated with thyroid-related disorders especially hypothyroidism at cut off value of TSH = 29.1 and also associated with hyperprolactinemia at cut off value of prolactin = 45.1.
Keywords: Abnormal uterine bleeding; Thyroid Disorders; Prolactin level; Perimenopausal Women; Abnormal Uterine Bleeding .

INTRODUCTION

Any form of bleeding that does not fall within the usual range in terms of amount, frequency, duration, and cyclicity is referred to as abnormal uterine bleeding (AUB) **[1]**.This is a prevalent presentation that impacts around one-third of patients who visit gynecological clinics**[2].** It occurs in 15%–20% between the menarche and the menopause in women **[3].**

Thyroid problems are strongly linked to abnormal uterine hemorrhage. Thyroid dysfunction must thus be assessed in all AUB patients **[8].**The mechanism linking thyroid disorders to AUB may be explained by changes in the thyroid stimulating hormone (TSH) response, an increase in prolactin, an alteration in the luteinizing hormone (LH) response, an impact on the peripheral conversion of androgens to estrogens, an alteration in the sex hormone binding globulin (SHBG) and a disruption in the coagulation pathways, which results in menorrhagia and affects the lipid profile **[4].** Additionally, hypothyroidism reduces the production of sex hormone-binding globulin (SHBG) and modifies peripheral oestrogen intake, leading to abnormal pituitary feedback **[6]**. The production of (SHBG) rises significantly in hyperthyroidism. Estrogen metabolism is disturbed and there is an increase in the synthesis of estrogens from androgens in the periphery **[7]**.

Elevated blood prolactin levels are known as hyperprolactinemia, and its prevalence ranges from 0.4% in the general adult population to 9%–17% in women who have menstrual disorders **[9].**Hyperprolactinemia can disrupt corpus luteum function and follicular maturation. They can also block the hypothalamus's normal pulsatile release of gonadotropin-releasing hormone. Additionally, it causes insufficient luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release, in amounts insufficient to trigger a healthy ovarian response **[10].** Prolactin and thyroid hormone levels in perimenopausal individuals presenting with unexplained uterine bleeding were measured in the current investigation. So, this study aimed to find out the relationship between thyroid disorders and prolactin level with abnormal uterine bleeding in perimenopausal women.

METHODS

This Cross sectional study was conducted on 63 patients aged from 40-55 years attending the outpatient clinic of Obstetrics and Gynecology Department, Zagazig University hospital and Tallerak Central Hospital complaining from Abnormal uterine bleeding. The study was authorized by our local ethics commission (IRB#10149/30-11-2022). The objectives of the study were explained to the women before inclusion in the study. Consent was obtained in writing, informed by each participant. The protocol for the study complied with the Helsinki Declaration (1975), which is the World Medical Association's guideline of ethics for research involving human subjects.

Inclusion Criteria were perimenopausal women with abnormal uterine bleeding, age (40-55) years, no obvious cervical and genital lesions, no evidence of any haematological disorder. Exclusion criteria: Age (<40 or >55) years, uncontrolled HTN & DM, suspected pelvic infection, profusely bleeding patient requiring therapeutic curettage, pregnant women, women with IUCD, women with haematological disorders ,women with fibroid.

Every woman underwent a thorough clinical checkup and history taking. The patient often lies supine on an examination table in the office, with their knees bent and their feet in supportive stirrups, while the pelvic examination is conducted. The general gynecologic examination also includes an examination of the abdomen. The conventional methods of examination, auscultation, percussion, and palpation should be used to examine the abdomen. The size of masses and other abdominal and pelvic tissues, such as the liver, can be assessed by percussion, as can any accumulation of fluid in the abdomen, such as ascites. Palpation is used to check for masses, organ enlargement, and pain.

When performing a pelvic examination, there may be a temptation to concentrate on inserting the speculum to collect cytology specimens. It is imperative for the examiner to consistently remember to check the external genitalia for normal look and hair distribution initially. Notable are any lesions or anomalies in development. It is important to look for and feel for superficial and subcutaneous lesions on the skin.

A speculum is used to examine the vagina. In order to avoid the delicate suburethral area, the speculum blades might be inserted at an oblique to horizontal angle but never vertically. The blades are moved to the vaginal apex using consistent posterior pressure. The cervix can then be softly exposed by opening the speculum. Sometimes the cervix can be seen by gently swaying the woman. For lesions, the cervix and vagina are examined.

Transvaginal ultrasound examination was performed with endovaginal transducer of 5 -.5 MHz frequency on voluson 730 pro-machine (GE Healthcare, Austria). Laboratory investigation including Complete blood count, PT, PTT, INR, Tests for liver and kidney function, blood glucose fasting, Urine pregnancy test to exclude pregnancy.

Thyroid Disorders:

Specific investigations include thyroid gland hormones (TSH, free T3 and free T4) by enzyme-linked immunosorbent assay (ELISA). The quantitave determination of thyroid Stimulating Hormone (TSH) concentration in human serum by a Micro Plate Immunoassay. Kit (BioCheck, Inc. 323 Vintage Park Drive Foster City, CA 94404). Catalog number BC-1001. Normal references range of TSH (0.4-6) miu/ml.

Free triiodothyronine (FT3) Quantitative Measurement of Human Serum Concentration Using Microplate Enzyme Immunoassay. Level of FT3 are thought to reflect amount of T3 available to the cell and may therefore determine the clinical metabolic status of T3 kit. Kit (BioCheck, Inc. 323 Vintage Park Drive Foster City, CA 94404). Catalog number: BC-1006. Normal reference range (1.5-4.1) pg/dl.

The Quantitative Determination of Free Thyroxine (FT4) Concentration in Human serum by Microplate Enzym Immunoassey. Kit (BioCheck, Inc. 323 Vintage Park Drive Foster City, CA 94404). Catalog number: BC-1008. Normal reference range: (0.8-1.9) ng/dl.

Prolactin level assessment:

Using the electrochemiluminescence immunoassay, serum PRL was ascertained "ECLIA" by using "cobas e 411" immunoassay

analyzer and Elecsys prolactin II reagent kits. Normal reference range; (20-25) ng/ml.

Principles of the assay: Two monoclonal antibodies that are particularly targeted against human PRL are used in the experiment. With the majority of macroprolactin forms, both antibodies exhibit minimal reactivity. The test principle is known as the "sandwich principle," and the assay takes 18 minutes altogether".

Reagents and working solutions: M Streptavidin-coated microparticles (transparent cap), 1 bottle and 6.5 ml Streptavidin-coated microparticles 0.72 mg/ml.

Reagent handling: The kit's reagents have been put together to form an unbreakable, ready-to-use unit.

Steps of the assay:

First incubation; 10uL the material forms an initial interaction with a prolactin-specific monoclonal antibody that has been biotinylated. Second incubation: ruthenium complex (Ru(bpy)-labeled monoclonal prolactin-specific antibody and streptavidin-coated microparticles are added. This results in the formation of a sandwich complex, which is then coupled to the solid phase by the interaction of biotin and streptavidin. The microparticles are magnetically attracted to the electrode surface of the measurement cell upon aspiration of the reaction mixture into it. ProCell is then used to remove the unbound materials. A photomultiplier is used to measure the chemiluminescent emission that is induced when a voltage is applied to the electrode. The reagent barcode provides a master curve, and an instrument-specific 2-point calibration produces a calibration curve that is used to determine the results.

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences was used to verify, enter, and analyze the data for this investigation (SPSS) version 17 (2022). Data were expressed as mean ± SD to quantitative data or numbers and percentages for categorical variables. Chi-square (x2), Fisher exact test/t-test and one way analysis of variance (one way ANOVA) were used when appropriate. Parametric Mann-Whitney U test was used to establish the difference in PRL levels between patients and controls. Propability (P) between groups is considered statistically non significant (NS) if P>0.05, Statistically significant (S*) if P< 0.05 and is considered statistically highly significant (HS*) if P< 0.001.

RESULTS

Table 1; showed that no significant difference between the studied patients regarding to age, parity and BMI .

Table 2; showed that no significant difference between the studied patients regarding to menstrual history.

Table 3; showed that 71.43% of patients represented with euthyroidism, Hypothyroidism represents 17.46% , Hyperthyroidism represents 3.17%, Subclinical hypothyroidism represents 6.35% of patients while Subclinical hyperthyroidism was in 1.58% of patients. There was significant differences between studied patients as regard to hypothyroidism, hyperthyroidism and Euthyroidism.

Table 4; showed that 79.4% of patients represented with Normal prolactin , 20.6% of patients represented with Hyperprolactinemia. That there was highly significant differences between studied patients as regard to distributions of cases according to thyroid function tests and serum prolactin level.

Table 5; showed that Hypothyroidism represents 17.46% of patients, Hyperthyroid 3.17%, Subclinical hypothyroidism 6.35% of patients while Subclinical hyperthyroidism was in 1.58% of patients. 79.4% of patients represented with Normal prolactin, 20.6% of patients represented with Hyperprolactinemia. There was highly significant differences between studied patients as regard to distributions of cases according to thyroid function tests and serum prolactin level.

Table 6; showed that 12.7% of patients represented with normal thyroid function and hyperProlactinemia, abnormal thyroid function and normal Prolactin represented in 20.63%, patients with normal thyroid function and Prolactin represents 58.73% , patients with abnormal thyroid function and hyperProlactinemia represents 7.93%. There was highly significant differences between studied patients as regard to distributions of cases according to thyroid function tests and serum prolactin level.

Table 7; showed that there was positive significant Correlation between abnormal uterine bleeding, hyperthyroidism, hypothyroidism, HMB and hyperProlactinemia in studied patients. that there was positive Correlation between perimenopausal and hyperprolactinaemia at cut off value of prolactin = 45.1 (figure 1). There was positive Correlation between Perimenopausal bleeding and hypothyroidism at cut off value of TSH = 29.1 (figure 2).

Table (1): Basic characteristics data of the studied patients (N=63).

	Sample : (n=63)	χ2	P value
Age (Mean ± SD)	53± 1.11	0.92	0.131 (NS)
BMI (kg/m^2) (Mean ± SD)	21.60 ± 3.42	0.61	0.27 (NS)
Parity			
Nullipara {N (5%)}	7 (33.3%)	1.16	0.28 (NS)
Primipara {N (5%)}	8 (38.2%)		
Multipara {N (5%)}	48 (76.19%)		

This table shows that no significant difference between the studied patients regarding age, parity and BMI.

Table (2): Clinical picture of the studied patients (N=63).

Clinical picture	Total sample (n=63) No(%)	P value
Type of bleeding		
Menorrhagia(HMB)	5 (7.9%)	0.437 (NS)
Metromenorrhagia	10(15.8%)	
Polymenorrhagia	8 (12.6%)	
Postmenopausal bleeding	40(63.2%)	
Duration of bleeding		
<3 months	14 (22.5)	0.213 (NS)
3-6 months	17 (26.8)	
6-12 months	12 (19.0)	
>12 months	20 (31.7)	
Amount of bleeding		
Mean ± SD	5.6 ±1.6	0.321 (NS)

This table shows that no significant difference between the studied patients regarding to menstrual history.

Table (3): Distribution of patients according to thyroid function tests (N=63).

	Total sample (n=63) No(%)	P value
Euthyroid	45 (71.43%)	0.02*
Hypothyroidism	11 (17.46%)	0.001**
Subclinical hypothyroidism	4 (6.35%)	0.42
Hyperthyroid	2 (3.17%)	0.05*
Subclinical Hyperthyroid	1 (1.58%)	0.72

significant** *** highly significant**

This table shows that 71.43% of patients represented with euthyroidism, Hypothyroidism represents 17.46%, Hyperthyroidism represents 3.17%, Subclinical hypothyroidism represents 6.35% of patients while Subclinical hyperthyroidism was in 1.58% of patients. There was significant differences between studied patients as regard to hypothyroidism, hyperthyroidism and Euthyroidism.

Table (4): Distribution of patients according to Prolactin level (N=63).

	Total sample: (n=63) No(%)	P value
Normal prolactin	50 (79.4%)	0.02*
Hyperprolactinemia	13 (20.6%)	0.004**

***significant** ****highly significant** This table shows that 79.4% of patients represented with Normal prolactin , 20.6% of patients represented with Hyperprolactinemia. There was significant differences between studied patients as regard to Hyperprolactinemia and normal prolactin cases.

Table (5): Distribution of patients according to thyroid function and Prolactin level in the studied patients (N=63).

	Total (n=63) No(%)	P value
Hyperprolactinemia	13(20.6%)	0.01*
Hypothyroidism	11(17.46%)	0.04*
Subclinical hypothyroidism	4(6.35%)	0.43
Hyperthyroid	2 (3.17%)	0.001**
Subclinical Hyperthyroid	1 (1.58%)	0.32

***significant** ****highly significant**
This table shows that there was highly significant differences between studied patients as regard to distributions of cases according to thyroid function tests and serum prolactin level.

Table (6): Patients with normal thyroid function and hyper Prolactinemia, abnormal thyroid function and normal Prolactin, patients of normal thyroid function and Prolactin level in the studied patients (N=63).

	Total No(%)	P value
Patients with normal thyroid function and hyperProlactinemia	8 (12.7%)	0.01*
Patients with abnormal thyroid function and normal serum Prolactin	13(20.63%)	0.004**
patients with normal thyroid function and serum Prolactin	37(58.73%)	0.04*
patients with abnormal thyroid function and hyperProlactinemia	5 (7.93%)	0.03*
Total	63 (100%)	0.005**

***significant** ****highly significant**
This table shows that there was highly significant differences between studied patients as regard to distributions of cases according to thyroid function tests and serum prolactin level.

Table (7): Correlation between abnormal uterine bleeding (HMB), hyperthyroidism, hypothyroidism and hyperProlactinemia in studied groups.

	R	P	Sig.
Hyperthyroidism	0.06	< 0.05	S
Hypothyroidism	0.1	< 0.05	S
hyperprolactinemia	0.06	<0.05	S
Heavy menstrual bleeding	0.1	<0.05	S

Table 7; showed that there was positive significant Correlation between abnormal uterine bleeding, hyperthyroidism, hypothyroidism, HMB and hyperProlactinemia in studied patients.

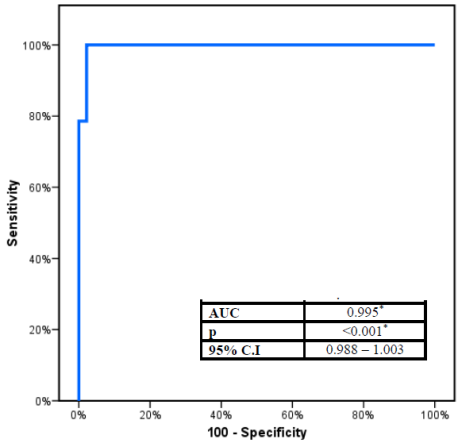

Figure (1): ROC curve for serum prolactin level to predict perimenopausal bleeding.

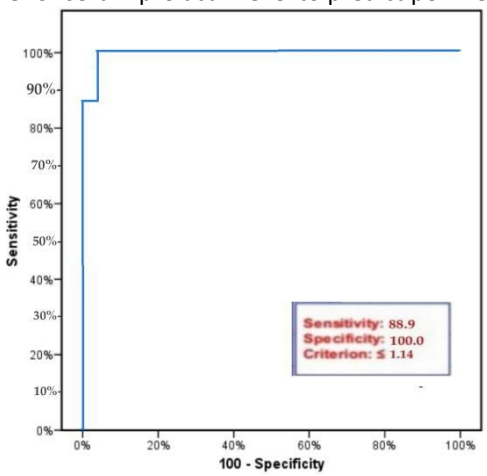

Figure (2): ROC curve for hypothyroidism to predict perimenopausal bleeding

DISCUSSION

In the present study a total of 63 patients with AUB were included between ages of 40-55 years ,which is correlating to **Bhavani et al [11]** 92.8% of menstrual abnormalities were noted in the women between the ages of 35-50 years **[11].** Also another study done by **Mohapatra et al[12]** revealed that the age group had the highest incidence of AUB 30-39 years (39%) **[12].**

In this study, menorrhagia represented (7.9%), polymenorrhagia (12.6%), metromenorrhagia (15.8%), post menopausal bleeding (63.2%). These finding are in agree with the study done by **Begum [8]** menorrhagia (45%), polymenorrhagia (17%) **[8].**

Also the study done by **Jadeja *et al*** further incorporated menorrhagia and polymenorrhagia into the description of aberrant uterine bleeding **[13].** According to other research, menorrhagia is the most prevalent kind of AUB **[14].**

In our study, the complaint of heavy menstrual bleeding represented 7.9% of women and 15.8% with complaints of shortened cycles. This disagree with the finding of Parveen et al they reported that 45% of women in their study reported having excessive menstrual bleeding, and 5% of them complained of shortened cycles **[15].** The small sample size in our study could be the cause of this discrepancy

In present study group no woman had structural abnormalities unlike to study done by **Bhavani et al**, 5.4% had fibroid and5.4% had ovarian cyst **[11]**.

In this study the prevalence of hyperprolactinemia is 20.6% in women with abnormal uterine bleeding this was in contrast to **Shin et al.** They found that 53% of women in the age group with AUB had the condition of 21-30 years **[17].** Another study observed a prevalence of 15-20% in women with AUB **[14].**

Being the most frequent kind, subclinical hypothyroidism is widespread among females with thyroid issues. Both hypothyroidism and hyperthyroidism can cause irregular menstruation. According to this study, hypothyroidism is a type of 23.8% of women with AUB and hyperthyroidism did present in 4.76% among them. These results are slightly higher than those of a prior study by Al-Hakeim, which discovered that among women with monthly irregularities, hypothyroidism was present in 16.1% of them and hyperthyroidism was present in 3.4% of them **[18].** The two studies' differing findings regarding

thyroid dysfunction may be the result of small sample sizes and regional differences.

After compiling the data from patients with subclinical and hypothyroidism, we discovered that 23.8% of women were hypothyroidism4.76 % of women were hyperthyroidism and 71.43 % were euthyroid which is correlating with study done by **Sharma et al [19]** (22% hypo, 14% hyper, 64% euthyroid) **[19]**. And linking to other research conducted by **Byna et al** (21.8% hypo, 12.72% hyper, 64.5% euthyroid) **[4].**

The current investigation demonstrated a strong correlation between hypothyroidism and women with AUB. This outcome is consistent with the findings of other earlier investigations **[20]**. **Whitaker et al** He reported that one of the common conditions that need to be evaluated in women experiencing irregular uterine bleeding is hypothyroidism **[21].** There have been reports of a significant frequency of hypothyroidism in Iraq, particularly in the Kurdistan region **[18].** It is unclear exactly how hypothyroidism affects the menstrual cycle and how it works. Some authors, however, linked this relationship to erratic or absent ovulation, which raises estrogen and lowers luteinizing hormone and causes monthly bleeding **[21] .**

TSH and T3 receptors have been found in the ovaries, which suggests that TSH and T3 have a direct impact on steroidogenesis and that estrogen has a direct impact on thyroid hormone secretion **[22] .**

The current study revealed that among women experiencing irregular menses, there was a noteworthy rise in the prevalence of thyroid diseases +ve substantial correlation between TSH and the perimenopausal phase, with a P value of (0.01)Similarly, **Attia et al [23]** reported significantly increased values of total and free T3/T4 among women with menorrhagia.

Of the 135 women with irregular periods in the research, 26 percent had elevated TSH levels **[24].** Thyroid dysfunction treatment may be able to correct irregular menstruation and maintain a patient's ability to become pregnant; some researchers have come to the conclusion that any woman experiencing irregular menses should have her thyroid function checked **[25].**

The current investigation assessed the frequency of thyroid issues and hyperprolactinemia in AUB patients. Patients with AUB had greater rates of hypothyroidism, as seen by higher levels of free T3/T4 and raised TSH, along with a higher incidence of hyperprolactinemia.

These results prompted the research institutions to examine all perimenopausal women with AUB for elevated levels of prolactin and thyroid hormone. In comparison, just 3.2% of the women who had regular menses had a raised prolactin level; in the majority of these cases, the elevation was small but persistent, thus we do not think that screening should be done for everyone. The prevalence of hyperprolactinemia among patients with menstruation-related issues has been assessed in the past; the majority of these studies included individuals who experienced oligomenorrhea or amenorrhea **[26].**

Based on financial concerns, the National Institute for Health and Care Excellence guidelines for the management of AUBrecommend against the routine testing of prolactin and thyroid hormones **Salvatore et al [27]**, whereas a review from the American Academy of Family Physicians **Johar et al [28]** suggests that people with AUB should have their TSH and prolactin levels measured.

Long-standing theories link thyroid issues to hyperprolactinemia, while some research has found no connection between prolactin and thyroid hormones **[29] .**

In humans, a connected mechanism regulates the release of prolactin and TSH. The pituitary thyrotrophs and lactotrophs have demonstrated varying sensitivity to the common stimulatory and inhibitory chemicals, indicating the possibility of a shared regulation mechanism **[28].** The present investigation demonstrated a clear correlation between hyperprolactinemia and aberrant TSH, suggesting a shared mechanism influencing the menstrual cycle.

This study limitations included sample size and a brief follow-up time compared to other studies. Thus, the study's findings might not accurately represent the situation throughout the entire nation.

CONCLUSIONS

In conclusion, we concluded that Abnormal uterine bleeding is strongly associated with thyroid-related disorders especially hypothyroidism at cut off value of TSH > (29.1) and also associated with hyperprolactinemia at cut off value of serum prolactin > (45.1).

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