The Relationship between Thyroid Disorders and Hyperprolactinemia in Perimenopausal Women with Abnormal Uterine Bleeding

Ali El-Shabrawy Ali, Safaa Abdel-salam Ibrahim, Asmaa Abdelaziz Mostafa Mohamed, Mai mostafa zaitoun

Obstetrics and Gynecology Department, Faculty of Medicine, Zagazig university, Egypt

Corresponding author: Asmaa Abdelaziz Mostafa Mohamed

Email: asmaaelbehery670@gmail.com

Article History: **Received:** 26.05.2023 **Revised:** 28.06.2023 **Accepted:** 25.07.2023

Abstract: Abnormal uterine bleeding (AUB) is a common complication in perimenopausal period with many different mechanisms, one of these causes may be due to thyroid disorders and abnormal prolactin level.

Keywords: AUB, Thyroid, Hyperprolactinemia.

DOI:10.48047/ecb/2023.12.10.988

Introduction:

Abnormal Uterine Bleeding (AUB) is defined as any type of bleeding that does not fall within the normal range for amount, frequency, duration and cyclicity **(1).**

It is one of the most common presentations affecting one -third of the patients attending to gynecology clinics **(2).** It occurs in 15%–20% of women between menarche and menopause **(3).**

The international Federation of Gynecology and Obstetrics(FIGO) created a classification system for the several etiologies of AUB ,that separates structural and non-structural causes of bleeding with the acronym PALM COEIN (Polyp, Adenomyosis, Leiomyoma, Malignancy, Coagulopathy, Ovulatory, Endometrial, Iatrogenic and Not otherwise classified) (**4).**

Perimenopause is considered a period of transition before the onset of menopause, starting with menstrual irregularity, and ending after 1 year of amenorrhea, at an average age of 47 years **(5).**

Menstrual abnormality is primarily a disorder of hypothalamo-pituitary-ovarian axis through direct or indirect effect on target organ **(6**).

Thyroid disorders are common in females, The mechanism by which the thyroid disorders is associated with AUB may be explained by altering thyroid stimulating hormone (TSH) response, increasing prolactin levels, altering luteinizing hormone (LH) response, affecting peripheral conversion of androgens to estrogens, altering sex hormone binding globulin (SHBG) and affecting coagulation pathways by interrupting the production of coagulation factors VII, VIII, IX, and XI, causing menorrhagia, it also has effect on lipid profile **(7).**

Among women with hypothyroidism, hyperprolactinemia is induced by thyrotropin-releasing hormone (TRH). This

stimulation altered the pulsatile secreation of the Gonadotropin-releasing hormone (GnRH) which leads to defect or delay in Luteinizing hormone(LH)response leading to luteal phase defect and anovulation **(8).**

Hypothyroidism also lowers the synthesis of sex hormone-binding globulin (SHBG) and affects the peripheral consumption of estrogen causing aberrant pituitary feedback (**9)**.

In hyperthyroidism, the production of (SHBG) increases substantially. The synthesis of estrogens from androgens in the periphery is augmented, and estrogen metabolism is disrupted (**10).**

Abnormal uterine bleeding has a strong association with thyroid disorders. The most common type of disorder is subclinical hypothyroidism. Thus, all patient of AUB must be evaluated for thyroid dysfunction**(11)**.

Hyperprolactinemia is a condition of elevated serum levels of prolactin ,its prevalence varies from 0.4% in the normal adult population to as high as 9%–17% among women with menstrual conditions(**6).**

A high serum prolactin level can disturb follicular maturation and corpus luteum function , and leads to inhibition of the normal pulsatile secretion of gonadotropin-releasing hormone in the hypothalamus. It also provokes deficient secretion of luteinizing hormone(LH) and follicle-stimulating hormone(FSH), in amounts which become not adequate to induce a proper ovarian response (**12).**

Abnormal uterine bleeding

Definition:

Abnormal Uterine Bleeding (AUB) is defined as any type of bleeding that does not fall within the normal range for amount, frequency, duration and cyclicity **(25)**

Etiology & pathophysiology:

Fédération International de Gynécologie et d'Obstétrique (FIGO) further created a classification system for several etiologies of AUB this classification system separates structural and non-structural sources of bleeding with the acronym **PALM-COEIN**: ((**P**olyp, **A**denomyosis, **L**eiomyoma, **M**ali gnancy (and hyperplasia), **C**oagulopathy, **O**vulatory disorders, **E**ndometrial, **I**atrogenic and **N**ot otherwise classified The 'PALM' are structural causes which are assessed visually (imaging and histopathology) and the 'COEIN' are non-structural)) **(26)**

Perimenopause

The perimenopausal period or climacteric begins with the irregularity of the menstruation cycle and extends up to 1 year after permanent cessation of menses**(26)**

It refers to the time period in the late reproductive years generally in the late 40s to early 50s. During this climacteric period, menstrual cycles become occasionally anovulatory due to a gradual decrease in the recruitment of ovarian follicles with a subsequent decline in the level of oestradiol. This downturn of the hormons causes increased incidence of prolonged cycles of amenorrhoea alternating with heavy menstrual bleeding **(27).**

Thyroid disorders and AUB

Thyroid disorders are common in the female population, with approximately 0.8 per 1000 women per year developing hyperthyroidism and 3.5 per 1000 per year developing spontaneous hypothyroidism **(18).**

The ovulatory disorder is the most common cause of AUB which occurs secondary to thyroid dysfunction. Many studies like Danese MD et al. and Douglas L Wilansky et al. said that any menstrual irregularity in non-pregnant women justifies screening for thyroid disorders **(28)** thus thyroid dysfunction may have profound effects on the female reproductive system. Both hypothyroidism and hyperthyroidism are associated with a variety of changes in reproductive function, including delayed onset of puberty, anovulatory cycles and abnormally high fetal wastage **(17).**

Abnormality of menstruation is primarily a disorder of hypothalamo-pituitary-ovarian axis.Thyroid hormones are thought to affect the menstrual pattern directly through an effect on ovarian-specific thyroid hormone receptors**(29)** and indirectly via their effects on sex hormone binding globulin, prolactin, and gonadotropin-releasing hormone secretion, and on coagulation factors **(20)**

The mechanism by which the thyroid disorders is associated with AUB :

It may be explained by altering thyroid stimulating hormone (TSH) response, increasing prolactin levels, altering luteinizing hormone (LH) response, affecting peripheral conversion of androgens to estrogens, altering sex hormone binding globulin (SHBG) and affecting coagulation pathways by interrupting the production of coagulation factors VII, VIII, IX, and XI, causing menorrhagia, it also has effect on lipid profile **(7)**

Hyperprolactinemia

Hyperprolactinemia is a condition of elevated serum levels of prolactin, a 198-amino-acid protein (23 kD) produced in the lactotroph cells of the anterior pituitary gland **(5).**

Hyperprolactinemia is one of the most common endocrine disorders of the hypothalamic–pituitary axis in young women and is associated with ovulatory dysfunction that results in menstrual irregularities**(30)**

The prevalence of hyperprolactinemia varies from 0.4% in the normal adult population to as high as 9%–17% among women with menstrual conditions such as amenorrhea or polycystic ovarian syndrome**(15)**

There is a known relationship between hyperprolactinemia and reproductive disorders, amenorrhea, and irregular bleeding **(31)**

The mechanism by which the hyperprolactinemia is associated with AUB:

A high serum prolactin level can disturb follicular maturation and corpus luteum function , and leads to inhibition of the normal pulsatile secretion of gonadotropin-releasing hormone in the hypothalamus. It also provokes deficient secretion of luteinizing hormone and

follicle-stimulating hormone, in amounts not adequate to induce a proper ovarian response **(12)**

Relationship between Thyroid Disorders and Hyperprolactinemia in Perimenopausal Women with AUB:

Perimenopausal abnormal uterine bleeding (AUB) is defined as uterine blood flow that is erratic **(1).** This is one of the most prevalent presentations in gynecology clinics where patients experience blood flow that does not meet the typical bleeding characteristics such as volume, occurrence, duration, and/or cycles **(2).** AUB is a frequently occurring disorder that affects 15-20% of women between the phases of early puberty and menopause. AUB may present as sexual malfunction, irregular menstrual cycle, and early menopause. The beginning of clinically overt hypothyroidism or hyperthyroidism is anticipated by menstrual disturbances **(13).**

In many cases of AUB, after ruling out various causes such as cervical or uterine pathology, or pregnancy, patients are usually managed by hormonal treatment or blind surgical therapy **(14).**

Hyperprolactinemia is one of the most common endocrine disorders of the hypothalamic–pituitary axis in young women and is associated with ovulatory dysfunction that results in menstrual irregularities **(30)**

A high serum prolactin level can disturb follicular maturation and corpus luteum function **(15).**

And leads to inhibition of the normal pulsatile secretion of gonadotropin-releasing hormone in the hypothalamus. It also provokes deficient secretion of luteinizing hormone(LH) and follicle-stimulating hormone(FSH), in amounts not adequate to induce a proper ovarian response (**12)**.

The ovulatory disorder is the most common cause of AUB which occurs secondary to thyroid dysfunction **(16).** Thus thyroid dysfunction may have profound effects on the female reproductive system. Both hypothyroidism and hyperthyroidism are associated with a variety of changes in menstrual cycle **(17).**

Thyroid hormones are thought to affect the menstrual pattern directly through an effect on ovarian-specific thyroid hormone receptors and indirectly via their effects on sex hormone binding globulin, prolactin, and gonadotropin-releasing hormone secretion, and on coagulation factors **(19).**

Several studies have shown that 15%–26% of menstrual cycle disorders result from thyroid dysfunction, also highlighted the importance of thyroid function tests in patients with menorrhagia and concluded that medical treatment given in an appropriate timeframe can resolve the symptoms **(20).**

Among women with hypothyroidism, hyperprolactinemia is induced by thyrotropin-releasing hormone (TRH). This stimulation modifies the pulsation of the Gonadotropin-releasing hormone (GnRH). The alteration results in anovulation and luteal phase deficiencies due to hindered response of luteinizing hormone (LH) (**8).**

Thyroid hormones also regulate the interaction of the follicle-stimulating hormone (FSH) and LH receptors; an effect that is significantly important in the production of progesterone hormone **(9)**.

Hypothyroidism also lowers the synthesis of sex hormone-binding globulin (SHBG) and affects the peripheral consumption of estrogen. The abnormal activity results in aberrant pituitary feedback **(21).**

Moreover, it also interrupts the production of coagulation factors such as Factor VII, VIII, IX, and XI, thereby instigating menorrhagia **(10).**

In cases of hyperthyroidism, the production of SHBG increases substantially. The synthesis of estrogens from androgens in the periphery is augmented, and estrogen metabolism is disrupted **(10).**

There exists a strong relationship between the thyroid hormone and regular steroid activity. The activity is crucial for the ovaries to function. The clinical management of thyroid dysfunction is essential to regulate the menstrual cycle **(22).**

The presence of menstrual abnormalities, sterility, and comorbidities are common among women with disrupted thyroid function **(23).**

So screening by evaluating prolactin and thyroid hormone levels is recommended for all patients with AUB, even in the absence of galactorrhea **(24).**

References:

1. **Goldstein, S. R., & Lumsden, M. A. (2017).** Abnormal uterine bleeding in perimenopause. *Climacteric*, *20*(5), 414-420.
2. **Bacon, J. L. (2017).** Abnormal uterine bleeding: current classification and clinical management. *Obstetrics and Gynecology Clinics*, *44*(2), 179-193.
3. **Singh, S., Best, C., Dunn, S., et al. (2018).** No. 292-Abnormal uterine bleeding in pre-menopausal women. *Journal of Obstetrics and Gynaecology Canada*, *40*(5), e391-e415.
4. **Huguelet, P. S., Buyers, E. M., Lange-Liss, J. H., et al. (2016).** Treatment of acute abnormal uterine bleeding in adolescents: what are providers doing in various specialties?. *Journal of Pediatric and Adolescent Gynecology*, *29*(3), 286-291.
5. **Delamater, L., & Santoro, N. (2018).** Management of the perimenopause. *Clinical obstetrics and gynecology*, *61*(3), 419.
6. **Speroff, L., Fritz, M. A. (2005)**. Clinical Gynecologic Endocrinology And Infertility. 7th ed., Philadelphia, PA: Lippincott Williams and Wilkins; p. 402. 547, 549
7. **Byna, P., Siddula, S., Kolli, S., et al. (2015).** Thyroid abnormality in perimenopausal women with abnormal uterine bleeding. *Int J Res Med Sci*, *3*(11), 3250-3.
8. **Koyyada, A., & Orsu, P. (2020).** Role of hypothyroidism and associated pathways in pregnancy and infertility: Clinical insights. *Tzu-Chi Medical Journal*, *32*(4), 312.
9. **Thaler, M. A., Seifert-Klauss, V., &Luppa, P. B. (2015)**. The biomarker sex hormone-binding globulin–from established applications to emerging trends in clinical medicine. Best practice & research Clinical endocrinology & metabolism, 29(5), 749-760.
10. **Ordookhani, A., &Burman, K. D. (2017).** Hemostasis in hypothyroidism and autoimmune thyroid disorders. *International journal of endocrinology and metabolism*, *15*(2).

11. **Begum, M. (2021)**. Association between Thyroid Disorders and Abnormal Uterine Bleeding in Reproductive Ages in a Private Medical College Hospital, Dhaka, Bangladesh. *SchInt J ObstetGynec*, *4*(11), 476-480.
12. **Bargiota, S. I., Bonotis, K. S., Messinis, I. E., et al. (2013).** The effects of antipsychotics on prolactin levels and women's menstruation. *Schizophrenia research and treatment*, *2013*.
13. **Singh, S., Best, C., Dunn, S. et al. (2013).** Abnormal uterine bleeding in pre-menopausal women. *Journal of obstetrics and gynaecology Canada*, *35*(5), 473-475.
14. **Warner, P. E., Critchley, H. O., Lumsden, M. A. et al. (2004).** Menorrhagia I: measured blood loss, clinical features, and outcome in women with heavy periods: a survey with follow-up data. American journal of obstetrics and gynecology, 190(5), 1216-1223.
15. **Fraser, I. S., & Zhuang, G. L. (1990).** Polymers of prolactin and their clinical significance. Obstetrical & Gynecological Survey, 45(8), 515-520.
16. **Thakur, M., Maharjan, M., Tuladhar, H. et al. (2020).** Thyroid dysfunction in patients with abnormal uterine bleeding in a tertiary care hospital: a descriptive cross-sectional study. *JNMA: Journal of the Nepal Medical Association*, *58*(225), 333.
17. **Singh, L., Agarwai, C. G., Chowdhary, S. R. et al. (1990).** Thyroid profile in infertile women.
18. **Taylor, P. N., Albrecht, D., Scholz, A. et al. (2018).** Global epidemiology of hyperthyroidism and hypothyroidism. *Nature Reviews Endocrinology*, *14*(5), 301-316.
19. **Vanderpump, M. P. J., Tunbrldge, W. M. G., French, J., et al. (1995).** The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clinical endocrinology, 43(1), 55-68.
20. **Poppe, K., Velkeniers, B., & Glinoer, D. (2007).** Thyroid disease and female reproduction. *Clinical endocrinology*, *66*(3), 309-321.
21. **Lecomte, P., Lecureuil, N., Lecureuil, M. et al. (1995).** Age modulates effects of thyroid dysfunction on sex hormone binding globulin (SHBG) levels. *Experimental and clinical endocrinology & diabetes*, *103*(05), 339-342.
22. **Birjandi, B., Ramezani Tehrani, F., Amouzegar, A., et al. (2021).** The association between subclinical hypothyroidism and TPOAb positivity with infertility in a population-based study: Tehran thyroid study (TTS). *BMC Endocrine Disorders*, *21*, 1-9.
23. **Al-Jaroudi, D., Yassin, S., Al Enezi, N., et al. (2018).** Hypothyroidism among subfertile women. *Clinical and Experimental Obstetrics & Gynecology*, *45*(1), 63-67.
24. **Hamid, A. M. A., Borg, T. F., & Madkour, W. A. (2015).** Prevalence of hyperprolactinemia and thyroid disorders among patients with abnormal uterine bleeding. *International Journal of Gynecology & Obstetrics*, *131*(3), 273-276.
25. **Goldstein, S. R., & Lumsden, M. A. (2017).** Abnormal uterine bleeding in

perimenopause. Climacteric, 20(5), 414-420.

26. **Munro, M. G., Critchley, H. O., Broder, M. S., & Fraser, I. S. (2011).** FIGO Working Group on Menstrual Disorders FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet, 113(1), 3-13.
27. **Kotdawala, P., Kotdawala, S., & Nagar, N. (2013**). Evaluation of endometrium in peri-menopausal abnormal uterine bleeding. Journal of mid-life health, 4(1), 16.
28. **Thakur, M., Maharjan, M., Tuladhar, H., Dwa, Y., Bhandari, S., Maskey, S., & Bajracharya, M. (2020).** Thyroid dysfunction in patients with abnormal uterine bleeding in a tertiary care hospital: a descriptive cross-sectional study. JNMA: Journal of the Nepal Medical Association, 58(225), 333.
29. **Doufas, A. G., & Mastorakos, G. (2000).** The hypothalamic-pituitary-thyroid axis and the female reproductive system. Annals of the New York Academy of Sciences, 900(1), 65-76.
30. **Lee, D. Y., Oh, Y. K., Yoon, B. K., & Choi, D. (2012).** Prevalence of hyperprolactinemia in adolescents and young women with menstruation-related problems. American journal of obstetrics and gynecology, 206(3), 213-e1.
31. **Eftekhari, N., Mirzaei, F., & Karimi, M. (2008).** The prevalence of hyperprolactinemia and galactorrhea in patients with abnormal uterine bleeding. Gynecological Endocrinology, 24(5), 289-291.