



A Study Protocol to Assess the Correlation of Endometrial Morphology with Concerned Hormone Levels in Patients of Abnormal Uterine Bleeding

Tanvi Bhardwaj^{a*#}, Kishor Hiwale^{a≡} and Sunita Vagha^{a°}

^a Department of Pathology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi (Meghe), Wardha, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i64B35425

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/81047>

Study Protocol

Received 25 October 2021
Accepted 29 December 2021
Published 30 December 2021

ABSTRACT

Background: Abnormal-uterine-bleeding (AUB) is caused due to numerous systemic or functional etiologies. Patients may come with metrorrhagia, menorrhagia, intermenstrual bleeding and polymenorrhea. The underlying pathology can be ascertained by histological variations of endometrium considering the age, the phase of menstrual cycle and the use of any exogenous hormones. This study aims to assess the correlation between endometrial changes and concerned hormone levels.

Methodology: This will be a Prospective study conducted for two years in Histopathology Department of Pathology, JNMC, Wardha. Total 65 female patients with complaint of irregular uterine bleeding will be included in this study. The histomorphology patterns of endometrial lesions will be studied and classified according to WHO classification. The collected data will be analysed using appropriate statistical methods.

Results: A Significant correlation is expected between endometrial changes and concerned hormone levels.

Conclusion: Conclusion will be drawn from the results obtained from the study.

[#] Junior Resident;

[≡] Professor;

[°] Professor and Head;

*Corresponding author: E-mail: tanvitiwari.491@gmail.com;

Keywords: Abnormal-uterine-bleeding (AUB); estrogen; progesterone; endometrium; histopathology.

1. INTRODUCTION

The definition of Abnormal- uterine-bleeding (AUB) is any form of bleeding which is not within the normal range of quantity, frequency, duration or cyclicity. AUB, which involves both acute and chronic AUB, is thought to be a symptom of potential uterine or systemic illness. In all age categories, it is the most prevailing complaint [1]. In adolescents, vaginal bleeding which occurs before menarche is referred to abnormal, while in females of child bearing and premenopausal age, any variation in menstrual period, frequency, duration or amount of flow, as well as bleeding between cycles, are considered as an abnormal sign.

There are systemic or functional etiologies for the AUB. Patients may come with metrorrhagia, menorrhagia, intermenstrual bleeding and polymenorrhea. The underlying pathology can be ascertain by histological variations of endometrium considering the age , the phase of menstrual cycle and the use of any exogenous hormones [1]. Other factors may be psychological stress, weight (obesity, anorexia, or rapid change), exercise, endocrinopathy, neoplasm, medication, or unexplained etiology, according to the studies carried out [2]. The frequency of abnormal uterine bleeding in patients is more prevalent in the age group of 40 to 49 years, where the prevalence in the population pool was around 64 percent [3].

The word abnormal-uterine-bleeding (AUB) encompasses both organic and non-organic causes. Dysfunctional-uterine-bleeding (DUB) is actually a subtype of AUB that, due to non-organic etiology, includes irregular bleeding. In 50 percent of women with AUB, it is present . For abnormal-uterine bleeding, endometrial biopsy is generally indicated to rule out organic pathology. Age and menstrual history are of particular significance since, according to age and menstrual status, the causes of abnormal-uterine-bleeding vary. In women of the reproductive age group, pregnancy complications, including abortion, are normal, while atrophy and organic pathologies are seen more commonly in postmenopausal women [1-3].

Only by ruling out the organic causes after the histopathological exam can a diagnosis of dysfunctional-uterine-bleeding be made. In DUB, there are three trends usually seen. The first is

referred to as "estrogen breakthrough bleeding," which happens from a "persistent follicle" in the continuous production of estrogen. The proliferative endometrium grows in size, thus increasing its own blood supply, and there is breakthrough bleeding. The second is known as "estrogen withdrawal bleeding," which is due to "failed follicle," i.e. 2, subnormal estrogen is released by the follicles. Both of these causes are anovulation-accredited. The third one is "ovulatory endometrium" due to defects in the follicular/luteal process [2-4].

Hypothyroidism is a common cause of multiple disorders in women of reproductive age, ranging from sexual dysfunction, menstrual defects and infertility. The first menstrual symptoms for women with hypothyroidism are disordered cycles and irregular blood flow [5].

As part of a hysterectomy specimen, the endometrium may be examined . DUB cases, depending significantly on the age and clinical history of the patient, may have structural or functional causes. Some studies have shown infertility as the most common sign of endometrial biopsy and endometrium in the secretory process as the most common morphological pattern [6].

A lot of women with fibroids are completely asymptomatic. However, in many women, gynaecological services with AUB and associated iron-deficiency anaemia are most frequently present. Everyday life is frequently interrupted for women with uterine fibroids, and fibroids are a leading sign of hysterectomy [7].

The length and heaviness of bleeding episodes in the form of variance, perimenopausal women facing menstrual issues experience cycle irregularity. Follicular growth is irregular during this process, leading to variability in the amount of oestrogen. Therefore in order to understand its potential consequences for reproductive cancers and other health outcomes, detailed characterization of sex hormone dynamics during perimenopause is important [8].

Some adolescents do not know that their patterns of bleeding are abnormal, although it is recognized that menstrual cycles during puberty are sometimes irregular. AUB and/or AUB alone may have long-term health effects, affect the quality of life and have an effect on school attendance [9].

The irreversible cessation of menstruation arising from the absence of follicular function of the ovary is menopause. Bleeding is labeled as postmenopausal bleeding 12 months after the last period of menstruation (PMB). Around 3 percent of menopausal women are affected by this condition and require prompt and thorough evaluation [10].

Abnormal uterine bleeding can occur in different forms at any age and has various modes of presentation. Excessive uterine bleeding can result from a wide range of conditions during reproductive age, from physiological processes to malignant lesions that include organic, systemic, and hormonal responses. Adenomyoma, endometrial polyps, ovarian tumors, pelvic inflammatory disease (PID), endometrial hyperplasia, endometrial carcinoma, hormonal dysfunction (such as hypothyroidism), and hypothalamic-pituitary disorders can be induced by fibromyoma. Abnormal uterine bleeding happens without any systemic causes or any organic lesions of the genital tract in a significant number of patients and the term dysfunctional uterine bleeding is used for this [11].

The normal cyclic physiological changes that occur during the reproductive cycle in the endometrium of females are regulated by the cyclical release of ovarian estrogen and progesterone. Concentration of receptors for these hormones also varies respectively. In hyperplasia's and endometrial cancers, especially type I Estrogen and progesterone hormones are also expressed. The level of these hormones gives a prognostic information. They also offer the option of hormone therapy. The key factor involved in the pathogenesis of Dysfunctional-Uterine-Bleeding is hormonal imbalance. This imbalance is best studied by endometrium histopathological assessment. Abnormal bleeding can be caused by well-defined pathological conditions such as chronic endometritis, endometrial polyp, submucosal leiomyomas [12].

1.1 Research Gap

The present study aims to study the correlation of morphological findings of endometrium with concerned hormone levels in patients of abnormal-uterine-bleeding at AVBRH and to correlate the histopathological findings in endometrium with concerned hormonal level in patients of AUB.

1.2 Research Question

With the understanding of changes in endometrium in patients of AUB in correlation with concerned hormone level, the following research question is framed-

“Does correlation of morphological findings of endometrium with concerned hormone levels in patients of abnormal-uterine-bleeding.”

2. METHODOLOGY

2.1 Study Design

Observational, analytical and prospective.

2.2 Place of Study

Department of Pathology, JNMC, Sawangi(Meghe), Wardha, Maharashtra.

2.3 Duration

2020 to 2022 (2 years)

2.4 Methods

- A detailed clinical history regarding age, clinical features, radiological findings and probable diagnosis of the patients will be obtained who have abnormal uterine bleeding.
- The grossed specimens will be then processed in tissue processor and paraffin blocks will be prepared. Sections will be cut and stained by H and E stains. The slides will be assessed under microscopy.
- The histomorphology patterns of endometrial lesions will be studied and classified according to WHO classification.
- The collected data will be tabulated and results will be calculated and analyzed by using appropriate statistical methods.

2.5 Sample Size – 65 Patients

The sample size was calculated by using Krejci and Morgan formula with desired error of margin:

$$n = (Z \alpha/2)^2 \times p \times (1-p) / d^2$$

where,

$Z^{\alpha/2}$ is the level of significance at 5% i.e. 95% confidence interval = 1.96

p = prevalence of AUB in women = 9% = 0.09

$d = \text{desired error of margin} = 7\% = 0.07$

$$n = 1.96^2 \times 0.09 \times (1 - 0.09) / 0.07^2$$

$n = 64.20$

$n = 65$ patients needed in the study

$n = 65$

2.5.1 Inclusion criteria

- All patients clinically and USG diagnosed cases of AUB, endometrial sampling, hormonal assessment, will be selected in this study group.

2.5.2 Exclusion criteria

- Patients with non-endometrial conditions of abnormal-uterine-bleeding.
- Patients with uterine-bleeding due to Intrauterine Devices.
- Patients presenting with abnormal-uterine-bleeding due to Pregnancy and its related complications.

2.6 Statistical Analysis

Statistical analysis will be carried out by using 'chi-square-test' where a value of $P < 0.05$ will be considered to indicate statistical-significance.

3. EXPECTED RESULTS

The study will be conducted for a period of 2 years and all the observations will be depicted in a well-tabulated master chart.

4. DISCUSSION

Tara et al. conducted a cross-sectional prospective study in the outpatient clinic of Maternity Teaching Hospital in Erbil city from 1st of September, 2017 to 30th of June, 2018 on 100 women. The aim of the study was to highlight the significant association between high thyroid stimulating hormone level and women with abnormal uterine bleeding ($p=0.002$). The study concludes that the thyroid dysfunction is a common cause of abnormal-uterine-bleeding among females of reproductive age group [5].

Ifeyinwa Mary Asuzu et al. A cross-sectional research was performed on specimens collected over a one-year period at the Department of Pathology of Premier Hospital, Abuja. Four hundred and eighty-six endometrial biopsy and curettage samples were examined from women

with irregular uterine bleeding submitted to the histopathology laboratory. The research concludes that retained products of pregnancy are the most common source of abnormal-uterine-bleeding in this population [6].

Lucy Whitaker et al. conducted a prospective study with the aim that AUB also co-exists with fibroids, but the relationship between the two remains incompletely understood and a menstrual bleeding complaint may be incidental to the identification of fibroids in many women. The study concludes. The care must remain individualized and involve the effect of pressure symptoms, the need for fertility retention and the need for contraceptives, as well as the control of their AUB to achieve enhanced quality of life [7].

MaltiKumariMaurya et al. A prospective research was performed to assess the clinical characteristics and histopathological results of irregular uterine bleeding and to compare the hormone profile in perimenopausal women. The study concludes that intermenstrual bleeding can represent a troubling symptom of endometrial malignancy in perimenopausal females. Further management and result can be predicted by histopathological endometrium trend and clinicopathological variables [8].

Selin Elmaoğulları et al. A prospective research was performed to establish that because of the immature hypothalamic-pituitary-ovarian axis and a related bleeding disorder in about 20 percent of HMB cases, anovulatory cycles are the leading etiology of HMB. In general, AUB is a likely cause of endocrine disorders such as hypothyroidism, polycystic ovarian syndrome and hyperprolactinemia. The study concludes that the AUB has been one of the key problems of adolescent gynecology, and the AUB is the most frequent anovulatory HMB presentation.. Anovulatory processes in most teenagers are normally hormonal and resolve spontaneously as the hypothalamic-pituitary-ovarian axis matures [9].

Pushpa Singh et al. conducted a prospective study withThe purpose of this research was to study endometrial thickness by transvaginal sonography and to compare it with the cytological pattern assessed by endometrial aspiration and the histopathological pattern of hysteroscopic biopsy. The study concludes that the role of endometrial thickness in the diagnosis of patients at high risk, especially with comorbid conditions, cannot be undermined. In selected

cases of PMB by hysteroscopy, histopathological examination is mandatory for ruling out malignancy [10].

Mitali Mahapatra et al. conducted a prospective study with the aim study the various aetiopathological factors responsible for AUB in women ages 20-55 years, and to correlate the clinical presentation with ultrasonography, hysteroscopy, laparoscopy and histopathological finding. The study concludes that it is seen that incidence of AUB is more common in 5th decade of life and in multiparous women. Menorrhagia is the most common bleeding pattern followed by metrorrhagia. Histopathological examination of the endometrium revealed that whatever may be the pathology, proliferative endometrium is the most common pattern [11].

Few other related studies were reviewed [13-15]. Studies on abnormal uterine bleeding were also reported by Gadge et al. [16], Kalambe et al. [17] and Selvanathan et al. [18-32].

5. CONCLUSION

Conclusion will be drawn from the results obtained from the study.

CONSENT

As per international standard or university standard, patients' written consent will be collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval will be collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bhat R, Sudhamani S, Roplekar P. Histopathological study of endometrium in abnormal uterine bleeding in perimenopausal and postmenopausal women. *J Sci Soc.* 2019;46(3):95-98.
2. Kumar D. Clinico-pathological correlation of abnormal uterine bleeding. *International journal of Medical and Health Research.* 2016;2(2):63-64.
3. Kathleen G, Patil MS. histopathological correlation of endometrial sample simple and post menopausal women with abnormal uterine bleeding. *IP Journal of Diagnostic Pathology and Oncology.* 2019; 4(1):32-38.
4. Jewson M, Purohit P, Lumsden MA. Progesterone and abnormal uterine bleeding/menstrual disorders. *Best Practice & Research Clinical Obstetrics & Gynaecology.* 2020;S15216 9342030081X. *J Gynecol Women's Health. Thyroid Dysfunction and Abnormal Uterine Bleeding.* 2019;15(4).
5. Asuzu I, Olaofe O. Histological pattern of endometrial biopsies in women with abnormal uterine bleeding in a hospital in north central nigeria. *International Journal of Reproductive Medicine.* 2018;5.
6. Whitaker L, Critchley HOD. Abnormal uterine bleeding. *Best Pract Res ClinObstetGynaecol.* 2016;34:54-65.
7. Maurya MK. Clinicopathological evaluation of abnormal uterine bleeding (AUB) and its correlation with biochemical hormone profile in perimenopausal women. *J Clin Exp Pathol.* 2018;08 [cited 2020 Sep 6]
8. Elmaogullari S, Aycan Z. Abnormal Uterine Bleeding In Adolescents. *Jcrpe.* 2018 ;10(3):191-7.
9. Singh P, Dwivedi P, Mendiratta S. Correlation of Endometrial Thickness with the Histopathological Pattern of Endometrium in Postmenopausal Bleeding. *J Obstet Gynaecol India.* 2016; 66(1):42-6.
10. Mahapatra M, Mishra P. Clinicopathological evaluation of abnormal uterine bleeding. *J Health Res Rev.* 2015;2(2):45.
11. Kumar V, Abbas AK, Fausto N, Robbins SL, Cotran RS. Robbins and Cotran pathologic basis of disease. Philadelphia, Elsevier Saunders; 2005.
12. Radhikabai P, Borkar K. Evaluation of Abnormal Uterine Bleeding Patients by Conventional Dilatation and Curettage and Hysteroscopically Guided Dilatation and Curettage." *Journal of Datta Meghe Institute of Medical Sciences University.* 2019;14(4):303-9. Available: https://doi.org/10.4103/jdmimsu.jdmimsu_165_19.

13. Daga S, Phatak S. Sonography Evaluation of Abnormal Uterine Bleeding in Perimenopausal Women with Pathological Correlation. *Journal of Datta Meghe Institute of Medical Sciences University*. 2019;14(4):288–92. Available:https://doi.org/10.4103/jdmimsu.jdmimsu_99_19.
14. Wankhade A, Vagha S, Shukla S, Bhake A, Laishram S, Agrawal D, Rastogi N, Wankhade M. To Correlate Histopathological Changes and Transvaginal Sonography Findings in the Endometrium of Patients with Abnormal Uterine Bleeding. *Journal of Datta Meghe Institute of Medical Sciences University*. 2019;1(14):11–15. Available:https://doi.org/10.4103/jdmimsu.jdmimsu_70_18.
15. Gadge AN, Acharya S, Shukla S Phatak. Comparative Study of Transvaginal Sonography and Hysteroscopy for the Detection of Endometrial Lesions in Women with Abnormal Uterine Bleeding in Perimenopausal Age Group. *Journal of SAFOG*. 2018;10(3): 155–60. Available:<https://doi.org/10.5005/jp-journals-10006-1580>.
16. Kalambe M, Jungari M, Chaudhary A, Kalambe A, Shrivastava D. Palm Coein Figo Classification System for Causes of Abnormal Uterine Bleeding (Aub) in Non Gravid Women of Reproductive Age Group in a Peri Urban Tertiary Care Hospital. *International Journal of Current Research and Review*. 2020;12(15):128–33. Available:<https://doi.org/10.31782/IJCRR.2020.121523>.
17. Selvanathan S, Acharya N, Singhal S. Quality of Life after Hysterectomy and Uterus-Sparing Hysteroscopic Management of Abnormal Uterine Bleeding or Heavy Menstrual Bleeding.” *Journal of Mid-Life Health*. 2019;10(2):63–69. Available:https://doi.org/10.4103/jmh.JMH_15_19.
18. James SL, Castle CD, Dingels ZV, Fox JT, Hamilton EB, Liu Z, Roberts NL, Sylte DO, Bertolacci GJ, Cunningham M, Henry NJ. Estimating global injuries morbidity and mortality: methods and data used in the Global Burden of Disease 2017 study. *Injury Prevention*. 2020; 26(Suppl 2):i125-53.
19. Kumar A, Chery L, Biswas C, Dubhashi N, Dutta P, Dua VK, Kacchap M, Kakati S, Khandeparkar A, Kour D, Mahajan SN. Malaria in South Asia: prevalence and control. *Acta tropica*. 2012 Mar 1;121(3):246-55.
20. Chole RH, Patil RN, Basak A, Palandurkar K, Bhowate R. Estimation of serum malondialdehyde in oral cancer and precancer and its association with healthy individuals, gender, alcohol, and tobacco abuse. *Journal of cancer research and therapeutics*. 2010 Oct 1;6(4):487.
21. Pradhan S, Madke B, Kabra P, Singh AL. Anti-inflammatory and immunomodulatory effects of antibiotics and their use in dermatology. *Indian journal of dermatology*. 2016 Sep;61(5):469.
22. Acharya S, Shukla S, Mahajan SN, Diwan SK. Acute dengue myositis with rhabdomyolysis and acute renal failure. *Annals of Indian Academy of Neurology*. 2010 Jul;13(3):221.
23. Gadbail AR, Chaudhary M, Patil S, Gawande M. Actual Proliferating Index and p53 protein expression as prognostic marker in odontogenic cysts. *Oral Diseases*. 2009 Oct;15(7):490-8.
24. Prasad N, Bhatt M, Agarwal SK, Kohli HS, Gopalakrishnan N, Fernando E, Sahay M, Rajapurkar M, Chowdhary AR, Rathi M, Jeloka T. The adverse effect of COVID pandemic on the care of patients with kidney diseases in India. *Kidney International Reports*. 2020 ;5(9):1545-50.
25. Walia IS, Borle RM, Mehendiratta D, Yadav AO. Microbiology and antibiotic sensitivity of head and neck space infections of odontogenic origin. *Journal of maxillofacial and oral surgery*. 2014; 13(1):16-21.
26. Lohe VK, Degwekar SS, Bhowate RR, Kadu RP, Dangore SB. Evaluation of correlation of serum lipid profile in patients with oral cancer and precancer and its association with tobacco abuse. *Journal of Oral Pathology & Medicine*. 2010;39(2): 141-8.
27. Korde S, Sridharan G, Gadbail A, Poornima V. Nitric oxide and oral cancer: A review. *Oral oncology*. 2012;48(6):475-83.
28. Gondivkar SM, Gadbail AR. Gorham-Stout syndrome: a rare clinical entity and review of literature. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2010;109(2):e41-8.
29. Gadbail AR, Chaudhary M, Gawande M, Hande A, Sarode S, Tekade SA, Korde S, Zade P, Bhowate R, Borle R, Patil S. Oral

- squamous cell carcinoma in the background of oral submucous fibrosis is a distinct clinicopathological entity with better prognosis. *Journal of Oral Pathology & Medicine*. 2017;46(6):448-53.
30. Gadre PK, Ramanojam S, Patankar A, Gadre KS. Nonvascularized bone grafting for mandibular reconstruction: myth or reality?. *Journal of Craniofacial Surgery*. 2011;22(5):1727-35.
 31. Sorte K, Sune P, Bhake A, Shivkumar VB, Gangane N, Basak A. Quantitative assessment of DNA damage directly in lens epithelial cells from senile cataract patients. *Molecular Vision*. 2011;17:1.
 32. Basak S, Rajurkar MN, Mallick SK. Detection of *Blastocystis hominis*: a controversial human pathogen. *Parasitology Research*. 2014;113(1): 261-5.

© 2021 Bhardwaj et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:
<https://www.sdiarticle5.com/review-history/81047>