

DOI: <https://dx.doi.org/10.18203/2320-1770.ijrcog20223471>

Original Research Article

Analysis of endometrial biopsy reports from adult women with abnormal uterine bleeding, a cross-sectional descriptive study

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Received: 23 November 2022

Revised: 12 December 2022

Accepted: 13 December 2022

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ABSTRACT

Background: Abnormal uterine bleeding is a common complaint in most women of different ages that prompts seeking gynecologic care. This study aimed to analyze and age-classify the prevalence of endometrial pathologies in women with abnormal uterine bleeding.

Methods: This is a cross-sectional and a descriptive study, conducted at the obstetrics and gynecology department of the American Mission Hospital in the Kingdom of Bahrain on 88 patients who presented with abnormal uterine bleeding between January 2019 and January 2020.

Results: Eighty-eight women with abnormal uterine bleeding demonstrated a fluctuating pattern of twenty endometrial pathologies distributed among five age groups in the range of 30-71. The mean age of the study cohort was 44.9 ± 7.65 years; 55% of which were reported in the 41-50 age group. Benign endometrial polyp was reported as the most common pathology, accounting for 47.8% of the cohort. Although benign endometrial polyp was significantly the highest overall finding in all three age groups younger than 60, disordered proliferative endometrium was the highest reported single pathology in the age group 41-50, ($N=10$, $p \leq 0.0001$).

Conclusions: This study demonstrated that benign endometrial polyp was the most common finding in women with abnormal uterine bleeding. This information could be essential for patient guidance and awareness of the benefits of endometrial biopsy. Eventually, the prediction of the potential endometrial pathology in women with abnormal uterine bleeding is vital for early disease management.

Keywords: Abnormal uterine bleeding, Benign disease of uterus, Cancer of the endometrium, Endometrial hyperplasia

INTRODUCTION

Abnormal uterine bleeding (AUB) is one of the most frequent complaints that prompts seeking gynecologic care, reporting over 70% of consults in both perimenopausal and postmenopausal years.¹ AUB affects 10-30% of women of reproductive age, with an adverse impact on their quality of life.² Variation in the normal

menstrual cycle pattern in the perimenopausal age group may be due to physiological hormonal changes. Nevertheless, the risk of other pathologies varying from an endometrial polyp to benign endometrial hyperplasia to atypical hyperplasia and endometrial carcinoma should always be considered. By definition, AUB is defined as a menstrual flow outside of the normal volume, duration and frequency. The term 'AUB' encompasses a set of

abnormalities, namely, abnormal volume, frequency, duration, and regularity, in addition to intermenstrual bleeding, in accordance with the latest classification system established by the international federation of gynecology and obstetrics (FIGO). FIGO classifies the etiology of AUB under the PALM-COEIN system that outlines structural causes, which may be identified via imaging or histopathology, and non-structural causes that may be identified by clinical assessment or laboratory investigations.³ Besides the clinical assessment and routine laboratory investigations, endometrial sampling is a key investigation in the assessment of AUB. The gold standard investigation for evaluation of AUB is a histopathological examination, which is a necessary tool for tailoring the treatment approach.⁴ In the past, the primary diagnostic test was dilatation and curettage, but this has now been replaced by endometrial biopsy in the office setting (pipelle biopsy) and hysteroscopic directed endometrial biopsy.⁵ The preferred sampling method is office-based biopsy, whereas hysteroscopic dilation and curettage are reserved for when office sampling fails or is inadequate, or cannot be performed.² The sensitivity for pipelle biopsy is comparable to that for hysteroscopic directed biopsy.⁶ As for abnormal uterine bleeding, the American College of Obstetricians and Gynecologists (ACOG) published age-based guidelines on the indications of endometrial sampling.¹⁹ In women younger than forty-five, endometrial biopsy is indicated only if abnormal uterine bleeding is persistent. Endometrial biopsy should also be considered if there is a history of unopposed estrogen exposure, failed medical treatment, or for women at high risk of endometrial cancer. Women above 45 years should undergo endometrial biopsy as part of the workup for the diagnosis of abnormal uterine bleeding, according to ACOG guidelines. Furthermore, women diagnosed with AUB must have menstrual cycles longer than 35 days or shorter than 21 days. Moreover, some characteristics of bleeding must be present, including heavy bleeding during periods, bleeding or spotting after sex or between periods, and postmenopausal bleeding. Finally, an irregular cycle must be present that lasts for 7-9 days.⁷ The purpose of this cross-sectional study was twofold, to determine the clinical spectrum of various causes of AUB, and to identify correlations (if any) among the associated histopathological findings in the different age groups. The findings of this study were helpful to predict the potential endometrial pathology in women with abnormal uterine bleeding, which is vital for early disease management. The study included women in the reproductive age group as well as women in peri and postmenopausal age groups.

METHODS

Study setting and design

This is a cross-sectional and a descriptive study conducted at the American Mission Hospital, which is a private hospital in the Kingdom of Bahrain, in

collaboration with the obstetrics and gynecology department between January 2019 to January 2020.

Participants and study size

The electronic medical records of 98 cases presenting with abnormal uterine bleeding in a one-year period between January 2019 and January 2020 were collected. The demographic characteristics such as age and the presenting complaints were collected to have a fixed background picture of our cohort. Endometrial pathologies were diagnosed on histopathology via dilatation and curettage (D&C), pipelle office biopsy, or hysteroscopic directed endometrial biopsy. The inclusion criteria included all women above the age of 30 who presented with AUB and had an endometrial biopsy. Additionally, patients with idiopathic uterine bleeding were also included in the study and those with leiomyoma, cervical, vaginal pathology, or bleeding disorders were excluded. The age group of patients was identified between 30 -71 years. Eighty-eight cases were included and divided into five age groups: 30-40, 41-50, 51-60, 61-70, and above 70. Ten patients were excluded from the study due to missing data from the electronic medical records, inaccurate data, patients not opting for the biopsy procedure or inadequate sample (Figure 1). This retrospective study was approved by the research ethics committee of the American mission hospital on April 14th, 2021. It should be noted that, among the 88 patients in this study, more than half of the cohort had hysteroscopic directed endometrial biopsy and among the rest, they were mainly office-based pipelle biopsy. About 10 patients had DNC procedure.

Quantitative variables

Our variables were analyzed by coding and inserting them into the IBM SPSS. The variables include age, presenting complaint and the histopathological diagnosis. Cross-tabulation was used to analyse our categorical variable, which is the age group and examine its association with the diagnosis. Frequency tables were used to represent the number of people in each age group as well as the proportion of patients who presented with specific complaints and were clinically diagnosed.

Data sources and measurement

The original data was collected directly from the electronic medical records of the American mission hospital. The data consisted of categorical-nominal variables and the ages were just used as labels for the classifying the categories.

Statistical methods

Continuous variables were represented as the mean and standard deviation. Discrete variables were expressed as frequencies and percentages with 95% confidence interval. Chi-square test was used to compare the

observed versus the expected prevalence of each pathology, p value less than 0.05 is considered statistically significant. All analyses were performed using SPSS version 23 (IBM Corp, Armonk, NY, USA).

RESULTS

Endometrial biopsy of the 88 patients showed a wide spectrum of pathologies in patients with different age

groups who presented with AUB. In our study, 88 patients were included with varying differences and pathologies. The main demographic characteristics of the patients included their age and presenting complaints. For instance, over half of all patients who presented with AUB was reported in the age groups 41-50 representing 55% and 34.8% patients presented with menorrhagia, which counts for the most common presenting complaint.

Table 1: The incidence of the 20 pathologies found per each age group.

Pathological findings	N	%	Age groups (years)				
			30-40	41-50	51-60	61-70	>70
Atypical endometrial hyperplasia with endometrial adenocarcinoma	1	1.1	0	0	1	0	0
Atypical endometrial hyperplasia with endometrial polyp	1	1.1	0	0	1	0	0
Atypical endometrial hyperplasia	2	2.3	1	1	0	0	0
Benign non atypical endometrial hyperplasia	12	13.6	4	4	2	2	0
Benign non atypical endometrial hyperplasia with endometrial polyp	1	1.1	0	1	0	0	0
Stage 2 endometrial carcinoma	1	1.1	0	0	1	0	0
Endometrial adenofibroma	1	1.1	0	0	0	1	0
Benign endometrial polyp	16	18.2	6	7	3	0	0
Benign endometrial polyp and disordered proliferative endometrium	9	10.2	3	6	0	0	0
Inactive endometrium	5	5.7	0	4	1	0	0
Strips of non-neoplastic endometrial glands	1	1.1	0	0	0	0	1
Benign endocervical and endometrial polyp	2	2.3	1	1	0	0	0
Benign endometrial polyp and Benign non atypical endometrial hyperplasia	1	1.1	0	1	0	0	0
Benign endometrial polyp with proliferative endometrium	11	12.5	5	6	0	0	0
Benign endometrial polyp with secretory endometrium	1	1.1	0	1	0	0	0
Proliferative endometrium	4	4.5	1	3	0	0	0
Disordered proliferative endometrium	13	14.8	2	10	1	0	0
Weak proliferative endometrium	1	1.1	1	0	0	0	0
Secretory endometrium with decidualized stroma	2	2.3	0	2	0	0	0
Decidualized endometrium (Exogenous hormone effect)	3	3.4	1	2	0	0	0

Therefore, most of the endometrial biopsies were taken from women in the same age group 41-50 (55%, N=49) followed by 30-40 (28%, N=25), 51-60 (12.3%, N=11), and above 70 years (1.1%, N=1). Thus, the mean age of patients with AUB was 44.9±7.65 years in this study. Prolonged heavy cycle was the second most common (28%) clinical spectrum, also most commonly occurring in the age group of 41-50. The third most common clinical spectrum was women presenting with postmenopausal bleeding and irregular periods (12.4%). The least common presenting complaint was post coital bleeding (1.1%). The incidence of biopsy pathologies reported was significantly different from one age group to another. The pathologies were documented as single or multiple findings, and thus several pathologies had low percentages of incidence but overall increased percentages of pathology such as disordered proliferative endometrium. A total of five to six pathologies have been reported, including single and multiple pathologies. Interestingly, the endometrial polyp was found to be the

most the common pathology with an overall percentage of 17.9% in all age groups, followed by disordered proliferative endometrium, 14.6%, and benign non-atypical endometrial hyperplasia, 13.4%. The incidence of multiple pathology was relatively less than single pathology, with the most common multiple pathology being endometrial polyp with proliferative endometrium, as shown in (Table 1). Endometrial polyp was reported as the most common pathology in all women who reported AUB with a percentage of 47.8%. In particular, the overall incidence of endometrial polyp, as a multiple finding and single finding, was significantly the highest in all three age groups younger than 60, as shown in (Table 2). However, disordered proliferative endometrium was the highest reported single pathology in the age group 41-50, (N=10 single out of 16). A total of 11 patients presented with post-menopausal bleeding and it showed that this age group although did not reach statistical significance, premalignant and malignant findings were the most prominent features. Benign

endometrial polyp and benign non-atypical endometrial hyperplasia were the most common histological finding

in the post-menopausal age group (72.7%).

Table 2: Most common pathological findings compared between age groups.

Pathological finding	N (%) ^a						P value between the age groups
	Age groups (years)						
	Total (N=87)	30-40 (N=25)	41-50 (N=49)	51-60 (N=11)	61-70 (N=3)	>70 (N=1)	
Atypical endometrial hyperplasia	4 (4.6)	1 (4)	1 (2.1)	2 (18.2)	0 (0)	0 (0)	0.4779*
Benign non atypical endometrial hyperplasia	14 (16)	4 (16)	6 (12.3)	2 (18.2)	2 (66.7)	0 (0)	0.1149*
Benign endometrial polyp	42 (47.8)	15 (60)	23 (47)	4 (36.4)	0 (0)	0 (0)	<0.0001*
Disordered proliferative endometrium	22 (25)	5 (20)	16 (32.7)	1 (9.1)	0 (0)	0 (0)	<0.0001*
Inactive endometrium	5 (5.7)	0 (0)	4 (8.2)	1 (9.1)	0 (0)	0 (0)	0.0174*

*The two-tailed P value from Chi square test, a: percentage of cases with this pathological finding out of total number of cases in this specific age group

It is noteworthy that none of the women in this age group presented with atypical endometrial hyperplasia. Benign non-atypical endometrial hyperplasia was the most commonly occurring and almost the only finding seen in the age group 61-70, (N=2 patients). There were four cases of atypical endometrial hyperplasia was most prevalent in the age group 38-51. Similarly, two cases of endometrioid carcinoma were seen in the age group 51-60.

DISCUSSION

The presented data illustrate several endometrial pathologies of women with abnormal uterine bleeding. AUB is a common female disorder across women of reproductive age, affecting 10-30%.² The results showed comparable demographic characteristics such as age and presenting complaints with the available literature. For example, the mean age in our study was 44.9±7.65 years. Biopsy samples were mostly taken from patients in the age group 41-50 (55%) as these were the patients who most presented with AUB. Similarly, in a study on a larger population (6458 participants), the mean age at the time of sampling was 49.5± 9; (n=4466), between 40 and 55 years.⁸ Furthermore, post-coital bleeding was the least frequent presented complaint in our study, accounting for only one patient. Indistinguishable findings were found in a study conducted by Pillai et, al, which evaluated the trends in clinical presentations of 88 outpatient women with AUB. The sample size being similar to our sample size, almost half (40%) of the study population aged 48-51, presented with menorrhagia and dysmenorrhea as the most common associated symptom. Similarly, the study showed only a few patients (N=3), with post coital bleeding.⁹ Focused studies are essential to evaluate the association between the presenting complaint and the pathological finding. In fact, this association can be simply used for patient guidance towards endometrial

biopsy. Regarding the endometrial sampling under the age of 45, American college of obstetricians and gynecologists (ACOG) practice bulletin 128, (July 2012, Reaffirmed 2019), mentions that the primary role of endometrial sampling in patients with AUB is to determine whether carcinoma or premalignant lesions are present; considering the fact that other pathologies related to bleeding may also be found. ACOG recommends that endometrial sampling be performed in patients with AUB, who are older than 45, as a first-line test, which was one of the criteria in our study.¹⁰⁻¹⁸ According to ACOG, in the case of younger than 45-year-old women, endometrial sampling should be performed only when a history of unopposed estrogen exposure exists e.g., PCOS, obesity, or failed management and persistent AUB.¹⁹ In this study, the above guidelines were strictly followed when endometrial sampling was performed in younger than 45 subjects. Several women in our younger cohort had persistent AUB with risk factors, which mainly included obesity and PCOS. There was one case of a woman on tamoxifen in the younger group after a lumpectomy for breast cancer. There were also women who had not responded to treatment with oral progesterone therapy and hence required an endometrial biopsy as per ACOG guidelines. It is worth noting that 33 subjects in our study were of Indian origin and 25 were from Bahrain, and the rest were from other nationalities. The prevalence of PCOS and obesity in the two significant ethnic cohorts in this study (Indian and Bahraini) are well established and seen very commonly in this region. Among the total 88 cases we studied, 12 were postmenopausal and 76 were premenopausal women with the highest incidence of AUB in the age group 41-50. Although we evaluated all risk factors (for both the pre- and post-menopausal age groups) including diabetes, hypertension, nulliparity, PCOS and obesity; we did not find any predictor despite including clinical variables for the prediction of premalignant/malignant endometrial

pathology in premenopausal women with AUB. These findings are consistent with the study of Giannella et al.¹⁸ We discuss the most common histopathological findings noted in our patients in order of frequency.

Benign endometrial polyp

Overall, benign endometrial polyp was the most common finding on histopathological examination with an overall percentage of 47.7%. Moreover, it was also noticed that endometrial polyp was the most common pathology in all age groups younger than 60. Interestingly, the previously mentioned study by Pillai et al. reported that endometrial polyp was the least detected pathology in the population being studied.⁹ In our study, the age inclusion criteria of all women including benign endometrial polyps women was more than 30 which complies with a study of 686 women stating that polyps are rare (0.9%) in women below the age of 30, and the prevalence increased with age, Driesler et al.¹⁰ It is estimated that in 20-40% of AUB patients, endometrial polyp was identified, with noticeable prevalence with increasing age. It is thought that endometrial polyp is caused by unopposed oestrogen stimulation that results in proliferation and hyperplasia in the endometrial glands and stroma leading to the formation of a polyp.^{8,11} A study by Antunes et al. has evaluated the records of 475 patients who were diagnosed with endometrial polyp. A total of 17 patients (2.74%) were identified with carcinomatous polyps most of whom were in the postmenopausal period.¹¹ In contrast to these findings, a study by Orveito et al determined that no malignancy was detected in the histopathological examination of endometrial polyps. Similarly, in our study, no malignancy was detected in patients with histopathology report of endometrial polyps.¹² It is worth mentioning that most of the similar studies show disordered proliferative endometrium or proliferative endometrium to be a more common finding than benign endometrial polyp.

Disordered proliferative endometrium

Abnormal uterine bleeding was commonly seen in the age group 41-50 (N=49), with most patients in this age group presenting with multiple endometrial patterns including proliferative endometrium, disordered proliferative endometrium and secretory endometrium. A total of 22 cases showed disordered proliferative pattern with highest incidence of (N=16, 32.7%) in the 41-50 age group. In contrast to our finding, a prospective study was done by Parmar et. al, on 102 AUB patients and considered disordered proliferative endometrium as the most common endometrial lesion (n= 44, 45%) in women aged 30-40 years.⁴ Histopathological examination has shown a various physiological process in the endometrium, including proliferative, secretory, and menstrual, were causes for AUB. Disordered proliferative endometrium is characterized when the endometrium is either inappropriate proliferative phase or a hyperplastic endometrial appearance.⁸ A study by Cho

Namm et al included 447 women and concluded different patterns of endometrium. The endometrium was in the proliferative phase in 73% of the cases, whereas 34.4% of cases had secretory endometrium and only 32% had disordered proliferative endometrium. In contrast, the incidence of disordered proliferative pattern was significant in our study. A total of 41 women were identified with different proliferative patterns, of which 53% belonged to the disordered proliferative endometrium. The remaining women were found to have normal proliferative endometrium (39%) and the least category was found to have secretory endometrial hyperplasia. One of the most common pathologies in our study was endometrial hyperplasia (N=19, 21.3%) with the highest incidence found in the age group of 41-50 (N=7, 14%). On categorizing the types of endometrial hyperplasia. According to WHO, there are 2 main categories of endometrial hyperplasia -hyperplasia without atypia and atypical hyperplasia/endometroid intraepithelial neoplasia. The hyperplasia without atypia is considered to be benign pathologies caused by anovulation and corpus luteum insufficiency. Atypical hyperplasia category is thought to be more conjugated with invasive endometrial carcinoma.¹⁴ In hyperplasia without atypia the risk of progression to cancer is minimal; 1-3% within 10 years in women of all age groups.¹⁵ whereas in patients with atypical endometrial hyperplasia upto 60% patients may have coexisting invasive cancer or are at extremely high risk of developing cancer. A study by Sofie et, al, conducted on 773 patients reported that more than half (N=457, 59.1%) of the cases diagnosed with endometrial hyperplasia developed endometrial cancer.¹⁶ This is in stark contrast to our findings, where of the 19 women with endometrial hyperplasia, 21% (n=4) patients showed atypia whereas 79% (N=15) patients were without atypia. None of the patients with atypia had coexisting endometrial cancer.

Endometrial carcinoma

Endometrial carcinoma accounted for 2 out of 88 cases, both in the age group 50-55 years. Interestingly, one of the patients presented with a perimenopausal heavy period and was 51 years old. The other woman presented at age 55 with a history of post-menopausal and post coital bleeding which is an unusual symptom for endometrial cancer. Although our study had only 2 cases of endometrial cancer both the cases were in the age group of perimenopause and menopause reemphasizing the importance of endometrial biopsy in this age group. A study by Sajitha et al analyzed 156 endometrial biopsies of patients with AUB, of which patients were seen to have endometrial carcinoma, mostly over 55 years of age.¹⁷

Limitations

The retrospective nature of the study, as well as the relatively small sample size were the major limitations. In particular, the mean age of the study, which lies in the

age group 40-51, was the main age group for most of the significant results. Therefore, this type of study can be prone to reporting and selection bias. Finally, the loss of long-term follow-up was a major weakness in determining disease progression, especially, the premalignant endometrial pathologies. Our study is limited by the small sample size, nevertheless it signifies the importance of performing endometrial biopsies in patients presenting with abnormal uterine bleeding, especially in the peri and post-menopausal women. Finally, although, with 88 subjects, the sample size in this study might be deemed small, the results of this study provided insightful information on the characteristics of abnormal uterine bleeding among women of different ages. We believe that future larger studies can be built upon the findings of this study. Nevertheless, several recent studies reported a similar sample size e.g., Pillai et al which included 88 patients, and its findings were consistent with those of this study).⁹ It should also be noted that, despite the relatively small sample size, 33 of the women in our study were of Indian origin and 25 were from Bahrain, and the rest were from other nationalities, which provided a diverse demographic group of subjects for the study.

CONCLUSION

This study was conducted to determine the clinical spectrum of endometrial causes of AUB and report the associated histopathological findings in the different age groups. Benign endometrial polyp was found to be the most common finding in patients with abnormal uterine bleeding, followed by disordered proliferative endometrium. This is essential information for patient guidance and awareness of the benefits of endometrial biopsy. Eventually, the prediction of the potential endometrial pathology in women with abnormal uterine bleeding is vital for early disease management. To conclude, health issues of this magnitude require multidisciplinary efforts from governments, research and scientific bodies, health care systems, and international entities.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Keshta MS, Keshta AS, Husain M, Gomaa HN, Ehiwario J, Gupta A, et al. Analysis of endometrial biopsy reports from adult women with abnormal uterine bleeding, a cross-sectional descriptive study. *Int J Reprod Contracept Obstet Gynecol* 2023;12:32-8.