



# The role of Histopathology, Endometrium Thickness and Obstetric History in Abnormal Uterine Bleeding

## Anormal Uterin Kanamada Histopatoloji, Endometrial Kalınlık ve Obstetrik Öykü Karşılaştırması

Abnormal Uterine Bleedings

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### Özet

**Amaç:** Anormal uterin kanamada (AUK) klinik, ultrason bulgularını değerlendirmek ve histopatolojik sonuçlarla karşılaştırmak. **Gereç ve Yöntem:** Toplam 404 AUK'li bayan hasta; Grup I: 18-39 yaş, Grup II: 40-50 yaş, Grup III: >50 yaş olarak sınıflandırıldı. Yaş, parite, kanama paterni, menstruel öykü, laboratuvar sonuçları, ultrason ve histopatolojik bulgular değerlendirildi. **Bulgular:** AUK ile başvuranların yaklaşık yarısı premenopozal grupta idi [196 (48.51%)], bunları postmenopozal grup [150(37.13%)] ve reproduktif yaş grubu takip ediyordu [58(14.36%)]. En sık görülen kanama paterni menometroraji olup bunu metroraji takip ediyordu. 306 (75.74%) hastada endometrial patolojiler izlenirken 98 (24.26%) hastada normal menstruel pattern izlendi. Endometrium kanseri 7(1.7%) bayanda izlendi. Reproduktif periyotta hormonal düzensizlik patern en sık patolojiydi. Premenopozal ve postmenopozal yaş gruplarında endometrial polip dominant patolojiydi. Tüm kanser vakaları postmenopozal gruptaydı. Üçten daha az doğum yapanlardan 4(19.04%) bayanda kanser izlenirken, ≥3 doğum yapanlardan 1(4.76%)'inde görüldü. Vajinal doğum yapanların 4'ünde kanser izlenirken sadece sezeryan ile doğum yapanlarda hiç kanser izlenmedi. Endometrial kalınlığı <4mm olan 109 hastadan, 15(13.76%)'inde düzensiz endometrial proliferasyon ve polip, 1 (0.92%)'inde endometrioid kanser mevcuttu. Endometrial kalınlığı >4mm 295 hastadan, 30 (10.17%)'unda endometrial hiperplazi, 6(2.03%)'ında endometrium kanseri izlendi. **Tartışma:** Transvajinal ultrasonografi endometrial kalınlık ve uterin patolojileri değerlendirmede tanısal metod olarak kullanılabilir. Fakat tekrarlayan uterin kanamalarda ultrason bulgularını dikkate almadan endometrial örneklemeye yapılmamalıdır.

### Anahtar Kelimeler

Anormal Uterin Kanama; Endometrial Kalınlık; Parite; Histopatoloji

### Abstract

**Aim:** To evaluate the clinical manifestations of abnormal uterine bleeding (AUB), ultrasonography findings and compare with histopathological results. **Material and Method:** A total of 404 women with AUB were classified as; Group I: 18-39 years, Group II: 40-50 years, Group III: >50 years old. Age, parity, bleeding pattern, menstrual history, laboratory results, ultrasonography and histopathological findings were evaluated. **Results:** Almost half presented with AUB were in the premenopausal group [196 (48.51%)], followed by 150(37.13%) postmenopausal group and 58(14.36%) reproductive age group. The most common bleeding pattern was menometrorrhagia followed by metrorrhagia. Endometrial pathologies were observed in 306 (75.74%) and normal menstrual pattern in 98 (24.26%) participants of AUB. Endometrium cancer was seen in 7 (1.7%) women. In the reproductive period most common pathology was hormonal imbalance pattern. Endometrial polyp was the dominant pathology in premenopausal and postmenopausal age groups. All malignancy cases were in the postmenopausal age group. Malignancy was in 4(19.04%) women who gave birth < 3 and in 1(4.76%) who had ≥3 children. Four women with vaginal delivery had malignancy whereas no malignancy was seen in women with only cesarean history. Among 109 women who had endometrial thickness <4mm, 15(13.76%) had irregular endometrial proliferation and polyp, 1 (0.92%) had endometrioid CA. Of 295 women who had endometrial thickness >4mm, 30 (10.17%) had endometrial hyperplasia, 6(2.03%) had endometrium cancer. **Discussion:** Transvaginal ultrasonography can be used as diagnostic method to evaluate endometrial thickness and differentiate uterine pathologies. However in the case of recurrent uterine bleeding, endometrial sampling should be performed disregarding ultrasonography findings.

### Keywords

Abnormal Uterine Bleeding; Endometrial Thickness; Parity; Histopathology

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## Introduction

Abnormal uterine bleeding (AUB) which has a negative impact on women's health, is the most common gynecologic pathology in the reproductive period. The incidence is 9-14% among reproductive women and it is responsible for 25% of gynecologic pathology [1-4]. AUB is classified as structural or non-structural (formerly called dysfunctional uterine bleeding) according to patient's history (severity, the incidence, the time and period-pre or postmenopausal), physical examination and imaging methods (ultrasonography, hysteroscopy or hydrososonography). The structural AUB may be caused by benign pathologies such as uterine fibroids, endometrial polyps, chronic endometritis or endometrial carcinoma [5, 6]. Since AUB is the most common symptom in endometrial carcinoma [2, 7, 8]. The correct diagnosis of the etiology of AUB is important to choose the correct treatment. Besides transvaginal ultrasonography, saline infusion sonohistography, hysteroscopy and coagulation tests, endometrial sampling and histopathological diagnosis are also necessary [3, 4, 9, 10]. Endometrial sampling is especially required for women above 40 years of age in the evaluation process of AUB. The measurement of endometrium thickness with transvaginal ultrasonography before endometrial sampling may prevent unnecessary invasive interventions.

In this study we aimed to evaluate the clinical manifestations, TVUS findings and evaluate the clinical and radiologic findings with hispathological sampling results.

## Material and Method

The participants were selected from women who admitted to Mevlana University Obstetrics and Gynecology Department with AUB between June 2013-March 2016. The study was approved by Mevlana University Clinical Ethics Committee. (Ethics Ref No: 26857650/215)

In this study 907 women with AUB and had dilatation and curettage were retrospectively reviewed. Age, parity, bleeding pattern, menstrual history, laboratory results (complete blood count, thyroid stimulating hormone (TSH), prolactin (PRL), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2)), ultrasonography findings and histopathologic evaluations were all evaluated. Women who had AUB due to first trimester pregnancy complications, thyroid function dysfunctions, hyperprolactinemia, cervicitis or vaginitis or bleeding due to any gynecologic interventions were excluded.

A total of 404 women suitable for inclusion criteria were included in the study. Women were classified into three groups according to age; Group I: 18-39 years old (reproductive period), Group II: 40-50 years old (premenopausal period), Group III: >50 years old (postmenopausal period). Bleeding patterns were classified as menorrhagia, metrorrhagia, menometrorrhagia, chronic hypermenorrhagia, intermenstrual bleeding and postmenopausal bleeding. Endometrial thickness was evaluated in transvaginal ultrasonography and cut-off value was accepted as 4 mm.

### Terms Used to Describe Abnormal Uterine Bleeding:

**Postmenopausal Bleeding:** Bleeding after physiologic cessation (12 months or more after) of menstruation.

**Menometrorrhagia:** Bleeding at irregular, non-cyclic intervals

and with heavy flow (>80 ml) or long duration (>7 days).

**Menorrhagia:** Bleeding occurs at normal intervals (21 to 35 days) but with heavy flow (>80 ml) or long duration (>7 days) per cycle.

**Metrorrhagia:** Uterine bleeding at irregular and more frequent than normal intervals.

**Intermenstrual /irregular bleeding:** Uterine bleeding of variable amounts occurring between regular menstrual periods. Histopathological evaluation were classified into eight classifications as inadequate material, normal endometrium (proliferative endometrium, secretory endometrium, menstrual endometrium), hormonal imbalance (asynchronous, stromal glandular destruction, endometrium under progesterone effect, decidual reaction), atrophic endometrium (atrophic, inactive or low proliferative), endometritis (acute or chronic), irregular proliferation and endometrial polyp, endometrial hyperplasia (simple with / without atypia, complex with/without atypia, malign endometrium disorders (endometriosis, mucinous). The correlation of histopathologic results with clinic complaints, parity, method of birth and transvaginal ultrasonography findings (TVUS) were evaluated. Uterine structural pathology which may cause AUB was also recorded.

**Statistical Analysis:** Statistical analyses were performed with SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). Distribution of the data was determined by the Shapiro-Wilk test. Continuous variables were expressed as mean  $\pm$  standard deviation or median (minimum-maximum). Categorical values were expressed as n (%).

## Results

The mean age of 404 was  $51 \pm 3.70$  years. All participants were married. Only 28 of the women were nulliparous. The mean parity of the rest 376 women was  $3 \pm 1.27$ , 324 women delivered vaginally, 24 had cesarean section (C/S) and 28 women had both vaginal delivery and C/S. The participants were classified into 3 groups according to ages. Most of the women presented with AUB [n=196 (48.51%)] were in the premenopausal group (Group II), followed by 150(37.13%) postmenopausal age group (Group III) and 58(14.36%) reproductive age group (Group I). The mean ages of the groups were  $33 \pm 4.20$  in Group I,  $42 \pm 1.57$  in Group II and  $57 \pm 5.36$  in Group III.

The median endometrium thickness of women on transvaginal ultrasonography was 18 mm. Table 1 shows clinical symptoms of women. The most common bleeding pattern was menometrorrhagia which was presented by 152 women (37.62%) followed by metrorrhagia 94 women (23.27%).

Major histological patterns observed were presented in Table

Table 1. The clinical characteristics of patients with abnormal uterine bleeding.

Clinical Symptoms	Group I	Group II	Group III	Total
postmenopausal bleeding	-	-	77(%51.4)	77(19.1)
menometrorrhagia	14(%24.2)	98(%50)	47(%31.4)	152(%37.6)
menorrhagia	8(%13.8)	29(%14.8)	4(%2.6)	41(%10.1)
metrorrhagia	27(%46.5)	45(%22.9)	22(%14.6)	94(%23.3)
intermenstruel bleeding	9(%15.5)	24(%12.3)	-	40(%9.9)
TOTAL	58(%100)	196(%100)	150(%100)	404(%100)

II. Normal menstrual pattern was seen in 84 patients (20.80%), endometrial polyp and endometrial proliferation disorders in 177 (43.81%), endometrial hyperplasia in 30 (7.43%), and endometrial carcinoma was noted in 7(1.73%) participants. Among 84 women with normal menstrual pattern, secretory endometrium was the most common pattern in 46(54.76%) participants, followed by proliferative pattern endometrium in 38(45.24%) participants. Among 30 participants of endometrial hyperplasia, 24 participants (80%) had simple endometrial hyperplasia without atypia whereas 6 participants (20%) were complex endometrial hyperplasia without atypia. Endometrium cancer was seen in 7 participants, 5 had the diagnosis of endometrioid and 2 participants had mucinous carcinoma.

The frequency of endometrial pathologies was observed in different age groups. In reproductive most common pathology was hormonal imbalance pattern followed by endometrial polyp, whereas endometrial polyp was the dominant pathology in premenopausal and postmenopausal age groups. In postmenopausal age group atrophic endometrium and endometrial hyperplasia followed endometrial polyp pathology (Table II). On the other hand the frequency of endometrial carcinoma was quite low 7(4.67%). All malignancy cases were in postmenopausal age group. The rest 397 of 404 women (98.27%) had benign histopathological spectrum. Co-existing pathology such as myom, adenomyosis was seen in 111 cases of total 404 par-

ticipants, 8(13.8%) in Group I, 54(25.7%) in Group II and 49 (36%) in Group III.

When histopathologic diagnosis was compared with parities of women, in 28 nulliparous only 2 (7.14%) had normal histologic findings, the rest 26 (92.86%) had pathologic findings. Among the pathologies 2 (7.14%) had malignancy. The number of total malignant cases were 21 (75%). The frequency of malignancy was 4(19.04%) in women who gave birth <3 and 1(4.76%) in women who had 3 or more children (Table III).

The delivery method was considered and among 324 women who had vaginal delivery 4 (1.23%) had malignancy. Of 28 women who had both vaginal and C/S delivery history 1 patient (3.57%) had endometrium cancer whereas no patient experienced malignancy who had only C/S delivery history. Endometrial polyp was the most common (46.30%) pathology in women who had vaginal delivery and endometrial hyperplasia was mostly seen in nulliparous women (42.86%) (Table III).

Among 109 women who had endometrial thickness <4mm, 15(13.76%) had irregular endometrial proliferation and polyp, 1 (0.92%) had endometrioid CA. The rest 93 (85.32%) had normal histology. Of 295 women who had endometrial thickness ≥4mm 97 (32.88%) had normal pathology, 162 (54.92%) had irregular proliferation and polyp, 30 (10.17%) had endometrial hyperplasia, 6(2.03%) had endometrium cancer (Table III).

## Discussion

Abnormal uterine bleeding (AUB) is defined as a bleeding pattern which differs in frequency, duration, and amount from the normal pattern during a normal menstrual cycle or after menopause [11]. AUB, may present different clinics such as oligomenorrhea, polymenorrhea, menorrhagia. AUB may be due to structural (such as pregnancy complications, anatomic uterine pathologies or endometrial neoplasia) or nonstructural causes (such as hormonal imbalance, acquired or congenital bleeding diathesis) [5, 6]. Therefore, setting out the etiology is important to give the right treatment. Detailed history, physical and pelvic examination, laboratory tests and radiologic imaging results are necessary. In reproductive period endometrium cancer risk is low so that TVUSG is the main diagnostic method and endometrial sampling is required only if necessary [3]. TVUSG is an important diagnostic parameter in detecting structural

Table 2. The histopathological classification of the groups

Histopathological diagnosis	Group I	Group II	Group III	Total
	N (%)	N (%)	N (%)	N (%)
Insufficient material	0(0)	2 (1.02)	12 (8.00)	14(3.46)
Normal endometrium	28 (48.28)	44 (22.45)	10 (6.67)	84 (20.80)
Hormonal imbalance	23 (39.66)	30 (15.31)	0(0)	51 (12.62)
Atrophic endometrium	0(0)	0 (0)	25(16.66)	25 (6.19)
Chronic endometritis	0(0)	15 (7.65)	1(0.67)	16 (3.97)
Irregular proliferation/ Endometrial polyp	6 (10.34)	91 (46.43)	80(53.33)	177 (43.81)
Endometrial hyperplasia	1 ( 1.72)	14 (7.14)	15(10.00)	30 (7.42)
Malignancy	0 (0)	0 (0)	7( 4.67)	7 (1.73)
Total	58 (14.36)	196 (48.51)	150(37.13)	404(100)

Table 3. Histopathological evaluations according to endometrial thickness, parity and delivery mode . TVUS: transvaginal ultrasonography, C/S: cesarean. Insufficient material, hormonal imbalance and endometritis findings are added to normal histology group

TVUS	Endometrial thickness	Normal histology	Irregular Proliferation+ Polip	Endometrial Hyperplasia	Malignancy	Total
		N (%)	N (%)	N (%)	N (%)	N (%)
Parity	4mm<	93 (85.4)	15 (13.7)	0 (0)	1 (0.9)	109 (100)
	4mm>	97 (32.9)	162 (54.9)	30 (10.2)	6 (2.0)	295 (100)
	0	2 (7.1)	12 (42.9)	12 (42.9)	2 (7.1)	28 (100)
	1	11 (29.7)	11 (29.7)	12 (32.5)	3 (8.1)	37 (100)
	2	37 (56.9)	23 (35.4)	4 (6.2)	1 (1.5)	65 (100)
Mode of Delivery	≥3	140 (51.1)	131 (47.8)	2 (0.7)	1 (0.4)	274 (100)
	Vaginal Delivery	158 (48.8)	150 (46.3)	12 (3.7)	4 (1.2)	324 (100)
	C/S	11 (45.8)	11 (45.8)	2 (8.4)	0 (0)	24 (100)
	Vaginal delivery+C/S	19 (67.8)	4 (14.3)	4 (14.3)	1 (3.6)	28 (100)
	Nullipar	2 (7.1)	12 (42.9)	12 (42.9)	2 (7.1)	28 (100)

causes of AUB such as fibroids, polyps, pelvic mass or endometrial hyperplasia [7]. Moreover, endometrial sampling for histopathological evaluation is needed especially in premenopausal or postmenopausal period for the differential diagnosis of AUB [3, 4, 9, 10].

Nonstructural or dysfunctional uterine bleeding (DUB) due to hormonal irregularities are mainly seen in adolescents [5]. However, we could not evaluate DUB in adolescents since there was no participant at this age group. Proliferative endometrium or endometrial hyperplasia due to unopposed estrogen in the reproductive ages may also cause AUB [12]. In the reproductive age group in our study menometrorrhagia was the most common symptom and hormonal imbalance was the most common histopathologic evaluation. In the literature, endometrial neoplasia is reported as a cause of AUB in reproductive period [13]. However in our study there was no case of endometrial neoplasia in reproductive age group.

In the premenopausal age group the most common symptom was menometrorrhagia and dominant histopathological finding was irregular proliferative endometrium and/or endometrial polyp followed by hormonal imbalance, and endometrial hyperplasia. These findings of our study was similar with the findings of Jetley et al, [6]. There was no endometrial neoplasia finding in Group II (premenopausal age).

In the literature 10% of the postmenopausal bleeding was reported to be associated with endometrium cancer [7], and 90% of endometrium cancer cases were told to have AUB as a major symptom [2,7]. Similarly, in this study all cases with endometrium cancer were in the postmenopausal age group. Similar with our findings, in the literature endometrium cancer risk is reported to increase with aging and peaks at 50-70 ages [2, 7, 14]. In this study, in 14 cases endometrial materials were inadequate for any diagnostic opinion. It has been told that biopsy results without any diagnostic opinion are enough to rule out malignancy [15].

Varying incidence of endometrial hyperplasia (EH) was reported in the literature. Mariam Abid reported 5%, Behnamfar et al 10% and Jyotsana 22.6% incidence of endometrial hyperplasia, [4, 16, 17 ]. In this study we reported the incidence of EH as 7.42% of total participants, 10% of postmenopausal women and 1.73% of women in the reproductive group.

Transvaginal ultrasonography is a simple, non-invasive imaging method used for the evaluation of anatomic abnormalities which may cause AUB [2, 18]. However, there is no consensus on the cut-off value for endometrial thickness [2, 7, 19, 20 ]. Gull B et al. reported that in cases with endometrial thickness <4mm endometrial carcinoma was not associated and his findings coincided with other studies in the literature [2, 19-22]. However, Buyuk E reported cutoff of 6 mm for endometrial thickness [23]. Davidson KG et al reported that in 5-10% of cases false negative evaluation of endometrium thickness with ultrasonography may occur so that in women with high-risk for cancer endometrial sampling may be considered irrespective to ultrasonography findings [24].

Karlsson et al. reported that 97% sensitivity and 81% specificity of TVUS when compared with dilatation and curettage(D&C) results in differentiating normal and pathological endometrium [19]. Auslender et al told that when endometrial thickness

3mm was accepted as cut-off value, unnecessary D&C ratios decreased 45% and endometrial pathologies would not be underdiagnosed [25]. In this study we evaluated the endometrial thickness with TVUS before dilatation and curettage. The cut-off value for endometrial thickness was accepted as 4 mm. Only in one patient, endometrial thickness could not be evaluated with TVUS, endometrial cancer was diagnosed. Our findings coincide with Dimitraki and Joongiler findings who reported that endometrial thickness may not be evaluated on transvaginal ultrasonography in high grade endometrium cancer and underdiagnosed [2,7]. Of 7 endometrium cancer cases 6 had >4mm endometrial thickness, and this situation showed that TVUS has an important role in the first-line diagnosis of endometrial pathologies. In one case endometrium was so thin that the thickness could not be measured. Therefore, as it has been reported in the literature, in the case of clinic findings such as menstrual irregularities or fibroids especially in the postmenopausal period, endometrial sampling should be performed even in the case that endometrial thickness is <4mm (7,26-28).

### Conclusion

Endometrial hyperplasia and endometrium cancer are more often in postmenopausal women with AUB. Transvaginal ultrasonography when used as a first line diagnostic method to evaluate endometrial thickness and differentiate uterine pathologies would prevent unnecessary invasive procedures. However in the case of recurrent abnormal uterine bleeding endometrial sampling should be performed disregarding TVUS findings.

### Competing interests

The authors declare that they have no competing interests.

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