



Research Article

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## “Not Yet Classified” Abnormal Uterine Bleeding in Reproductive-age Women

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### Abstract

**Objective:** Abnormal uterine bleeding (AUB) is a common problem among women in reproductive age. Not always is their cause easy to establish and in those cases not yet classified abnormal uterine bleeding is diagnosed.

The aim of this study was the analysis of the clinical and histopathological results of the endometrium evaluation in women with initially diagnose of not yet classified bleeding who had undergone curretage, because of prolonged bleeding.

**Methods:** The study was conducted among 78 women aged between 21 and 42 years with prolonged uterine bleeding. Not yet classified uterine bleeding diagnose was based on patient history and physical examination. The percentage of the histopathological findings that confirmed the initial diagnose was evaluated and two groups of women, those with normal and abnormal endometrium in the aspects of clinical data (age, parity, BMI (body mass index) and menstruation bleeding pattern were compared.

**Results:** The initial diagnose of non classified uterine bleeding was confirmed only in 42.3% of women. The further results of abnormal uterine bleeding were as follows: endometrial polyps in 30.8%, hormonal imbalance in 14%, hyperplasia of the endometrium in 6% and endometritis in 4%. The only statistically significant parameter was frequent occurrence of regular than irregular menstrual cycles in a group of women with non classified uterine bleeding.

**Conclusion:** Histopathological examination of the endometrium enabled to find the cause of bleeding in more than a half of women with initially recognized non classified uterine bleeding. Besides the higher incidence of regular cycles in the group of women with confirmed not yet classified bleeding, no differences depending on age, parity, BMI, length and amount of menstrual bleeding were observed among women with abnormal uterine bleeding.

### Keywords:

Abnormal uterine bleeding; Curettage; Endometrial polyps; Endometrial hyperplasia; Endometritis; Hormonal disorders

## Introduction

Abnormal uterine bleeding is one of the most frequent health problems reported by women. The prevalence of abnormal uterine

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bleeding (AUB) is estimated at 11-13% of women in general population and increases with age, up to 24% at the age of 36-42 [1]. From this, only 30% of them seek medical advice [2].

Regardless the cause, uterine bleedings are very awkward, worrying, have negative influence on the quality of life and one of the most frequent reason of outpatients visits to gynecologists [3]. However, despite a standard diagnostic procedure, including the patient history, blood tests, the gynecology examination, the transvaginal ultrasonography (TVS), the cause of the bleeding can not be identified in 40- 50 % of the cases [4]. In such cases, non classified uterine bleeding are diagnosed by exclusion. Mostly, they concern women of reproductive age, and has no relevance to pregnancy, structural pelvic alterations, hormonal imbalance, hormonal contraception or chronic diseases [5]. They may occur in both normal ovulatory and non-ovulatory cycle [6].

Prolonged bleeding as well as heavy bleeding require curettage or biopsy and histopathological examination of endometrium. It is expected that the microscopic examination indicates the real cause of the bleeding and allows implementation of effective treatment, however its result does not always solves the problem. However, it is not known, how often it happens and whether there are any factors characteristic for non classified uterine bleeding.

## Aim of the Study

The aim of this study was both the analysis of the clinical data, histopathological examination of endometrium in reproductive-age women with not yet classified abnormal uterine bleeding who had undergone curretage because of prolonged bleeding and the attempt to find factors that may distinguish women with undiagnosed cause from women with diagnosed cause of the bleeding.

## Material and Methods

Participants of the study were 78 women with not yet classified functional bleeding, aged between 21 and 42 (the mean of the age 33.7). The subjects were selected amongst those attending 1<sup>st</sup> Department of Obstetrics and Gynecology, Warsaw Medical University, Warsaw, Poland. Exclusion criteria were: pregnancy, chronic disease, abnormal gynecological and ultrasound examination, uterine fibroids, and any known causes of bleeding. Parity, BMI (body mass index), menstrual cycle regularity, length and amount of bleeding were determined in all women. Cycles 25 to 35 days and menstrual bleeding lasting up to 7 days were accepted as normal. Although curretage is not the standard method of the initial diagnostic procedure of the endometrium, it was performed in all women because of the prolonged and/or heavy bleeding.

The obtained material was delivered for histopathological examination. For statistical analysis the dependent variables were analysed taking into account histopathological findings, age, parity, cycle regulatory and amount of menstrual bleeding. The statistical tests used Chi-square test. Values were regarded statistically significant when  $p < 0.001$ .

## Results

In the group of women with initially diagnosed not yet classified uterine bleeding the results of histopathological evaluation showed no

abnormalities of endometrium in 42.3% of them (Table 1). Although a coherence of patterns with cycle's phase was more frequently typical for proliferation phase (58.6%) than secretory phase (41.4%) the difference was not statistically significant.

The histopathological evaluation allowed to set diagnosed in 57.7% of women. The findings were as follows: endometrial polyps (30.8%), hormonal disorders (14.1%), endometrial hyperplasia (7.7%) and endometritis (5.1%).

Further analyses were done between two groups, first group consisted of women in whom no abnormalities were found in the histopathological evaluation, the second group consisted of women with pathologies of endometrium. Table 2 shows the results of histopathological examination based on aged, parity, BMI, menstruation regularity, length and amount of menstrual bleeding.

No abnormalities in endometrium were observed in 57.6 % of women at and under the age of 35 and in 42.4 % over 35, in 48.5 % of pulliparous and 51.5 % of nulliparous, in 15.2% underweight, 54.5 % with normal body weight, 12.1% overweight and 18.2% obese. In this group of women regular cycles were observed in 84.8%, bleeding shorter than 7 days in 42.4%, longer than 7 days in 57.6%, in 54.5% of women bleeding was normal and in 45.5% heavy.

The histopathological evaluation showed abnormalities in 46.7% of women at and under the age of 35, and in 53.5% over 35, 35.6% were pulliparous and 64.4 % nulliparous. The hystopathological pathologies were found in 11.1% underweight, 46,7% with normal weight, 20% overweight and 22.2% of obese women. The majority of women in these group have regular cycle (62.2% vs 37.8%), prolonged (66.7% vs 33.3%), and moderate bleeding (53.3 vs 46.7%). The statistical analysis showed that only regular menstrual bleeding were statistically significant more frequent in women with both functional bleeding intially diagnosed and not yet classified (p<0,05). However, the difference was not statistically significant in the group of women that histopathological examination indicated the cause of bleeding.

Statistical analysis of other chosen clinical data did not show statistically significant differences, which suggests that none of them was represented more frequently in the study group of women with undiagnosed cause of bleeding.

## Discussion

The terminology and etiology of abnormal bleeding in nongravid women of reproductive-age, that was introduced by International Federation of Gynecology and Obstetrics (FIGO) in 2011 and refers to the acronym PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified), forms the basis for diagnosis and as follows therapy of such disorders [5].

In this classification, among abnormal uterine bleeding, that are not related to stuctural anomalies, there is one category – not yet classified. Women with such bleeding are the most problematic as far as the therapy is concerned. For these reasons, the determination of the characteristic factors distinguishing them from women with bleeding possible to determine seems to be important. In any case, it should be considered whether a tissue sample is needed for diagnosis and which follows biopsy or curretage is needed. The results of the study show that in women with undiagnosed prolonged or heavy abnormal uterine bleedings, regardless of age, histopathological examination indicates the cause in almost 58%. This confirms the findings of other

authors, that significant number of endometrial samples revealed pathology rendering endometrial curetting and biopsy an important procedure [7]. It's hard to agree with the statement that endometrial biopsy is recommended for women with uterine functional bleeding, in whom three-month empirical therapy was failed [6].

The histopatological evaluation confirmed the intial diagnosis of the bleeding not yet classified in approximately 42% of women. A compliance between endometrium pattern and the phase of the cycle was found more frequent in proliferative compared to secretory phase of the cycle. Although the difference was not statistically significant. One of the explanation of this findings may be the effect of hormonal fluctuations during the menstrual cycle on blood vessels haemodynamics in young women [8]. Both estrogen and progesterone are needed to maintain the integrity and stability of the endometrium. At the proliferative phase of the cycle, estradiol controls structural changes such as endometrial cells proliferation, endometrium growth and angiogenesis. During the secretory phase, both estrogens and progesterone activity influence the remodeling of endometrium with further glandular development, stroma oedema and vascular proliferation that leads to the density coiling of the spiral vessels [8].

**Table 1:** Histopathological results in reproductive-age women with abnormal bleeding.

Histopathological result	Number of women (%)
Endometrium normal	33 (42,3)
Endometrium polyposa	24 (30,8)
Endometrium dyshormonal	11 (14,1)
Hyperplasia endometrii	6 (7,7)
Endometritis	4 (5,1)

**Table 2:** The analysis of the clinical data and histopathological findings in reproductive-age women with initially diagnosed non yet classified uterine bleedings.

	Normal endometrium N=33	Abnormal endometrium N=45
Age <35	19 (57.6%)	21 (46.7%)
Age >35	14 (42.4%)	24 (53.3%)
p*	0,964	0.655
Pulliparous	16 (48.5%)	16 (35.6%)
Nulliparous	17 (51.5%)	29 (64.6%)
p*	0,841	0,051
BMI <18,5 kg/m <sup>2</sup>	5 (15.5%)	5 (11.1%)
BMI 18,5-24,9 kg/m <sup>2</sup>	18 (54.5%)	21 (46.7%)
BMI 25,0-29,9 kg/m <sup>2</sup>	4 (12.1%)	9 (20%)
BMI>30,0 kg/m <sup>2</sup>	6 (18.2%)	10 (22.2%)
p*	0,002	0,006
Regular menstrual cycle	28 (84.8 %)	28 (62.2%)
Irregular menstrual cycle	5 (15.2%)	17 (37.8%)
p*	<0,001	0,102
Menstrual bleeding<7 days	14 (42.4 %)	15 (33.3%)
Menstrual bleeding>7 days	19 (57.5%)	30 (66.7%)
p*	0,383	0,025
Moderate bleeding	18 (54.5%)	24 (53.3%)
Hypermenorrhoe	15 (45.5%)	21 (46.7%)
	0,729	0,656

**Note:** p - The level of statistical significance

In maintenance and disruption of the functional layer of endometrium and in the maintainance of integrity of the blood vessels the extracellular matrix plays the crucial role. Changes that occur are regulated, among all, by the activity of matrix metalloproteinase and prostaglandins which are under the control of steroid hormones. [9,10]. It is assumed that slight, transient and clinically non significant changes can cause disruption of functional layer and bleeding, but this hypothesis requires further study.

In the examined group of women age, parity, BMI, the length and amount of menses bleeding remained irrelevant. However, statistically significant in more women regular than irregular menstrual cycle were observed. Idiopathic factor was also noted as the most common cause of bleeding in young and reproductive-age women by other authors [11].

Endometrial polyps, are the second cause of bleeding regarding frequency. Polyps lesions were not visible in ultrasound examination probably due to bleeding and their small size. Polyps as well as submucosal myomas and hyperplasia are impossible to detect in ultrasound examination in 18% of women [12]. Increased incidence of polyps along with increasing age and body weight was also reported by other authors [13].

It is estimated that disorders in hormone secretion are the cause of bleeding in about 27% of all abnormal bleedings [14]. In our study, they were observed in 14% of women. These results suggest that estrogen release disorders may be an etiological factor. It is well established that estrogen accounts for 80%, and progesterone for 20%, of all ovary hormones disfunctions [14]. It is worthwhile to mention that abnormal uterine bleeding may be a symptom of other different hormonal disturbances, such as hypothyroidism or hyperprolactinemia. The disorders relate mainly to the cycle length and amount of menstrual bleeding, abnormal bleeding were observed occasionally [15,16].

The results regarding endometrial hyperplasia seem interesting. They indicate no difference occurrence in young women, thus lacking the commonly deemed risk factor as women's age [17]. This may indicate that among the reproductive-age women, incidence of endometrial hyperplasia is not dependent on age. Similarly, to other authors, we observed hyperplasia more often in nulliparous patient with overweight or obesity, and prolonged menstrual bleeding [18,19].

Endometritis that was found in histopathological examination in the study group could be either a primary cause of bleeding or it could have developed due to prolonged bleeding for other reasons.

## Conclusions

The results showed that in 58% of women with initially not yet classified abnormal uterine bleeding, based on histopathological evaluation of endometrium several disorders can be diagnosed, i.e. structures, that are undetectable in gynecological and invisible in ultrasound examinations. Besides, the higher incidence of regular cycles were present in the group of women with confirmed not yet classified bleeding. Moreover no difference was shown on age, parity, BMI, length and amount of menstrual bleeding were observed among women with abnormal uterine bleeding.

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Top