Clinical, histopathological and therapeutic considerations in non-neoplastic abnormal uterine bleeding in menopause transition

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Abstract
With the decline of ovarian hormonal function, from the fifth decade of life, women enter the menopause transition, during which bleeding becomes irregular in duration and time of occurrence. Secondary to ovarian dysfunction, developmental and maturation endometrial anomalies occur, which are clinically translated by abnormal uterine bleeding, which in many cases at this age can be caused by organic lesions (fibroma, polyps, endometritis, endometrial hyperplasia, adenomyosis, etc.). The retrospective study included a total of 256 patients with abnormal uterine bleeding in menopause transition. Statistics showed that the incidence of these types of bleeding increases with age (64.5%) and parity (30.5%), with symptoms consisting mostly in different clinical forms of abnormal uterine bleeding (62.1%), and leiomyomas prevailing at histopathological examination (49.6%). Progesterone replacement therapy was the first therapeutic choice for correcting these types of bleeding. Progesterone therapy is useful not only for therapeutic purposes to amend the bleeding, but also as a precaution against the development of endometrial carcinoma. Progestogens cancel the proliferative and mitogenic effect of estrogens, even when administered in sequential regimen 10–12 days per month.

Keywords: perimenopause metrorrhagia, biopsy, progestogens.

Introduction
Menopause transition includes a period of about 4–5 years before menopause, sometimes even several months, characterized by varying degrees of somatic and psychological changes that reflect the change in the ovarian cycle [1]. This period begins gradually and may be announced by the presence of discrete symptoms during the middle and terminal 5th decade of life. In some women, the most significant symptom is an irregular menstrual period, which must be carefully evaluated to determine whether it is the consequence of low estrogen levels or an associated pathology [2, 3]. The terminology of abnormal uterine bleeding includes the following clinical entities [4–6]: oligomenorrhea, polymenorrhea, menorrhagia, menometrorrhagia, metrorrhagia, midcycle spotting, dysfunctional uterine bleeding, abnormal acute uterine bleeding. The treatment for abnormal uterine bleedings in menopause transition is either hormonal or surgical, depending on the patient’s symptoms and diagnosis.

The standard approach is cyclical therapy with progestogenic agents for 10 days between the 16th and the 25th days to provoke the deprivation bleeding and reduce the risk of endometrial hyperplasia and carcinoma [7].

Progesterone replacement therapy is indicated for menstrual cycle disturbances during perimenopause, due to anovulatory or dysovulatory cycles when the endometrium is mostly under the influence of estrogens.

The surgical treatment of abnormal bleeding should be reserved for cases unresponsive to medical treatment, in which the histopathological examination dictates a first choice hysterectomy, or when the medical therapy is not indicated (progesterone hypersensibility, severe liver failure, history of thromboembolic disease, stroke, occult hematuria).

The alternative therapy of abnormal uterine bleeding (Lady 4® – Oenothera biennis extract, Turnera diffusa, Panax ginseng, royal jelly; Gynease® – Symplocos racemosa extract, Glycyrrhiza glabra, Asparagus racemosa), is addressed to patients who refuse the administration of hormone therapy, thus non-compliant to this type of medication take into consideration with the utmost reluctance.

Materials and Methods
Between January 1 and December 31, 2009, a number of 256 patients with abnormal uterine bleeding and various clinical symptoms were examined in the No. 1 Clinic of Obstetrics and Gynecology, Emergency County Hospital, Craiova. The diagnostic protocol included the following investigations: endovaginal ultrasound and endometrial biopsy by dilatation and curettage (146 cases – 57%), hysteroscopy with endometrectomy (87 cases – 34%), and aspiration using the 23 Volkman cannula (23 cases – 9%) (Figure 1).

The clinical and laboratory evolution of the patients were followed up, with recommendation for a particular type of therapy.
Results

For the study group we assessed the following parameters: age and parity, dominant clinical type of abnormal uterine bleeding, the histopathological correspondent, and the type of therapy (Table 1).

Table 1 – Distribution of patients on age and parity

<table>
<thead>
<tr>
<th>Parity</th>
<th>41–45-year-old</th>
<th>%</th>
<th>46–52-year-old</th>
<th>%</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>0.8</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>2.7</td>
</tr>
<tr>
<td>I</td>
<td>6</td>
<td>2.3</td>
<td>10</td>
<td>3.9</td>
<td>16</td>
<td>6.3</td>
</tr>
<tr>
<td>II</td>
<td>25</td>
<td>9.8</td>
<td>17</td>
<td>6.6</td>
<td>42</td>
<td>16.4</td>
</tr>
<tr>
<td>III</td>
<td>31</td>
<td>12.1</td>
<td>55</td>
<td>21.5</td>
<td>86</td>
<td>33.6</td>
</tr>
<tr>
<td>High multiparity</td>
<td>27</td>
<td>10.5</td>
<td>78</td>
<td>30.5</td>
<td>105</td>
<td>41</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>35.5</td>
<td>165</td>
<td>64.5</td>
<td>256</td>
<td>100</td>
</tr>
</tbody>
</table>

Of 256 patients, 165 (64.5%) were between 46 and 52-year-old with 78 (30.5%) high multiparous, indicating that the incidence of abnormal uterine bleeding increases with age and parity.

The dominant symptom of abnormal bleeding was: menometrorrhagia – 89 patients (34%), followed by metrorrhagia – 48 patients (18%), hypermenorrhea – 38 (15%), polymenorrhea – 32 (13%), menorrhagia – 27 (11%), and intermenstrual uterine bleeding – 22 (9%).

The retrospective study on 159 patients (62.1%) indicated that symptoms consisted of: menorrhagia-hypermenorrhea, menorrhagia-polymenorrhea, menorrhagia-intermenstrual bleeding.

The analysis of histopathological results revealed the following morphological aspects in menopause transition: leiomyomata – 127 cases (49.6%); endometrial polyps – 33 cases (12.9%); adenomyosis – 25 cases (9.8%); chronic non-specific endometritis – 19 (7.5%); atrophic endometrium – 18 cases (7%); dysfunctional uterine bleeding – 27 cases (10.5%) of which secretory endometrium – 22 cases (8.6%), endometrium with disorganized proliferation seen as a bridge between normal proliferation and hyperplasia – five cases (1.9%), endometrial hyperplasia – seven cases (2.7%) of which simple hyperplasia without atypia with squamous metaplasia – three cases (1.2%) and complex hyperplasia with atypia – four cases (1.6%).

Besides highlighting the patient’s hormonal status, the biopsic curettage also aims at excluding the endometrial adenocarcinoma, which is more often encountered during this period.
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The 127 uterine leiomyomas had a submucous or intramural localization, with 23 cases associated with localized endometrial atrophy, moderate or even severe (Figure 4). Most cases were highly cellular leiomyomas (83 cases), while the rest of them (44 cases) were forms with diffuse hyalinization, marked edema or hemorrhagic infiltration (Figure 5).

Endometrial polyps were diagnosed in 33 cases corresponding to the following aspects: functional polyps (12 cases) and hyperplastic polyps (Figure 6). Functional polyps showed a normal proliferative endometrium appearance, while hyperplastic polyps showed a similar appearance to simple hyperplasia without atypia, but with limited pattern. In all cases, the endometrium adjacent to the polyps showed a normal proliferative appearance or different degrees of atrophy.

Adenomyosis was present in 25 of the cases with abnormal uterine bleeding that were investigated. In all cases, there were multiple areas of adenomyosis, with the appearance of normal proliferative endometrium or sometimes with cystic transformation and appearance of simple hyperplasia without atypia.

There were 27 cases with HUD, out of which 24 in patients with anovulatory and dysovulatory cycles: proliferative endometrium – eight cases, secretory endometrium – 11 cases, endometrium with disorganized proliferation – five cases, and three cases in patients with ovulatory cycle. In patients with anovulatory cycles we encountered a proliferative phase pattern, with the presence of fibrinous microthrombi, areas of stromal collapse and surface syncytial papillary metaplasia (Figure 7).

Non-specific chronic endometritis were present in 19 of the cases investigated, 15 cases with mild forms and the other four with severe ones. In mild forms, the lympho-plasmocytic inflammatory infiltrate was focal, situated beneath the surface endometrium, and in the four cases of severe endometritis, it was diffuse, both beneath the surface epithelium as well as periglandular, with the glands showing reactive atypia (Figure 8).

Diffuse endometrial atrophy was diagnosed in 18 cases, of which 12 with mild atrophy, four with moderate atrophy and two cases of severe atrophy (Figure 9).

We noticed a decrease in the thickness of the endometrium, the disappearance of the folds and the horizontalization, at least in certain areas, of the surface epithelium, a decrease in the number of endometrial glands and of their lumen, and the atrophy of the glandular and surface epithelium to cubical and pseudopavimentous aspects, the reduction of the endometrial stroma with an increase in collagen fibers.

The endometrium with disorganized proliferation (Figure 10) was seen in five cases, in patients aged between 41 and 45 years, showing dilated cystic glands or even a complex pattern with glandular budding along tubular glands with the same pattern as the normal proliferating endometrium.

Endometrial hyperplasia was diagnosed in 12 cases: nine cases were hyperplasia without atypia, two cases were complex hyperplasia without atypia and one case showed hyperplasia with atypia. In simple hyperplasia without atypia the proliferating endometrial glands showed mostly changes in shape and dimensions, with random disposition within the endometrial stroma, leading to a variety of architectural patterns (Figure 11).

Complex hyperplasia without atypia was characterized by a variable glandular architecture, with highly branching glands, with budding towards the stroma or intraluminal pseudopapillary protrusions, but with a constant scarce interglandular stroma (Figure 12).
There was only one case where the pattern corresponded to a complex hyperplasia with atypia in which atypical glands showed obvious nuclear stratification, loss of nuclear polarity and frequent mitoses, revealing a generally disorganized pattern (Figure 13).

In menopause transition, the therapeutic methods used to stop abnormal uterine bleedings were: progesterone replacement therapy in 167 cases (64%), alternative therapy in 27 cases (11%), dilation and curettage in 17 cases (7%), hysterectomy in 13 cases (5%) and estrogen/progesterative hormone therapy in seven cases (3%). Twenty-five cases (10%) refused the medical treatment and were excluded from the study group after performing the curettage with biopsy (Figure 14).

Hormonal and alternative therapies were administered for six months, and hysterectomy was performed either because of the histopathological examination, or because of persisting hemorrhage despite an adequate hormonal therapy.
uterine bleeding in menopausal transition may be [2, 15, 16]; dysfunctional uterine bleeding, endometrial atrophy, endometrial polyp, endometrial hyperplasia, endometrial metaplasia, adenomyosis, uterine fibroma, chronic non-specific endometritis.

Dysfunctional uterine bleeding (DUB) is a disorder with a hormonal imbalance as etiopathogenic substrate, without organic cause. In our study, we found DUB in 10.5% of cases as a mechanism for abnormal uterine bleeding in menopause transition.

DUB often involves a mechanism of anovulation, but most anovulatory bleedings are the result of what has been termed “estrogen effect”. In the absence of ovulation and the production of progesterone, the endometrium responds to estrogen stimulation by proliferation. This endometrial proliferation with no periodic removal results in the rupture of the fragile endometrial tissue. Healing of the endometrium is irregular and asynchronous. Stimulation by relatively low levels of estrogen causes prolonged and irregular bleeding, while sustained high levels lead to episodes of amenorrhea followed by heavy acute bleeding. In our study, proliferative endometrium was revealed in eight cases (3.12%), compared with the Bhosle A and Fonseca M study which revealed that dysfunctional uterine bleeding represented by proliferative endometrium was found in 66.1% of cases, with the Jordan University study – 53% of cases, the Zion Hospital and the LTMMC study – 66.1% of cases and the study of Michail G et al. – 9.8% [17, 18].

In addition to anovulation, dysovulation is equally incriminated in the occurrence of DUB, coupled with a controversial clinical entity, of luteal phase defect (LPD)-type, which is manifested by an insufficient production of progesterone by the corpus luteum and, therefore, an inadequate development of the secretory endometrium [19]. Clinically, patients have premenstrual or intermenstrual bleeding, irregular, prolonged menstrual cycles. In our study, 11 patients (4.29%) had secretory endometrium. Endometrium with disorganized proliferation is encountered during the perimenopause interval in women who have sporadic anovulatory cycles and in women receiving estrogen therapy and it is considered an intermediate step between the normal proliferative endometrium and endometrial hyperplasia. In our study, this pathology was found in five cases (1.95%).

Endometrial atrophy, the result of premature ovarian failure with estrogen deficiency in patients during menopause, was identified in 18 cases (7.0%). Among the authors cited above, only Michail G et al. reported endometrial atrophy in 21.9% in a group of 84 patients [18]. Although postmenopausal uterine bleeding should raise the suspicion of endometrial hyperplasia or carcinoma, the most common cause of bleeding at this stage of life is by far endometrial atrophy. In a study of patients with postmenopausal uterine bleeding, 15% were diagnosed with various types of hyperplasia and 56% with endometrial atrophy [20].

Endometrial polyps were diagnosed in 12.9% of patients hospitalized in the clinic and represent the most common benign tumor, having as cause an increased estrogen secretion, which leads to hyperplasia of the basal endometrial layer.
Endometrial hyperplasia is a multiplication of endometrial glands which leads to mucosal thickening and occurs because of an endogenous (chronic anovulation) or exogenous (hormone replacement therapy) "prolonged estrogen stimulation". This injury is especially characteristic in perimenopausal and postmenopausal patients, but can also occur in young women during their reproductive life, usually those with "polycystic ovarian disease". Predisposing factors are similar to those of endometrial carcinoma: obesity, nulliparity, diabetes, hypertension, ovarian tumors, which are associated with an estrogen-type hormonal secretion.

Clinically, the lesion is manifested by abnormal, sometimes heavy uterine bleeding. Endometrial hyperplasia with morphological and biological alterations of endometrial glands and stroma may precede or coexist with endometrial cancer.

Our study reports endometrial hyperplasia in five cases, of which four cases (1.6%) with complex hyperplasia with atypia and three cases (1.2%) with simple hyperplasia without atypia, one with squamous metaplasia.

The classification adopted by WHO and the International Society of Gynaecological Pathology in 1994 divides endometrial hyperplasia in two categories, simple and complex, each of them having two subcategories, with or without atypia.

Classification of endometrial hyperplasia (WHO System, 1994):
- simple hyperplasia;
- complex (adenomatous) hyperplasia;
- simple atypical hyperplasia;
- complex atypical hyperplasia (atypical adenomatous).

According to [21], the terminology of endometrial morphological lesions refers to two broad classes: benign endometrial hyperplasia and endometrial intraepithelial neoplasia (EIN). The WHO system subclassifies endometrial hyperplasia according to architectural complexity and cytological atypia. Today it is known that estrogen effects unbalanced by progesterone and precancerous lesions are distinct entities. The physiological endometrial response to an abnormal estrogen stimulus defines endometrial hyperplasia generally with polyclonal proliferation, while monoclonal characteristics belong to noninvasive neoplasia and define endometrial intraepithelial neoplasia (EIN) [22].

In our study, endometrial hyperplasia represented 2.7% of the causes of uterine bleeding in menopausal patients. The analysis of the seven cases of endometrial hyperplasia showed a clear predominance of cases with hyperplasia without atypia, compared with the cases with complex hyperplasia with and without atypia. Most endometrial hyperplasias develop during menopause and are associated with anovulation, whereas postmenopausal patients with endometrial hyperplasia are usually under unantagonised estrogen replacement therapy. Patients with endometrial hyperplasia typically show abnormal uterine bleeding. Anastasiadis PG et al. disclose an endometrial hyperplasia prevalence of approximately 20% of patients investigated by biopsy for abnormal bleeding [23]. Taddei GL et al. [24] found in a study on a series of 1075 patients with abnormal uterine bleeding, a prevalence for endometrial hyperplasia of 20.2%, while 9.2% of patients were diagnosed with carcinoma. In the same study, taking into account only postmenopausal patients, hyperplasia represented 23.4%, with the prevalence of endometrial carcinoma increased to 12.3%.

Endometrial metaplasia can be epithelial or non-epithelial. Epithelial metaplasia may have several variants: squamous, mucinous, with ciliated, clear, or eosinophilic cells. The criteria for this classification developed by the WHO are both cytological and architectural. The changes address hyperestrogenism, are common in menopause transition and may occur in the case of several lesions: endometrial polyps, endometritis, endometrial hyperplasia and, the same sample from uterine scraping may contain different types of metaplasia. Non-epithelial metaplasia (stromal: cartilage, bone, smooth muscle) is much more rare and is not specific to perimenopause. In our study, we encountered a case of squamous epithelial metaplasia, associated with simple hyperplasia without atypia.

Adenomyosis is a lesion characterized by the presence within the myometrium of foci consisting of glands and endometrial stroma, located at distance of the junction between the endometrium and the myometrium. It occurs more frequently during perimenopause, being a lesion detected in 20% of surgically treated gynecological cases. It is rarely detected by transcervical endometrial resection, when the sample contains fragments of myometrium with basal endometrium and a variable quantity of functional endometrium. Frequently, the diagnosis of adenomyosis is a retrospective one, on the hysterectomy sample. Clinically, it is associated with heavy and prolonged abnormal menstrual bleeding and dysmenorrhea, frequently occurring one week before the onset of the menstruation. Histopathological examination revealed that in 25 patients (9.8%) menstrual irregularities were due to adenomyosis, although the clinical and ultrasound examinations revealed that the number of such patients was higher (24%).

Most patients with uterine fibroids associated with recurrent bleeding are treated by hysterectomy. In our study, leiomyomas are responsible for abnormal uterine bleeding in 127 patients (49.65%) and the data concurs with the results from the studies performed in DHQ Hospital and Nishtar Hospital Multan – 54.8% and Bombay Hospital – 54% [17].

In the study group of patients in menopause transition, non-specific chronic endometritis as an etiology of abnormal uterine bleeding was found in 19 patients (7.5%), which was a lower reporting rate than other studies in the literature: Jordan University – 14%, Michail G et al. – 20.7% [18].

Clinically, chronic endometritis is usually manifested by intermenstrual vaginal bleeding and sometimes menorrhagia, being diagnosed in 3–10% of women with irregular uterine bleeding who undergo endometrial biopsy [14]. Recent studies which followed the association between the diagnosis of chronic endometritis with clinical data indicated the absence of statistically
significant associations with symptoms (abnormal metrorrhagia, chronic pelvic pain), the latter being reported only in pathological inflammatory history of patients (infections of the reproductive system, salpingitis) [25].

The sensitivity of endometrial biopsy in detecting uterine abnormalities is reported in the literature to be 96%. Dilatation and curettage of the uterus are considered the gold standard for the diagnosis of endometrial cancer, but can not be seen as a therapeutic gesture for abnormal uterine bleeding; moreover, it limits the access to the region of the uterine horns, which makes perihysteroscopic biopsy a superior technique [26].

**Conclusions**

The diagnosis of perimenopause bleeding and prognostic evaluation is based on the histopathological examination of the endometrium after biopsy. Special attention should be paid to women showing an endocrine-metabolic risk profile for this type of cancer.

In the study group, menstrual irregularity was seen mainly in the 46–52-year-old group (64.5%) and in 35% of high multiparous patients.

The dominant symptom was represented by menometrorrhagia (34%), noting that in 62.1% of cases the symptoms consisted in association of abnormal uterine bleeding clinical signs: menorrhagia-hypermenorrhea, menorrhagia-polymenorrhoea, menorrhagia intermenstrual bleeding.

From the histopathological point of view, in our study leiomyofibromas were the most common cause of abnormal uterine bleeding (49.6%).

The abnormal uterine bleeding is the result of hyperestrogenic conditions in which the endometrium is in the proliferative phase (3.12% in our study) and, if untreated, may lead to endometrial adenocarcinoma.

Progestrone hormone therapy was used for 64% of patients. The choice for progesterone substitution therapy in menopause remains an individual decision that requires careful consideration of symptoms, risk factors, and the risk/benefit ratio.

**References**


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