Endometrial proliferative lesions associated with uterine fibromatosis

ANCA DANIELA BRĂILA1, DIANA VANIOVA KLIMENTOVA1, C. M. DAMIAN2, M. B. BRĂILA1

1)Department of Obstetrics and Gynecology
2)Department of Anatomy
University of Medicine and Pharmacy of Craiova
Emergency County Hospital, Craiova

Abstract
Hysteroscopy and uterine curettage are required in cases of atypical hyperplasia in premenopause and in all cases of hyperplasia with/without atypia in postmenopausal women. Biopsic curettage is the method of choice in the diagnosis of endometrial pathology. Transvaginal ultrasound and Doppler examination are useful in assessing the risk of endometrial hyperplasia or endometrial cancer in postmenopausal women with/without continuous replacement therapy, but cannot replace endometrial biopsy to exclude endometrial cancer diagnosis. Medical treatment with progesterone containing drugs addresses endometrial hyperplasia without atypia. Surgical treatment is recommended for premenopausal and postmenopausal patients with uterine fibromatosis associated with atypical hyperplasia as well as patients with adenocarcinoma. Risk of progression to malignancy requires clinical and histopathological monitoring to avoid insufficient treatment of lesions with evolutive risk and aggressive treatment of lesions without risk.

Keywords: biopsic curettage with histopathological examination, hyperplasia, adenocarcinoma, hysteroscopy, ultrasound examination, uterine fibromatosis.

Introduction
In both endometrial proliferative lesions and uterine fibromatosis, the etiopathogenic substrate is almost always represented by absolute or relative chronic hyperestrogenism, which is not counterbalanced by progesterone, premenopause being characterized by anovulatory cycles showing an increased risk of developing these diseases [1–3]. Hyperestrogenism affects both the endometrium resulting in hyperplasia and adenocarcinoma, and the myometrium resulting in the development of diffuse or circumscribed fibromatosis.

The frequency of the association between atypical endometrial hyperplasia and endometrial carcinoma varies between 17% and 52% with a variable rate of progression to carcinoma between 1% and 28%, depending on the severity of the lesion, which led to the terminology of endometrial intraepithelial neoplasia (EIN) [4–6].

Endometrial biopsy is indicated for abnormal uterine bleeding or the presence of atypical glandular cells detected on Babes–Papanicolaou cytology.

Within the uterus, the following factors were identified: EGF, TGF-α, TGF-β, IGF, PDGF (platelet-derived growth factor), VEGF (vascular endothelial growth factor), IL1 and IL6.

Production of platelet-activating factor (PAF) is regulated by ovarian steroids. Endothelin ET1 causes vasoconstriction and FGF (fibroblast growth factor) IS involved in angiogenesis [1, 7, 8].

Intracytoplasmic protein phosphorylation initiates changes in gene expression, cell metabolism and cell division. Cyclical variability of several growth factors, their receptors and their regulatory proteins, support their steroid dependence [9, 10].

Ligands, namely estrogen and progesterone, induce through specific receptors (ER and PR) effects on various cellular constituents of the endometrium and myometrium [11, 12].

3D ultrasound investigation with measurement of endometrial volume is more efficient than the measurement of endometrial thickness alone. An endometrial volume of 13 mL has a sensitivity of 100% for endometrial cancer [13–16].

Hysteroscopy is the ideal clinical method for the diagnosis and conservative management of endometrial hyperplasia. Tissue sampling and histopathological examination establish the histopathological diagnosis with a sensitivity of almost 100% [1, 17–19].

Histopathological examination is the only investigation, which can clarify the diagnosis, as well as the severity and extent of proliferative lesions [20–22].

Materials and Methods
The study was conducted over a period of five years, between 2006 and 2010, the biological material being represented biopsy samples obtained during uterine curettage and total hysterectomy specimens from patients hospitalized in the Second Clinic of Obstetrics and Gynecology of the Emergency County Hospital of Craiova.

We included patients aged between 41 and 60 years.
with uterine fibromatosis and excessive menstrual disorders clinically expressed by metrorrhagia or menometrorrhagia.

The cases were divided into two groups:
(a) Group I, consisting of patients between 41 and 50-year-old;
(b) Group II, consisting of patients between 51 and 60-year-old.

Clinical examination of patients included gynecological examination, cardiovascular examination with EKG investigation, consultation by a nutrition and metabolism physician for patients with a history of obesity and diabetes or blood glucose levels over 120 mg/dL.

Common laboratory investigations were performed: complete blood count, ESR, fibrinogen, INR, Quick test, Howell’s time, glucose, blood urea, serum creatinine, uric acid, liver tests (SGOT, SGPT), urine analysis.

Specific investigations consisted of transvaginal ultrasound, hysteroscopy and fractional biopsy curettage. Transvaginal ultrasound revealed the structure, size and shape of the uterus, targeting the myometrium as well as the endometrial thickness, the status of the cervix, ovaries and Douglas pouch. Color Doppler and Power Doppler were used to study pelvic vasculature.

Hysteroscopy was performed only for patients without any suspicion of endometrial adenocarcinoma and without heavy bleeding.

During fractional biopsy curettage, endometrial fragments were sampled that were evaluated in the Pathology Laboratory of the Emergency County Hospital of Craiova.

For the period during which the study was conducted, we recorded a total of 553 patients in the fourth and fifth decades of life who had uterine fibromatosis and who underwent diagnostic surgery – biopsy curettage, or therapeutic surgery – total hysterectomy.

Group I consisted of 360 patients between 41 and 50 years, and Group II of 193 patients aged between 51 and 60.

Histopathological analysis of the biopsy material sampled during uterine curettage allowed the following classification of endometrial proliferative lesions: simple or complex endometrial hyperplasia without atypia, simple or complex endometrial hyperplasia with atypia, endometrial carcinoma.

Patients with uterine fibromatosis and simple or complex hyperplasia without atypia received progesterone treatment while in patients with atypical hyperplasia or endometrial carcinoma radical surgery was indicated.

Results

The study included a total of 553 cases over a period of five years (from 2006 to 2010).

Of the total of 553 cases, 360 patients were assigned to Group I (those aged between 41 and 50 years) and 193 patients were assigned to Group II (those aged between 51 and 60 years).

Group I, patients aged between 41 and years, accounting for 360 cases (65%), is clearly superior to Group II of 193 patients (35%), aged 51 to 60 years (Figure 1), due to the ovarian physiological decline objectified by physiological and histological changes.

Figure 1 – Distribution of cases in the study groups.

Table 1 shows the case distribution between 2006 and 2010.

Table 1 – Distribution of cases according to age group and year

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>59</td>
<td>28</td>
</tr>
<tr>
<td>2007</td>
<td>69</td>
<td>31</td>
</tr>
<tr>
<td>2008</td>
<td>76</td>
<td>39</td>
</tr>
<tr>
<td>2009</td>
<td>74</td>
<td>48</td>
</tr>
<tr>
<td>2010</td>
<td>82</td>
<td>47</td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>360</td>
<td>193</td>
</tr>
<tr>
<td>%</td>
<td>65</td>
<td>35</td>
</tr>
</tbody>
</table>

Transvaginal ultrasound is controversial as selection method for biopsy in patients with postmenopausal uterine bleeding with high risk of endometrial pathology (Table 2).

Table 2 – Endometrial thickness as measured by ultrasound examination

<table>
<thead>
<tr>
<th>Patients</th>
<th>Endometrial thickness [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min.</td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td>4</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>5</td>
</tr>
</tbody>
</table>

Hysteroscopic analysis revealed in the first batch an increased incidence of endometrial hyperplasia without atypia – 255 cases (70%). In Group II, we observed an increased incidence of hyperplasia with atypia – 53 cases (48%). We must mention that diagnostic hysteroscopy was not performed in patients with suspicion of endometrial cancer.

Histopathological analysis of endometrial biopsies from the two groups revealed endometrial hyperplasia in Group I; in Group II, there were 53 cases with endometrial hyperplasia but also endometrial carcinoma. In Group I (patients aged between 41 and 50 years), histopathological examination revealed hyperplasia types in Table 3.

Table 3 – Distribution of cases in Group I according to histopathological examination

<table>
<thead>
<tr>
<th>Endometrial hyperplasia</th>
<th>No. of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple without atypia</td>
<td>137</td>
<td>38</td>
</tr>
<tr>
<td>Complex without atypia</td>
<td>118</td>
<td>33</td>
</tr>
<tr>
<td>Simple with atypia</td>
<td>62</td>
<td>17</td>
</tr>
<tr>
<td>Complex with atypia</td>
<td>43</td>
<td>12</td>
</tr>
</tbody>
</table>
In terms of histopathology, the first group of 360 patients there is an increased frequency of hyperplasia without atypia, simple (137 cases, 38%) and complex (118 cases, 33%) (Figure 2).

We mention that in this group there were no cases with endometrial carcinoma.

In Group II (patients aged between 51 and 60 years), histopathological examination showed an endometrium with the proliferative lesions presented in Table 4.

In the second group of 193 patients, the percentages change in favor of hyperplasia with atypia, simple (45 cases, 23%) and complex (48 cases, 25%), and also endometrial cancer (53 cases, 27%) (Figure 3).

Microscopic examination established the diagnosis of certainty, both for hyperplasia with or without atypia and uterine adenocarcinoma (Figures 4–7).
The microscopic appearance of simple endometrial hyperplasia without atypia shows increased numbers of endometrial glands lined by a simple cuboidal epithelium, without atypia, that reduce the inter-glandular stroma with a glands/stroma ratio of 2/1; a particular aspect is cystic glandular hyperplasia in which some glands show cystic dilations, maintaining the simple hyperplasia without atypia appearance.

Simple hyperplasia with atypia is characterized by increased number of endometrial glands with a glands/stroma ratio of 2/1, but the glandular epithelium may show stratification and pseudo-stratification, sometimes squamous or eosinophilic metaplasia with the presence of cellular atypia at this level.

Complex hyperplasia without atypia is characterized by a marked increase in endometrial glands with different shapes and sizes lined by epithelium, some with pseudo-stratification, even a “back to back” disposition, but no atypical glandular epithelium.

In complex hyperplasia with atypia, there is an increase in the number of endometrial glands giving the “back to back” appearance, with lining stratified epithelium with cytonuclear atypia, some even showing intraluminal papilliferous projections, down to the appearance of adenocarcinoma in situ; the two histological aspects coexisted in some cases.

In terms of therapeutic conduct, in the first group 255 patients received progesterone therapy, and for the other 105 patients total hysterectomy was indicated. In the second group, 47 patients received hormonal therapy and 146 underwent radical surgery (Table 5).

Table 5 – Therapeutic conduct in the two study groups

<table>
<thead>
<tr>
<th>Therapeutic conduct</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>255 70</td>
<td>47 24.5</td>
</tr>
<tr>
<td>Surgery</td>
<td>105 30</td>
<td>146 75.5</td>
</tr>
</tbody>
</table>

Discussion

After the age of 40 years, the estrogen-progesterone balance begins to change in favor of the estrogens. Initially, relative estrogenemia by lowering progesterone, and later absolute estrogenemia by complete absence of progesterone, leave their mark on the endometrium through proliferative lesions and also on the myometrium through uterine fibromatosis.

In terms of endometrial thickness, measured by transvaginal ultrasound in patients diagnosed with endometrial hyperplasia and those diagnosed with endometrial cancer, the maximum endometrial thickness 15 mm in patients with hyperplasia and 20 mm in patients diagnosed with cancer.

Hysteroscopy analysis in the first batch, in simple endometrial hyperplasia, revealed a thickened endometrium with characteristic bushy, velvety appearance, with increased, pink-rose-like submucosal blood supply. In polypoid hyperplasia, the thickened endometrium shows pink-whitish elongated protrusions of varying sizes, sometimes with surface microbleeds. Glandular-cystic hyperplasia shows prominent translucent cysts with tree-like fine blood supply. In adenomatous simple hyperplasia, the endometrium is thick, dense, festooned, sometimes multi-layered, pink-whitish, sometimes bright and/or with cerebroid aspect. In this group, there was an increased incidence of endometrial hyperplasia without atypia (255 cases, 70%).

Adenomatous hyperplasia with atypia had a higher incidence in Group II (53 cases, 48%). In terms of hysteroscopy, endometrial architecture is altered, with irregular budding, sometimes even vegetant appearance, depending on the mild, moderate or severe form. The vasculature is thicker, twisted, with pathognomonic “corkscrew” appearance of the vessels.

In the first group, therapeutic management consisted of hormonal therapy in 255 patients (70%) and surgery in 105 patients (30%).

In the second group, the following therapeutically scheme was used: hormonal therapy in 47 cases (25%) and radical surgery in 146 patients (75%).

The objectives of hormonal therapy are: correction of menometorrhagia, transformation of the proliferative endometrium into a hypoplastic or atrophic one, avoidance of relapses, minimized risks, especially metabolic and cardiovascular ones. From the existing groups of hormone drugs we used progestins such as Lutenyl, Arefam, Utrogestan in short and long administration. Hormonal treatment in the first group was indicated in cases of hyperplasia without atypia, simple (137 cases, 38%) and complex (118 cases, 33%).

Abdominal or vaginal hysterectomy in benign proliferative lesions of the endometrium with menometorrhagia unresponsive to hormonal treatment was performed in cases with hyperplasia with atypia and in patients over 45 years with uterine fibromatosis. Hormonal treatment in the second group was indicated in patients with hyperplasia without atypia, simple (17 cases, 9%) and complex (30 cases, 16%).

Classical or laparoscopic hysterectomy was performed in patients with simple or complex hyperplasia with atypia.

Excision surgery was the main treatment in endometrial cancer, along with physical agents and hormonal medication. The surgical procedure consisted of total extended hysterectomy with pelvic lymphadenectomy and ablation of a large vaginal collar.

Discussion

Endometrial biopsy, ultrasound examination and hysteroscopy can be used as a diagnostic tripod for detecting endometrial proliferative lesions. The increased incidence of endometrial hyperplasia without atypia was present in the 41–50 years age group (255 patients, 70%).

In the group of patients between 51 and 60 years of age, there is an increased incidence of endometrial hyperplasia with atypia and endometrial adenocarcinoma (146 patients, 75%).

Hormonal therapy has proven beneficial in cases of simple or complex hyperplasia without atypia.

Total hysterectomy with bilateral annexectomy was
the indication of choice for patients with hyperplasia with atypia, simple or complex and in cases over 45-year-old with associated uterine fibromatosis.

In some cases, respecting the conditions, indications and contraindications, complex radio-therapeutic oncstatic treatment and ultra-radical surgery (total enlarged organs and contraindications, complex radio-therapeutic oncological treatment and pelvic lymphadenectomy) were performed.

References

Corresponding author
Anca Daniela Brăila, Teaching Assistant, MD, Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, 2–4 Petru Rareș Street, 200349 Craiova, Romania; Phone +40761–326 917, e-mail: ancabraila@yahoo.com

Received: August 22nd, 2012
Accepted: October 25th, 2012