Descriptive epidemiology of endometrial hyperplasia in patients with abnormal uterine bleeding

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Summary

Purpose of investigation: To evaluate the prevalence and epidemiologic characteristics of endometrial hyperplasias in women with abnormal uterine bleeding.

Methods: We performed a retrospective analysis on data gained grom 294 patients with histologically documented endometrial hyperplasia (with or without atypia), detected among 1,469 women who underwent fractional dilatation and curettage in our department due to abnormal uterine bleeding from 1986 to 1998. Epidemiologic characteristics were abstracted from the patients' medical charts.

Results: 294/1469 women were found with endometrial hyperplasia (258 without atypia and 36 atypical hyperplasias). Thirty-six of them were under 40 years of age. Four of the detected endometrial hyperplasias progressed to endometrial carcinoma (one with simple hyperplasia, two with complex and one with atypical hyperplasia). Obesity and hypertension were justified as risk factors in our study population.

Conclusions: The prevalence of endometrial hyperplasia according to our data was 20%. There were statistically significant differences in most epidemiologic parameters between the two types of hyperplasia. The progression of four endometrial hyperplasias to endometrial adenocarcinoma indicates the need for intense follow-up even in cases where patients undergo conservative therapy.

Key words: Endometrial hyperplasia; Risk factors; Prevalence; Endometrial carcinoma.

Introduction

Endometrial hyperplasia (EH) is a pathologic condition that is usually associated with abnormal uterine bleeding, the symptom that commonly brings the patient to the attention of the gynecologist.

Hyperplasia of the endometrium results from estrogenic stimulation of the endometrium without the usual cyclic modification of progesterone and, therefore, is almost invariably found in anovulatory women. Although it is a situation that usually affects perimenopausal or postmenopausal women it can also be found in younger patients who are anovulatory [1].

The association between unopposed estrogen and endometrial hyperstimulation is well recognised. The endometrial response to unopposed estrogen can be viewed as a spectrum of changes ranging from the benign to the malignant. This concept is supported by specimens from hysterectomies performed for endometrial adenocarcinoma, in which adjacent areas frequently show hyperplastic changes. As unopposed estrogen stimulation continues, the degree of endometrial abnormality increases. If hyperestrogenism persists, endometrial hyperplasia of varying degrees will develop and may eventually progress to endometrial adenocarcinoma. Clinical manifestations of endometrial hyperstimulation are the same for both hyperplasia and carcinoma, consisting mainly of abnormal bleeding. The bleeding has no specific pattern, and may be either postmenopausal, metrorrhagic or menorrhagic [2].

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Ferency [3] and Kurmann *et al.* [4] reported: "there is an increasing recognition that endometrial hyperplasias can be divided into two broad groups, those that are associated with a risk of eventual development of an invasive endometrial adenocarcinoma and those which are devoid of such a risk". There is also a now generally accepted agreement that the critical difference between these two groups is the presence or absence of cytological atypia. Fox [5] has proposed the following classification: I. Hyperplasia without cytological atypia. II. Hyperplasia with cytological atypia. Included in the group without cytological atypia are two morphologically distinct entities, one with architectural abnormalities and one lacking any architectural aberrations, the former being classed as a "complex" hyperplasia and the latter as a "simple" hyperplasia (previously known as "cystic glandular hyperplasia"). Any hyperplasia showing cytological atypia is classed as an "atypical" hyperplasia and there are no compelling reasons for subdivision of this group.

The presence of cytological atypia is the single most important predictor of malignant potential and resistance to medical therapy. Distinguishing between atypical hyperplasia and endometrial carcinoma can be difficult, particularly in small endometrial samples [2], and the presence of arbitrarily defined endometrial stromal invasion is determinative [4].

Recent studies declare that atypical hyperplasia is not directly related to excess estrogenic stimulation, but it may represent an autonomous neoplastic growth of the endometrium [6].

The aim of the present study was to assess the prevalence of endometrial hyperplasia (with and without

atypia), to evaluate the presence of selected risk factors in each type of hyperplasia in our study population and finally to discuss the risk of hyperplastic lesions progressing to carcinoma.

Materials and Method

From January 1986 to December 1998, 1,469 women aged 23-79 years presenting with abnormal uterine bleeding were treated in our department. Abnormal uterine bleeding (AUB) was considered as an increase in blood loss during menses or in the length of menses (menorrhagia), or an increase in the number of bleeding episodes (polymenorrhea), or irregular bleeding episodes that occur at frequent intervals during menses and in postmenopause [7].

None of these patients were undergoing hormonal replacement therapy, nor were pregnant, receiving tamoxifen or oral contraceptives.

All patients, after histologic diagnosis of EH without atypia were subjected to progesterone therapy and follow-up protocol, while patients with atypical EH were prompted to undergo surgical treatment. Up to 1995 the follow-up protocol comprised endometrial thickness measurement every 6 months by transvaginal sonography and D&C in case of symptoms (AUB) or thick endometrium. We used a 10 mm cut-off limit for endometrial thickness in premenopausal women (double layer) and a 5 mm cut-off limit in postmenopausal women.

From 1995 and on hysteroscopy was added to the protocol as an initial diagnostic routine method in cases of AUB as well as prior to every endometrial biopsy or D&C needed in patient follow-up. All samples were obtained under general anesthesia except for patients with contraindications for general anesthesia, whose biopsies were carried out under paracervical block.

Obesity, diabetes mellitus, hypertension, menopausal status and subfertility which are generally accepted as risk factors for EH, were included in our analysis.

We estimated obesity by Body Mass Index (BMI) which is body weight (in kg) divided by height (in meters)^2.

To evaluate our results we used frequency tables and the x^2 test for proportions.

Results

From the 1,469 women (716 pre and 753 postmenopausal) submitted to D&C due to AUB, 294 were found with EH. After 1995 (when hysteroscopy was established as a routine diagnostic procedure in our clinic) 76 EH were detected (69 without atypia and 7 atypical).

Table 1 describes the prevalence of EH in our study population, classified by the presence of atypia. The cumulative prevalence of EH was 20% (294/1469). In detail, the prevalence of EH whithout atypia was 17.6% and of atypical EH 2.4%. The prevalence of EH in postmenopausal women was 15.6% (118/753). Atypical EH in the same group accounted for 3.6%. (27/753).

Table 2 displays the distribution of selected risk factors for each type of EH in our patients. The analysis of our data suggests that there is a statistically significant difference between the two types of EH regarding most risk factors for the disease, with diabetes mellitus being an exception.

Table 1. — *Prevalence of endometrial hyperplasia in patients with A.U.B.*

Type of hyperplasia	No of patients	Prevalence %
Without atypia	258	17.6
Atypical	36	2.4
Total	294	20.0

Table 2. — *Distribution of risk factors for endometrial hyperplasia.*

Risk factor	Type of hyperplasia				
	Without atypia (n=258)		Atypical (n=36)		
	n	%	n	%	p
Obesity					
</=25	38	14.7	11	30.5	
26-29	197	76.3	22	61.1	<0.001
>/=30	23	9	3	8.4	
Diabetes Mellitus					
Yes	31	12	4	11.1	<0.9
No	227	88	32	88.9	
Hypertension					
Yes	150	58.1	28	77.8	<0.05
No	108	41.9	8	22.2	
Menopause					
Yes	91	35.2	27	75	<0.01
No	167	64.8	9	25	
Subfertility					
Yes	24	9.3	9	25	<0.01
No	234	90.7	27	75	

Table 3. — *Progression of endometrial hyperplasia to cancer.*

Type of hyperplasia	Patient's age	Time of cancer detection
Without atypia		
• Simple	46	3 years
• Complex	36	1 year
• Complex	40	1.5 years
• Atypical	58	6 months

Of further significance is the detection of endometrial carcinoma in four cases of endometrial hyperplasia that progressed to carcinomas (Table 3). All four patients were detected after 1995 and were hysteroscopically diagnosed and followed-up. Another three patients with documented complex hyperplasia as first diagnosis develeped endometrial adenocarcinoma while under progesterone therapy. However, we cannot describe the malignancy's appearance as "progression to cancer", since these patients were diagnosed before 1995 and, therefore, they were not hysteroscopically followed-up.

The first patient presented simple hyperplasia at the age of 46. After cessation of the menses at 47, the woman had recurrent metrorrhagia and she underwent two D&Cs in two years time. The histological diagnosis of the first D&C was simple hyperplasia, while the second showed endometrial adenocarcinoma of endometrioid type.

Two women with complex hyperplasias aged 36 and 40 developed endometrial carcinoma in one and one and a half years, respectively. The first one underwent one D&C and the second one two D&Cs due to recurrent hemorrhage.

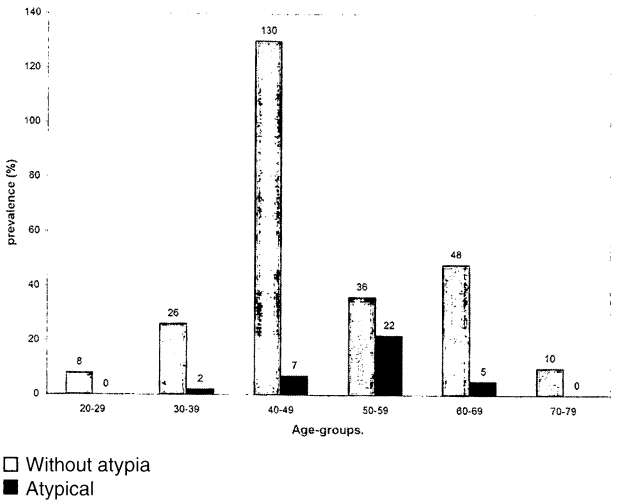

Figure 1. — Distribution of endometrial hyperplasias in women with abnormal uterine bleeding by age.

One woman with atypical hyperplasia, aged 58, developed endometrial carcinoma in six months. The patient with this atypical pattern of hyperplasia refused surgical treatment and underwent another D&C due to recurrent haemorrhage. The histological diagnosis showed adenocarcinoma of the endometrium of endometrioid type. The patient was submitted to total hysterectomy and histologic examination of the uterus revealed the coexistence of atypical hyperplasia adjacent to endometrial cancer.

The distribution of both types of EH (atypical and without atypia) according to age is described in Figure 1. The peak incidence of EH without atypia is observed in the 5th decade of life while the respective one for atypical hyperplasia appears a decade later. The presence of 36 women (34 with EH without atypia and 2 with atypical EH) under 40 years of age (2.4%) is of great interest.

Discussion

EH, defined as abnormally increased proliferation of endometrial glands of irregular size and shape has recently been divided – following proposals by the International Society of Gynecological Pathologists and the World Health Organization – into two categories based on the presence or absence of cytological atypia, and further classified as simple or complex according to the extent of architectural abnormalities [8]. In recent studies a different origin of atypical EH has been demonstrated based on information of clonal analysis and genetic alterations in endometrial biopsy samples. In detail, the monoclonal pattern of atypical hyperplasia and endometrial carcinoma has been justified in contrast to polyclonal origin in hyperplasias without atypia [9, 10].

It appears that cytologic atypia is useful in identyfying a patient with a significantly increased likelyhood of developing carcinoma; the presence of superimposed glandular complexity and crowding places the patient at greater risk [4, 8].

According to our data, the progression of EH to malignancy was 4.3% for hyperplasias without atypia (3/69). The results of our study are consistent with some authors' opinions about the possible progression of hyperplasia to carcinoma [8, 11]. Kurman *et al.* [4] found that progression to carcinoma occurred in only 1% of patients with simple hyperplastic lesions, 3% of patients with complex hyperplasias and 23% of patients with atypical hyperplasias.

Fox *et al.* [12] reported that approximately 1/3 of patients with an atypical endometrial hyperplasia will eventually develop an invasive adenocarcinoma of the endometrium.

Ho *et al.* [13] referring to the risk of endometrial cancer development in patients with EH, reports a 27.6% incidence of endometrial carcinoma in cases of EH with atypia and 3.4% in those without atypia.

Baak *et al.* [14] described a cumulative risk of 15% for endometrial hyperplasia to progress to a metachronous endometrial carcinoma.

We cannot affirm that atypical hyperplasias progress to cancer because all our patients with atypical hyperplasia were surgically treated according to our protocols. The only patient with atypical hyperplasia who developed endometrial cancer, localized at the same place with hyperplasia, refused to undergo surgical treatment immediately after inizial diagnosis.

The coexistence of atypical hyperplasia with endometrial cancer found in the hysterectomy specimen of that patient is in accordance with previous reports. Gordon and Ireland [15] reported that of patients with atypical hyperplasia in curetting specimens, approximately 25% will have an associated well-differentiated carcinoma of the endometrium, if a hysterectomy is performed. Janicek and Rosenhein [16] described a 43% concurrent endometrial cancer in patients who undergo hysterectomy for "atypical hyperplasia".

There have been numerous investigators in the past who have evaluated obesity, parity, diabetes mellitus, age, and menopause as risk factors for endometrial hyperplasia [17-19]. Our study results indicate that there are statistically significant differences in the distribution of risk factors among patients presenting EH with or without atypia. Obesity (BMI>25) prevails in patients with EH without atypia against those with atypia ($p<0.001$). Diabetes mellitus presents a similar distribution in the two sub-populations, while hypertension is of a marginal significance. On the other hand, menopause and subfertility are more commonly met in patients with atypical EH ($p<0.01$).

The cumulative prevalence of hyperplasia in postmenopausal women in our study was 15.6%, while the incidence of atypical EH in the same group was 3.6%. These numbers resemble the ones reported by Gredmark *et al.* [19] who found 7.2% frequency of adenomatous and atypical EH in postmenopausal women with AUB.

Lee and Scully [20] reported ten cases of complex endometrial hyperplasia in patients between 15-20 years. Patients of such age were not included in our study population, but we found 36 women (34 with EH without

atypia and 2 with atypical EH) less than 40 years of age. Bearing in mind the malignant potential of EH, as mentioned above, the considerable percentage of young reproductive women with hyperplastic lesions (36/294, 12.2%) indicates the need for intense follow-up of these women, even if they are under therapeutic protocols.

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